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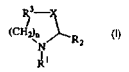
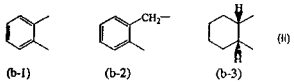
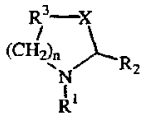
最終頁に続く

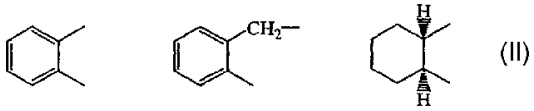
(54)【発明の名称】トリペプチジルペプチダーゼ阻害剤

(57)【要約】
【化１】



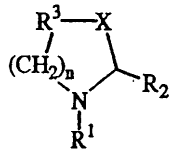






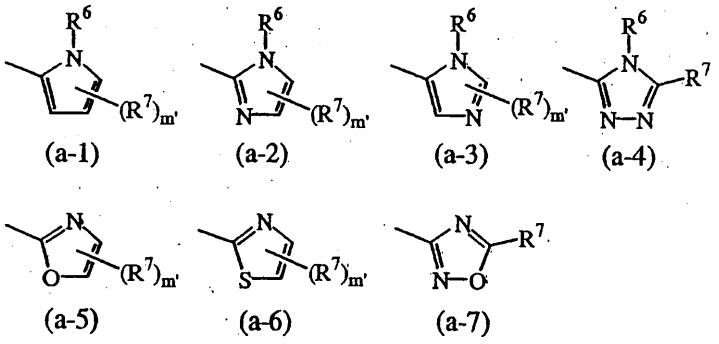
本発明は、内因性神経ペプチド、例えばコレシストキニン（ＣＣＫ）の不活性化に関与する膜トリペプチジルペプチダーゼの阻害剤である式（Ｉ）の新規化合物に関する。さらに本発明は、そのような化合物を製造する方法、該化合物を含んでなる製薬組成物ならびに該化合物の医薬としての使用に関する。（Ｉ）において、ｎは整数（０）もしくは（１）であり；Ｘは、Ｏ；Ｓ；または－（CR^4R^5）$_m$－［式中、ｍは整数（１）もしくは（２）であり；R^4およびR^5は各々互いに独立して水素もしくはC_{1-4}アルキルである］を表し；R^1は、場合によっては、ヒドロキシ；C_{1-6}アルキルオキシカ

【特許請求の範囲】
【請求項１】
式（Ｉ）
【化１】



(I),

の化合物、その立体化学的異性型、またはその製薬的に許容しうる付加塩
｛式中、
ｎは、整数０もしくは１であり；
Ｘは、Ｏ；Ｓ；または－（ＣＲ^{4}Ｒ^{5}）$_{m}$－［式中、ｍは整数１もしくは２であり；Ｒ^{4}およびＲ^{5}は各々互いに独立して水素もしくはＣ$_{1-4}$アルキルである］を表し；
Ｒ^{1}は、場合によっては、ヒドロキシ；Ｃ$_{1-6}$アルキルオキシカルボニル；アミノＣ$_{1-6}$アルキルカルボニル［式中、Ｃ$_{1-6}$アルキル基はＣ$_{3-6}$シクロアルキルにより場合によっては置換されている］；モノ－およびジ（Ｃ$_{1-4}$アルキル）アミノＣ$_{1-6}$アルキルカルボニル；アリールにより置換されているアミノカルボニル；Ｃ$_{1-6}$アルキルカルボニルオキシＣ$_{1-6}$アルキルカルボニル；Ｃ$_{1-6}$アルキルオキシカルボニルアミノＣ$_{1-6}$アルキルカルボニル［式中、アミノ基はＣ$_{1-4}$アルキルにより場合によっては置換されている］；カルボニル基を介して結合されるアミノ酸残基；アミノにより置換されているＣ$_{1-6}$アルキル；またはアリールカルボニルであり；
Ｒ^{2}は、
【化２】

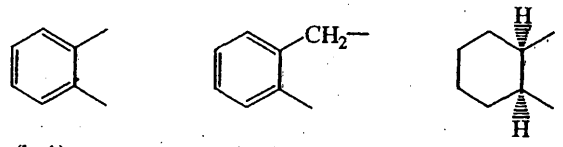


(a-1) (a-2) (a-3) (a-4)

(a-5) (a-6) (a-7)

［式中、ｍ’は、整数１もしくは２であり；
Ｒ^{6}は、水素もしくはＣ$_{1-4}$アルキルであり；
Ｒ^{7}は、互いに独立して水素；ハロ；アミノ；ヒドロキシ；トリフルオロメチル；Ｃ$_{1-6}$アルキル；ヒドロキシ、ヒドロキシカルボニル、Ｃ$_{1-4}$アルキルオキシカルボニル、アミノカルボニル、モノ－もしくはジ（Ｃ$_{1-4}$アルキル）アミノカルボニル、アミノ、またはモノ－もしくはジ（Ｃ$_{1-4}$アルキル）アミノにより置換されているＣ$_{1-4}$アルキル；フェニル；アミノカルボニル；ヒドロキシカルボニル；Ｃ$_{1-4}$アルキルオキシカルボニル；Ｃ$_{1-4}$アルキルカルボニル；またはＣ$_{1-4}$アルキルオキシカルボニルＣ$_{1-4}$アルキルアミノカルボニルである］
から選ばれる５員の複素環であるか；
あるいはＲ^{2}は、ベンズイミダゾールか、またはハロ、トリフルオロメチル、Ｃ$_{1-4}$アルキル、ヒドロキシ、ヒドロキシカルボニルもしくはＣ$_{1-4}$アルキルオキシカルボニルから各々独立して選ばれる置換基１もしくは２個により置換されているベンズイミダゾールであり；

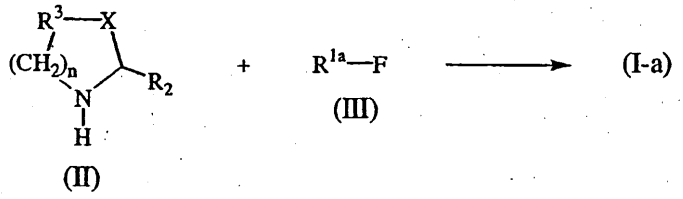
R^3は、ハロもしくはフェニルメチルにより場合によっては置換されている二価の基－CH_2CH_2－であるか；
あるいはR^3は、式
【化３】



(b-1) (b-2) (b-3)

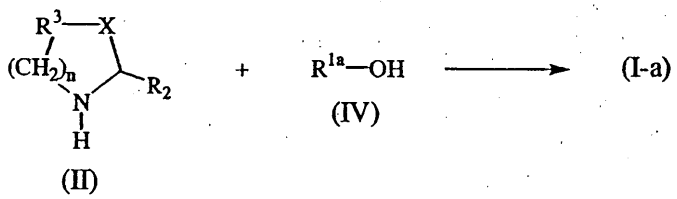
［式中、該（ｂ－１），（ｂ－２）もしくは（ｂ－３）は、ハロ、ヒドロキシ、C_{1-6}アルキル、C_{1-6}アルキルオキシ、ニトロ、アミノ、シアノ、トリフルオロメチル、フェニル、または各々独立してハロ、ヒドロキシ、シアノ、C_{1-6}アルキル、C_{1-6}アルキルオキシ、ニトロ、シアノおよびトリフルオロメチルから選ばれる置換基１もしくは２個により置換されているフェニル、から各々独立して選ばれる置換基１、２もしくは３個により場合によっては置換されていてもよい］の二価の基であり；
アリールは、フェニルか、またはアミノ、ニトロもしくはヒドロキシカルボニルにより置換されているフェニルである｝。
【請求項２】
ｎが０であり、そしてR^3がハロもしくはメトキシにより場合によっては置換されている式（ｂ－１）の基である、請求項１において請求される化合物。
【請求項３】
ｎが０であり、R^3がハロもしくはメトキシにより場合によっては置換されている式（ｂ－１）の基であり、そしてＸが－CH_2－もしくは－CH_2CH_2－を表す、請求項１において請求される化合物。
【請求項４】
が式（ａ－２），（ａ－４），（ａ－６）もしくは（ａ－７）の基である、先行請求項のいずれかに記載の化合物。
【請求項５】
R^1がC_{1-6}アルキルカルボニル、アミノC_{1-6}アルキルカルボニルもしくはアミノ酸である、先行請求項のいずれかに記載の化合物。
【請求項６】
製薬学的に許容しうるキャリヤーおよび治療上有効量の請求項１～５のいずれかにおいて請求される化合物を含んでなる製薬学的組成物。
【請求項７】
治療上有効量の請求項１～５のいずれかにおいて請求される化合物が製薬学的に許容しうるキャリヤーと緊密に混合される、請求項６において請求される製薬学的組成物の製造方法。
【請求項８】
医薬として使用するための、請求項１～５のいずれかにおいて請求される化合物。
【請求項９】
式（Ｉ）の化合物の製造方法であって、
ａ）式（ＩＩ）の中間体が、反応に不活性な溶媒中、そして場合によっては適当な塩基の存在下で、式（ＩＩＩ）の中間体と反応され、それによってR^{1a}がアミノにより置換されているC_{1-4}アルキル以外のすべてのR^1置換基を表す式（Ｉ）の化合物として定義される、式（Ｉ－ａ）の化合物を生成するか；または

【化４】



b）式（ＩＩ）の中間体が式（ＩＶ）の中間体と反応され、それによって式（Ｉ－ａ）の化合物を生成するが；

【化５】



この場合、上記反応スキームにおいて、基R^1、R^2、R^3、および整数ｎは請求項１において定義されたとおりであるか；

ｃ）または、式（Ｉ）の化合物が、技術上既知の変換反応にしたがって各々他の化合物に転化されるか；または所望であれば、式（Ｉ）の化合物が酸付加塩に転化されるか、または反対に、式（Ｉ）の化合物の酸付加塩がアルカリを用いて遊離の塩基形態に転化され；そして所望であれば、その立体化学的異性型を製造する、方法。

【発明の詳細な説明】

【０００１】

（技術分野）

本発明は、内因性神経ペプチド、例えばコレシストキニン（ＣＣＫ）の不活性化に関与する膜トリペプチジルペプチダーゼの阻害剤である式（Ｉ）の新規化合物に関する。さらに本発明は、そのような化合物を製造する方法、該化合物を含んでなる製薬組成物ならびに該化合物の医薬としての使用に関する。

【０００２】

コレシストキニン（ＣＣＫ）は、腸および脳において多面作用（ｐｌｅｉｏｔｒｏｐｉｃ）の生物学的効果を発揮するホルモンおよびニューロンペプチドのファミリーである。ＣＣＫの作用は、CCK_AおよびCCK_B受容体によって媒介される。ＣＣＫは、CCK_Aアゴニストによって増進される食物摂取の制御（Ｓｍｉｔｈ Ｇ．Ｐ．ｅｔ ａｌ．，Ｊ．Ａｎｎ．Ｎ．Ｙ．Ａｃａｄ．Ｓｃｉ．，７１３，２３６－２４１（１９９４））、およびCCK_Bアンタゴニストによって低下される不安の制御（Ｗｏｏｄｒｕｆｆ Ｇ．ｅａｌ．，Ｒｅｖ．Ｐｈａｒｍａｃ．，３１，４６９－５０１（１９９１））において生理学的役割を有することが知られている。

【０００３】

トリペプチジルペプチダーゼＩＩ（ＴＰＰ ＩＩ）は、ＣＣＫ不活性化ペプチダーゼである。ＴＰＰ ＩＩは、コレシストキニンに応答するニューロンならびに非ニューロン細胞において見いだされている。ＴＰＰ ＩＩは、ＣＣＫ－８不活性化に関与する神経ペプチダーゼであると考えられる（Ｒｏｓｅ Ｃ．ｅｔ ａｌ．，Ｎａｔｕｒｅ，３８０，４０３－４０９（１９９６））。

【０００４】

ＴＰＰ ＩＩは胃腸管におけるＣＣＫ－８不活性化において必要とされる。外因性のＣＣＫは食物摂取を低下させ、そして満足という行動的付随状況を惹起する。食物摂取はCCK_A受容体アゴニストの全身的投与によって増進される（Ｓｍｉｔｈ Ｇ．Ｐ．ｅｔ ａｌ．，Ｊ．Ａｎｎ．Ｎ．Ｙ．Ａｃａｄ．Ｓｃｉ．，７１３，２３６－２４１（１９９４）

）。内因性ＣＣＫ制御の食物摂取は、ホルモン起源よりもむしろニューロン性であると考えられ、そして迷走神経の求心線維における末梢CCK_A受容体に作用する（Ｓｍｉｔｈ　Ｇ．Ｐ．ｅｔ　ａｌ．，Ａｍ．Ｊ．Ｐｈｙｓｉｏｌ．，２４９，Ｒ６３８－Ｒ６４１（１９８５））。

【０００５】

ＴＰＰ　ＩＩの阻害剤は、ＣＣＫニューロンの機能を研究する上で有用な道具であり、そして過食、肥満、胃腸運動に関する問題および精神病症候群のような障害の治療のための有用な薬物になるであろう。

【０００６】

１９９６年１１月１４日公表のＷＯ－９６／３５８０５は、胃腸および精神障害の治療において有用な内因性神経ペプチドの不活性化に関わる膜トリペプチジルペプチダーゼの阻害剤を開示している。１９９９年７月８日公表のＷＯ－９９／３３８０１は、摂食障害、肥満、精神病症候群および関連する精神医学障害の治療において有用なＣＣＫ不活性化トリペプチジルペプチダーゼ（ＴＰＰ　ＩＩ）阻害性化合物を開示している。

【０００７】

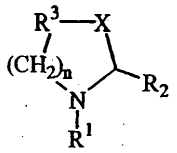
本発明の化合物は、R^2置換基の性質によって、引用されている技術上既知の化合物とは構造的に異なる。

【０００８】

本発明は、式（Ｉ）

【０００９】

【化６】



(I),

【００１０】

の化合物、その立体化学的異性型、またはその製薬的に許容しうる付加塩に関していて、

式中、

ｎは、整数０もしくは１であり；

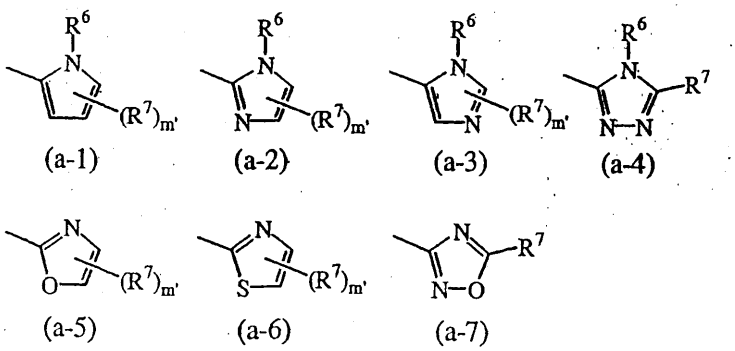
Ｘは、Ｏ；Ｓ；または－（CR^4R^5）$_m$－［式中、ｍは整数１もしくは２であり；R^4およびR^5は各々互いに独立して水素もしくはC_{1-4}アルキルである］を表し；

R^1は、場合によっては、ヒドロキシ；C_{1-6}アルキルオキシカルボニル；アミノC_{1-6}アルキルカルボニル［式中、C_{1-6}アルキル基はC_{3-6}シクロアルキルにより場合によっては置換されている］；モノ－およびジ（C_{1-4}アルキル）アミノC_{1-6}アルキルカルボニル；アリールにより置換されているアミノカルボニル；C_{1-6}アルキルカルボニルオキシC_{1-6}アルキルカルボニル；C_{1-6}アルキルオキシカルボニルアミノC_{1-6}アルキルカルボニル［式中、アミノ基はC_{1-4}アルキルにより場合によっては置換されている］；カルボニル基を介して結合されるアミノ酸残基；アミノにより置換されているC_{1-6}アルキル；またはアリールカルボニルであり；

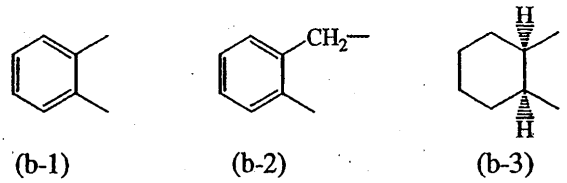
R^2は、

【００１１】

【化７】



【００１２】
［式中、ｍ’は、整数１もしくは２であり；
R^6は、水素もしくはC_{1-4}アルキルであり；
R^7は、互いに独立して水素；ハロ；アミノ；ヒドロキシ；トリフルオロメチル；C_{1-6}アルキル；ヒドロキシ、ヒドロキシカルボニル、C_{1-4}アルキルオキシカルボニル、アミノカルボニル、モノ－もしくはジ（C_{1-4}アルキル）アミノカルボニル、アミノ、またはモノ－もしくはジ（C_{1-4}アルキル）アミノにより置換されているC_{1-4}アルキル；フェニル；アミノカルボニル；ヒドロキシカルボニル；C_{1-4}アルキルオキシカルボニル；C_{1-4}アルキルカルボニル；またはC_{1-4}アルキルオキシカルボニルC_{1-4}アルキルアミノカルボニルである］
から選ばれる５員の複素環であるか；
あるいはR^2は、ベンズイミダゾールか、またはハロ、トリフルオロメチル、C_{1-4}アルキル、ヒドロキシ、ヒドロキシカルボニルもしくはC_{1-4}アルキルオキシカルボニルから各々独立して選ばれる置換基１もしくは２個により置換されているベンズイミダゾールであり；
R^3は、ハロもしくはフェニルメチルにより場合によっては置換されている二価の基－CH_2CH_2－であるか；
あるいはR^3は、式
【００１３】
【化８】



【００１４】
［式中、該（ｂ－１），（ｂ－２）もしくは（ｂ－３）は、ハロ、ヒドロキシ、C_{1-6}アルキル、C_{1-6}アルキルオキシ、ニトロ、アミノ、シアノ、トリフルオロメチル、フェニル、または各々独立してハロ、ヒドロキシ、シアノ、C_{1-6}アルキル、C_{1-6}アルキルオキシ、ニトロ、シアノおよびトリフルオロメチルから選ばれる置換基１もしくは２個により置換されているフェニル、から各々独立して選ばれる置換基１、２もしくは３個により場合によっては置換されていてもよい］の二価の基であり；
アリールは、フェニルか、またはアミノ、ニトロもしくはヒドロキシカルボニルにより置換されているフェニルである。
【００１５】
本明細書において使用される用語「アミノ酸残基」は、グリシン、アラニン、バリン、ロイシン、イソロイシン、メチオニン、プロリン、フェニルアラニン、トリプトファン、セリン、スレオニン、システイン、チロシン、アスパラギン、グルタミン、アスパラギン酸

、アスパラギン酸のエステル、グルタミン酸、グルタミン酸のエステル、リジン、アルギニン、およびヒスチジンアミノ酸残基であって、これらは、分子の残りの窒素原子にそれらのカルボニル基を介して結合されていて、そして一般に「Ｒ－ＣＨ（NH_2）－ＣＯ－」によって表すことができる。

【００１６】

前述の定義において使用されるように、ハロは、一般にフルオロ、クロロ、ブロモおよびヨードであり；C_{1-4}アルキルは、例えば、メチル、エチル、プロピル、ブチル、１－メチルエチル、２－メチルプロピルおよびそれに類するもののような炭素原子１～４個をもつ直鎖および分枝鎖の飽和炭化水素基を定義し；C_{1-6}アルキルは、C_{1-4}アルキルならびに炭素原子５もしくは６個をもつそれらの高級同族体、例えば２－メチルブチル、ペンチル、ヘキシルおよびそれに類するものを含むことを意味し；C_{3-6}シクロアルキルは、一般に、シクロプロピル、シクロブチル、シクロペンチルおよびシクロヘキシルであり；C_{3-6}アルケニルは、炭素原子３～６個をもつ直鎖および分枝鎖の不飽和炭化水素基、例えばプロペニル、ブテニル、ペンテニルもしくはヘキセニルを定義し；C_{1-2}アルカンジイルは、メチレンもしくは１，２－エタンジイルを定義し；C_{1-5}アルカンジイルは、炭素原子１～５個を含有する二価の直鎖もしくは分枝鎖炭化水素基、例えば１，２－エタンジイル、１，３－プロパンジイル、１，４－ブタンジイル、１，５－ペンタンジイル、およびそれらの分枝異性体を定義し；C_{1-6}アルカンジイルは、C_{1-5}アルカンジイルおよび炭素原子６個をもつその高級同族体、例えば１，６－ヘキサンジイルおよびそれに類するものを含む。用語「ＣＯ」は、カルボニル基を指す。

【００１７】

先に使用されたような用語「立体化学的異性型」は、式（Ｉ）の化合物が保持してもよいすべての可能な立体異性型を定義する。他に記述または指示されなければ、化合物の化学的名称は、すべての可能な立体化学的異性型の混合物を指し、該混合物は、塩基性分子構造をもつすべてのジアステレオマーおよび鏡像異性体を含む。より特別には、立体形成中心は、Ｒ－もしくはＳ－立体配置を有してもよく；二価の環式（部分）飽和基における置換基は、ｃｉｓ－もしくはｔｒａｎｓ－立体配置のいずれを有してもよい。二重結合を含む化合物は、該二重結合においてＥもしくはＺ－立体化学を有してもよい。式（Ｉ）の化合物の立体化学的異性型は、明らかに本発明の範囲内に包含されることを意図する。

【００１８】

上記のような製薬的に許容しうる付加塩は、製薬的に許容しうる酸付加塩を含み、そして式（Ｉ）の化合物が形成することができる治療的に活性な無毒の酸付加塩型を含むことを意味する。製薬的に許容しうる酸付加塩は、そのような適当な酸により塩基型を処理することによって都合よく得ることができる。適当な酸は、例えば、ハロゲン化水素酸のような無機酸、例えば塩化水素酸もしくは臭化水素酸、硫酸、硝酸、リン酸およびそれに類する酸；または、有機酸、例えば、酢酸、プロパン酸、ヒドロキシ酢酸、乳酸、ピルビン酸、シュウ酸（すなわちエタン二酸）、マロン酸、コハク酸（すなわちブタン二酸）、マレイン酸、フマール酸、リンゴ酸、酒石酸、クエン酸、メタンスルホン酸、エタンスルホン酸、ベンゼンスルホン酸、ｐ－トルエンスルホン酸、シクラミン酸、サリチル酸、ｐ－アミノサリチル酸、パモ酸およびそれに類する酸を含む。

【００１９】

本発明の化合物が酸性部分を担持する場合は、適当な製薬的に許容しうる塩基付加塩が可能であり、これらは、アルカリ金属塩、例えばナトリウムもしくはカリウム塩；アルカリ土類金属塩、例えばカルシウムもしくはマグネシウム塩；および適当な有機リガンドと形成される塩基付加塩、例えば第１級、第２級、第３級もしくは第４級アンモニウム塩、例えばモルホリニル、ｔｅｒｔ－ブチルアミンおよび類するものを含む。

【００２０】

反対に、該塩型は、適当な塩基で処理することによって遊離塩基型に変換することもできる。

【００２１】

また、先に使用された用語付加塩は、式（Ｉ）の化合物ならびにその塩が形成できる溶媒和物も包含する。そのような溶媒和物は、例えば、水和物、アルコラートおよびそれに類するものである。

【００２２】

興味ある化合物は、１つ以上の次の制限が適合する式（Ｉ）のそれらの化合物である：

ａ）ｎは０である；

ｂ）R^3は、場合によってはハロもしくはメトキシにより置換されている式（ｂ－１）の基である；

ｃ）Ｘは、－CH_2－もしくは－CH_2CH_2－を表す；

ｄ）R^2は、R^6が水素である式（ａ－２）の基である；

ｅ）R^2は、式（ａ－２），（ａ－４），（ａ－６）もしくは（ａ－７）の基である；

ｆ）R^2は、場合によってはメチル、ヒドロキシ、ハロ、トリフルオロメチル、メチルオキシカルボニルもしくはヒドロキシカルボニルにより置換されているベンズイミダゾールである；

ｇ）R^1は、C_{1-6}アルキルカルボニル、アミノC_{1-6}アルキルカルボニルもしくはアミノ酸である。

【００２３】

特別な化合物は、ｎが０であり、そしてR^3が場合によってはハロもしくはメトキシにより置換されている式（ｂ－１）の基である、式（Ｉ）のそれらの化合物である。

【００２４】

好適な化合物は、ｎが０であり、R^3が場合によってはハロもしくはメトキシにより置換されている式（ｂ－１）の基であり、そしてＸが－CH_2－を表す、式（Ｉ）のそれらの化合物である。

【００２５】

他の好適な化合物は、ｎが０であり、R^3が場合によってはハロもしくはメトキシにより置換されている式（ｂ－１）の基であり、そしてＸが－CH_2CH_2－を表す、式（Ｉ）のそれらの化合物である。

【００２６】

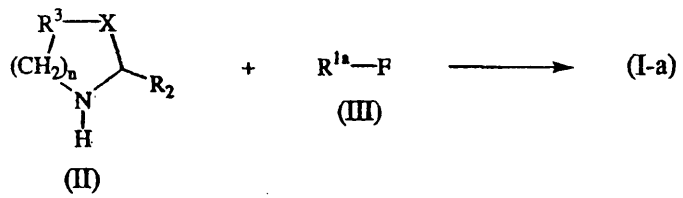
なお他の好適な化合物は、R^1がC_{1-6}アルキルカルボニル、アミノC_{1-6}アルキルカルボニルもしくはアミノ酸である、式（Ｉ）のそれらの化合物である。

【００２７】

R^{1a}が、アミノにより置換されているC_{1-4}アルキル以外のすべてのR^1置換基を表す式（Ｉ）の化合物として定義される、式（Ｉ－ａ）の化合物は、反応に不活性な溶媒、例えばジクロロメタンもしくはクロロホルム中、４－メチル－モルホリンの存在下で、式（ＩＩ）の中間体を式（ＩＩＩ）の中間体と反応させることによって製造することができる。撹拌は反応の速度を増進できる。反応は、便利には、室温～反応混合液の還流温度の範囲の温度において実施でき、そして所望ならば、反応はオートクレーブ中、高圧下で実施されてもよい。場合によっては、該反応は酸加水分解段階へと続いて、酸に不安定な保護基、例えばｔｅｒｔ－ブチルオキシカルボニルが除去される。

【００２８】

【化９】



(II)

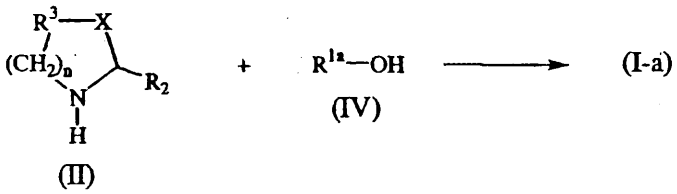
【００２９】

あるいはまた、式（Ｉ－ａ）の化合物は、反応に不活性な溶媒、例えばジクロロメタン中

、適当な活性化剤、例えばクロロギ酸イソブチルの存在下、適当な塩基、例えばトリエチルアミンの存在下で、式（ＩＩ）の中間体を式（ＩＶ）の中間体と反応させることによって製造することができる。場合によっては、該反応は酸加水分解段階へと続いて、酸に不安定な保護基、例えばｔｅｒｔ－ブチルオキシカルボニルが除去される。

【００３０】

【化１０】

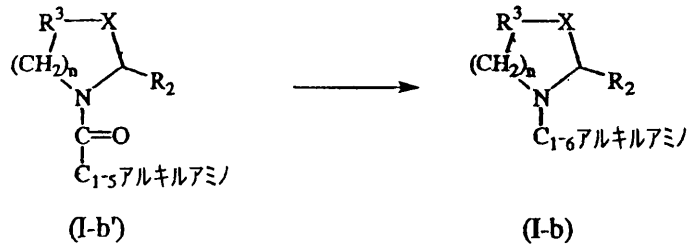


【００３１】

R^1が、アミノにより置換されているC_{1-4}アルキルを表す式（Ｉ）の化合物として定義される式（Ｉ－ｂ）の化合物は、便利には、R^1がアミノC_{1-5}アルキルカルボニルを表す対応する出発化合物（Ｉ－ｂ’）を、適当な還元反応にかけることによって製造することができる。適当な還元反応は、例えば、ボラン－テトラヒドロフラン錯体による処理であってもよい。

【００３２】

【化１１】

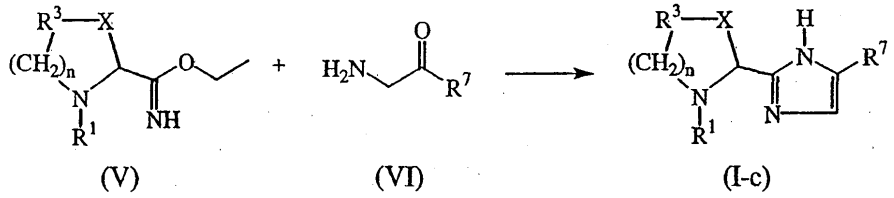


【００３３】

R^2が基（ａ－２）［式中、R^6は水素であり、そしてR^7はイミダゾール部分の３位に位置する］を表す式（Ｉ）の化合物として定義される式（Ｉ－ｃ）の化合物は、適当な溶媒、例えばメタノール中、酢酸カリウムの存在下で式（Ｖ）の中間体を式（ＶＩ）の中間体と反応させることによって製造することができる。

【００３４】

【化１２】



【００３５】

さらに、式（Ｉ）の化合物は、技術上既知の基変換反応にしたがって式（Ｉ）の化合物を各々他の化合物に転化することによって製造されてもよい。

【００３６】

出発材料および若干の中間体、例えば式（ＩＩＩ）、（ＩＶ）および（ＶＩ）は既知の化合物であり、そして市販品として得られるか、または当該技術分野において一般に既知の慣用の反応操作にしたがって製造されてもよい。

【００３７】

式（Ｉ）の化合物および中間体のあるものは、例えば、R^2置換基を担持している炭素原子のような、ＲもしくはＳ立体配置において存在するそれらの構造における１つ以上の立体形成中心を有してもよい。

【００３８】

ＣＡＳ命名協定にしたがえば、既知絶対配置の２つの立体形成中心が分子中に存在する場合、ＲもしくはＳ記述子は、最低番号のキラル中心、基準中心（ｒｅｆｅｒｅｎｃｅ ｃｅｎｔｅｒ）（Ｃａｈｎ－Ｉｎｇｏｌｄ－Ｐｒｅｌｏｇ ｓｅｑｕｅｎｃｅ ｒｕｌｅに基づいて）に指定される。第２の立体形成中心の配置は、関連記述子［Ｒ＊，Ｒ＊］もしくは［Ｒ＊，Ｓ＊］を用いて指示され、この場合、Ｒ＊は常に基準中心として特定され、そして［Ｒ＊，Ｒ＊］は同じキラリティーをもつ中心を示し、そして［Ｒ＊，Ｓ＊］は異なるキラリティーの中心を示す。例えば、分子中の最低番号のキラル中心がＳ配置をもち、そして第２の中心がＲである場合、立体記述子はＳ－［Ｒ＊，Ｓ＊］として特定される。

【００３９】

先に記述された方法において製造された式（Ｉ）の化合物は、技術上既知の分割操作にしたがって、互いに分離できる鏡像異性体のラセミ混合物の形態において合成されてよい。式（Ｉ）のラセミ化合物は、適当なキラル酸との反応によって対応するジアステレオマー塩型に転化されてもよい。次いで、該ジアステレオマー塩型は、例えば、選択もしくは分別結晶化によって分離され、そして鏡像異性体が、アルカリによってそれから遊離される。式（Ｉ）の化合物の鏡像異性型を分離する代替方式は、キラル固定相を用いる液体クロマトグラフィーを必要とする。また、該純粋な立体化学的異性型は、反応が立体化学的に起きるならば、適当な出発材料の対応する純粋な立体化学的異性型から得られてもよい。好ましくは、特定の立体異性体が所望される場合、該化合物は、立体特異的製造法によって合成されるであろう。これらの方法は、有利には、鏡像異性体として純粋な出発材料を使用することができる。

【００４０】

式（Ｉ）の化合物、製薬的に許容しうる塩およびそれらの立体異性型は、薬理学的実施例Ｃ－１において証明されるように、内因性神経ペプチド、例えばコレシストキニン（ＣＣＫ）の不活性化に関与する膜トリペプチジルペプチダーゼの阻害剤である。

【００４１】

それらのＴＰＰ ＩＩ阻害特性に鑑みて、本発明は、ＴＰＰ ＩＩ活性に関連する症状もしくは障害、例えば摂食障害、肥満、精神病症候群および関連する精神医学障害の治療において有用である。

【００４２】

式（Ｉ）の化合物の利用に鑑みて、また、本発明は、摂食障害、肥満、精神病症候群および関連する精神医学障害を罹患しているヒトを含む温血動物（一般に本明細書では患者と呼ばれる）を治療する方法を提供することが次ぎにくる。結果的に、治療方法は、ＴＰＰ ＩＩの活性を阻害し、そして／または症状、例えば摂食障害、肥満、精神病症候群および関連する精神医学障害を罹患している患者を軽減するために提供される。

【００４３】

したがって、医薬としての式（Ｉ）の化合物の使用は、ＣＣＫ不活性化ペプチダーゼトリペプチジルペプチダーゼ（ＴＰＰ ＩＩ）の阻害剤として作用を提供し、そして／または摂食障害、特に肥満の治療のため、および／または精神病症候群および関連する精神医学障害の治療のために提供されるが、この使用は式（Ｉ）の化合物の治療上の有効量を含有する。また、ＴＰＰ ＩＩの活性を阻害し、そして／または摂食障害、肥満、精神病症候群および関連する精神医学障害を治療する医薬の製造のために、式（Ｉ）の化合物の使用が提供される。両予防的および治療的処置が期待される。

【００４４】

若干の本発明の化合物、特に化合物（１５３）～（１８１）は、オピオイド活性、例えばデルター－オピオイド（δ）、ミュー－オピオイド（μ）および／またはカッパー－オピオイ

ド（κ）活性をまた有することが信じられている。オピオイド活性は薬理学的実施例Ｃ．２およびＣ．３において記述されるようなアッセイを用いて測定できる。

【００４５】

本発明の製薬組成物を製造するために、有効成分としての、塩基もしくは酸付加塩型における特定の化合物の有効量が、製薬的に許容しうるキャリアーとの直接混合物において組み合わされるが、このキャリアーは、投与に望ましい製剤の形態に応じて広範な種々の剤形をとることができる。これらの製薬組成物は、好ましくは経口的、肛門内、または非経口的注射による投与に適している単位用量剤形において望ましくは存在する。例えば、経口投薬形態の組成物を製造するでは、例えば、懸濁剤、シロップ剤、エリキシル剤、および液剤のような経口液状製剤の場合には、水、グリコール、油、アルコール等：あるいは散剤、丸剤、カプセル剤および錠剤の場合には、固形キャリアー、例えば澱粉、糖、カオリン、滑沢剤、結合剤、崩壊剤等のような、すべての通常の製薬媒質が使用できる。投与が容易であることから、錠剤およびカプセル剤が、もっとも有利な経口投薬単位形態を代表していて、この場合には、固形製薬キャリアーが使用されることは明らかである。非経口組成物では、他の成分が、例えば溶解性を助けるために含まれてもよいけれども、キャリアーは、通常は、少なくとも大部分、滅菌水を含むであろう。注射用液剤は、例えば、キャリアーが、生理食塩水溶液、グルコース溶液もしくは生理食塩水とグルコース溶液の混合液を含む状態で製造されてもよい。また、注射用懸濁剤も製造することができ、この場合には適当な液状キャリアー、懸濁化剤等が使用されてもよい。経皮投与に適する組成物では、キャリアーは、添加物が皮膚に対して有意な悪影響を惹起しない少ない割合で何らかの性質をもつ適当な添加物と場合によっては組み合わされて、場合によっては、浸透促進剤および／または適当な湿潤剤を含有する。該添加物は、皮膚への投与を容易にし、そして／または所望の組成物を製造するのに役立つであろう。これらの組成物は、種々の方法、例えば経皮パッチとして、スポット・オンとして、軟膏剤として投与されてもよい。対応する塩基型以上のそれらの高い水溶性により、（Ｉ）の酸付加塩は、水性組成物の製造において明らかに一層適している。

【００４６】

投与の簡易性および用量の均一性のために、用量単位形態において前述の製薬組成物を製剤化することは特に得策である。本明細書において使用される用量単位形態は、ここでは１回の用量として適当な物理的に分割された単位を指し、各単位は、必要な製薬キャリアーと一緒になって所望の治療効果を生むように計算された有効成分の予め決定された量を含有している。そのような用量単位形態の例は、錠剤（刻み目をつけたり、コーティングされた錠剤を含む）、カプセル剤、丸剤、粉末包装剤、ウェーファー剤、注射用液剤もしくは懸濁剤、ティースプーン量剤、テーブルスプーン量剤など、およびそれらの分けられた集合物である。

【００４７】

経口投与では、製薬組成物は、固形用量形態、例えば、錠剤（のみ込める剤形および噛める剤形の両方）、カプセル剤もしくはゲルキャップ剤（ｇｅｌｃａｂｓ）等の形態をとってもよく、これらは、製薬的に許容しうる添加物、例えば結合剤（例えば予めゲル化されたトウモロコシ澱粉、ポリビニルピロリドンもしくはヒドロキシプロピルメチルセルロース）；賦形剤（例えば乳糖、微結晶セルロースもしくはリン酸カルシウム）；滑沢剤（例えばステアリン酸マグネシウム、タルクもしくはシリカ）；崩壊剤（例えばポテト澱粉もしくはナトリウム澱粉グリコレート）；または湿潤剤（例えばラウリル硫酸ナトリウム）を用いる慣用の手段によって製造される。錠剤は、当該技術分野において周知の方法によってコーティングされてもよい。

【００４８】

経口投与のための液状製剤は、例えば、液剤、シロップ剤もしくは懸濁剤の形態をとってもよく、あるいは、それらは、使用前に水もしくは他の適当な溶媒とともに構成するための乾燥生成物として提供されてもよい。そのような液状製剤は、場合によっては、製薬的に許容しうる添加物、例えば、懸濁化剤（例えばソルビトールシロップ、メチルセルロー

ス、ヒドロキシプロピルメチルセルロースもしくは水素化食用油脂）；乳化剤（例えばレシチンもしくはアラビアゴム）；非水性溶媒（例えばアーモンド油、油性エステルもしくはエチルアルコール）；および保存剤（例えばｐ－ヒドロキシ安息香酸メチルもしくはプロピルまたはソルビン酸）を用いて慣用の手段によって製造されてもよい。

【００４９】

製薬的に許容しうる甘味剤は、好ましくは、少なくとも１種の強い甘味剤、例えばサッカリン、サッカリンナトリウムもしくはカルシウム、アスパルテーム、アセスルファームカリウム、シクラミン酸ナトリウム、アリテーム、ジヒドロカルコン甘味剤、モネリン、ステビオシドもしくはスクラロース（４，１’，６’－トリクロロ－４，１’，６’－トリデオキシガラクトスクロース）、好ましくはサッカリン、サッカリンナトリウムもしくはカルシウム、および場合によってはかさ張る甘味剤、例えばソルビトール、マンニトール、フルクトース、スクロース、マルトース、イソマルト、グルコース、水素化グルコースシロップ、キシリトール、カラメルもしくは蜂蜜を含む。

【００５０】

強い甘味剤は、便利には、低濃度で使用される。例えば、サッカリンナトリウムの場合には、濃度は、最終製剤の総容量に基づいて、０．０４％～０．１％（ｗ／ｖ）の範囲であってもよく、そして好ましくは、低用量製剤では約０．０６％および高用量製剤では約０．０８％である。かさ張る甘味剤は、効果的には、約１０％～約３５％、好ましくは約１０％～１５％（ｗ／ｖ）の範囲の比較的大量で使用することができる。

【００５１】

低用量製剤における苦み成分を遮蔽できる製薬的に許容しうる着香剤は、好ましくは、果実フレーバー、例えばチェリー、ラズベリー、黒スグリもしくはストロベリーフレーバーである。２種の着香剤の組み合わせ物は、非常に良好な結果をもたらすであろう。高用量製剤では、より強い着香剤、例えば、Ｃａｒａｍｅｌ　Ｃｈｏｃｏｌａｔｅフレーバー、Ｍｉｎｔ　Ｃｏｏｌフレーバー、Ｆａｎｔａｓｙフレーバーおよび類似の製薬的に許容しうる強い着香剤が必要とされるであろう。各着香剤は、最終組成物において、０．０５％～１％（ｗ／ｖ）の濃度範囲で存在してもよい。該強い着香剤の組み合わせ物は有利に使用される。好ましくは、製剤の酸性条件下で、味および色のいかなる変化もしくは損失を受けない着香剤が使用される。

【００５２】

また、本発明の化合物は、デポ製剤として製剤化されてもよい。そのような長く作用する製剤は、移植（例えば皮下もしくは筋肉内）によるか、または筋肉内注射によって投与されてもよい。かくして、例えば、本化合物は、適当な高分子もしくは疎水性材料（例えば許容しうる油中の乳液として）またはイオン交換樹脂とともに、あるいは難溶性誘導体、例えば難溶性塩として製剤化されてもよい。

【００５３】

本発明の化合物は、注射、便利には静脈内、筋肉内もしくは皮下注射による、例えば大量（ｂｏｌｕｓ）注射もしくは連続静脈内注入による非経口投与のために製剤化されてもよい。注射用製剤は、添加される保存剤とともに、単位用量形態において、例えばアンプルもしくは多用量容器において存在してもよい。本組成物は、油性もしくは水性溶媒における懸濁剤、液剤または乳剤のような形態をとってもよく、そして製剤化剤、例えば等張化剤、懸濁化剤、安定化剤および／または分散剤を含有してもよい。あるいはまた、有効成分は、使用前に適当な溶媒、例えば無菌の発熱物質不含水を用いて構成するための粉末形態において存在してもよい。

【００５４】

また、本発明の化合物は、例えばココアバターもしくは他のグリセリドのような慣用の坐剤基質を含有する、坐剤もしくは滞留浣腸剤のような肛門内組成物において製剤化されてもよい。

【００５５】

鼻内投与では、本発明の化合物は、例えば、液状噴霧剤、散剤として、またはドロップ剤

の形態で使用されてもよい。
【００５６】
実験の部
これ以後に記述される操作において、次の略語が使用された：「ＡＣＮ」はアセトニトリルを表し；「ＴＨＦ」は、テトラヒドロフランを表し；「ＤＣＭ」はジクロロメタンを表し；そして「ＭＩＫ」はメチルイソブチルケトンを表す。
【００５７】
若干の化学薬剤では、化学式、例えば、ジクロロメタンについてCH_2Cl_2、メタノールについてCH_3OH、アンモニアについてNH_3、塩酸についてＨＣｌ、水酸化ナトリウムについてＮａＯＨ、炭酸水素ナトリウムについて$NaHCO_3$、そして炭酸ナトリウムについてNa_2CO_3が使用された。
【００５８】
それらの場合には、実の立体化学配置に対するさらなる引用なしに、最初に単離された立体化学的異性型が「Ａ」と命名され、そして第２番目は「Ｂ」と命名された。
【００５９】
調製用液体クロマトグラフィーは、ＹＭＣ　ＯＤＳ－Ａカラム（３０ｘ１００ｍｍ、５ミクロン、温度：周囲温度、流速：３５ｍＬ／ｍｉｎ、移動相：ａ）１０／９０アセトニトリル／０．１％トリフルオロ酢酸を含有する水、ｂ）９０／１０アセトニトリル／０．１％トリフルオロ酢酸を含有する水、勾配：９分間にわたってＡからＢへの直線勾配、２５４ｎｍにおけるＵＶ検出）を用いる半調製用ＨＰＬＣユニットにおいて実施された。
【００６０】
Ａ．中間体の製造
実施例Ａ．１
ａ）２，３－ジヒドロキシ－１Ｈ－インドール－２－カルボキサミド（０．０３０ｍｏｌ）をトリクロロメタン（４００ｍｌ）中に懸濁した。混合液を０℃に冷却した。トリエチルアミン（０．０４５ｍｏｌ）を添加した。塩化アセチル（０．０４５ｍｏｌ）を２分かけて添加した。３０分後、ＴＬＣは反応が不完全であったことを示した。フラスコをなお冷却しながら、さらなるトリエチルアミン（６．２６ｍｌ）を、続いて１５分後にはさらなる塩化アセチル（３．２１ｍｌ）を添加した。ＴＬＣは反応がなお不完全であったことを示した。反応液を継続して撹拌し、０℃に冷却し、そしてさらなるトリエチルアミン（６．２６ｍｌ）を添加した。２分かけて、さらなる塩化アセチル（３．２１ｍｌ）を正味添加した。ＴＬＣは６０分後に８０％完了を示し、そしてさらに３０分後には進行しなかった。塩化アセチルおよびトリエチルアミンの第３回分量を添加した。さらに１５分後、氷冷水（２００ｍｌ）を添加した。混合液を１０分間撹拌し、濾過し、そして水（３ｘ１００ｍｌ）およびトリクロロメタン（２ｘ７５ｍｌ）により洗浄した。サンプルを一夜乾燥させて、（Ｓ）－１－アセチル－２，３－ジヒドロ－１Ｈ－インドール－２－カルボキサミド４．７１ｇを得た
（Ｓ）－１－アセチル－２，３－ジヒドロ－１Ｈ－インドール－２－カルボニトリル（中間体２，ｍｐ．１３４－１３５℃）３．１２ｇ（８３％）を得た。
【００６１】
ｃ）中間体（２）（０．０１５１ｍｏｌ）をジエチルエーテル（２００ｍｌ）に懸濁した。エタノール（０．０２１４ｍｏｌ）を添加し、そして混合液を０℃に冷却した。ＨＣｌ（気体）を４５分間吹き込んだ。混合液を氷浴から除去し、そして撹拌した。２０分後、残渣を側壁上に集めた。壁を引っ掻き、そして白色固形物を析出させた。１時間後、サンプルを濾過し、ジエチルエーテルで洗浄し、素早く風乾して、（Ｓ）－エチル　１－アセチル－２，３－ジヒドロ－１Ｈ－インドール－２－カルボキシイミデート・一塩酸塩３．９９ｇを得た（中間体３）。同様に、エチル　１－アセチル－２，３－ジヒドロ－１Ｈ－インドール－２－カルボキシイミデート１塩酸（中間体６）を、１－アセチル－２，３－ジヒドロ－１Ｈ－インドール－２－カルボニトリルから出発して製造した。
【００６２】

実施例Ａ．２

ａ）５－クロロ－２，３－ジヒドロキシ－１Ｈ－インドール－２－カルボン酸メチルエステル（０．００７６１ｍｏｌ）をメタノール（２５ｍｌ）中に溶解し、そして０℃に冷却した。NH_3を１０分間吹き込んだ。フラスコに栓をし、そして室温まで暖めた。混合液を一夜撹拌した。ＴＬＣは反応がほとんど完了したことを示した。サンプルを±１／３容量まで濃縮し、冷却し、そして濾過し、得られる固形物を氷冷メタノール（２ｍｌ）で洗浄し、次いで空気中で乾燥して、５－クロロ－２，３－ジヒドロ－１Ｈ－インドール－２－カルボキサミド（中間体７，ｍｐ．１５１－１５２℃）０．７４ｇを得た。

【００６３】

ｂ）トリエチルアミン（０．０２０８０ｍｏｌ）を、トリクロロメタン（７００ｍｌ）に溶解した中間体（７）（０．０９６３２ｍｏｌｅ）に添加した。混合液を５℃に冷却した。塩化アセチル（０．２４８０ｍｏｌｅ）を撹拌しながら２分かけて添加した。５分後、沈殿が生成した。氷浴を除去し、そして容器を１５分間放置した。氷水（２５０ｍｌ）を添加し、そして混合液を１０分間撹拌した。サンプルを濾過し、そして水およびトリクロロメタンにより洗浄した。固形物を水（２００ｍｌ）に懸濁し、そして１０分間渦巻きさせた。トリクロロメタン（２００ｍｌ）を添加し、そして混合液を撹拌し、次いで濾過し、そして水およびトリクロロメタンで洗浄し、次いで一夜風乾させて、１－アセチル－５－クロロ－２，３－ジヒドロ－１Ｈ－インドール－２－カルボキサミド（中間体８）１９．７１ｇを得た。

【００６４】

ｃ）トリエチルアミン（０．４１２９１ｍｏｌｅ）を、０℃においてジクロロメタン（５００ｍｌ）に懸濁した中間体（８）（０．０８２５８ｍｏｌｅ）に添加した。塩化トリクロロアセチル（０．２０６４５ｍｏｌｅ）を１０分かけて添加した。反応が緩慢に見える場合は、さらなる分量のトリエチルアミン（２０ｍｌ）、次いでさらなる塩化トリクロロアセチル（７．６ｍｌ）を添加し、そして混合液を低温で２時間撹拌した。氷浴を除去し、そして混合液を２時間放置した。これは暗色の反応液をもたらし、これを０℃に再冷却した。氷冷水（１５０ｍｌ）を徐々に添加し、そして混合液を５分間撹拌した。層を分離させ、そして有機相を洗浄（氷冷３ＮＨＣｌ、飽和$NaHCO_3$）し、乾燥し、濾過し、そして濃縮した。残渣を氷冷ジエチルエーテル（４０ｍｌ）中で粉砕した。濾過、氷冷ジエチルエーテル（１０ｍｌ）による洗浄により、１－アセチル－５－クロロ－２，３－ジヒドロ－１Ｈ－インドール－２－カルボニトリル（中間体９，ｍｐ．１４０－１４２℃）１５．１３ｇを得た。

【００６５】

ｄ）ＨＣｌ（２Ｍ溶液として）を、ガスの発生が示されるまで中間体（９）に徐々に添加した。次いで、調製したＨＣｌ（ジエチルエーテル中２Ｎ）を添加して停止させ、そしてジエチルエーテル中に懸濁したＨＣｌ（１５０ｍｌ）、次いでエタノール（０．０４２ｍｏｌｅ）を添加した。混合液を０℃に冷却し、そしてＨＣｌ（気体）を、オイルを析出させながら１時間かけて添加した。反応液をジエチルエーテルでｌ　１に希釈した。さらなるオイルの沈殿があり、そして１時間放置後は固形物の生成はなかった。ジエチルエーテルをデカントして除いた。残渣を希釈した（ジエチルエーテル，５００ｍｌ）。固形物が生成し始め、そして混合液を２時間撹拌した。サンプルを濾過し、ジエチルエーテルで洗浄した。サンプルを真空下に放置して、エチル　１－アセチル－５－クロロ－２，３－ジヒドロ－１Ｈ－インドール－２－カルボキシイミデート・一塩酸塩（中間体１０）６．４１ｇを得た。

【００６６】

実施例Ａ．３

ａ）ＤＣＭ（５０ｍｌ）中ジカルボン酸ビス（１．１－ジメチルエチル）エステル（０．０７６１５ｍｏｌ）を、０℃においてＤＣＭ（１５０ｍｌ）中２，３－ジヒドロ－１Ｈ－インドール－２－メタノール（０．０７６１５ｍｏｌ）に５分かけて添加した。混合液を放置して室温に暖め、そして一夜撹拌した。混合液を減圧下で濃縮し、そしてＫｏｇｅｌ

Ｒｏｈｒ蒸留にかけて、１．１－ジメチルエチル２，３－ジヒドロ－２－（ヒドロキシメチル）－１Ｈ－インドール－１－カルボキシレート（中間体１１）１１．９８ｇを得た。

【００６７】

ｂ）Ｄｅｓｓ－Ｍａｒｔｉｎ　Ｒｅａｇｅｎｔ（０．０１１ｍｏｌ）を、ＤＣＭ（３５ｍｌ）中に溶解した中間体１１（０．０１０ｍｏｌ）に正味１分かけて添加した。１５分後、氷浴を除去し、そして混合液を放置して室温に暖めた。さらなるＤｅｓｓ－Ｍａｒｔｉｎ　Ｒｅａｇｅｎｔ（０．３３ｇ）を添加し、そして混合液をさらに３０分間撹拌した。混合液を０℃に再冷却し、そして飽和$NaHCO_3$水溶液（１００ｍｌ）中に溶解することを試みた$Na_2S_2O_3$（２５ｇ）の部分懸濁液／溶液により徐々に処理した。１０分後、混合液を氷から除去し、そして層を分離させた。さらなるＤＣＭを添加し、そして混合液を濾過した。有機相を濾過液から分離し、そして合わせた有機相を乾燥し、濾過し、濃縮し、そしてフラッシュカラムクロマトグラフィー（溶出液：１０％酢酸エチル：ヘキサン、３：１酢酸エチル：ヘキサン（５ｍｌ）にサンプルを溶解する）を通して精製して、１．１－ジメチルエチル２－ホルミル－２，３－ジヒドロ－１Ｈ－インドール－１－カルボキシレート（中間体１２，ｍｐ．８５－８７℃）を得た。

【００６８】

実施例Ａ．４

ピリジン（５０ｍｌ）中１－アセチル－２，３－ジヒドロ－１Ｈ－インドール－２－カルボニトリル（０．００９８８ｍｏｌ）およびトリエチルアミン（０．０１９７ｍｏｌ）の溶液を、バブラーを介して硫化水素（ガス）により室温で２時間処理し、そして得られた飽和反応混合液を密閉し、そして１６時間放置した。反応混合液を氷水スラリー２００ｍｌ中に注入した。かさのある沈殿が生成した。混合液を氷浴において再冷却し、そして沈殿を吸引濾過によって回収し、冷水で洗浄し、そして風乾して、１－アセチル－２，３－ジヒドロ－１Ｈ－インドール－２－カルボチオアミド（中間体１３，ｍｐ．１９４－１９５℃）１．６２ｇを得た。

【００６９】

実施例Ａ．５

１－アセチル－２，３－ジヒドロ－１Ｈ－インドール－２－カルボニトリル（０．０１３２ｍｏｌ）を水（５４ｍｌ）とともに処理し、そして得られる懸濁液を連続してNa_2CO_3（０．００７２６ｍｏｌ）および$NH_2OH.HCl$（０．０１４５ｍｏｌ）により処理した。混合液をエタノール（２６ｍｌ）と処理し、そして８０－９０℃に加熱した。反応温度に達した時点で、混合液はなお懸濁液であった。さらなるエタノール２６ｍｌを添加して澄明溶液を得た。反応液を２．５時間加熱し、そして撹拌しながら室温まで冷却した。かさのある沈殿が生成し、これを吸引濾過によって回収し、冷蒸留水で洗浄し、そして風乾して、１－アセチル－２，３－ジヒドロ－Ｎ’－ヒドロキシ－１Ｈ－インドール－２－カルボキシイミドアミド（中間体１４，ｍｐ．２０４－２０５℃）２．２３ｇを得た。

【００７０】

実施例Ａ．６

１－アセチル－２－（４－エチル－１Ｈ－イミダゾル－２－イル）－２，３－ジヒドロ－１Ｈ－インドール（０．００３５ｍｏｌ）およびＨＣｌ，６Ｎ（５０ｍｌ）を窒素雰囲気下で合わせた。反応混合液を直ちに加熱し、そして加熱を３．５時間継続した。混合液を室温まで冷却させ、次いで、ジエチルエーテル（２ｘ７５ｍｌ）で抽出し、０℃に冷却し、アルカリ化（冷却３ＮＮａＯＨにより）し、次いで、クロロホルム（３ｘ６０ｍｌ）で抽出した。合わせた有機相を乾燥、濾過し、そして溶媒を蒸発して、２－（４－エチル－１Ｈ－イミダゾル－２－イル）－２，３－ジヒドロ－１Ｈ－インドール（中間体１５）０．７９ｇを得た。

【００７１】

実施例Ａ．７

ａ）メタノール（６００ｍｌ）中５－フルオロ－１Ｈ－インドール－２－カルボン酸，エチルエステル（０．１２１ｍｏｌ）の懸濁液に、Ｍｇ（０．３６ｍｏｌ）を添加した。混合液をアルゴン下の３口丸底フラスコに室温で入れた。反応液の温度を密にモニターした。約１０分後、混合液は、最初は徐々に、次いでさらに激しく発泡を始めた。反応温度を氷浴の断続的な適用によって１５～２５℃に維持した。３０分後、発泡は遅くなった。混合液を室温で３日間撹拌させた。混合液をクロロホルム６００ｍｌと飽和NH_4Cl溶液５００ｍｌ間で分配した。有機層を$MgSO_4$で乾燥し、そして褐色オイルまで濃縮した。オイルをエーテル中に溶解し、そして３ＮＨＣｌで抽出した。水層をエーテルで洗浄し、３ＮＮａＯＨで塩基性にし、そしてクロロホルムで抽出した。抽出液を$MgSO_4$で乾燥し、そして濃縮して、メチル５－フルオロ－２，３－ジヒドロ－１Ｈ－インドール－２－カルボキシレート（中間体１６）１３．９１ｇを得た。

【００７２】

ｂ）Ａｒ下で氷浴で冷却されたメタノール（０．６ｍｌ）中２MNH_3に、メタノール（１５０ｍｌ）に溶解した中間体（１６）（０．０５７４ｍｏｌ）を添加した。この混合液を室温まで暖め、そしてアルゴン下で６時間撹拌した。反応液を１５０ｍｌまで濃縮し、そして濾過した。固形物を少量の冷メタノールで洗浄し、そして乾燥して、５－フルオロ－２，３－ジヒドロ－１Ｈ－インドール－２－カルボキサミド（中間体１７，ｍｐ．１９７－１９９℃）２．３３ｇを得た。

【００７３】

ｃ）アルゴン下で氷浴で冷却したＤＣＭ（３０ｍｌ）中中間体（１７）（０．００９４ｍｏｌｅ）の混合液に、トリエチルアミン（０．０３１ｍｏｌｅ）、続いて塩化アセチル（０．０３１ｍｏｌｅ）を添加した。得られる混合液を放置して室温に戻した。６時間撹拌後、混合液を氷浴で冷却し、そして水５０ｍｌを添加した。混合液を約２０分間撹拌し、濾過し、そして固形物を乾燥して、１－アセチル－５－フルオロ－２，３－ジヒドロ－１Ｈ－インドール－２－カルボキサミド（中間体１８，ｍｐ．２３２－２３５℃）１．５８ｇを得た。

【００７４】

ｄ）アルゴン下で氷浴で冷却したＤＣＭ（３０ｍｌ）中中間体（１８）（０．００７６ｍｏｌｅ）の懸濁液に、トリエチルアミン（０．０２２８ｍｏｌｅ）、続いて塩化トリクロロアセチル（０．０１１５ｍｏｌｅ）を添加した。混合液を放置して室温に戻し、そして６時間撹拌した。混合液を水、２ＮＨＣｌおよび飽和$NaHCO_3$で洗浄した。有機層を乾燥し、そして濃縮した。濃縮物をエーテル中で粉砕し、そしてヘキサン中５０％酢酸エチルで溶出するシリカゲルカラムにおいて精製した。所望の画分を合わせ、そして濃縮した。残渣をエーテル中で粉砕し、そして固形物を濾過によって回収し、そして乾燥させて、１－アセチル－５－フルオロ－２，３－ジヒドロ－１Ｈ－インドール－２－カルボニトリル（中間体１９，ｍｐ．９３－９５℃）０．３０ｇを得た。

【００７５】

ｅ）中間体（１９）（０．００４ｍｏｌｅ）およびＨＣｌ／ジエチルエーテル（６０ｍｌ）をアルゴン下で氷浴において冷却した。エタノール（０．００７５ｍｏｌｅ）を添加した。ＨＣｌを、混合液が均質になるまで５０分間溶液中に吹き込んだ。混合液を放置して徐々に室温まで暖め、そして４時間撹拌した。エーテルをデカントして除き、そしてメタノールに溶解した。メタノール溶液を真空濃縮し、そして残渣を次の段階のためにそのまま使用される、エチル　１－アセチル－５－フルオロ－２，３－ジヒドロ－１Ｈ－インドール－２－カルボキシイミデート・一塩酸塩（中間体２０）を得た。

【００７６】

実施例Ａ．８

ａ）２，３－ジヒドロ－５－メトキシ－１Ｈ－インドール－２－カルボン酸，メチルエステル（０．０８４ｍｏｌ）およびメタノール（５００ｍｌ）中２MNH_3を合わせ、そしてアルゴン下室温で１週間にわたって撹拌した。溶液を１００ｍｌまで濃縮し、氷浴で冷却し、そして濾過した。固形物を少量の冷メタノールで洗浄し、そして乾燥した。残渣を

メタノール／ＡＣＮ中で粉砕し、そして濾過して、２，３－ジヒドロ－５－メトキシ－１Ｈ－インドール－２－カルボキサミド（中間体２１，ｍｐ．２２８－２２９℃）４．５６ｇを得た。

【００７７】

ｂ）トリエチルアミン（０．０１０６ｍｏｌｅ）、次いで塩化アセチル（０．０１０６ｍｏｌｅ）を、アルゴン下で氷浴で冷却したＤＣＭ（４０ｍｌ）中中間体（２１）（０．００３２ｍｏｌｅ）溶液に添加した。混合液を放置して徐々に室温に暖め、そして一夜撹拌した。混合液を氷浴で冷却し、そして氷冷水（３０ｍｌ）を添加した。１０分間撹拌後、混合液を濾過し、そして固形物を一夜乾燥させた。残渣を水５０ｍｌに懸濁した。懸濁液を３０分間撹拌させ、濾過し、そして一夜乾燥して、１－アセチル－２，３－ジヒドロ－５－メトキシ－１Ｈ－インドール－２－カルボキサミド（中間体２２，ｍｐ．１９６－１９７℃）０．４０ｇを得た。

【００７８】

ｃ）アルゴン下、氷浴で冷却したＤＣＭ（１５０ｍｌ）中中間体（２２）（０．０２２ｍｏｌｅ）の懸濁液に、トリエチルアミン（０．０６６ｍｏｌｅ）、次いで塩化トリクロロアセチル（０．０３３ｍｏｌｅ）を添加した。混合液を放置して徐々に室温まで一夜暖めた。混合液を水、２ＮＨＣｌおよび飽和ＮａＨＣＯ$_3$で洗浄した。有機相を乾燥し、濃縮し、そしてエーテル中で粉砕し、そして固形物を回収して、１－アセチル－２，３－ジヒドロ－５－メトキシ－１Ｈ－インドール－２－カルボニトリル（中間体２３，ｍｐ．１０８－１１０℃）を得た。

【００７９】

ｄ）氷浴において冷却した１ＭＨＣｌ／ジエチルエーテル（２００ｍｌ）中、中間体（２３）（０．０１５４ｍｏｌｅ）およびエタノール（０．０２３１ｍｏｌｅ）の溶液に、ＨＣｌ（ガス）を６０分間吹き込んだ。氷冷を４５分間維持し、そして混合液を室温において真空下で油性沈殿２００ｍｌまで濃縮した。残渣を粉砕して褐色固形物にして、これはジエチルエーテルをデカント除去した後オイルになった。残渣をジエチルエーテルで２回洗浄し、メタノールに溶解し、そしてさらなる合成のためにさらなる精製なしに使用される、エチル　１－アセチル－２，３－ジヒドロ－５－メトキシ－１Ｈ－インドール－２－カルボキシイミデート・一塩酸塩（中間体２４）を得た。

【００８０】

実施例Ａ．９

ＤＣＭ（２５ｍｌ）に溶解した（Ｓ）－２－（ｔｅｒｔ－ブトキシカルボニルアミノ）酪酸（０．０１０ｍｏｌ）を－１０℃の冷却浴中に置いた。ピリジン（０．０１０ｍｏｌ）、続いて２，４，６－トリフルオロ－１，３，５－トリアジン（０．０３４５ｍｏｌ）を添加した。混合液を窒素下で撹拌した。１時間後、氷冷水（７５ｍｌ）を添加した。さらなるＤＣＭ（４５ｍｌ）を添加し、そして混合液を振盪した。有機相を分離し、氷冷水で再び洗浄し、次いで有機相を乾燥し、濾過し、そして濃縮して（Ｓ）－１，１－ジメチルエチル［１－（フルオロカルボニル）プロピル］－カルバメート（中間体２５）２．２９ｇを得た。

【００８１】

実施例Ａ．１０

化合物（８）（０．００１７０ｍｏｌ）をＨＣｌ，６Ｎ（２０ｍｌ）中に溶解し、そして直ちに、窒素下で１００℃の油浴において２００分間暖めた。加熱を止め、そしてサンプルを０℃に冷却した。３ＮＮａＯＨ（３５ｍｌ）を徐々に添加した。アルカリ化は飽和ＮａＨＣＯ$_3$により完結させた。サンプルをクロロホルムで抽出した。合わせた有機相を乾燥、濾過し、そして（Ｓ）－２，３－ジヒドロ－２－（４－プロピル－１Ｈ－イミダゾル－２－イル）－１Ｈ－インドール（中間体５）を生成している得られる溶液をさらなる精製なしにさらなる合成において使用した。

【００８２】

実施例Ａ．１１

エタノール（１８０ｍｌ）中中間体（１３）（０．００８４４ｍｏｌ）の混合液を一定分量の１－ブロモ－２－ブタノン（０．００８５ｍｏｌ）で処理し、そして１６時間加熱還流させた。反応混合液を室温まで冷却し、エーテルおよび１ＭＮａＯＨ（水溶液）間に抽出した。有機画分を$MgSO_4$で乾燥し、そして真空濃縮して暗色固形物を得て、これをシリカゲルのフラッシュカラムクロマトグラフィー（溶出液：１００％ＤＣＭ～９７：３ＤＣＭ／ジエチルエーテル）にかけて、２－（４－エチル－２－チアゾリル）－２，３－ジヒドロ－１Ｈ－インドール（中間体４）０．９１ｇを得た。

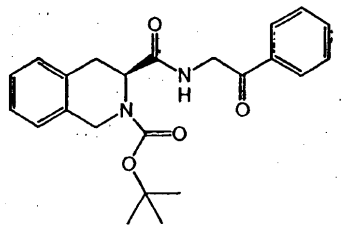
【００８３】

実施例Ａ．１２

３－（２－オキソ－２－フェニル－エチルカルバモイル）－３，４－ジヒドロ－１Ｈ－イソキノリン－２－カルボン酸ｔｅｒｔ－ブチルエステル

【００８４】

【化１３】



【００８５】

３，４－ジヒドロ－１Ｈ－イソキノリン－２，３－ジカルボン酸－２－ｔｅｒｔブチルエステル（２．７７ｇ，１０ｍｍｏｌ）および２－アミノ－１－フェニル－エタノン（１．７１ｇ，１０ｍｍｏｌ）、およびＨＯＢＴ（１－ヒドロキシベンゾトリアゾール）（２．７０ｇ，２０ｍｍｏｌ）をジクロロメタン（１００ｍｌ）に溶解した。溶液を０℃に冷却し、次いで（４－ジメチルアミノ－ブチル）－エチル－カルボジイミド（２．９９ｇ，１２ｍｍｏｌ）を、続いてＮＭＭ（Ｎ－メチル－モルホリン）（１．３１ｇ，１３ｍｍｏｌ）を添加した。次いで反応混合液を室温まで温めた。７２時間後、反応混合液を水で抽出し、そして有機相を連続して$NaHCO_3$、２Ｎクエン酸および$NaHCO_3$で抽出し、$MgSO_4$で乾燥し、濾過し、そして濃縮して黄色泡状物として表題の化合物を得た。化合物を示す液体クロマトグラフィー（ＬＣ）は８６％純度（２１４ｎｍ）であり、そしてさらなる精製なしに使用した。

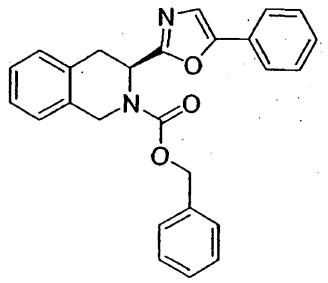
【００８６】

実施例Ａ．１２ａ

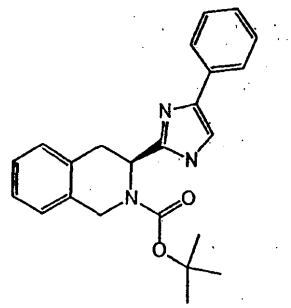
３－（２－オキソ－２－フェニル－エチルカルバモイル）－３，４－ジヒドロ－１Ｈ－イソキノリン－２－カルボン酸ベンジルエステル（実施例Ａ．１２の３－（２－オキソ－２－フェニル－エチルカルバモイル）－３，４－ジヒドロ－１Ｈ－イソキノリン－２－カルボン酸ｔｅｒｔ－ブチルエステルと類似の方式において製造される）の$POCl_3$による脱水は、次の中間化合物を生成する：

【００８７】

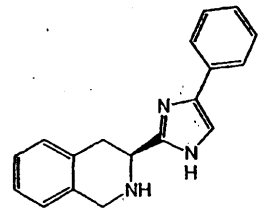
【化１４】



【００８８】
ＣＢＺ基は、ヨードトリメチルシランによる処理によって得られるオキサゾールから容易に除去される。得られるノルーアミンオキサゾール中間体は、その類似体イミダゾール中間体について記述された類似の操作にしたがって化合物１７０へと進めることができる。
【００８９】
実施例Ａ．１３
３－（４－フェニル－１Ｈ－イミダゾル－２－イル）－３，４－ジヒドロ－１Ｈ－イソキノリン－２－カルボン酸ｔｅｒｔ－ブチルエステル
【００９０】
【化１５】

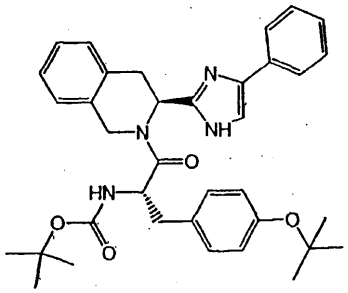


【００９１】
先の実施例Ａ．１２において製造した生成物（３．５５ｇ，９ｍｍｏｌ）、NH_4OAc（酢酸アンモニウム）（２０．８ｇ，２７０ｍｍｏｌ）およびＡｃＯＨ（酢酸）（３０ｍＬ）を室温において合体し、そして反応混合液を約３時間蒸気浴上で加温した。次いで、反応混合液を室温に冷却し、そして氷スラリー混合物（４００ｇ）中に注入した。この混合液に、濃水酸化アンモニウム（５０ｍｌ）およびエチルエーテルを添加した。層を分離し、そして水相を第２分量のエチルエーテルで洗浄した。有機相を合わせ、$MgSO_4$で乾燥し、濾過し、そして減圧下で濃縮して褐色泡状物を得た。このサンプルを調製用ＨＰＬＣによって精製して、白色粉末として精製した表題の化合物を得た。ＬＣは、サンプルが２１４ｎｍにおいて純度９６％であることを示した。
測定ＭＷ（MH^+）：３７６
実施例Ａ．１４
３－（４－フェニル－１Ｈ－イミダゾル－２－イル）－１，２，３，４－テトラヒドロ－イソキノリン
【００９２】
【化１６】



【００９３】
トリフルオロ酢酸（ＴＦＡ）（４ｍｌ）を試験管中で約０℃に冷却した。次いで、この冷溶媒に先の実施例Ａ．１３において製造した生成物（０．７５ｇ，２ｍｍｏｌ）を添加した。反応混合液を約４５分間かけて室温まで暖めた。過剰のＴＦＡをN_2ガスの気流下で除去した。残渣をジクロロメタン（１５ｍｌ）および飽和$NaHCO_3$間に分配した。次いで、水相を第２分量のジクロロメタンで再抽出し、そして有機相を合わせ、$MgSO_4$で乾燥し、そして濾過して、ジクロロメタン溶液において表題の化合物を得た。濾液はさらなる精製もしくは単離なしに次の段階（実施例Ａ．１５）において使用した。
測定ＭＷ（MH^+）：２７６
実施例Ａ．１５
［１－（４－ｔｅｒｔ－ブトキシ－ベンジル）－２－オキソ－２－［３－（４－フェニル－１Ｈ－イミダゾル－２－イル）－３，４－ジヒドロ－１Ｈ－イソキノリン－２－イル］－エチル］－カルバミン酸ｔｅｒｔ－ブチルエステル

【００９４】
【化１７】

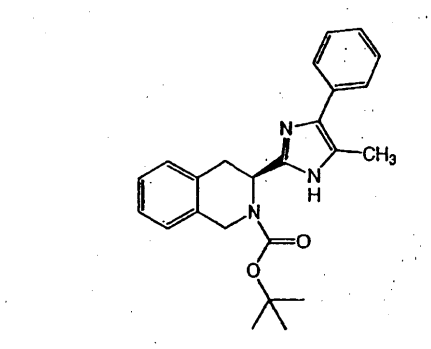


【００９５】
２－ｔｅｒｔ－ブトキシカルボニルアミノ－３－（４－ｔｅｒｔ－ブトキシ－フェニル）－プロピオン酸（０．７４ｇ，２．２ｍｍｏｌ，０．２６ｍｌ）をジクロロメタン（４０ｍｌ）に溶解し、そして反応混合液を約０℃に冷却した。次いで、この溶液にＮＭＭ（０．２１ｇ，２．１ｍｍｏｌ）、続いてクロロギ酸イソブチル（０．２７ｇ，２ｍｍｏｌ）を添加し、そして溶液を約１．２５時間放置した。次いで、反応混合液に実施例Ａ．１４において製造した生成物（０．５５ｇ，２ｍｍｏｌ）を添加し、そして反応混合液を約１６時間撹拌した。次いで、反応混合液を水、飽和$NaHCO_3$、２Ｎクエン酸、飽和$NaHCO_3$で抽出し、$MgSO_4$で乾燥し、濾過し、そして濃縮して泡状物として表題の化合物を得た。測定ＭＷ（MH^+）：５９５．
臭素は、この中間化合物のイミダゾール部分の５位に、クロロホルム中０℃において該中間化合物を１当量のBr_2と反応させることによって導入できる。
塩素は、この中間化合物のイミダゾール部分の５位に、該中間化合物をＮ－クロロスクシンイミドと反応させることによって導入できる。

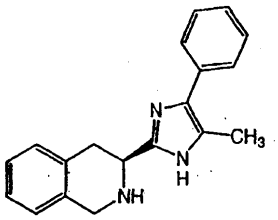
【００９６】
実施例Ａ．１６
３－（５－メチル－４－フェニル－１Ｈ－イミダゾル－２－イル）－３，４－ジヒドロ－１Ｈ－イソキノリン－２－カルボン酸ｔｅｒｔ－ブチルエステル

【００９７】

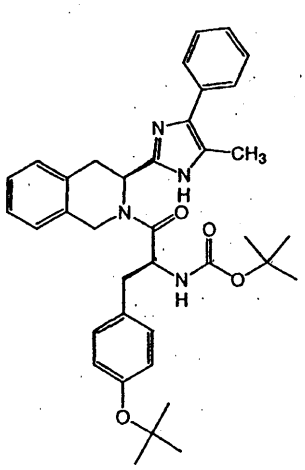
【化１８】



【００９８】
３－ホルミル－３，４－ジヒドロ－１Ｈ－イソキノリン－２－カルボン酸ｔｅｒｔ－ブチルエステル（１．８３ｇ，７ｍｍｏｌ）をＡｃＯＨ（２５ｍＬ）と合わせ、これに１－フェニル－プロパン－１，２－ジオン（３．１１ｇ，２１ｍｍｏｌ）およびNH_4OAc（１３．４９ｇ，１７５ｍｍｏｌ）を直ちに添加した。次いで反応混合液を蒸気浴上に置き、約２０分間アルゴン雰囲気下で加熱した。反応混合液を氷浴において冷却し、次いで氷スラリー（４４ｇ）に添加した。得られる混合液を、濃NH_4OH（５０ｍｌ）の添加によって塩基性にして、次にジエチルエーテル（各１５０ｍｌ）で２回抽出した。合わせた有機相を$MgSO_4$で乾燥し、濾過し、そして濃縮して粗生成物を得た。この物質を調製用ＨＰＬＣによって精製して、白色固形物として表題の化合物を得た。
測定ＭＷ（MH^+）：３９０
実施例Ａ．１７
３－（５－メチル－４－フェニル－１Ｈ－イミダゾル－２－イル）－３，４－ジヒドロ－１Ｈ－イソキノリン
【００９９】
【化１９】



【０１００】
約０℃に冷却したＴＦＡ溶液（５ｍｌ）に、実施例Ａ．１６において製造した化合物（１．１０ｇ，２．８２ｍｍｏｌ）を添加し、そして反応混合液を約３０分間撹拌した。次いで反応混合液を氷浴から除き、そして室温まで暖めた。過剰のＴＦＡをN_2の気流下で除去した。残渣を飽和$NaHCO_3$およびジクロロメタン間に分配した。水相を第２分量のジクロロメタンで洗浄し、そして有機相を合わせた。合わせた有機相を$MgSO_4$で乾燥し、次いで濾過して、ジクロロメタンにおける溶液として表題の生成物を得て、これをさらなる精製もしくは単離なしに使用した。
【０１０１】
実施例Ａ．１８
［１－（４－ｔｅｒｔ－ブトキシ－ベンジル）－２－［３－（５－メチル－４－フェニル－１Ｈ－イミダゾル－２－イル）－３，４－ジヒドロ－１Ｈ－イソキノリン－２－イル］－２－オキソ－エチル］－カルバミン酸ｔｅｒｔ－ブチルエステル
【０１０２】
【化２０】



【０１０３】
２－ｔｅｒｔ－ブトキシカルボニルアミノ－３－（４－ｔｅｒｔ－ブトキシ－フェニル）－プロピオン酸（０．７４ｇ，２．２ｍｍｏｌ）を約０℃に冷却したジクロロメタン（６０ｍｌ）に溶解した。次いで、反応混合液にＮＭＭ（０．３０ｇ，２．９７ｍｍｏｌ）、続いてクロロギ酸イソブチル（０．３９ｇ，２．８２ｍｍｏｌ，０．３７ｍｌ）を添加した。溶液を約９０分間０℃に静置した。次いで、反応混合液に実施例Ａ．１７において製造した生成物（２．８２ｍｍｏｌ）をジクロロメタン溶液として添加した。反応混合液を次いで室温まで暖めた。１６時間後、反応混合液を連続的に水、飽和$NaHCO_3$、２Ｎクエン酸、飽和$NaHCO_3$で抽出し、次いで$MgSO_4$で乾燥し、濾過し、そして濃縮して粗生成物を得た。この物質を調製用ＨＰＬＣによって精製して、白色泡状物として表題の生成物を得た。
測定ＭＷ（MH^+）：６０９
Ｂ．最終化合物の製造
実施例Ｂ．１
４－メチルモルホリン（０．００３ｍｏｌ）をクロロホルム（８０ｍｌ）に溶解した中間体（５）（０．００３ｍｏｌ）に添加した。０℃に冷却後、中間体（２５）（０．００３ｍｏｌ）を正味オイルとして添加した。２７分後、反応混合液を水、飽和$NaHCO_3$およびブラインで洗浄し、乾燥し、濾過し、そして濃縮して、［２Ｓ－［１（Ｒ＊），２Ｒ＊］］－１，１－ジメチルエチル［１－［［２，３－ジヒドロ－２－（４－プロピル－１Ｈ－イミダゾル－２－イル）－１Ｈ－インドル－１－イル］－カルボニル］プロピル］－カルバメート（化合物１４）を得た。
【０１０４】
実施例Ｂ．２
メタノール（２００ｍｌ）中中間体（３）（０．０４７ｍｏｌｅ）に、酢酸カリウム（０．１９９ｍｏｌｅ）を添加した。混合液をアルゴン下で加熱還流した。これに、メタノール（９５ｍｌ）中１－アミノ－２－ペンタノン塩酸塩（０．０９４ｍｏｌｅ）溶液を４５分かけて徐々に添加した。添加が終了した後、混合液を還流下で一夜撹拌させ、次いで濃縮した。濃縮物をＤＣＭ中に採取し、そして飽和$NaHCO_3$で洗浄した。水相をＤＣＭで抽出した。合わせた有機抽出液を乾燥し、そして固形残渣まで濃縮した。残渣をジエチルエーテルおよびＡＣＮによる粉砕によって精製し、そして場合によってはカラムクロマトグラフィーによってさらに精製して、（Ｓ）－１－アセチル－２，３－ジヒドロ－２－（４－プロピル－１Ｈ－イミダゾル－２－イル）－１Ｈ－インドール（化合物８，ｍｐ．１７４－１７５℃）５．８３ｇを得た。
【０１０５】
実施例Ｂ．３
中間体（１２）（０．００１０１ｍｏｌｅ）、２，３－ヘキサンジオン（０．００４ｍｏｌｅ）および酢酸アンモニウム（０．０２５ｍｏｌｅ）を酢酸（４ｍｌ）中に合わせて入

れ、直ちに１５分間蒸気浴上に置いた。室温で２時間後、反応液を氷水（１００ｍｌ）中に注ぎ、３ＮＮａＯＨで塩基性にして、ジエチルエーテルで抽出（２回）した。有機相を合わせ、乾燥、濾過、そして濃縮した。残渣をジエチルエーテル中に採取し、濃縮し、次いで調製用ＬＣによって精製して、１，１－ジメチルエチル２，３－ジヒドロ－２－（５－メチル－４－プロピル－１Ｈ－イミダゾル－２－イル）－１Ｈ－インドール－１－カルボキシレート（化合物９９）０．４４０ｇを得た。
同様に、化合物（８０）は、中間体（１２）をそれぞれ１，１，１－トリフルオロ－３，３－ジブロモアセトンのアルデヒドと反応させることによって製造された。
【０１０６】
実施例Ｂ．４
Ｎ－［（１，１－ジメチルエトキシ）カルボニル］－Ｎ－メチル－Ｌ－アラニン（０．００１８１ｍｏｌ）をＤＣＭに溶解し、そして０℃に冷却した。トリエチルアミン、次いでクロロギ酸イソブチル（０．００１８１ｍｏｌ）を添加し、そして混合液を０℃で７０分間撹拌した。ＤＣＭ（６ｍｌ）中中間体（５）（０．００１８１ｍｏｌ）を添加した。混合液を室温まで暖め、そして一夜撹拌した。混合液を抽出（水、飽和$NaHCO_3$）し、乾燥し、濾過し、そして濃縮した。残渣をＨＰＬＣによって精製した。純粋画分を回収し、そして溶媒を蒸発させて、［２Ｓ－［１（Ｒ＊），２Ｒ＊］］－１，１－ジメチルエチル［２－［２，３－ジヒドロ－２－（４－プロピル－１Ｈ－イミダゾル－２－イル）－１Ｈ－インドル－１－イル］－１－メチル－２－オキソエチル］メチル－カルバメート（化合物６３，ｍｐ．７７－８０℃）０．３８０ｇを得た。
【０１０７】
実施例Ｂ．５
氷浴中で予め冷却した両化合物１４（０．００７３ｍｏｌｅ）およびトリフルオロ酢酸（５ｍｌ）を合わせ、そして窒素下で徐々に室温まで戻した。１時間後、混合液を濃縮した。濃縮物を水に溶解し、そしてジエチルエーテルで抽出した。水相を飽和$NaHCO_3$で塩基性にして、クロロホルムで２回抽出した。合わせた有機相を$MgSO_4$で乾燥し、そして濃縮した。残渣をエーテル中に溶解し、そしてエーテル中１ＭＨＣｌの３ｍｌと処理した。沈殿を濾過し、真空下で乾燥した。残渣を飽和$NaHCO_3$およびクロロホルム間に分配した。有機相を$MgSO_4$で乾燥し、そして濃縮した。濃縮液を、クロロホルム中５％ＭｅＯＨで溶出するＢｉｏｔａｇｅカラムにおいて精製した。残渣をエーテルに溶解し、そしてジエチルエーテル中１ＭＨＣｌの±２ｍｌと処理した。固形物を窒素下の濾過によって回収し、そして一夜真空下で乾燥して、［２Ｓ－［１（Ｒ＊），２Ｒ＊］］－α－エチル－２，３－ジヒドロ－β－オキソ－２－（４－プロピル－１Ｈ－イミダゾル－２－イル）－１Ｈ－インドール－１－エタンアミン二塩酸塩二水和物（化合物１５，ｍｐ．１３２－１４０℃）０．３６４ｇを得た。
【０１０８】
実施例Ｂ．６
ｎ－ブタノール（２００ｍｌ）中中間体（１３）（０．０１０２ｍｏｌｅ）の懸濁液を、ブタン酸ヒドラジド（０．０２５４ｍｏｌｅ）と処理し、１０分間撹拌し、次いで１０日間加熱還流した。反応液を冷却し、真空濃縮し、ＤＣＭ中と蒸留水間に分配した。濃縮した有機相を逆相調製用カラムクロマトグラフィーにかけて、１－アセチル－２，３－ジヒドロ－２－（５－プロピル－１Ｈ－１，２，４－トリアゾル－３－イル）－１Ｈ－インドール（化合物９１）を得た。
【０１０９】
実施例Ｂ．７
ａ）エタノール（２５ｍｌ）中化合物９１（０．４２ｇ）の溶液を、ＮａＯＨ水溶液（３Ｍ，２５ｍｌ）と処理し、そして反応混合液を２４時間還流した。反応液を冷却し、酢酸エチルで希釈し、そして冷却蒸留水で処理した。層を分離し、そして水性画分を酢酸エチルで５回抽出し、そして合わせた有機画分を乾燥し、濃縮し、そして調製用カラムクロマトグラフィーによって精製して、２，３－ジヒドロ－２－（５－プロピル－１Ｈ－１，２

，４－トリアゾル－３－イル）－１Ｈ－インドールを得た。
【０１１０】
ｂ）ＤＣＭ（５ｍｌ）中２，３－ジヒドロ－２－（５－プロピル－１Ｈ－１，２，４－トリアゾル－３－イル）－１Ｈ－インドール（０．０００１７ｍｏｌｅ）溶液をＮ－エチル－Ｎ－（１－メチルエチル）－２－プロパンアミン（０．０００７２ｍｏｌｅ）、次いで（２－フルオロ－２－オキソエチル）－９Ｈ－フルオレン－９－イル－カルバミン酸メチルエステル（０．０００７０ｍｏｌｅ）と処理した。反応液を室温で１５時間撹拌した。反応液をＤＣＭで希釈し、飽和$NaHCO_3$で２回処理し、そしてNa_2SO_4で乾燥し、そして濃縮した。残渣を逆相調製用カラムクロマトグラフィーにかけて、所望のモノ付加物０．０２ｇおよびビス付加物０．０２ｇを得たが、これは調製用クロマトグラフィー溶出液（水中０．１％トリフルオロ酢酸／アセトニトリル）による処理によって完全に所望のモノ付加物に転化された。これらを合わせて、Ｈ－フルオレン－９－イルメチル［２－［２，３－ジヒドロ－２－（５－プロピル－１Ｈ－１，２，４－トリアゾル－３－イル）－１Ｈ－インドル－１－イル］－２－オキソエチル］－カルバメート０．０３ｇを得た。
【０１１１】
ｃ）ＤＣＭ（１０ｍｌ）中Ｈ－フルオレン－９－イルメチル［２－［２，３－ジヒドロ－２－（５－プロピル－１Ｈ－１，２，４－トリアゾル－３－イル）－１Ｈ－インドル－１－イル］－２－オキソエチル］－カルバメート（０．０００６ｍｏｌｅ）溶液をピペリジン（０．０１０ｍｏｌｅ）と処理し、そして室温で１時間撹拌した。合わせた反応液を真空濃縮し、そして逆相調製用カラムクロマトグラフィーにかけて、２，３－ジヒドロ－β－オキソ－２－（５－プロピル－１Ｈ－１，２，４－トリアゾル－３－イル）－１Ｈ－インドール－１－エタンアミン　トリフルオロ酢酸塩（１：１）（化合物９２）０．０２ｇを得た。
【０１１２】
実施例Ｂ．８
ピリジン（１４０ｍｌ）中、中間体（１４）（０．００８９８ｍｏｌｅ）および塩化ブタノイルの混合液を、室温で４０時間撹拌し、次いで加熱還流した。２１時間後、反応液を冷却し、そして真空濃縮した。残渣をＤＣＭ中と飽和$NaHCO_3$間で抽出し、有機画分をNa_2SO_4で乾燥し、濾過し、そして濃縮した。残渣をシリカゲルフラッシュカラムクロマトグラフィー（溶出液，１００％CH_2Cl_2～９５／５CH_2Cl_2／エーテル）にかけて、１－アセチル－２，３－ジヒドロ－２－（５－プロピル－１，２，４－オキサジアゾル－３－イル）－１Ｈ－インドール（化合物８９，ｍｐ．９３－９４℃）を得た。
【０１１３】
実施例Ｂ．９
ａ）エタノール（６０ｍｌ）中化合物８９（０．００３５ｍｏｌｅ）溶液を、３ＭＮａＯＨ（６０ｍｌ）と処理し、そして反応混合液を５．５時間５５－６０℃に加熱した。反応液を氷浴中で急速に冷却し、ＤＣＭで希釈し、そして冷蒸留水で処理した。層を分離し、そして水性画分をＤＣＭで３回抽出した。有機画分を合わせ、１ＭＮａＯＨで１回洗浄し、そしてNa_2SO_4で乾燥し、真空濃縮した。残渣を調製用カラムクロマトグラフィーによって精製して、２，３－ジヒドロ－２－（５－プロピル－１，２，４－オキサジアゾル－３－イル）－１Ｈ－インドール０．４５ｇを得た。
【０１１４】
ｂ）ＤＣＭ（１０ｍｌ）中２，３－ジヒドロ－２－（５－プロピル－１，２，４－オキサジアゾル－３－イル）－１Ｈ－インドール（０．００１１ｍｏｌｅ）溶液をＮ－メチル－Ｎ－（１－メチルエチル）－２－プロパンアミン（０．４０ｍｌ）、次いで（２－フルオロ－２－オキソエチル）－９Ｈ－フルオレン－９－イル－カルバミン酸メチルエステル（０．６７ｇ）と処理した。反応液を室温で４０時間撹拌し、そして各Ｎ－メチル－Ｎ－（１－メチルエチル）－２－プロパンアミン、次いで（２－フルオロ－２－オキソエチル）

－９Ｈ－フルオレン－９－イル－カルバミン酸メチルエステルのその他の分量と処理し、そして室温で２日間撹拌した。反応液をＤＣＭで希釈し、飽和ＮａＨＣＯ$_3$で２回処理し、そしてＮａ$_2$ＳＯ$_4$で乾燥し、そして濃縮した。残渣を逆相調製用カラムクロマトグラフィーにかけて、９Ｈ－フルオレン－９－イルメチル［２－［２，３－ジヒドロ－２－（５－プロピル－１，２，４－オキサジアゾル－３－イル）－１Ｈ－インドル－１－イル］－２－オキソエチル］－カルバメート０．３５ｇを得た。

【０１１５】

ｃ）９Ｈ－フルオレン－９－イルメチル［２－［２，３－ジヒドロ－２－（５－プロピル－１，２，４－オキサジアゾル－３－イル）－１Ｈ－インドル－１－イル］－２－オキソエチル］－カルバメート（０．３５ｇ）をＤＣＭ（４０ｍｌ）に溶解し、ピペリジン（０．５０ｍｌ）と処理し、そして室温で１８間撹拌した。完了した反応液を真空濃縮し、そして逆相調製用カラムクロマトグラフィーにかけて、２，３－ジヒドロ－β－オキソ－２－（５－プロピル－１，２，４－オキサジアゾル－３－イル）－１Ｈ－インドール－１－エタンアミン　トリフルオロ酢酸塩（１：１）（化合物９０，ｍｐ．１６０－１６２℃）０．１３ｇを得た。

【０１１６】

実施例Ｂ．１０

２，３－ジヒドロ－２－（４－プロピル－１Ｈ－イミダゾル－２－イル）－１Ｈ－インドール（０．００２４ｍｏｌ）および１，３－イソベンゾフランジオン（０．００２６ｍｏｌ）を、アルゴン下の２５ｍｌ容ナシ型フラスコにおいて２時間１００℃に加熱した。混合液をメタノールに溶解し、そして１５時間加熱還流した。反応混合液を濃縮し、そしてＤＣＭ中に採取し、水および３ＮＮａＯＨで洗浄した。塩基性水性抽出液を６ＮＨＣｌで酸性にしてＤＣＭで抽出した。この有機抽出液をＭｇＳＯ$_4$で乾燥し、そして濃縮した。濃縮液をエーテル中で粉砕し、そして回収した。これをさらに酸性水溶液とともに、調製用液体クロマトグラフィーによって精製して、２－［［２－（４－エチル－１Ｈ－イミダゾル－２－イル）－２，３－ジヒドロ－１Ｈ－インドル－１－イル］カルボニル］－安息香酸　トリフルオロ酢酸塩（１：１）（化合物８５，ｍｐ．９８－１０３℃）０．２３ｇを得た。

【０１１７】

実施例Ｂ．１１

１－イソシアナト－２－ニトロ－ベンゼン（０．００２ｍｏｌ）をＴＨＦ（１０ｍｌ）中中間体（１５）（０．０１６ｍｏｌ）溶液に添加した。混合液をアルゴン下、室温で５時間撹拌した。混合液をヘキサンで希釈し、濾過し、そして乾燥させて、２－（４－エチル－１Ｈ－イミダゾル－２－イル）－２，３－ジヒドロ－Ｎ－（２－ニトロフェニル）－１Ｈ－インドール－１－カルボキサミド（化合物７７，ｍｐ．２０８－２０９℃）０．３４ｇを得た。

【０１１８】

実施例Ｂ．１２

化合物７７（０．０００６ｍｏｌ）、ラネーニッケル（０．０２ｇ；水中５０％スラリー）およびメタノール（２０ｍｌ）の混合液に、ヒドラジンを添加した。水（０．００３ｍｏｌ）。得られる混合液を２時間加熱還流した。室温に冷却後、混合液を注意してセライトを通して濾過し、そして濾液を濃縮した。残渣をエーテル中で粉砕し、そして濾過した。残渣を調製用液体クロマトグラフィーによって精製して、Ｎ－（２－アミノフェニル）－２－（４－エチル－１Ｈ－イミダゾル－２－イル）－２，３－ジヒドロ－１Ｈ－インドール－１－カルボキサミド　トリフルオロ酢酸塩（１：２）（化合物７９，ｍｐ．１０６－１０８℃）０．２４ｇを得た。

【０１１９】

実施例Ｂ．１３

ＴＨＦ（７０ｍｌ）中化合物１６（０．００６９７ｍｏｌｅ）混合液を一定分量づつの水素化ナトリウム（０．００７ｍｏｌｅ）と処理し、そして周囲温度において１６時間撹拌

した。ヨードメタン（０．００７１ｍｏｌｅ）を一定分量づつ導入した。周囲温度で２４時間撹拌後、さらなる水素化ナトリウム（０．００７ｍｏｌｅ）をアルゴン雰囲気下で一定分量づつ添加した。発泡が沈静した後フラスコを再び閉じ、そして１６時間撹拌した。完了した反応液を氷浴で冷却し、ＤＣＭ中に注入し、そして冷水と処理した。層を分離し、そして水相をＤＣＭにより３回抽出した。合わせた有機画分を飽和$NaHCO_3$で洗浄し、Na_2SO_4で乾燥し、そして濃縮した。残渣をフラッシュシリカゲルカラムクロマトグラフィー（溶出液，ＤＣＭ～エーテル～９：１エーテル／ＴＨＦ）にかけた。適当な画分を合わせた。残渣をエーテル中に採取し、そしてフリーザー内に置いた。結晶が析出して、１－アセチル－２－（４－エチル－１－メチル－１Ｈ－イミダゾル－２－イル）－２，３－ジヒドロ－１Ｈ－インドール（化合物１３２，ｍｐ．１０５－１０６℃）０．５５ｇ（２９．３％）を得た。第２セットの画分を合わせた。残渣をエーテル中に採取し、そしてフリーザー内に置いた。結晶の析出を観察し、１－アセチル－２－（４－エチル－１－メチル－１Ｈ－イミダゾル－２－イル）－２，３－ジヒドロ－１Ｈ－インドール（化合物１３３，ｍｐ．１３５－１３７℃）０．３８ｇを得た。

【０１２０】

実施例Ｂ．１４

化合物８０（０．００１ｍｏｌｅ）を１ＮＮａＯＨ（１２ｍｌ）に懸濁した。混合液を激しく撹拌し、そして窒素下で１時間８８℃に加熱した。室温で３時間撹拌後、混合液を０℃に冷却し、１ＭＨＣｌで徐々に中和して若干の固形物を沈殿させた。固形物を濾過し、氷冷水で洗浄した。水相を２回抽出し、乾燥、濾過、濃縮、そして乾燥して、１，１－ジメチルエチル２－（４－カルボキシ－１Ｈ－イミダゾル－２－イル）－２，３－ジヒドロ－１Ｈ－インドール－１－カルボキシレート（化合物１１７）０．１４０ｇを得た。

【０１２１】

実施例Ｂ．１５

１－ヒドロキシベンゾトリアゾール水和物（０．０００３６ｍｏｌｅ）、グリシンメチルエステル、塩酸塩（０．０００４７ｍｏｌｅ）、４－メチルモルホリン（０．０００５５ｍｏｌｅ）およびＮ’－（エチルカルボンイミドイル）－Ｎ，Ｎ－ジメチル－１，３－プロパンジアミン一塩酸塩（０．０００４７ｍｏｌｅ）を、０℃においてＤＣＭ（３０ｍｌ）に溶解した化合物１１７（０．０００３６ｍｏｌｅ）に添加した。混合液を窒素下で室温まで温め、そして一夜撹拌した。混合液を水、飽和$NaHCO_3$、２Ｎクエン酸、次いで飽和$NaHCO_3$で抽出し、乾燥し、濾過し、そして濃縮して、１，１－ジメチルエチル２，３－ジヒドロ－２－［４－［［（２－メトキシ－２－オキソエチル）アミノ］カルボニル］－１Ｈ－イミダゾル－２－イル］－１Ｈ－インドール－１－カルボキシレート（化合物１１８）０．１００ｇ（６９％）を得た。

【０１２２】

実施例Ｂ．１６

化合物６１（０．０００２８ｍｏｌ）を３ＮＮａＯＨ（３ｍｌ）と処理し、そして室温で２０分間撹拌させた。次いで、溶液を３ＮＨＣｌ　３ｍｌと処理し、そしてクロロホルムで抽出した。物質を水層に留めた。水層を調製用液体クロマトグラフィーによって精製して、２－［１－（アミノアセチル）－２，３－ジヒドロ－１Ｈ－インドル－２－イル］－１Ｈ－ベンズイミダゾール－５－カルボン酸一水和物トリフルオロ酢酸塩（１：２）（化合物６２、ｍｐ．２０８－２１１℃）０．１２ｇを得た。

【０１２３】

実施例Ｂ．１７

化合物１０２（０．００２３８ｍｏｌｅ）をメタノール４０ｍｌに溶解し、そして１ＮＫＯＨ（５０ｍｌ）と合わせた。反応液アルゴン下で一夜４０℃に加温した。加熱を５５－６０℃に上げて、さらに一夜加熱した。次いで反応液を室温まで冷却し、濾過し、そして０℃において１ＮＨＣｌで徐々に中和した。サンプルをＤＣＭで５回抽出し、合わせ、そしてNa_2SO_4で乾燥した。この有機溶液を濾過し、そしてさらなる精製なしにさらなる合成乾燥において使用される１，１－ジメチルエチル２－（４－カルボキシ－５－プロ

ピル－１Ｈ－イミダゾル－２－イル）－２，３－ジヒドロ－１Ｈ－インドール－１－カルボキシレート（化合物１０５）を得た。

【０１２４】

実施例Ｂ．１８

１－ヒドロキシベンゾトリアゾール水和物（０．００３１８ｍｏｌｅ）を、室温においてＤＣＭ（１６０ｍｌ）中化合物１０５（０．００１５９ｍｏｌｅ）溶液に添加した。Ｎ，Ｎ’－メタン－テトライル－ビスシクロヘキサンアミン（０．００２０６ｍｏｌｅ）を正味室温で添加した。６０分後、NH_3ガスを５分間吹き込み、そして固形物を析出させた。混合液を１週間静置させた。混合液を濾過し、そして濾液を飽和$NaHCO_3$で抽出した。有機相を$MgSO_4$で乾燥し、濾過し、そして濃縮した。残渣を液体クロマトグラフィーによって精製して、１，１－ジメチルエチル２－［４－（アミノカルボニル）－５－プロピル－１Ｈ－イミダゾル－２－イル］－２，３－ジヒドロ－１Ｈ－インドール－１－カルボキシレート（化合物１０６）０．２１ｇを得た。

【０１２５】

実施例Ｂ．１９

１－ヒドロキシベンゾトリアゾール水和物（０．００１５８ｍｏｌｅ）を、ＤＣＭ（８０ｍｌ）中化合物１０５（０．０００７９ｍｏｌｅ）溶液に添加した。グリシンメチルエステル塩酸塩（０．００１０３ｍｏｌｅ）、Ｎ’－（エチルカルボンイミドイル）－Ｎ，Ｎ－ジメチル－１，３－プロパンジアミン一塩酸塩（０．００１０３ｍｏｌｅ）および４－メチルモルホリン（０．００１０３ｍｏｌｅ）を添加した。ＴＨＦ（２５ｍｌ）を添加した。反応液を室温で３日間撹拌した。混合液を水で抽出した。有機相を飽和$NaHCO_3$、２Ｎクエン酸、飽和$NaHCO_3$で洗浄し、$MgSO_4$で乾燥し、濾過し、そして濃縮して、１，１－ジメチルエチル２，３－ジヒドロ－２－［４－［［（２－メトキシ－２－オキソエチル）アミノ］カルボニル］－５－プロピル－１Ｈ－イミダゾル－２－イル］－１Ｈ－インドール－１－カルボキシレート（化合物１０９）０．２０ｇを得た。

【０１２６】

実施例Ｂ．２０

化合物８１（０．０００５ｍｏｌｅ）を１ＮＮａＯＨ（６ｍｌ）に懸濁した。混合液を直ちに６０分間８０℃に加熱した。室温で、クロロホルム（６ｍｌ）次いで（２－フルオロ－２－オキソエチル）－１，１－ジメチルカルバミン酸エステル（０．００１ｍｏｌｅ）を添加した。混合液を一夜撹拌した。層を分離した。水相を冷却し、酸性にして、クロロホルムで２回抽出した。後者の有機相を合わせ、乾燥、濾過、そして濃縮した。サンプルを調製用ＨＰＬＣによって精製して、２－［１－［［［（１，１－ジメチルエトキシ）カルボニル］－アミノ］アセチル］－２，３－ジヒドロ－１Ｈ－インドル－２－イル］－１Ｈ－イミダゾール－４－カルボン酸（化合物１３８）０．０４０ｇを得た。

【０１２７】

実施例Ｂ．２１

エタノール（５ｍｌ）に溶解した化合物１４５（０．０００９７ｍｏｌｅ）に、エタノール中２１％ＮａＯＥｔ数滴を添加した。混合液をアルゴン下室温で撹拌した。３０分後に、さらにエタノール中２１％ＮａＯＥｔ２滴を添加した。１６時間後に、さらにエタノール中２１％ＮａＯＥｔ２滴を添加した。３０分後、混合液を濃縮し、そして水とＤＣＭ間に分配した。水相をさらなるＤＣＭで洗浄した。合わせた有機相を水で洗浄し、乾燥そして濃縮して、［２Ｓ－［１（Ｒ＊），２Ｒ＊］］－２，３－ジヒドロ－α－メチル－β－オキソ－２－（４－プロピル－１Ｈ－イミダゾル－２－イル）－１Ｈ－インドール－１－エタノール（化合物１４６）０．１９３ｇ（６６％）を得た。

化合物１４８は化合物１４７から出発して同様に製造された。

【０１２８】

実施例Ｂ．２２

アセトニトリル（１５ｍｌ）中化合物５８（０．００１９ｍｏｌｅ）の懸濁液に、無水酢酸（０．０７４ｍｏｌｅ）を添加した。アルゴン下室温で４時間撹拌した。無水酢酸さら

なる１．０ｍｌを添加し、そして反応液を一夜撹拌した。さらに６時間撹拌後、反応は完結した。混合液を濃縮し、そして残渣を飽和ＮａＨＣＯ$_3$とクロロホルム間に分配した。有機相を乾燥し、そして濃縮した。残渣をカラムクロマトグラフィーによって精製した。所望の画分を合わせ、エーテル中で粉砕し、そして回収して、１－［［１－［（４－クロロフェニル）アセチル］－４－（３－メトキシフェニル）－４－ピペリジニル］メチル］－１，３－ジヒドロ－２Ｈ－ベンズイミダゾル－２－オン（化合物１４９）０．３７ｇを得た。

【０１２９】

実施例Ｂ．２３

化合物１４９（０．００１２ｍｏｌｅ）およびＴＨＦ（２００ｍｌ）の溶液を光化学反応器内に入れ、そしてＵＶ光線を１４時間照射した。次いで混合液を窒素下室温において２日間放置した。混合液を濃縮した。濃縮液を、１：９ＤＣＭ中ＴＨＦで溶出するＢｉｏｔａｇｅカラムにおいて精製して、１－［２－（１－アセチル－２，３－ジヒドロ－１Ｈ－インドル－２－イル）－５－プロピル－１Ｈ－イミダゾル－４－イル］－エタノン（化合物１５０）０．０７７ｇを得た。

【０１３０】

実施例Ｂ．２４

ＴＨＦ１０ｍｌに溶解した化合物１３（０．００１０６ｍｌｏｅ）を、ＴＨＦ中の溶液であるＢＨ$_3$．ＴＨＦ（１９ｍｌ）と室温で処理した。次いで溶液を油浴に置き、そして一夜６０℃に加熱した。０℃に冷却後、溶液を３ＮＨＣｌ　１５ｍｌにより注意深く処理した。次いで溶液を室温まで暖め、そして４時間撹拌した。次いで混合液を０℃に再冷却し、そして３ＮＮａＯＨ　１２ｍｌで塩基性にして、次いで塩基性化の完結を固形Ｎａ$_2$ＣＯ$_3$により行った。層を分離し、水相をクロロホルムで再洗浄した。有機相を合わせ、少量の水相を分離し、そして有機相をＮａ$_2$ＳＯ$_4$で乾燥した。混合液を濾過し、そして濾液を減圧下で濃縮した。残渣を調製用液体クロマトグラフィーにかけて、［２Ｓ－［１（Ｒ＊），２Ｒ＊］］－２－（４－エチル－１Ｈ－イミダゾル－２－イル）－２，３－ジヒドロ－α－メチル－１Ｈ－インドール－１－エタンアミン　トリフルオロ酢酸塩（１：１）（化合物１２７）０．３３ｇを得た。

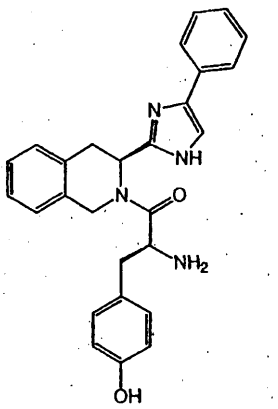
【０１３１】

実施例Ｂ．２５

３－アミノ－４－（４－ヒドロキシ－フェニル）－１－［３－（４－フェニル－１Ｈ－イミダゾル－２－イル）－３，４－ジヒドロ－１Ｈ－イソキノリン－２－イル］－ブタン－１－オン（化合物１５５）

【０１３２】

【化２１】



【０１３３】

ＴＦＡ（４ｍｌ）を約０℃に冷却し、次いで実施例Ａ．１５において製造した化合物（１．１０ｇ，１．８５ｍｍｏｌ）を添加した。反応混合液を約０．５時間静置した。次いで

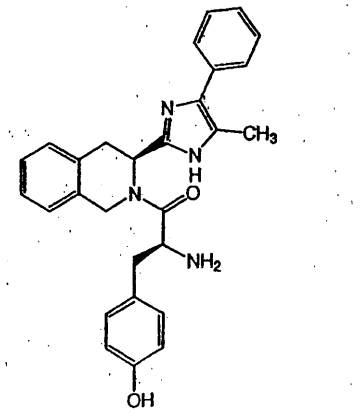
過剰のＴＦＡをN_2の気流下で除去して、褐色オイルを得た。オイルを調製用ＨＰＬＣにより精製して、白色固体として表題の化合物を得た。測定ＭＷ（MH^+）：４３９

実施例Ｂ．２６

２－アミノ－３－（４－ヒドロキシ－ベンジル）－１－［３－（５－メチル－４－フェニル－イミダゾル－２－イル）－３，４－ジヒドロ－１Ｈ－イソキノリン－２－イル］－プロパン－１－オン（化合物１５３）

【０１３４】

【化２２】



【０１３５】

約０℃に冷却したＴＦＡ溶液（４ｍｌ）に、実施例Ａ．１８において製造した化合物（０．２４ｇ，０．４ｍｍｏｌ）を添加し、そして反応混合液を約２０分間撹拌した。次いで反応混合液を氷浴から除き、そして室温まで暖めた。過剰のＴＦＡをN_2の気流下で除去して、粗生成物を得た。この物質を調製用ＨＰＬＣにより精製して、白色固体として表題の化合物を得た。

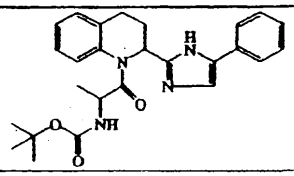
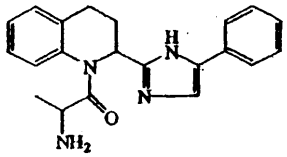
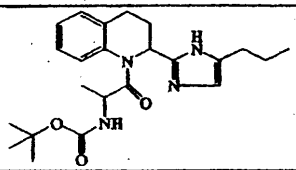
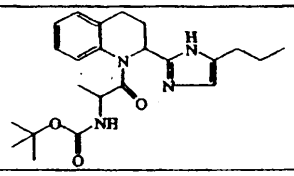
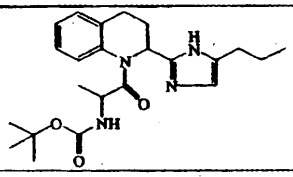
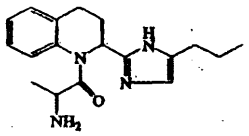
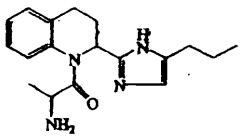
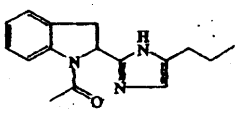
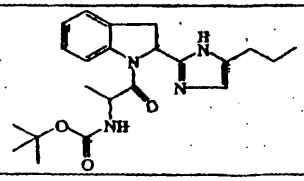
測定ＭＷ（MH^+）：４５３

表Ｆ－１は、前記実施例の１つにしたがって製造された化合物を列挙している。次の略語を表中で使用した：．$C_2HF_3O_2$はトリフルオロ酢酸塩を表し、．$2C_2H_2O_4$はエタン二酸塩を表し、そして．$C_{10}H_8O_3S$は２－ナフタレンスルホン酸塩を表す。該表Ｆ－１は、化合物の構造、これらの化合物が製造された実施例ナンバー、塩型、立体化学指標および融点（測定された場合）を列挙している。

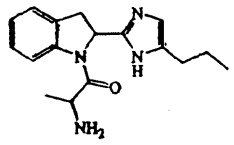
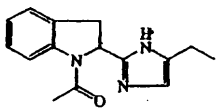
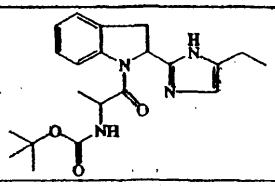
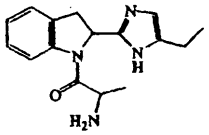
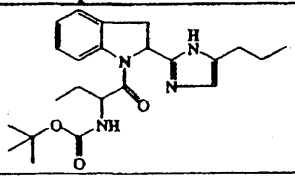
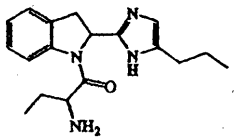
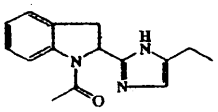
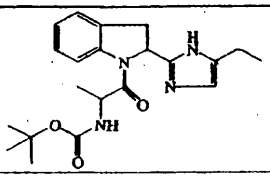
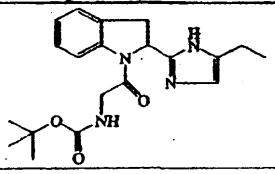
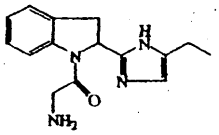
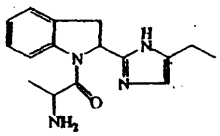
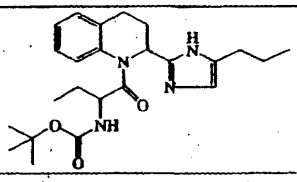
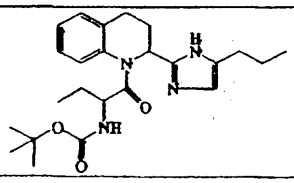
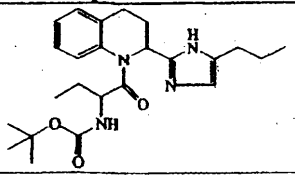
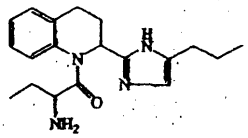
【０１３６】

【表１】

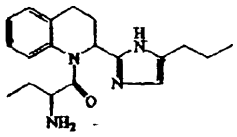
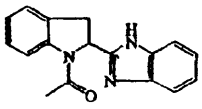
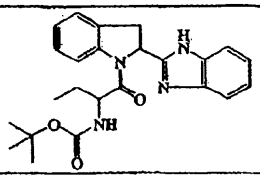
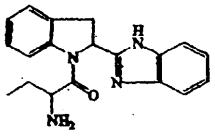
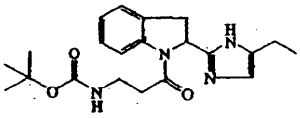
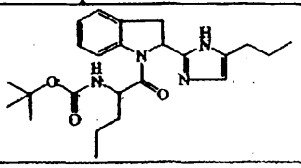
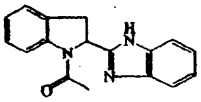
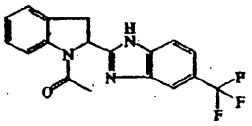
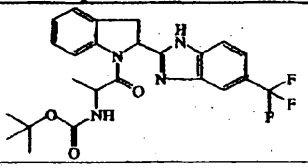
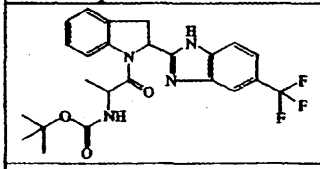
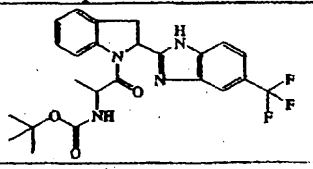
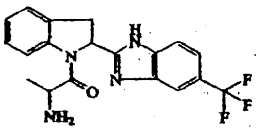
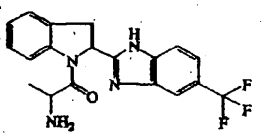
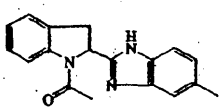
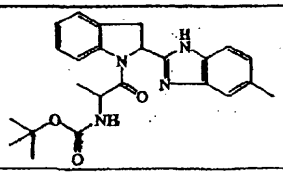
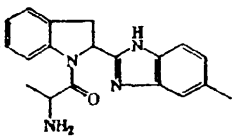
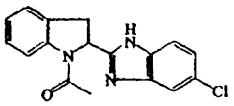
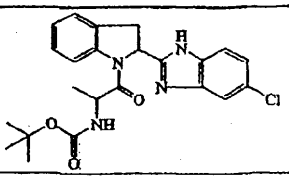
表F-1

		
Co. No. 1; Ex. B.1	Co. No. 2; Ex. B.5	Co. No. 3; Ex. B.1; [2R-[1(S*),2R*]] + [2S-(1(R*),2R*]]
		
Co. No. 4; Ex. B.1; [1(S),2A]	Co. No. 5; Ex. B.1; [1(S),2B]	Co. No. 6, Ex. B.5; [1(S),2A]
		
Co. No. 7; Ex. B.5; [1(S),2B]	Co. No. 8; Ex. B.2; (S); mp. 174-175°C	Co. No. 9; Ex. B.1; [2S-[1(R*),2R*]]

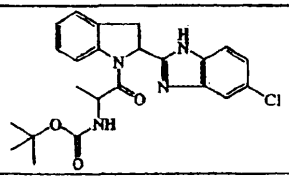
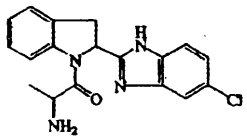
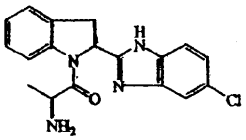
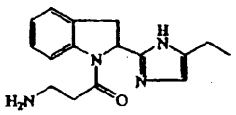
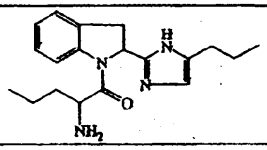
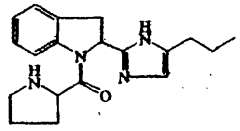
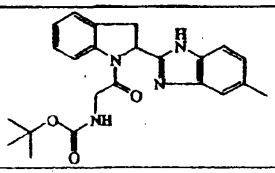
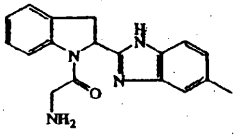
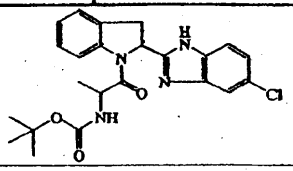
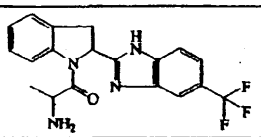
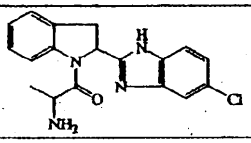
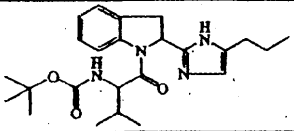
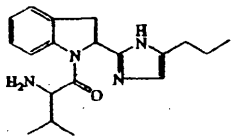
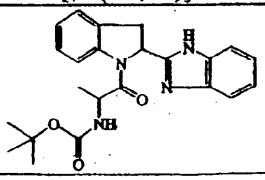
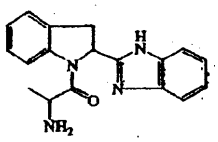
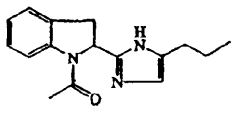
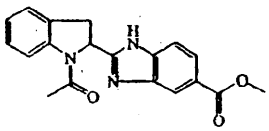
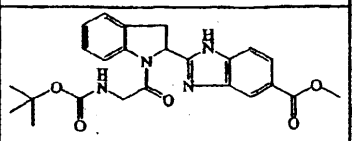
【０１３７】
【表２】

		
Co. No. 10; Ex. B.5; [2S-[1(R*),2R*]]	Co. No. 11; Ex. B.2; (S); mp. 136-139°C	Co. No. 12; Ex. B.1; [2S-[1(R*),2R*]]
		
Co. No. 13; Ex. B.5; [2S-[1(R*),2R*]]; mp. 116-118°C	Co. No. 14; Ex. B.1; [2S-[1(R*),2R*]]	Co. No. 15; Ex. B.5; .2HCl.2H$_2$O [2S-[1(R*),2R*]]; mp. 132-140°C
		
Co. No. 16; Ex. B.2	Co. No. 17; Ex. B.1; [2R-[1(S*),2R*]]; mp. 76-79°C	Co. No. 18; Ex. B.1; mp. 198-199°C
		
Co. No. 19; Ex. B.5; mp. 184-186°C	Co. No. 20; Ex. B.5; .H$_2$O [2R-[1(S*),2R*]]; mp. 73-74°C	Co. No. 21; Ex. B.1; [2R-[1(S*),2R*]] + [2S-[1(R*),2R*]]
		
Co. No. 22; Ex. B.1; [1(S),2A]	Co. No. 23; Ex. B.1; [1(S),2B]	Co. No. 24; Ex. B.5; .2C$_2$H$_2$O$_4$; [1(S),2A]; mp. >90°C

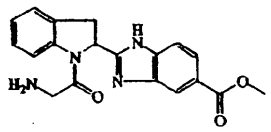
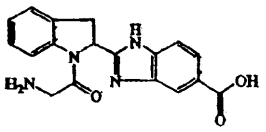
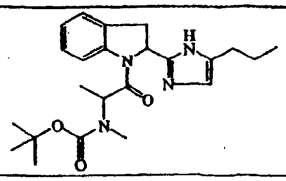
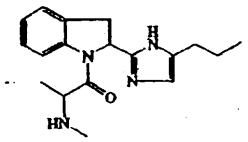
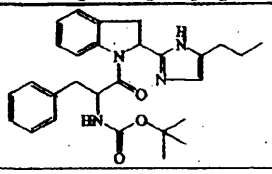
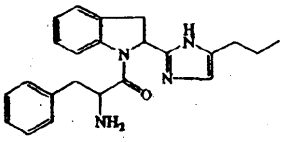
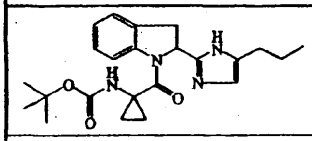
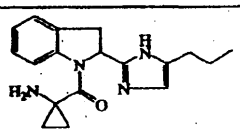
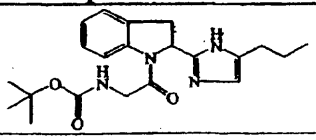
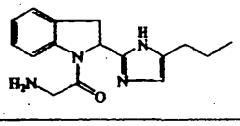
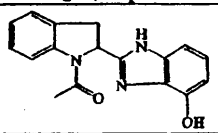
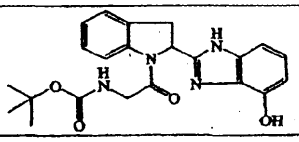
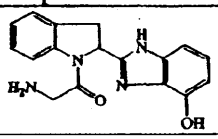
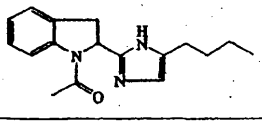
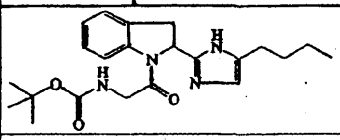
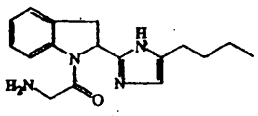
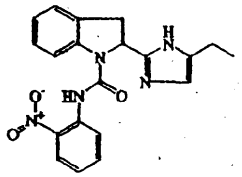
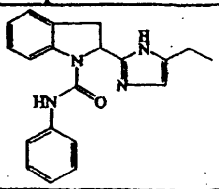
【０１３８】
【表３】

		
Co. No. 25; Ex. B.5; .2HCl.2H$_2$O [1(S),2B]; mp. >100°C	Co. No. 26; Ex. B.2; (S); mp. 208-210°C	Co. No. 27; Ex. B.4; [S-[1(R*),R*]; mp. 107-109°C
		
Co. No. 28; Ex. B.5; .3HCl; [S-[1(R*),R*]; mp. 240-242°C	Co. No.29 ; Ex. B.4; mp. 170-171°C	Co. No. 30; Ex. B.4; .C$_2$HF$_3$O$_2$; [S-(R*,R*)]; mp. 173-175°C
		
Co. No. 31; Ex. B.2; mp. 261-262°C	Co. No. 32; Ex. B.2; mp. 256-257°C	Co. No. 33; Ex. B.1; .C$_2$HF$_3$O$_2$; [R-(R*,S*)]
		
Co. No. 34; Ex. B.1; .C$_2$HF$_3$O$_2$; [S-(R*,R*)]	Co. No. 35; Ex. B.1; .C$_2$HF$_3$O$_2$; [R-(R*,S*)] + [S-(R*,R*]]	Co. No. 36; Ex. B.5; .2C$_2$HF$_3$O$_2$; [S-(R*R*)]
		
Co. No. 37; Ex. B.5; .2C$_2$HF$_3$O$_2$; [R-(R*,S*)] + [S-(R*,R*)]	Co. No. 38; Ex. B.2; mp. 214-216°C	Co. No. 39; Ex. B.1; [1(S)]; mp. 137-138°C
		
Co. No. 40; Ex. B.5; [1(S)]; mp. 198-203°C	Co. No. 41; Ex. B.2; mp. 221-222°C	Co. No. 42; Ex. B.1; .2C$_2$HF$_3$O$_2$; [R-(R*,S*)]

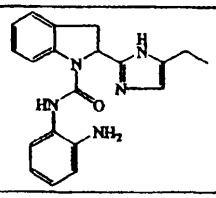
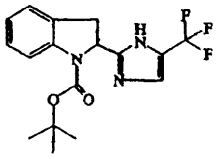
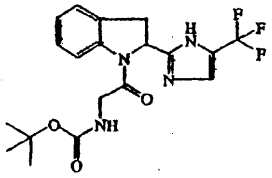
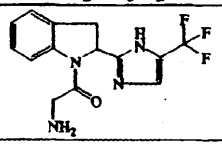
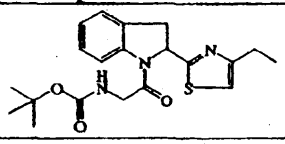
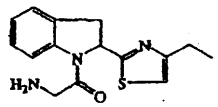
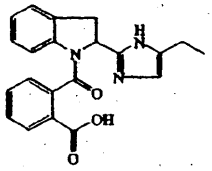
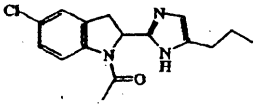
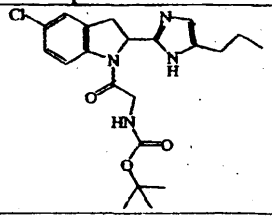
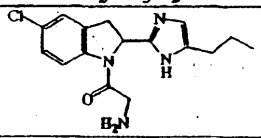
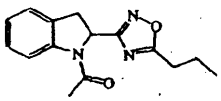
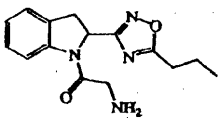
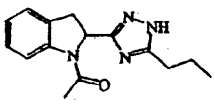
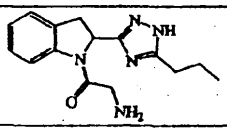
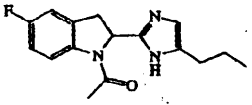
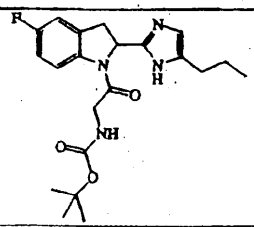
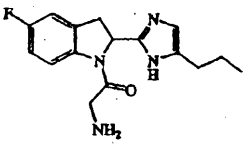
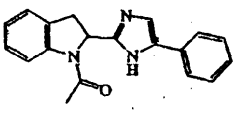
【０１３９】
【表４】

		
Co. No. 43; Ex. B.1; .$C_2HF_3O_2$; [S-(R*,R*)]	Co. No. 44; Ex. B.5; .$3C_2HF_3O_2$; [S-(R*,R*)]	Co. No. 45; Ex. B.5; .$2C_2HF_3O_2$; [R-(R*,S*)] + [S-(R*,R*)]
		
Co. No.46 ; Ex. B.5; mp. 158-160°C	Co. No. 47; Ex. B.5; .$2C_2H_2O_4$; [S-(R*,R*)]; mp. 135-137°C	Co. No. 48; Ex. B.5; .2HCl.$3H_2O$; [S-(R*,R*)]; mp. 85-87°C
		
Co. No. 49; Ex. B.4; .$H_2O.C_2HF_3O_2$; mp.	Co. No. 50; Ex. B.5; mp. 116-118°C	Co. No. 51; Ex. B.1; .$C_2HF_3O_2$; [R-(R*,S*)] + [S-(R*,R*)]
		
Co. No. 52; Ex. B.5; .$2C_2HF_3O_2$; [R-(R*,S*)]	Co. No. 53; Ex. B.5; .$H_2O.2C_2HF_3O_2$; [R-(R*,S*)]	Co. No. 54; Ex. B.4; .$C_2HF_3O_2$; [S-(R*,R*)]; mp. 66-68°C
		
Co. No. 55; Ex. B.5; .$C_{10}H_8O_3S.H_2O$; [S-(R*,R*)]; mp. 195-197°C	Co. No. 56; Ex. B.1; [S-(R*,R*)]; mp. 76-78°C	Co. No. 57; Ex. B.5; [S-(R*,R*)]; mp. 141-143°C
		
Co. No. 58; Ex. B.2; mp. 173-174°C	Co. No. 59; Ex. B.2; mp. 220-222°C	Co. No. 60; Ex. B.1; .H_2O; mp. 183°C

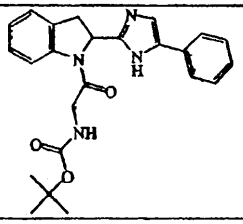
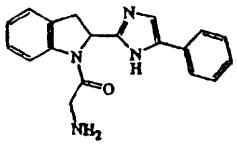
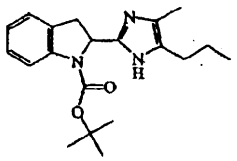
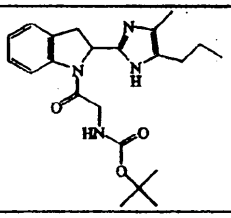
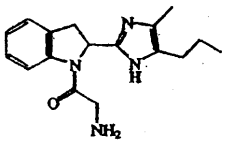
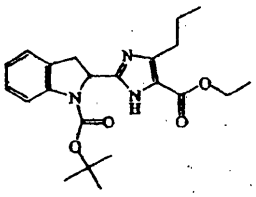
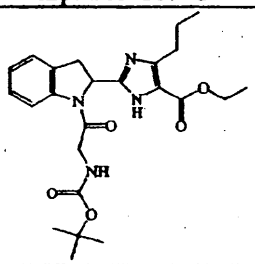
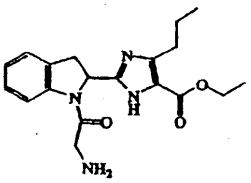
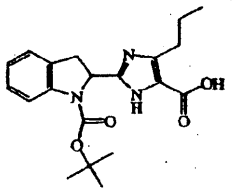
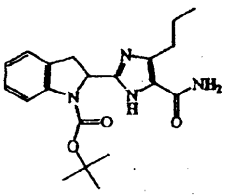
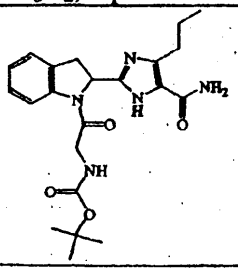
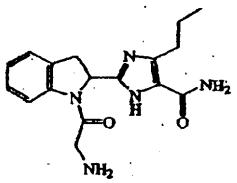
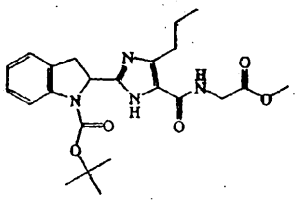
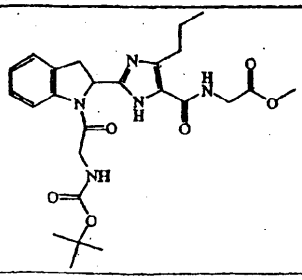
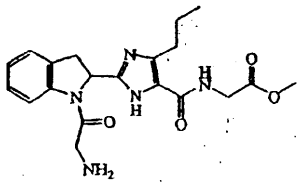
【０１４０】
【表５】

		
Co. No. 61; Ex. B.5; mp. 122°C	Co. No. 62; Ex. B.16; $.2H_2O.2C_2HF_3O_2$	Co. No. 63; Ex. B.4; [S-(R*,R*)]; mp. 77-80°C
		
Co. No. 64; Ex. B.5; [S-(R*,R*)]; mp. 137-138°C	Co. No. 65; Ex. B.1; [2S-[1(R*),2R*]]	Co. No. 66; Ex. B.5; $.C_2H_2O_4.2H_2O$; [2S-[1(R*),2R*]]; mp. 153-156°C
		
Co. No. 67; Ex. B.1; mp. 100-104°C	Co. No. 68; Ex. B.5; $.HCl.H_2O$; mp. 152°C	Co. No. 69; Ex. B.1
		
Co. No. 70; Ex. B.5; $.H_2O$; mp. 168-170°C	Co. No. 71; Ex. B.2; .2KCl; mp. 189-191°C	Co. No. 72; Ex. B.1; mp. 168°C
		
Co. No. 73; Ex. B.5; $.H_2O.2C_2F_3O_2$; mp. >300°C	Co. No. 74; Ex. B.2; mp. 191-192°C	Co. No. 75; Ex. B.1; mp. 214-216°C
		
Co. No. 76; Ex. B.5; mp. 158-160°C	Co. No. 77; Ex. B.11	Co. No. 78; Ex. B.11

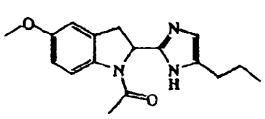
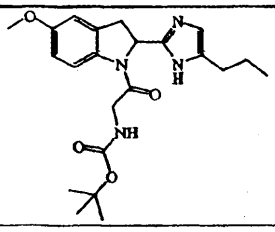
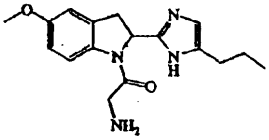
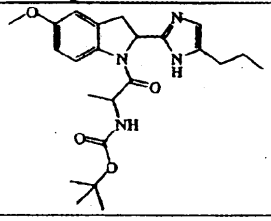
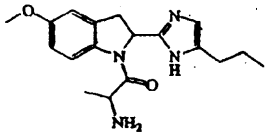
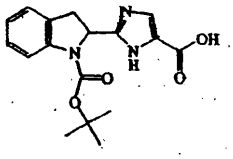
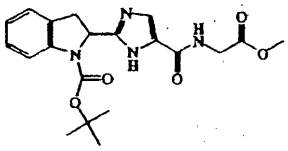
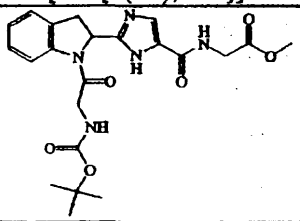
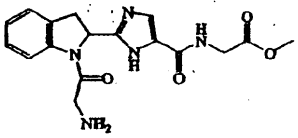
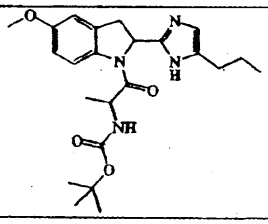
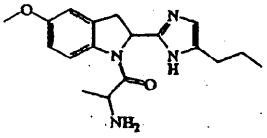
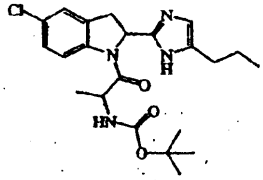
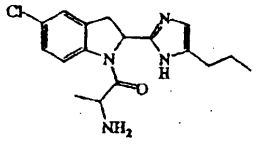
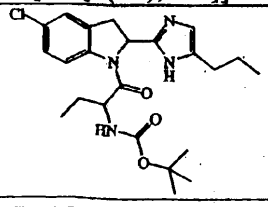
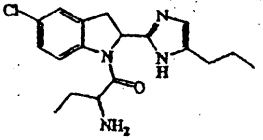
【０１４１】
【表６】

		
Co. No. 79; Ex. B.12; .2$C_2HF_3O_2$	Co. No. 80; Ex. B.3; mp. 179-181°C	Co. No. 81; Ex. B.1
		
Co. No. 82; Ex. B.5; mp. 186-188°C	Co. No. 83; Ex. B.1	Co. No. 84; Ex. B.5; .$C_4H_4O_4$; mp. 173-174°C
		
Co. No. 85; Ex. B.10; .$C_2HF_3O_2$	Co. No. 86; Ex. B.2; mp. 225-226°C	Co. No. 87; Ex. B.4;
		
Co. No. 88; Ex. B.5; mp. 193-195°C	Co. No. 89; Ex. B.8	Co. No. 90; Ex. B.9; .$C_2HF_3O_2$
		
Co. No. 91; Ex. B.6; mp.	Co. No. 92; Ex. B.7; .$C_2HF_3O_2$	Co. No. 93; Ex. B.2
		
Co. No. 94; Ex. B.1; .$C_2HF_3O_2$	Co. No. 95; Ex. B.5; .$C_2HF_3O_2$	Co. No. 96; Ex. B.2

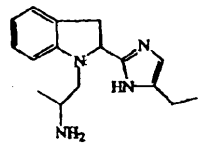
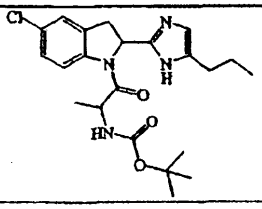
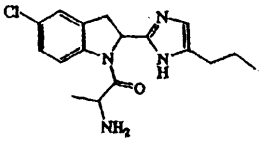
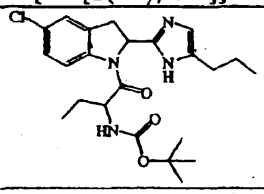
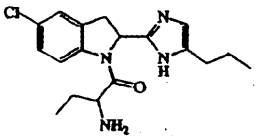
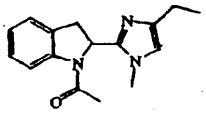
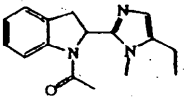
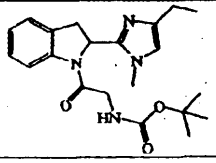
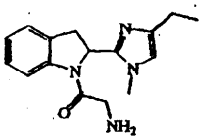
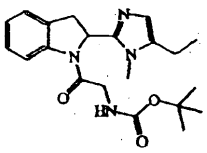
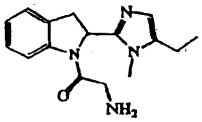
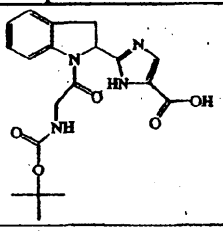
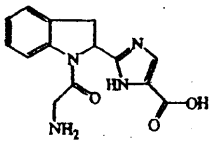
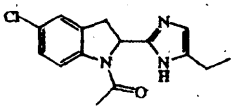
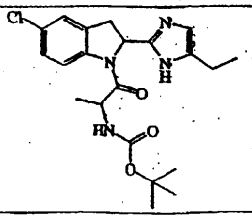
【０１４２】
【表７】

		
Co. No. 97; Ex. B.4	Co. No. 98; Ex. B.5; mp. 214-215°C	Co. No. 99; Ex. B.3
		
Co. No. 100; Ex. B.1; mp. 165-167°C	Co. No. 101; Ex. B.5; mp. 197-198°C	Co. No. 102; Ex. B.3
		
Co. No. 103; Ex. B.4	Co. No. 104; Ex. B.5; .$C_2HF_3O_2$; mp. 102-105°C	Co. No. 105; Ex. B.17
		
Co. No. 106; Ex. B.18	Co. No. 107; Ex. B.1	Co. No. 108; Ex. B.5; .$C_2HF_3O_2$; mp. 124-131°C
		
Co. No. 109; Ex. B.19	Co. No. 110; Ex. B.1	Co. No. 111; Ex. B.5; .$C_2HF_3O_2$; mp. 95-99°C

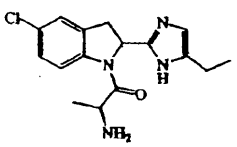
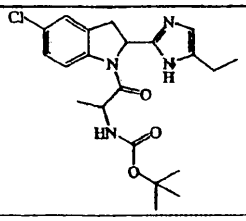
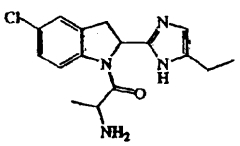
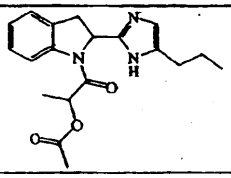
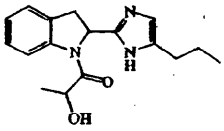
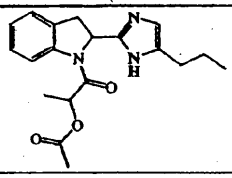
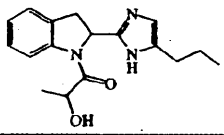
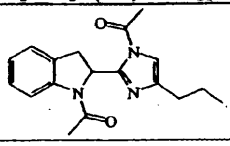
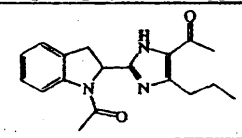
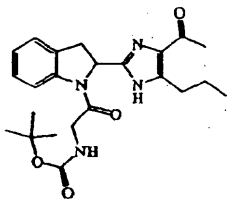
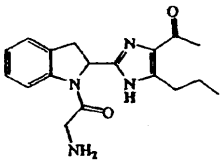
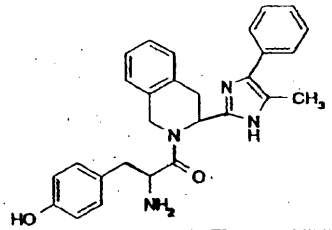
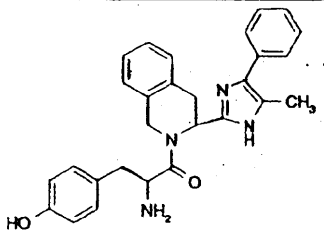
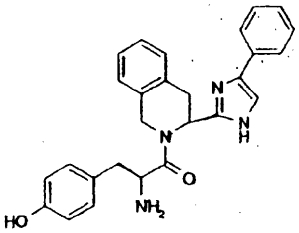
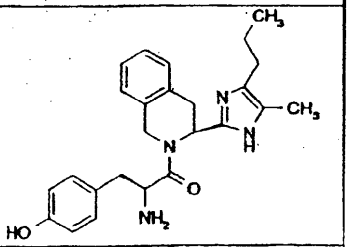
【０１４３】
【表８】

		
Co. No. 112; Ex. B.2; mp. 236-237°C	Co. No. 113; Ex. B.1; mp. 184-188°C	Co. No. 114; Ex. B.5; .$C_2HF_3O_2$
		
Co. No. 115; Ex. B.1; .$C_2HF_3O_2$ [2R-[1(S*),2R*]]	Co. No. 116; Ex. B.5; .$C_2HF_3O_2$ [2R-[1(S*),2R*]]	Co. No. 117; Ex. B.14
		
Co. No. 118; Ex. B.15	Co. No. 119; Ex. B.1	Co. No. 120; Ex. B.5; .$C_2HF_3O_2$
		
Co. No. 121; Ex. B.1; .$C_2HF_3O_2$ [2S-[1(R*),2R*]]	Co. No. 122; Ex. B.5; .$C_2HF_3O_2$ [2S-[1(R*),2R*]]	Co. No. 123; Ex. B.1; .$C_2HF_3O_2$ [2R-[1(S*),2R*]]
		
Co. No. 124; Ex. B.5; .$C_2HF_3O_2$ [2R-[1(S*),2R*]]	Co. No. 125; Ex. B.4; .$C_2HF_3O_2$ [2R-[1(S*),2R*]]	Co. No. 126; Ex. B.5; .$C_2HF_3O_2$ [2R-[1(S*),2R*]]

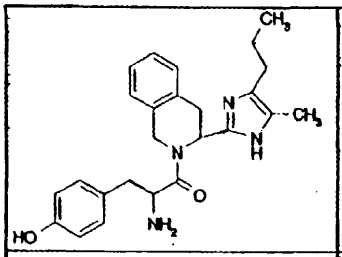
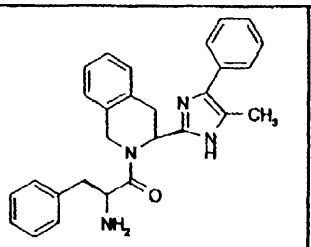
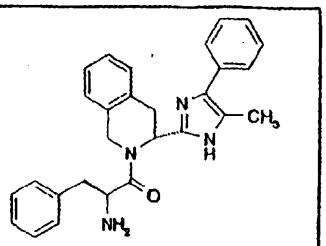
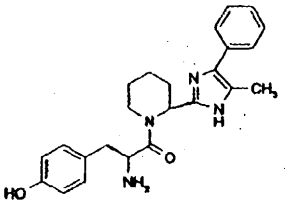
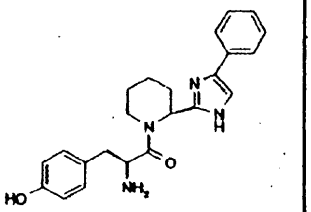
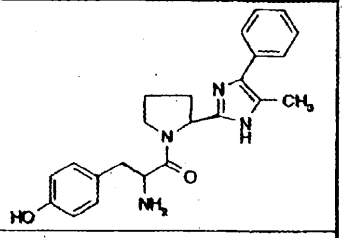
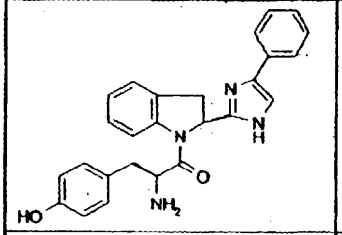
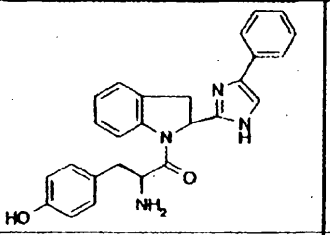
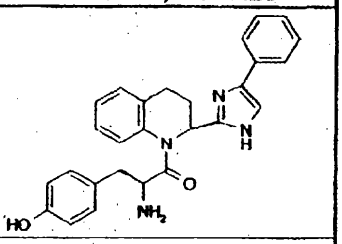
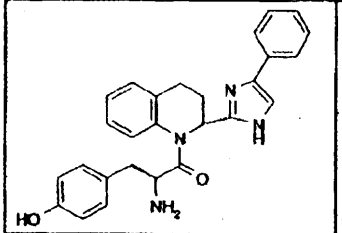
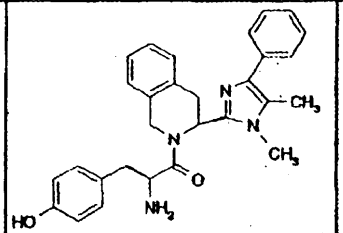
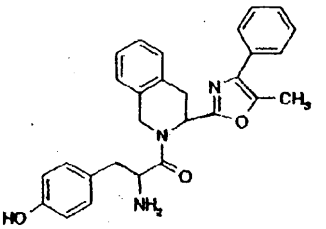
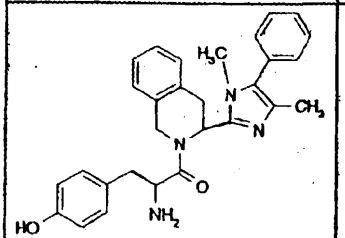
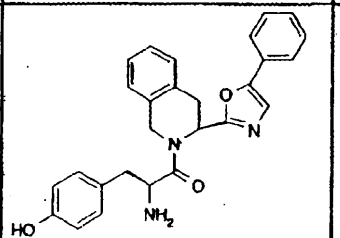
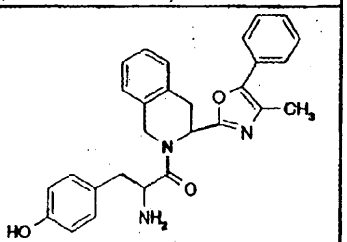
【０１４４】
【表９】

		
Co. No. 127; Ex. B.24; .$C_2HF_3O_2$; [2S-[1(R*),2R*]]	Co. No. 128; Ex. B.1; .$C_2HF_3O_2$; [2S-[1(R*),2R*]]	Co. No. 129; Ex. B.5; .$C_2HF_3O_2$; [2S-[1(R*),2R*]]
		
Co. No. 130; Ex. B.4; .$C_2HF_3O_2$; [2S-[1(R*),2R*]]	Co. No. 131; Ex. B.5; .HCl [2S-[1(R*),2R*]]; mp. 235-240°C	Co. No. 132; Ex. B.13
		
Co. No. 133; Ex. B.13	Co. No. 134; Ex. B.1	Co. No. 135; Ex. B.5; mp. 115-117°C
		
Co. No. 136; Ex. B.1	Co. No. 137; Ex. B.5; mp. 107-109°C	Co. No. 138; Ex. B.20
		
Co. No. 139; Ex. B.5; .$C_2HF_3O_2$	Co. No. 140; Ex. B.2	Co. No. 141; Ex. B.1; .$C_2HF_3O_2$; [2R-[1(S*),2R*]]

【０１４５】
【表１０】

		
Co. No. 142; Ex. B.5; [2R-[1(S*),2R*]]	Co. No. 143; Ex. B.1; .$C_2HF_3O_2$; [2S-[1(R*),2R*]]	Co. No. 144; Ex. B.5; [2S-[1(R*),2R*]]
		
Co. No. 145; Ex. B.1; [2S-[1(R*),2R*]]	Co. No. 146; Ex. B.21; [2S-[1(R*),2R*]]	Co. No. 147; Ex. B.1; [2R-[1(S*),2R*]]
		
Co. No. 148; Ex. B.21; [2R-[1(S*),2R*]]	Co. No. 149; Ex. B.22	Co. No. 150; Ex. B.23
		
Co. No. 151; Ex. B.1	Co. No. 152; Ex. B.5; .$C_2HF_3O_2$	Co. No.153; Ex. B.26
		
Co. No.154; Ex. B.26	Co. No.155; Ex. B.25	Co. No.156; Ex. B.26

【０１４６】
【表１１】

		
Co. No.157; Ex. B.26	Co. No.158; Ex. B.26	Co. No.159; Ex. B.26
		
Co. No.160; Ex. B.26	Co. No.161; Ex. B.25	Co. No.162; Ex. B.26
		
Co. No.163; Ex. B.25	Co. No.164; Ex. B.25	Co. No.165; Ex. B.25
		
Co. No.166; Ex. B.25	Co. No.167; Ex. B.25	Co. No.168; Ex. B.25
		
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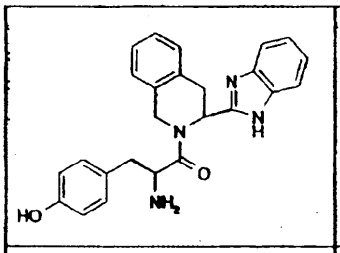
【０１４７】
【表１２】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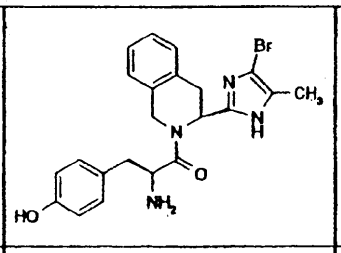
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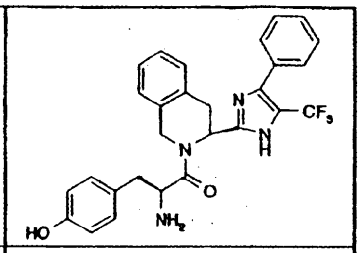
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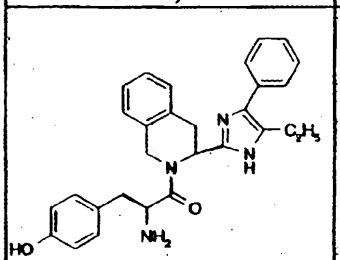
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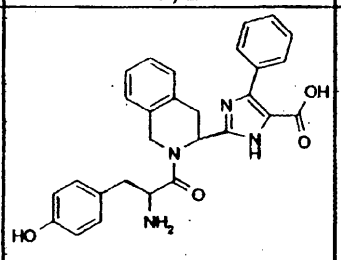
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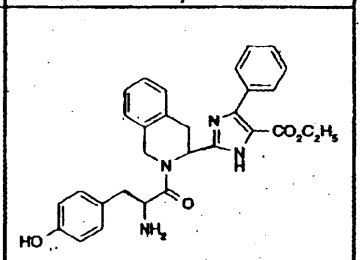
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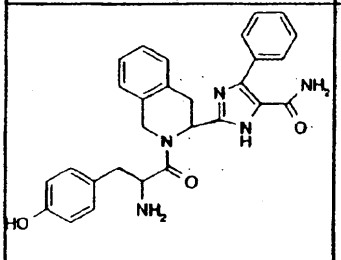
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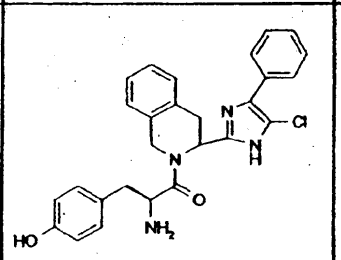
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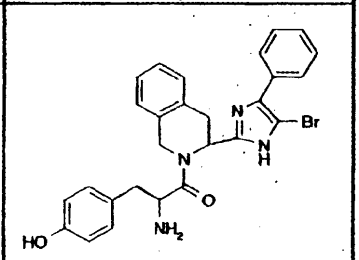
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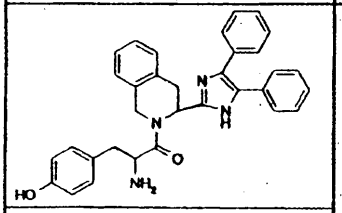
Co. No.181; Ex. B.26

【０１４８】

Ｃ．薬理学的実施例

Ｃ．１．トリペプチジルペプチダーゼＩＩ（ＴＰＰ　ＩＩ）の阻害

ＴＰＰ　ＩＩの阻害は、Ｎａｔｕｒｅ，３８０，４０３－４０９（１９９６）においてＣ．Ｒｏｓｅらによって記述されている操作を用いて測定された。

ＴＰＰ　ＩＩ活性は、１ｍＭ　ＤＴＴおよび１ｍＭ　ＥＧＴＡを含む５０ｍＭリン酸カリウムバッファーｐＨ７．５中、基質として１５μＭ　ＡＡＦ－ＡＭＣを用いて評価された。化合物は最終ＤＭＳＯ濃度１％において添加された。蛍光は４０５ｎｍにおいて測定された。式（Ｉ）の化合物の力価は$ＩＣ_{５０}$値、すなわち５０％阻害を与えるのに必要な濃度として表された。

【０１４９】

化合物６，１０，１３，１５，１９，２２，２４，２８，３０，４４，４７，４８，５４，５５，５７，６１，６２，６６，６８，７０，７３，７６，８２，８４，８８，９０，９２，９５，１０１，１０４，１０８，１１１，１１４，１１６，１２０，１２２，１２４，１２６，１２９，１３１，１３５，１４２および１４４が$１．０^{－５}$Ｍに等しいかまたはそれ以下の$ＩＣ_{５０}$値を有する。

【０１５０】

Ｃ．２ラットの脳δ－オピオイド受容体結合アッセイ

オスのＷｉｓｔａｒラット（１５０－２５０ｇ，ＶＡＦ，Ｃｈａｒｌｅｓ　Ｒｉｖｅｒ，Ｋｉｎｇｓｔｏｎ，ＮＹ）を頸部転位によって殺傷し、そしてそれらの脳を除去し、直ちに氷冷ＴｒｉｓＨＣｌバッファー（５０ｍＭ，ｐＨ７．４）中に入れる。前脳を、小丘の背面に始まり中脳－橋連結を腹側に通過する冠状横断によって、脳の残りの部分から分離する。離断の後、前脳をＴｒｉｓバッファー中でＴｅｆｌｏｎ（Ｒ）－ガラスホモジナイザーにおいてホモジナイズする。ホモジネートをＴｒｉｓバッファー１００ｍｌ当たり前脳組織１ｇ濃度に希釈し、そして３９，０００ＸＧで１０分間遠心する。ペレットを、Ｐｏｌｙｔｏｎホモジナイザーから数回の短いパルスにより同容量のＴｒｉｓバッファーに再懸濁する。この微粒調製物をδ－オピオイド結合アッセイのために使用する。δ－選択性ペプチドリガンド［^{3}Ｈ］ＤＰＤＰＥとともに２５℃でインキュベーション後、チューブ内容物を、Ｂｒａｎｄｅｌセルハーベスターにおいて Ｗｈａｔｍａｎ　ＧＦ／Ｂフィルターシートを通して濾過する。チューブおよびフィルターを１０ｍＭＨＥＰＥＳ（ｐＨ７．４）４ｍｌで３回洗浄し、そしてフィルターサークルに結合している放射能を、Ｆｏｒｍｕｌａ９８９シンチレーション液（Ｎｅｗ　Ｅｎｇｌａｎｄ　Ｎｕｃｌｅａｒ，Ｂｏｓｔｏｎ，ＭＡ）を用いてシンチレーションカウンターにおいて測定する。

【０１５１】

データは、対照の結合に比較した阻害％（単一濃度の試験化合物のみが評価される場合）またはK_i値（濃度範囲が試験される場合）のいずれかを計算するために使用する。

【０１５２】

阻害％は次のように計算する：

【０１５３】

【数１】

$$\left(1-\left[\frac{(\text{試験化合物 dpm}-\text{非特異的 dpm})}{(\text{全 dpm}-\text{非特異的 dpm})}\right]\right)\times 100\%$$

【０１５４】

K_i値は、ＬＩＧＡＮＤ（Ｍｕｎｓｏｎ，Ｐ．Ｊ．ａｎｄ　Ｒｏｄｂａｒｄ，Ｄ．，Ａｎａｌ．Ｂｉｏｃｈｅｍ．１０７：２２０－２３９，１９８０）データ解析プログラムを用いて計算する。

【０１５５】

Ｃ．３ラットの脳μ－オピオイド受容体結合アッセイ

オスのＷｉｓｔａｒラット（１５０－２５０ｇ，ＶＡＦ，Ｃｈａｒｌｅｓ　Ｒｉｖｅｒ，Ｋｉｎｇｓｔｏｎ，ＮＹ）を頸部転位によって殺傷し、そしてそれらの脳を除去し、直ちに氷冷ＴｒｉｓＨＣｌバッファー（５０ｍＭ，ｐＨ７．４）中に入れる。前脳を、小丘の背面に始まり中脳－橋連結を腹側に通過する冠状横断によって、脳の残りの部分から分離する。離断の後、前脳をＴｒｉｓバッファー中でＴｅｆｌｏｎ（Ｒ）－ガラスホモジナイザーにおいてホモジナイズする。ホモジネートをＴｒｉｓバッファー１００ｍｌ当たり前脳組織１ｇ濃度に希釈し、そして３９，０００ＸＧで１０分間遠心する。ペレットを、Ｐｏｌｙｔｏｎホモジナイザーから数回の短いパルスにより同容量のＴｒｉｓバッファーに再懸濁する。この微粒調製物をμ－オピオイド結合アッセイのために使用する。μ－選択性ペプチドリガンド［^{3}Ｈ］ＤＡＭＧＯとともに２５℃でインキュベーション後、チューブ内容物を、Ｂｒａｎｄｅｌセルハーベスターにおいて Ｗｈａｔｍａｎ　ＧＦ／Ｂフィルターシートを通して濾過する。チューブおよびフィルターを１０ｍＭＨＥＰＥＳ（ｐＨ７．４）４ｍｌで３回洗浄し、そしてフィルターサークルに結合している放射能を、Ｆｏｒｍｕｌａ９８９シンチレーション液（Ｎｅｗ　Ｅｎｇｌａｎｄ　Ｎｕｃｌｅａｒ，Ｂｏｓｔｏｎ，ＭＡ）を用いてシンチレーションカウンターにおいて測定する。

【０１５６】

データは、対照の結合に比較した阻害％（単一濃度の試験化合物のみが評価される場合）またはK_i値（濃度範囲が試験される場合）のいずれかを計算するために使用する。

【０１５７】

阻害％は次のように計算する：

【０１５８】

【数２】

$$\left(1-\left[\frac{(\text{試験化合物 dpm}-\text{非特異的 dpm})}{(\text{全 dpm}-\text{非特異的 dpm})}\right]\right) X\ 100\%$$

【０１５９】

K_i値は、ＬＩＧＡＮＤ（Ｍｕｎｓｏｎ，Ｐ．Ｊ．ａｎｄ Ｒｏｄｂａｒｄ，Ｄ．，Ａｎａｌ．Ｂｉｏｃｈｅｍ．１０７：２２０－２３９，１９８０）データ解析プログラムを用いて計算する。

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(74) Agent: **DE CORTE, Filip**; Janssen Pharmaceutica N.V., Patent Department, Turnhoutseweg 30, B-2340 Beerse (BE).

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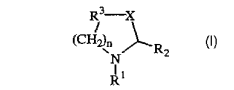
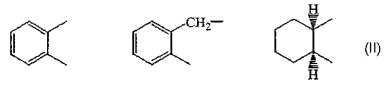
Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
— *of inventorship (Rule 4.17(iv)) for US only*
— *of inventorship (Rule 4.17(iv)) for US only*

[Continued on next page]

(54) Title: TRIPEPTIDYL PEPTIDASE INHIBITORS



(I)



(b-1) (b-2) (b-3) (II)

(57) Abstract: The present invention is concerned with novel compounds of formula (I) which are inhibitors of a membrane tripeptidyl peptidase responsible for the inactivation of endogenous neuropeptides such as cholecystokinis (CCKs). The invention further relates to methods for preparing such compounds, pharmaceutical compositions comprising said compounds as well as the use as a medicine of said compounds. (I) wherein n is an integer (0) or (1); X represents O; S; or -(CR^{4}R^5)$_m$- wherein m is an integer (1) or (2); R^4 and R^5 are each independently from each other hydrogen or C_{1-4}alkyl; R^1 is C_{1-6}alkylcarbonyl optionally substituted with hydroxy; C_{1-6}alkyloxycarbonyl; aminoC$_{1-6}$alkylcarbonyl wherein the C_{1-6}alkyl group is optionally substituted with C_{3-6}cycloalkyl; mono- and di(C_{1-4}alkyl)aminoC$_{1-6}$alkylcarbonyl; aminocarbonyl substituted with aryl; C_{1-6}alkylcarbonyloxyC$_{1-6}$alkylcarbonyl; C_{1-6}alkyloxycarbonylaminoC$_{1-6}$alkylcarbonyl wherein the amino group is optionally substituted with C_{1-4}alkyl; an amino acid; C_{1-6}alkyl substituted with amino; or arylcarbonyl; R^2 is an optionally substituted (5)-membered heterocycle, or R^2 is optionally substituted benzimidazole; R^3 is a bivalent radical -CH_2CH_2- optionally substituted with halo or phenylmethyl; or R^3 is a bivalent radical of formula (II).

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— *of inventorship (Rule 4.17(iv)) for US only*

Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TRIPEPTIDYL PEPTIDASE INHIBITORS

The present invention is concerned with novel compounds of formula (I) which are inhibitors of a membrane tripeptidyl peptidase responsible for the inactivation of endogenous neuropeptides such as cholecystokinins (CCKs). The invention further relates to methods for preparing such compounds, pharmaceutical compositions comprising said compounds as well as the use as a medicine of said compounds.

Cholecystokinins (CCKs) are a family of hormonal and neuronal peptides which exert pleiotropic biological effects in the gut and brain. The actions of CCK are mediated by CCK_A and CCK_B receptors. CCK is known to have a physiological role in the control of food intake, which is enhanced by CCK_A agonists (Smith G.P. et al., *J. Ann. N.Y. Acad. Sci.*, 713, 236-241 (1994)), and the control of anxiety, which is decreased by CCK_B antagonists (Woodruff G. et al., *Rev. Pharmac.*, 31, 469-501 (1991)).

Tripeptidyl peptidase II (TPP II) is a CCK inactivating peptidase. TPP II is found in neurons responding to cholecystokinin as well as in non-neuronal cells. TPP II is considered to be a neuropeptidase responsible for CCK-8 inactivation (Rose C. et al., *Nature*, 380, 403-409, (1996)).

TPP II could be involved in CCK-8 inactivation in the gastrointestinal tract. Exogenous CCK reduces food intake and elicits other behavioural concomitants of satiation. Food intake is increased by systemic administration of CCK_A receptor agonists (Smith G.P. et al., *J. Ann. N.Y. Acad. Sci.*, 713, 236-241 (1994)). Endogenous CCK-controlling food intake seems to be of neuronal rather than hormonal origin and acts upon peripheral CCK_A receptors on vagal afferent fibres (Smith G.P. et al., *Am. J. Physiol.*, 249, R638-R641 (1985)).

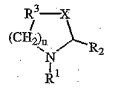
Inhibitors of TPP II are useful tools in investigating the functions of CCK neurons and may be useful drugs for the treatment of disorders such as over-eating, obesity, problems with gastrointestinal motility and psychotic syndromes.

WO-96/35805, published 14 November 1996, discloses inhibitors of a membrane tripeptidylpeptidase responsible for the inactivation of endogenous neuropeptides useful in treatment of gastrointestinal and mental disorders. WO-99/33801, published 8 July 1999, discloses CCK-inactivating tripeptidyl peptidase (TPP II) inhibiting compounds

useful in the treatment of eating disorders, obesity, psychotic syndromes and associated psychiatric disorders.

The compounds of the present invention differ from the cited art-known compounds structurally, by the nature of the R^2 substituent.

The present invention concerns compounds of formula (I)



(I),

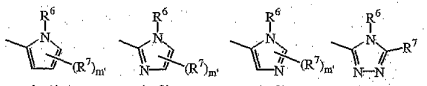
a stereochemically isomeric form thereof, or a pharmaceutically acceptable addition salt thereof, wherein

n is an integer 0 or 1;

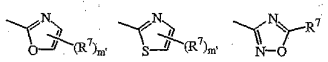
X represents O; S; or $-(CR^4R^5)_m-$ wherein m is an integer 1 or 2; R^4 and R^5 are each independently from each other hydrogen or C_{1-4}alkyl;

R^1 is C_{1-6}alkylcarbonyl optionally substituted with hydroxy; C_{1-6}alkyloxycarbonyl; aminoC_{1-6}alkylcarbonyl wherein the C_{1-6}alkyl group is optionally substituted with C_{3-6}cycloalkyl; mono- and di(C_{1-4}alkyl)aminoC_{1-6}alkylcarbonyl; aminocarbonyl substituted with aryl; C_{1-6}alkylcarbonyloxyC_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonylaminoC_{1-6}alkylcarbonyl wherein the amino group is optionally substituted with C_{1-4}alkyl; an amino acid residue bound via the carbonyl group; C_{1-6}alkyl substituted with amino; or arylcarbonyl;

R^2 is a 5-membered heterocycle selected from



(a-1) (a-2) (a-3) (a-4)



(a-5) (a-6) (a-7)

wherein m' is an integer 1 to 2;

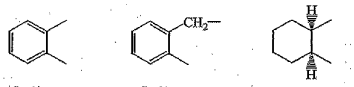
R^6 is hydrogen or C_{1-4}alkyl;

R^7 is independently from each other hydrogen; halo; amino; hydroxy; trifluoromethyl; C_{1-6}alkyl; C_{1-4}alkyl substituted with hydroxy,

hydroxycarbonyl, C_{1-4}alkyloxycarbonyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, amino, or mono- or di(C_{1-4}alkyl)amino; phenyl; aminocarbonyl; hydroxycarbonyl; C_{1-4}alkyloxycarbonyl; C_{1-4}alkylcarbonyl; or C_{1-4}alkyloxycarbonylC_{1-4}alkylaminocarbonyl;

or R^2 is benzimidazole, or benzimidazole substituted with one or two substituents each independently selected from halo, trifluoromethyl, C_{1-4}alkyl, hydroxy, hydroxycarbonyl, or C_{1-4}alkyloxycarbonyl;

R^3 is a bivalent radical $-CH_2CH_2-$ optionally substituted with halo or phenylmethyl; or R^3 is a bivalent radical of formula



(b-1) (b-2) (b-3)

wherein said (b-1), (b-2), or (b-3) optionally can be substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, nitro, amino, cyano, trifluoromethyl, phenyl, or phenyl substituted with one or two subsitutents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, nitro, cyano, and trifluoromethyl;

aryl is phenyl, or phenyl substituted with amino, nitro or hydroxycarbonyl.

The term "amino acid residues" as used herein are the glycine, alanine, valine, leucine, isoleucine, methionine, proline, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, esters of aspartic acid, glutamic acid, esters of glutamic acid, lysine, arginine, and histidine amino acid radicals which are bound via their carbonyl group to the nitrogen atom of the rest of the molecule and which can be generally represented by "R-CH(NH_2)-CO-".

As used in the foregoing definitions halo is generic to fluoro, chloro, bromo and iodo; C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methyl-ethyl, 2-methylpropyl and the like; C_{1-6}alkyl is meant to include C_{1-4}alkyl and the higher homologues thereof having 5 or 6 carbon atoms, such as, for example, 2-methyl-butyl, pentyl, hexyl and the like; C_{3-6}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; C_{3-6}alkenyl defines straight and branched chain unsaturated hydrocarbon radicals having from 3 to 6 carbon atoms, such as propenyl,

butenyl, pentenyl or hexenyl; C_{1-2}alkanediyl defines methylene or 1,2-ethanediyl; C_{1-5}alkanediyl defines bivalent straight or branched chain hydrocarbon radicals containing from 1 to 5 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, and the branched isomers thereof; C_{1-6}alkanediyl includes C_{1-5}alkanediyl and the higher homologues thereof having 6 carbon atoms such as, for example, 1,6-hexanediyl and the like. The term "CO" refers to a carbonyl group.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration. Compounds encompassing double bonds can have an E or Z-stereochemistry at said double bond. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

The pharmaceutically acceptable addition salts as mentioned hereinabove include pharmaceutically acceptable acid addition salts and are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (*i.e.* ethanedioic), malonic, succinic (*i.e.* butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable base addition salts are possible which include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and base addition salts formed with suitable organic ligands, e.g., primary, secondary, tertiary or quaternary ammonium salts, such as morpholinyl, tert-butylamino, and the like.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

Interesting compounds are those compounds of formula (I) wherein one or more of the following restrictions apply :

a) n is 0;
b) R^3 is a radical of formula (b-1) optionally substituted with halo or methoxy;
c) X represents $-CH_2-$ or $-CH_2CH_2-$;
d) R^2 is a radical of formula (a-2) wherein R^6 is hydrogen;
e) R^2 is a radical of formula (a-2), (a-4), (a-6), or (a-7);
f) R^2 is benzimidazole optionally substituted with methyl, hydroxy, halo, trifluoromethyl, methyloxycarbonyl, or hydroxycarbonyl;
g) R^1 is C_{1-6}alkylcarbonyl, aminoC_{1-6}alkylcarbonyl or an amino acid.

Particular compounds are those compounds of formula (I) wherein n is 0 and R^3 is a radical of formula (b-1) optionally substituted with halo or methoxy.

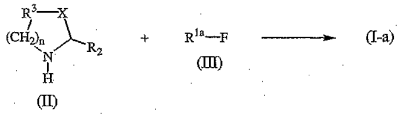
Preferred compounds are those compounds of formula (I) wherein n is 0, R^3 is a radical of formula (b-1) optionally substituted with halo or methoxy, and X represents $-CH_2-$.

Other preferred compounds are those compounds of formula (I) wherein n is 0, R^3 is a radical of formula (b-1) optionally substituted with halo or methoxy, and X represents $-CH_2CH_2-$.

Still other preferred compounds are those compounds of formula (I) wherein R^1 is C_{1-6}alkylcarbonyl, aminoC_{1-6}alkylcarbonyl or an amino acid.

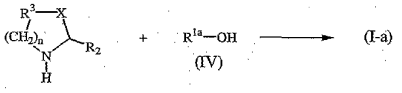
Compounds of formula (I-a), defined as compounds of formula (I) wherein R^{1a} represents all R^1 substituents other than C_{1-4}alkyl substituted with amino, can be prepared by reacting an intermediate of formula (II) with an intermediate of formula (III) in the presence of 4-methyl-morpholine, in a reaction-inert solvent such as, e.g. dichloromethane of chloroform. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried out at a temperature ranging between room temperature and the reflux temperature of the reaction mixture and, if desired, the reaction may be carried out in an autoclave at an increased pressure. Optionally said

reaction is followed by an acid hydrolysis step to remove acid labile protecting groups, such as a *tert*-butyloxycarbonyl.



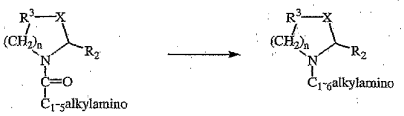
(II) (III) (I-a)

Alternatively, compounds of formula (I-a) can also be prepared by reacting an intermediate of formula (II) with an intermediate of formula (IV) in the presence of an appropriate activating agent, such as e.g. isobutyl chloroformate, in a reaction-inert solvent such as, e.g. dichloromethane, in the presence of a suitable base such as, e.g. triethylamine. Optionally said reaction is followed by an acid hydrolysis step to remove acid labile protecting groups, such as a *tert*-butyloxycarbonyl.



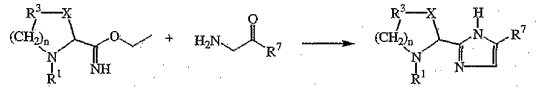
(II) (IV) (I-a)

Compounds of formula (I-b), defined as compounds of formula (I) wherein R^1 represents C_{1-6}alkyl substituted with amino, can conveniently be prepared by submitting the corresponding starting compounds (I-b') wherein R^1 represents aminoC_{1-5}alkylcarbonyl to an appropriate reduction reaction. Appropriate reduction reactions can be e.g. treatment with borane-tetahydrofuran complex.



(I-b') (I-b)

Compounds of formula (I-c), defined as compounds of formula (I) wherein R^2 represents a radical (a-2) wherein R^6 is hydrogen and R^7 is located at the 3-position of the imidazole moiety, can be prepared by reacting an intermediate of formula (V) with an intermediate of formula (VI) in the presents of potassium acetate in a suitable solvent such as methanol.



(V) (VI) (I-c)

The compounds of formula (I) may further be prepared by converting compounds of formula (I) into each other according to art-known group transformation reactions.

The starting materials and some of the intermediates, such as e.g. intermediates of formula (III), (IV) and (VI), are known compounds and are commercially available or may be prepared according to conventional reaction procedures generally known in the art.

Compounds of formula (I) and some of the intermediates may have one or more stereogenic centers in their structure, present in a R or a S configuration, such as, e.g. the carbon atom bearing the R^2 substituent.

Following CAS nomenclature conventions, when two stereogenic centers of known absolute configuration are present in a molecule, an *R* or *S* descriptor is assigned (based on Cahn-Ingold-Prelog sequence rule) to the lowest-numbered chiral center, the reference center. The configuration of the second stereogenic center is indicated using relative descriptors [*R*,R**] or [*R*,S**], where R* is always specified as the reference center and [*R*,R**] indicates centers with the same chirality and [*R*,S**] indicates centers of unlike chirality. For example, if the lowest-numbered chiral center in the molecule has an *S* configuration and the second center is *R*, the stereo descriptor would be specified as *S*-[*R*,S**].

The compounds of formula (I) as prepared in the hereinabove described processes may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from

the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (I), the pharmaceutically acceptable salts and stereoisomeric forms thereof are inhibitors of a membrane tripeptidyl peptidase responsible for the inactivation of endogenous neuropeptides such as cholecystokinis (CCKs) as evidenced in pharmacological example C-1.

In view of their TPP II inhibiting properties the compounds of the present invention are useful in treatment of conditions or disorders associated with TPP II activity such as, e.g. eating disorders, obesity, psychotic syndromes and associated psychiatric disorders.

In view of the utility of the compounds of formula (I), it follows that the present invention also provides a method of treating warm-blooded animals, including humans, (generally called herein patients) suffering from eating disorders, obesity, psychotic syndromes and associated psychiatric disorders Consequently a method of treatment is provided for inhibiting the activity of TPP II and/or relieving patients suffering from conditions, such as, for example, eating disorders, obesity, psychotic syndromes and associated psychiatric disorders.

Hence, the use of a compound of formula (I) as medicine is provided acting as an inhibitor of the CCK-inactivating peptidase tripeptidyl peptidase (TPP II) and/or for the treatment of eating disorders, especially obesity and/or for the treatment of psychotic syndromes and associated psychiatric disorders, which comprises a therepautically effective amount of a compound of formula (I). Also provided is the use of a compound of formula (I) for the manufacture of a medicine for inhibiting the activity of TPP II and/or treating eating disorders, obesity, psychotic syndromes and associated psychiatric disorders. Both prophylactic and therapeutic treatment are envisaged.

It is believed that some of the compounds of the present invention, in particular compounds (153) to (181), may also have opioid activity such as delta-opioid (δ), mu-opioid (μ) and/or kappa-opioid (κ) activity. Opioid activity can be measured using the assays as described in pharmacological examples C.2 and C.3.

To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. Acid addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

For oral administration, the pharmaceutical compositions may take the form of solid dose forms, for example, tablets (both swallowable-only and chewable forms), capsules or gelcaps, prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art.

Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means, optionally with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methylcellulose, hydroxypropyl methylcellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid).

Pharmaceutically acceptable sweeteners comprise preferably at least one intense sweetener such as saccharin, sodium or calcium saccharin, aspartame, acesulfame potassium, sodium cyclamate, alitame, a dihydrochalcone sweetener, monellin, stevioside or sucralose (4,1',6'-trichloro-4,1',6'-trideoxy*galacto*sucrose), preferably saccharin, sodium or calcium saccharin, and optionally a bulk sweetener such as sorbitol, mannitol, fructose, sucrose, maltose, isomalt, glucose, hydrogenated glucose syrup, xylitol, caramel or honey.

Intense sweeteners are conveniently employed in low concentrations. For example, in the case of sodium saccharin, the concentration may range from 0.04% to 0.1% (w/v) based on the total volume of the final formulation, and preferably is about 0.06% in the low-dosage formulations and about 0.08% in the high-dosage ones. The bulk sweetener can effectively be used in larger quantities ranging from about 10% to about 35%, preferably from about 10% to 15% (w/v).

The pharmaceutically acceptable flavours which can mask the bitter tasting ingredients in the low-dosage formulations are preferably fruit flavours such as cherry, raspberry, black currant or strawberry flavour. A combination of two flavours may yield very

good results. In the high-dosage formulations stronger flavours may be required such as Caramel Chocolate flavour, Mint Cool flavour, Fantasy flavour and the like pharmaceutically acceptable strong flavours. Each flavour may be present in the final composition in a concentration ranging from 0.05% to 1% (w/v). Combinations of said strong flavours are advantageously used. Preferably a flavour is used that does not undergo any change or loss of taste and colour under the acidic conditions of the formulation.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example as a sparingly soluble salt.

The compounds of the invention may be formulated for parenteral administration by injection, conveniently intravenous, intramuscular or subcutaneous injection, for example by bolus injection or continuous intravenous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multidose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as isotonizing, suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration the compounds of the invention may be used, for example, as a liquid spray, as a powder or in the form of drops.

Experimental part

In the procedures described hereinafter the following abbreviations were used : "ACN" stands for acetonitrile; "THF", which stands for tetrahydrofuran; "DCM" stands for dichloromethane; and "MIK" stands for methyl isobutyl ketone.

For some chemicals the chemical formula was used, e.g. CH_2Cl_2 for dichloromethane, CH_3OH for methanol, NH_3 for ammonia, HCl for hydrochloric acid, NaOH for sodium hydroxide, $NaHCO_3$ for sodium hydrogen carbonate, and Na_2CO_3 sodium carbonate.

In those cases the stereochemically isomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration.

Preparative liquid chromatography was performed on a semi-preparative HPLC unit using a YMC ODS-A column (30 x 100 mm, 5 micron, temperature : ambient, flow rate : 35 mL/min, mobile phase : a) 10/90 acetonitrile/ water with 0.1% trifluoroacetic acid, b) 90/10 acetonitrile/ water with 0.1% trifluoroacetic acid, gradient : linear gradient from A to B over 9 minutes, UV detection at 254 nm.

A. Preparation of the intermediates

Example A.1

a) 2,3-Dihydroxy-1*H*-indole-2-carboxamide (0.030 mol) was suspended in trichloromethane (400 ml). The mixture was cooled to 0°C. Triethylamine (0.045 mol) was added. Acetyl chloride (0.045 mol) was added over 2 minutes. After 30 minutes, TLC showed the reaction was incomplete. While the flask was still cool, more Triethylamine (6.26 ml) was added, followed 15 minutes later with more acetyl chloride (3.21 ml). TLC showed the reaction was still incomplete. The reaction was continued to allow to stir, cooled to 0°C, and more triethylamine (6.26 ml) was added. Over 2 minutes, more acetyl chloride (3.21 ml) was added neat. TLC showed 80% completion after 60 minutes, and no progress after 30 more minutes. A third portion of acetyl chloride and triethylamine was added. After an additional 15 minutes, ice cold water (200 ml) was added. The mixture was stirred for 10 minutes, filtered, and rinsed with water (3 x 100 ml) and trichloromethane (2 x 75 ml). The sample was allowed to dry overnight, yielding 4.71 g of (S)-1-acetyl-2,3-dihydro-1*H*-indole-2-carboxamide

yielding 3.12g (83%) of (S)-1-acetyl-2,3-dihydro-1*H*-indole-2-carbonitrile (intermediate 2, mp. 134-135°C).

c) Intermediate (2) (0.0151 mol) was suspended in diethylether (200 ml). Ethanol (0.0214 mol) was added, and the mixture was cooled to 0°C. HCl (gas) was bubbled in for 45 minutes. The mixture was removed from the ice bath and stirred. After 20 minutes, a residue collected on the wall sides. The walls were scratched, and a white solid precipitated out. After 1 hour the sample was filtered, rinsed with diethylether, air dried quickly, yielding 3.99 g of (S)-ethyl 1-acetyl-2,3-dihydro-1*H*-indole-2-carboximidate monohydrochloride (intermediate 3).

In analogy, ethyl 1-acetyl-2,3-dihydro-1*H*-indole-2-carboximidate monohydrochloride (intermediate 6) was prepared starting from 1-acetyl-2,3-dihydro-1*H*-indole-2-carbonitrile.

Example A.2

a) 5-chloro-2,3-dihydroxy-1*H*-indole-2-carboxylic acid, methyl ester (0.00761 mole) was dissolved in methanol (25 ml) and cooled to 0°C. NH_3 was bubbled in for 10 minutes. The flask was stoppered and allowed to warm to room temperature. The mixture was stirred overnight. TLC showed the reaction was mostly complete. The sample was concentrated to ± 1/3 volume, cooled, and filtered, rinsing resulting solid with ice cold methanol (2 ml) and then dried ion the air, yielding 0.74 g of 5-chloro-2,3-dihydro-1*H*-indole-2-carboxamide (intermediate 7, mp. 151-152°C).

b) Triethylamine (0.02080 mole) was added to intermediate (7) (0.09632 mole) dissolved in trichloromethane (700 ml). The mixture was cooled to 5°C. Acetyl chloride (0.2480 mole) was added over 2 minutes with stirring. After 5 minutes, a precipitate formed. The ice bath was removed, and the container allowed to sit for 15 minutes. Ice water (250 ml) was added, and the mixture was stirred for 10 minutes. The sample was filtered, rinsed with water and trichloromethane. The solid was suspended in water (200 ml), and swirled for 10 minutes. Trichloromethane (200 ml) was added and the mixture was stirred, then filtered and rinsed with water and trichloromethane, and then dried to the air overnight, yielding 19.71 g of 1-acetyl-5-chloro-2,3-dihydro-1*H*-indole-2-carboxamide (intermediate 8).

c) Triethylamine (0.41291 mole) was added to intermediate (8) (0.08258 mole) suspended in dichloromethane (500 ml) at 0°C. Trichloroacetyl chloride (0.20645 mole) was added over 10 minutes. When the reaction appeared sluggish, an additional portion of triethylamine (20 ml) and then more trichloroacetyl chloride (7.6 ml) were added, and the mixture was stirred for 2 hours at low temperature. The ice bath was removed, and the mixture was allowed to sit for 2 hours. This resulted in a darker

colored reaction, which was re-cooled to 0°C. Ice cold water (150 ml) was slowly added, and the mixture was stirred for 5 minutes. The layers were separated, and the organic phase was washed (ice cold 3N HCl, saturated $NaHCO_3$), dried, filtered, and concentrated . The residue was triturated in ice cold diethylether (40 ml). Filtration, rinsing with ice cold diethylether (10 ml), yielding 15.13 g of 1-acetyl-5-chloro-2,3-dihydro-1*H*-indole-2-carbonitrile (intermediate 9, mp. 140-142°C).

d) HCl (as a 2 M solution) was added slowly to intermediate (9) until gas evolution was noted. Then stopped adding the prepared HCl (2N in diethylether), and suspended HCl in diethylether (150 ml) and then ethanol (0.042 mole) was added. The mixture was cooled to 0°C and HCl (gas) was added over an hour, with an oil precipitating out. The reaction was diluted to 1 l with diethylether. More oil precipitates, and no solid formed after sitting for 1 hour. The diethylether was decanted off. The residue was diluted (diethylether, 500 ml). The solid begins to form, and the mixture was stirred for 2 hours. The sample was filtered, rinsing with diethylether. The sample was placed under vacuum, yielding 6.41g of ethyl 1-acetyl-5-chloro-2,3-dihydro-1*H*-indole-2-carboximidate monohydrochloride (intermediate 10).

Example A.3

a) Bis (1,1-dimethylethyl)ester dicarbonic acid (0.07615 mol) in DCM (50 ml) was added over 5 minutes to 2,3-dihydro-1*H*-indole-2-methanol (0.07615 mol) in DCM (150 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was concentrated under reduced pressure and submitted to a Kogel Rohr distillation, yielding 11.98 g of 1,1-dimethylethyl 2,3-dihydro-2-(hydroxymethyl)-1*H*-indole-1-carboxylate (intermediate 11).

b) Dess-Martin Reagent (0.011 mol) was added neat over 1 minutes to intermediate (11) (0.010 mol) dissolved in DCM (35 ml). After 15 minutes, the ice bath was removed, and the mixture was allowed to warm to room temperature. More Dess-Martin Reagent (0.33 g) was added, and the mixture was stirred for 30 minutes more. The mixture was re-cooled to 0°C and treated slowly with a partial suspension/solution of $Na_2S_2O_3$ (25 g) which had attempted to dissolve in a saturated aqueous $NaHCO_3$ (100 ml) solution. After 10 minutes, the mixture was removed from ice, and the layers were separated. More DCM was added, and the mixture was filtered. The organic was separated from the filtrate, and the combined organic phases were dried, filtered, concentrated and purified through flash column chromatography (eluent : 10% ethyl acetate: hexane, dissolving the sample in 3:1 ethyl acetate: hexane (5 ml)), yielding 1,1-dimethylethyl 2-formyl-2,3-dihydro-1*H*-indole-1-carboxylate (intermediate 12, mp. 85-87°C).

Example A.4

A solution of 1-acetyl-2,3-dihydro-1*H*-indole-2-carbonitrile (0.00988 mol) and Triethylamine (0.0197 mol) in pyridine (50 ml) was treated with hydrogen sulfide (gas) at room temperature via a bubbler for 2 hours and the resultant saturated reaction mixture was closed and allowed to set for 16 hours. The reaction mixture was poured into 200 ml of an ice water slurry. A voluminous precipitate formed. The mixture was recooled in an ice bath and the precipitate was collected by suction filtration, washed with cold water, and air dried, yielding 1.62 g of 1-acetyl-2,3-dihydro-1*H*-indole-2-carbothioamide (intermediate 13, mp. 194-195°C).

Example A.5

1-acetyl-2,3-dihydro-1*H*-indole-2-carbonitrile (0.0132 mole) was treated with water (54 ml) and the resulting suspension was treated sequentially with Na_2CO_3 (0.00726 mole) and $NH_2OH.HCl$ 0.0145 mole). The mixture was treated with ethanol (26 ml) and heated to 80-90°C. Upon achieving reaction temperature, the mixture was still a suspension. Added another 26 ml of ethanol which afforded a clear solution. The reaction was heated for 2.5 hours and cooled to room temperature with stirring. A voluminous precipitate formed which was collected by suction filtration, washed with cold distilled water, and air dried, yielding 2.23 g of 1-acetyl-2,3-dihydro-*N*'-hydroxy-1*H*-indole-2-carboximidamide (intermediate 14, mp. 204-205°C).

Example A.6

1-acetyl-2-(4-ethyl-1*H*-imidazol-2-yl)-2,3-dihydro-1*H*-indole (0.0035 mol) and HCl, 6N (50 ml) were combined under nitrogen atmosphere. The reaction mixture was heated immediately and the heating was continued for 3.5 hours. The mixture was allowed to cool to room temperature, then extracted with diethylether (2 x 75 ml), cooled to 0°C, alkalized (with cooled 3 N NaOH), then extracted with chloroform (3 x 60 ml). The combined organic layers were dried, filtered and the solvent was evaporated, yielding 0.79 g of 2-(4-ethyl-1*H*-imidazol-2-yl)-2,3-dihydro-1*H*-indole (intermediate 15).

Example A.7

a) To a suspension of 5-fluoro-1*H*-indole-2-carboxylic acid, ethyl ester (0.121 mole) in methanol (600 ml) was added Mg (0.36 mole). The mixture was in a 3-neck round bottom flask under argon at room temperature. The temperature of the reaction was monitored closely. After about 10 minutes, the mixture began to bubble, slowly at first and then more vigorously. The reaction temperature was maintained between 15 and

25°C with intermittent applications of an ice bath. After 30 minutes, the bubbling had slowed. The mixture was allowed to stir at room temperature for three days. The mixture was partitioned between 600 ml of chloroform and 500 ml of saturated NH_4Cl solution. The organic layer was dried over $MgSO_4$ and concentrated to a brown oil. The oil was dissolved in ether and extracted with 3N HCl. The aqueous layer was washed with ether, basified with 3N NaOH, and extracted with chloroform. The extract was dried over $MgSO_4$ and concentrated, yielding 13.91 g of methyl 5-fluoro-2,3-dihydro-1*H*-indole-2-carboxylate (intermediate 16).

b) To 2M NH_3 in methanol (0.6 mol), cooled in an ice bath under Ar, was added intermediate (16) (0.0574 mol) dissolved in methanol (150 ml). The mixture was allowed to warm to room temperature and stir under argon for 6 hours. The reaction was concentrated to 150 ml and filtered. The solid was rinsed with a small amount of cold methanol and allowed to dry, yielding 2.33 g of 5-fluoro-2,3-dihydro-1*H*-indole-2-carboxamide (intermediate 17, mp. 197-199°C).

c) To a mixture of intermediate (17) (0.0094 mole) in DCM (30 ml), cooled in an ice bath under argon, was added triethylamine (0.031 mole) followed by acetyl chloride (0.031 mole). The resulting mixture was allowed to return to room temperature. After stirring for 6 hours, the mixture was cooled in an ice bath and 50 ml of water was added. The mixture was allowed to stir about 20 minutes, was filtered and the solid was allowed to dry to obtain 1.58 g of 1-acetyl-5-fluoro-2,3-dihydro-1*H*-indole-2-carboxamide (intermediate 18, mp. 232-235°C).

d) To a suspension of intermediate (18) (0.0076 mole) in DCM (30 ml), cooled in an ice bath under argon, was added triethylamine (0.0228 mole) followed by trichloroacetyl chloride (0.0115 mole). The mixture was allowed to warm to room temperature and stir for 2 hours. The mixture was washed with water, 2N HCl, and saturated $NaHCO_3$. The organic layer was dried and concentrated. The concentrate was triturated in ether and purified on silica gel column, eluting with 50% ethyl acetate in hexane. The desired fractions were combined and concentrated. The residue was triturated in ether and the solid collected by filtration and allowed to dry, yielding 0.30g of 1-acetyl-5-fluoro-2,3-dihydro-1*H*-indole-2-carbonitrile (intermediate 19, mp. 93-95°C).

e) A solution of intermediate (19) (0.004 mole) and HCl/diethylether (60 mL) was cooled in an ice bath under argon. Ethanol (0.0075 mole) was added. HCl was bubbled into the solution for 50 minutes until the mixture became homogeneous. The mixture was allowed to slowly warm to room temperature and stir for 4 hours. The ether was decanted off and dissolved in methanol. The methanol solution was concentrated in

vacuum and the residue was used as is for the next step, yielding ethyl 1-acetyl-5-fluoro-2,3-dihydro-1*H*-indole-2-carboximidate monohydrochloride (intermediate 20).

Example A.8

a) 2,3-dihydro-5-methoxy-1*H*-indole-2-carboxylic acid methyl ester (0.084 mole) and 2M NH_3 in methanol (500 ml) were combined and stirred at room temperature under argon over the weekend. The solution was concentrated to 100 ml, cooled in an ice bath, and filtered. The solid was rinsed with a small amount of cold methanol and dried.The residue was triturated in methanol/ACN and filtered, yielding 4.56 g of 2,3-dihydro-5-methoxy-1*H*-indole-2-carboxamide (intermediate 21, mp. 228-229°C).

b) Triethylamine (0.0106 mole) then acetyl chloride (0.0106 mole) were added to a solution of intermediate (21) (0.0032 mole) in DCM (40 ml) cooled in an ice bath under argon. The mixture was allowed to slowly warm to room temperature and stir overnight. The mixture was cooled in an ice bath and ice cold water (30 ml) was added. After stirring for 10 minutes, the mixture was filtered, and the solid was allowed to dry overnight. The residue was suspended in 50 ml water. The suspension was allowed to stir for 30 minutes, filtered, and dried overnight, yielding 0.40 g of 1-acetyl-2,3-dihydro-5-methoxy-1*H*-indole-2-carboxamide (intermediate 22, mp. 196-197°C).

c) To a suspension of intermediate (22) (0.022 mole) in DCM (150 ml), cooled in an ice bath under argon, was added triethylamine (0.066 mole) then trichloroacetyl chloride (0.033 mole). The mixture was allowed to slowly warmed to room temperature overnight. The mixture was washed with water, 2N HCl, and saturated $NaHCO_3$. The organic phase was dried, concentrated and triturated in ether and the solid collected, yielding 1-acetyl-2,3-dihydro-5-methoxy-1*H*-indole-2-carbonitrile (intermediate 23, mp. 108-110°C).

d) To a solution of intermediate (23) (0.0154 mole) and ethanol (0.0231 mole) in 1M HCl/diethylether (200 ml), cooled in an ice bath was bubbled HCl (gas) for 60 minutes. The ice bath was maintained for 45 minutes, and the mixture was concentrated at room temperature under vacuum to 200 ml of an oily precipitate. The residue was triturated to a brown solid that became an oil after decanting off the diethylether. The residue was washed with diethylether twice, dissolved in methanol, and used without further purification for further synthesis, yielding ethyl 1-acetyl-2,3-dihydro-5-methoxy-1*H*-indole-2-carboximidate monohydrochloride (intermediate 24).

Example A.9

(S)-2-(Tert-butoxycarbonylamino)butyric acid (0.010 mol) dissolved in DCM (25 ml) was placed in a cooling bath at -10 °C. Pyridine (0.010 mol) was added, followed by

2,4,6-trifluoro-1,3,5-triazine (0.0345 mol). The mixture was stirred under nitrogen. After one hour, ice cold water (75 ml) was added. More DCM (45 ml) was added, and the mixture was shaken. The organic phase was separated, washed with ice cold water again (100 ml), then the organic phase dried, filtered, and concentrated to yield 2.29g of (S)-1,1-dimethylethyl [1-(fluorocarbonyl)propyl]-carbamate (intermediate 25).

Example A.10

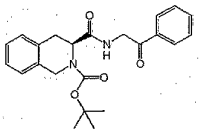
Compound (8) (0.00170 mol) was dissolved in HCl, 6N (20 ml), and immediately warmed in an oil bath at 100°C under nitrogen for 200 minutes. The heat was turned off, and the sample was cooled to 0°C. 3 N NaOH (35 ml) was slowly added. Basification was completed with saturated $NaHCO_3$. The sample was extracted with chloroform. The combined organic phases were dried, filtered, and the resulting solution was used without further purification in further synthesis, yielding (S)-2,3-dihydro-2-(4-propyl-1*H*-imidazol-2-yl)-1*H*-indole (intermediate 5).

Example A.11

A mixture of intermediate (13) (0.00844 mol) in ethanol (180 ml) was treated with 1-bromo-2-butanone (0.0085 mol) in one portion and heated to reflux for 16 hours. The reaction mixture was cooled to room temperature and extracted between ether and cold 1 M NaOH (aqueous). The organic fraction was dried over MgSO4 and concentrated in vacuo to afford a dark solid which was subjected to silica gel flash column chromatography (eluent 100% DCM to 97:3 DCM / diethyl ether), yielding 0.91 g of 2-(4-ethyl-2-thiazolyl)-2,3-dihydro-1*H*-indole (intermediate 4).

Example A.12

3-(2-oxo-2-phenyl-ethylcarbamoyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid tert butyl ester

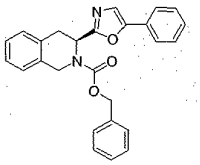


3,4-Dihydro-1*H*-isoquinoline-2,3-dicarboxylic acid-2-tertbutyl ester (2.77 g, 10 mmol) and 2-amino-1phenyl-ethanone (1.71 g, 10 mmol), and HOBT (1-hydroxybenzo-triazole) (2.70 g, 20 mmol) were dissolved in dichloromethane (100 ml). The solution was cooled to 0°C and then (4-dimethylamino-butyl)-ethyl-carbodiimide (2.29 g, 12 mmol) was added followed by NMM (N-methyl-morpholine) (1.31 g, 13 mmol).

The reaction mixture was then warmed to room temperature. After 72 hours the reaction mixture was extracted with water, and the organic phase extracted consecutively with saturated $NaHCO_3$, 2N citric acid and $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to yield the title product as a yellow foam. Liquid chromatography (LC) indicated the compound was 86% pure (214 nm), and was used without further purification.

Example A.12a

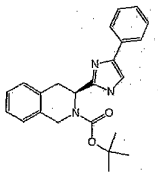
Dehydration of 3-(2-oxo-2-phenyl-ethylcarbamoyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid benzyl ester (prepared in a similar manner as 3-(2-oxo-2-phenyl-ethylcarbamoyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid tert butyl ester of Example A.12) with $POCl_3$ yields the following intermediate compound :



The CBZ group is readily removed from the resulting oxazole by treatment with iodotrimethylsilane. The resulting nor-amine oxazole intermediate can be carried on to compound 170 following similar procedures as described for its analogous imidazole intermediates.

Example A.13

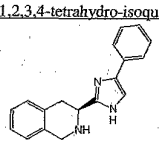
3-(4-phenyl-1H-imidazol-2-yl)-3,4,-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester



The product prepared in Example A.12 above (3.55g, 9mmol), NH_4OAc (ammonium acetate) (20.8g, 270 mmol) and AcOH (acetic acid) (30 mL) were combined at room

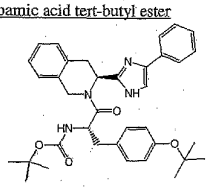
temperature and the reaction mixture was warmed on a steam bath for about 3 hours. The reaction mixture was then cooled to room temperature and poured into an ice slurry mix (400 g). To this mixture was added concentrated ammonium hydroxide (50 mL) and ethyl ether. The layers were separated, and the aqueous phase washed with a second portion of ethyl ether. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a brown foam. This sample was purified by preparative HPLC to yield the purified title compound as a white powder. LC indicated the sample was 96% pure at 214nm.
Measured MW (MH^+): 376

Example A.14
3-(4-phenyl-1H-imidazol-2-yl)-1,2,3,4-tetrahydro-isoquinoline



Triflouroacetic acid (TFA) (4mL) was cooled in a test tube to about 0°C. To the cool solvent was then added the product prepared in Example A.13 (0.75 g, 2 mmol) above. The reaction mixture was allowed to warm to room temperature over about 45 minutes. Excess TFA was removed under a stream of N_2 gas. The residue was partitioned between dichloromethane (15 mL) and saturated $NaHCO_3$. The aqueous phase was then re-extracted with a second portion of dichloromethane and the organic phases combined, dried over $MgSO_4$ and filtered, to yield the title compound in dichloromethane solution. The filtrate was used in the next step (Example A.15) without further purification or isolation.
Measured MW (MH^+): 276

Example A.15
[1-(4-tert-butoxy-benzyl)-2-oxo-2-[3-(4-phenyl-1H-imidazol-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-ethyl]-carbamic acid tert-butyl ester



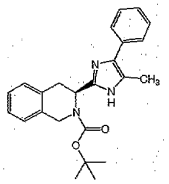
2-Tert-butoxycarbonylamino-3-(4-tert-butoxy-phenyl)-propionic acid (0.74 g, 2.2 mmol) was dissolved in dichloromethane (40 mL) and the reaction mixture cooled to about 0°C. To the solution was then added NMM (0.21 g, 2.1 mmol) followed by isobutyl chloroformate (0.27 g, 2 mmol, 0.26 mL) and the solution was allowed to stand for about 1.25 hours. To the reaction mixture was then added the product prepared in Example A.14 (0.55 g, 2 mmol) and the reaction mixture stirred for about 16 hours. The reaction mixture was then extracted with water, saturated $NaHCO_3$, 2N citric acid, saturated $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to yield the title product as a foam. Measured MW (MH^+): 595.

A bromine can be introduced at the 5-position of the imidazole moiety of this intermediate compound by reacting said intermediate compound with 1 equivalent of Br_2 at 0°C in chloroform.

A chlorine can be introduced at the 5-position of the imidazole moiety of this intermediate compound by reacting said intermediate compound with *N*-chloro-succinimide.

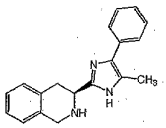
Example A.16

3-(5-methyl-4-phenyl-1H-imidazol-2-yl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester



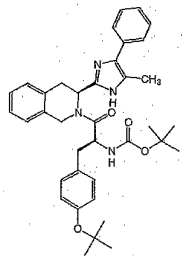
3-Formyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (1.83 g, 7 mmol) was combined with AcOH (25 mL) to which was immediately added 1-phenyl-propane-1,2-dione (3.11 g, 21 mmol) and NH_4OAc (13.49 g, 175 mmol). The reaction mixture was then placed on a steam bath and heated under an argon atmosphere for 20 minutes. The reaction mixture was cooled in an ice bath and then added to an ice slurry (44 g). The resulting mixture was basified by addition of concentrated NH_4OH (50 mL) and then extracted twice with diethyl ether (150 mL each). The combined organic phases were dried over MgSO4, filtered and concentrated to yield crude product. This material was purified by preparative HPLC to yield the title compound as a white solid. Measured MW (MH^+): 390

Example A.17
3-(5-methyl-4-phenyl-1H-imidazol-2-yl)-3,4,-dihydro-1H-isoquinoline



To a solution of TFA (5mL) cooled to about 0°C was added the compound prepared in Example A.16 (1.10 g, 2.82 mmol) and the reaction mixture stirred for about 30 minutes. The reaction mixture was then removed from the ice bath and allowed to warm to room temperature. Excess TFA was removed under a stream of N_2. The residue was partitioned between saturated $NaHCO_3$ and dichloromethane. The aqueous phase was washed with a second portion of dichloromethane and the organic phases combined. The combined organic phase was dried over Na_2SO_4, then filtered to yield the title product as a solution in dichloromethane, which was used without further purification or isolation.

Example A.18
[1-(4-tert-butoxy-benzyl)-2-[3-(5-methyl-4-phenyl-1H-imidazol-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-2-oxo-ethyl]-carbamic acid tert-butyl ester



2-Tert-butoxycarbonylamino-3-(4-tert-butoxy-phenyl)-propionic acid (0.74 g, 2.2 mmol) was dissolved in dichloromethane (60 mL), cooled to about 0°C. To the reaction mixture was then added NMM (0.30 g, 2.97 mmol), followed by isobutyl chloroformate (0.39 g, 2.82 mmol, 0.37 mL). The solution was allowed to stand at 0°C for about 90 minutes. To the reaction mixture was then added the product prepared in

Example A.17 (2.82 mmol) as a solution in dichloromethane. The reaction mixture was then warmed to room temperature. After 16 h the reaction mixture was extracted sequentially with water, saturated $NaHCO_3$, 2N citric acid, saturated $NaHCO_3$, then dried over $MgSO_4$, filtered and concentrated to yield crude product. This material was purified via preparative HPLC to yield the title product as a whitish foam.
Measured MW (MH^+): 609

B. Preparation of the final compounds

Example B.1

4-Methylmorpholine (0.003 mol) was added to intermediate (5) (0.003 mol) dissolved in chloroform (80 ml). After cooling to 0°C, intermediate (25) (0.003 mol) was added neat as an oil. After 27 minutes, the reaction mixture was washed with water, saturated $NaHCO_3$, and brine, dried, filtered, and concentrated, yielding [2S-[1(R*),2R*]]-1,1-dimethylethyl [1-[[2,3-dihydro-2-(4-propyl-1*H*-imidazol-2-yl)-1*H*-indol-1-yl]-carbonyl]propyl]-carbamate (compound 14).

Example B.2

To intermediate (3) (0.047 mole) in methanol (200 ml) was added potassium acetate (0.199 mole). The mixture was heated to reflux under argon. To this was slowly added a solution of 1-amino-2-pentanone hydrochloride (0.094 mole) in methanol (95 ml) over 45 minutes. After the addition was complete, the mixture was allowed to stir overnight at reflux, then concentrated. The concentrate was taken up in DCM and washed with saturated $NaHCO_3$. The aqueous layer was extracted with DCM. The combined organic extracts were dried and concentrated to a solid residue. The residue was purified by trituration with diethyl ether and ACN and optionally further purified by column chromatography, yielding 5.83 g of (S)-1-acetyl-2,3-dihydro-2-(4-propyl-1*H*-imidazol-2-yl)-1*H*-indole (compound 8, mp. 174-175°C).

Example B.3

Intermediate (12) (0.00101 mole), 2-3-hexanedione (0.004 mole), and ammonium acetate (0.025 mole) were combined in acetic acid (4 ml), and immediately placed on a steam bath for 15 minutes. After 2 hours at room temperature, the reaction was poured into ice water (100 ml), basified with 3N NaOH, and extracted with diethylether (twice). The organic phases were combined, dried, filtered, and concentrated. The residue was taken up in diethylether, concentrated and then purified by prep LC, yielding 0.440 g of 1,1-dimethylethyl 2,3-dihydro-2-(5-methyl-4-propyl-1*H*-imidazol-2-yl)- 1*H*-indole-1-carboxylate (compound 99).

Analogously, compound (80) was prepared by reacting intermediate (12) with the respective aldehyde of 1,1,1-trifluoro-3,3-dibromoacetone.

Example B.4

N-[(1,1-dimethylethoxy)carbonyl]-*N*-methyl- L-alanine (0.00181 mol) was dissolved in DCM and cooled to 0°C. Triethylamine (0.00181 mol), then isobutyl chloroformate (0.00181 mol) were added, and the mixture was stirred at 0°C for 70 minutes. Intermediate (5) (0.00181 mol) in DCM (6 ml) was added. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was extracted (water, saturated $NaHCO_3$), dried, filtered, and concentrated. The residue was purified by HPLC. The pure fractions were collected and the solvent was evaporated, yielding 0.380 g of [2S-[1(R*),2R*]]-1,1-dimethylethyl [2-[2,3-dihydro-2-(4-propyl-1*H*-imidazol-2-yl)-1*H*-indol-1-yl]-1-methyl-2-oxoethyl]methyl-carbamate (compound 63, mp. 77-80°C).

Example B.5

Compound 14 (0.0073 mole) and trifluoroacetic acid (5 ml), both precooled in an ice bath, were combined and allowed to slowly return to room temperature under nitrogen. After 1 hour, the mixture was concentrated. The concentrate was dissolved in water and extracted with diethylether. The aqueous layer was basified with saturated $NaHCO_3$ and extracted twice with chloroform. The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was dissolved in ether and treated with 3 ml of 1M HCl in ether. The precipitate was filtered and dried under vacuum. The residue was partitioned between saturated $NaHCO_3$ and chloroform. The organic layer was dried over $MgSO_4$ and concentrated. The concentrate was purified on a Biotage column, eluting with 5% MeOH in chloroform. The residue was dissolved in ether and treated with ±2 ml of 1M HCl in diethyl ether. The solid was collected by filtration under nitrogen and dried under vacuum overnight, yielding 0.364 g of [2S-[1(R*),2R*]]-α-ethyl-2,3-dihydro-β-oxo-2-(4-propyl-1*H*-imidazol-2-yl)-1*H*-indole-1-ethanamine dihydrochloride dihydrate (compound 15, mp. 132-140°C).

Example B.6

A suspension of intermediate (13) (0.0102 mole) in n-butanol (200 ml) was treated with butanoic acid hydazide (0.0254 mole), stirred for 10 minutes, and then heated to reflux for 10 days. The reaction was cooled, concentrated *in vacuo*, distributed between DCM and distilled water. The concentrated organic phase was subjected to reverse phase preparatory column chromatography to give 1-acetyl-2,3-dihydro-2-(5-propyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (compound 91).

Example B.7

a) A solution of the compound 91 (0.42g) in ethanol (25 ml) was treated with an aqueous NaOH solution (3 M, 25 mL) and the reaction mix was refluxed for 24 hours. The reaction was cooled, diluted with ethyl acetate, and treated with cold distilled water. The layers were separated and the aqueous fraction was extracted 5 times with ethyl acetate and the combined organic fractions were dried, concentrated and purified by preparatory column chromatography yielding 2,3-dihydro-2-(5-propyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole.

b) A solution of 2,3-dihydro-2-(5-propyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (0.00017 mole) in DCM (5 ml) was treated with *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (0.00072 mole) then (2-fluoro-2-oxoethyl)-9*H*-fluoren-9-yl-carbamic acid methyl ester (0.00070 mole). The reaction was stirred at room temperature for 15 hours. The reaction was diluted with DCM, treated twice with saturated $NaHCO_3$, and dried over Na_2SO_4 and concentrated. The residue was subjected to reverse phase prep column chromatography to obtain 0.02 g of the desired mono-adduct and 0.02g of a bis-adduct that was completely converted to the desired mono-adduct by treatment with the prep chromatography eluent (0.1% trifluoroacetic acid in water / acetonitrile). These were combined, yielding 0.03 g of *H*-fluoren-9-ylmethyl [2-[2,3-dihydro-2-(5-propyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl]-2-oxoethyl]-carbamate.

c) A solution of *H*-fluoren-9-ylmethyl [2-[2,3-dihydro-2-(5-propyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl]-2-oxoethyl]-carbamate (0.00006 mole) in DCM (10 ml) was treated with piperidine (0.010 mole) and stirred at room temperature for 1 hour. The completed reaction was concentrated in vacuo and subjected to reverse phase prep column chromatography, yielding 0.02 g of 2,3-dihydro-β-oxo-2-(5-propyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole-1-ethanamine trifluoroacetate (1:1) (compound 92).

Example B.8

A mixture of intermediate (14) (0.00898 mole) and butanoyl chloride (0.0094 mole) in pyridine (140 ml) was stirred at room temperature for 40 hours and then heated to reflux. After 21 hours the reaction was cooled and concentrated in vacuo. The residue was extracted between DCM and saturated aqueous $NaHCO_3$ and the organic fraction was dried over Na_2SO_4, filtered, and concentrated.The residue was subjected to silica gel flash column chromatography (eluent 100% CH_2Cl_2 to 95/5 CH_2Cl_2 / ether), yielding 1-acetyl-2,3-dihydro-2-(5-propyl-1,2,4-oxadiazol-3-yl)-1*H*-indole (compound 89, mp. 93-94°C).

Example B.9

a) A solution of compound 89 (0.0035 mole) in ethanol (60 ml) was treated with 3M NaOH (60 ml), and the reaction mix was heated to 55 - 60°C for 5.5 hours. The reaction was rapidly cooled in an ice bath, diluted with DCM, and treated with cold distilled water. The layers were separated and the aqueous fraction was extracted three times with DCM. The organic fractions were combined, washed once with 1M NaOH, and dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by prep column chromatography, yielding 0.45g of 2,3-dihydro-2-(5-propyl-1,2,4-oxadiazol-3-yl)-1*H*-indole.

b) A solution of 2,3-dihydro-2-(5-propyl-1,2,4-oxadiazol-3-yl)-1*H*-indole (0.0011 mole) in DCM (10 ml)was treated with *N*-methyl-*N*-(1-methylethyl)-2-propanamine (0.40 mL) then (2-fluoro-2-oxoethyl)-9*H*-fluoren-9-yl carbamic acid methyl ester (0.67 g). The reaction was stirred at room temperature for 40 hours and treated with another portion each of *N*-methyl-*N*-(1-methylethyl)-2-propanamine then (2-fluoro-2-oxoethyl)-9*H*-fluoren-9-yl carbamic acid methyl ester and stirred at room temperature for two days. The reaction was diluted with DCM, treated twice with saturated $NaHCO_3$, and dried over Na_2SO_4. and concentrated. The residue was subjected to reverse phase prep column chromatography, yielding 0.35 g of 9*H*-fluoren-9-ylmethyl [2-[2,3-dihydro-2-(5-propyl-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]-2-oxoethyl]-carbamate.

c) 9*H*-fluoren-9-ylmethyl [2-[2,3-dihydro-2-(5-propyl-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]-2-oxoethyl]-carbamate (0.35 g) was dissolved in DCM (40 ml), treated with piperidine (0.50 ml), and stirred at room temperature for 18 hours. The completed reaction was concentrated *in vacuo* and subjected to reverse phase prep column chromatograph, yielding 0.13 g of 2,3-dihydro-β-oxo-2-(5-propyl-1,2,4-oxadiazol-3-yl)-1*H*-indole-1-ethanamine trifluoroacetate (1:1) (compound 90, mp. 160-162°C).

Example B.10

2,3-dihydro-2-(4-propyl-1*H*-imidazol-2-yl)-1*H*-indole (0.0024 mol) and 1,3-isobenzofurandione (0.0026 mol) were heated to 100°C in a 25 ml pear shaped flask under argon for 2 hours. The mixture was dissolved in methanol and heated to reflux for 15 hours. The reaction mixture was concentrated and taken up in DCM, washed with water and 3 N NaOH. The basic aqueous extract was acidified with 6 N HCl and extracted with DCM. This organic extract was dried over $MgSO_4$ and concentrated. The concentrate was triturated in ether and collected. This was further purified, together with the acidic aqueous solution, by prep liquid chromatography, yielding 0.23 g of 2-[[2-(4-ethyl-1*H*-imidazol-2-yl)-2,3-dihydro-1*H*-indol-1-yl]carbonyl]- benzoic acid trifluoroacetate (1:1) (compound 85, mp. 98-103°C).

Example B.11

1-Isocyanato-2-nitro-benzene (0.002 mol) was added to a solution of intermediate (15) (0.016 mol) in THF (10 ml). The mixture was stirred at room temperature under argon for 5 hours. The mixture was diluted with hexanes, filtered, and allowed to dry, yielding 0.34 g of 2-(4-ethyl-1*H*-imidazol-2-yl)-2,3-dihydro-*N*-(2-nitrophenyl)-1*H*-indole-1-carboxamide (compound 77, mp. 208-209°C).

Example B.12

To a mixture of compound 77 (0.0006 mol), Raney Nickel (0.02 g; 50% slurry in water), and methanol (20 ml) was added hydrazin. Water (0.003 mol). The resulting mixture was heated to reflux for 2 hours. After cooling to room temperature, the mixture was carefully filtered through celite and the filtrate was concentrated. The residue was triturated in ether and filtered. The residue was purified by prep liquid chromatography, yielding 0.24 g of *N*-(2-aminophenyl)-2-(4-ethyl-1*H*-imidazol-2-yl)-2,3-dihydro-1*H*-indole-1-carboxamide trifluoroacetate (1:2) (compound 79, mp. 106-108°C).

Example B.13

A mixture of compound 16 (0.00697 mole) in THF (70 ml) was treated with of sodium hydride (0.007 mole) in one portion and stirred at ambient temperature for 16 hours. Iodomethane (0.0071 mole) was introduced in one portion. After stirring at ambient temperature for 24 hours, more sodium hydride (0.007 mole) was added in one portion under an argon atmosphere. The flask was restoppered after effervescence had subsided, and stirred for 16 hours. The completed reaction was cooled in an ice bath, poured into DCM, and treated with cold water. The layers were separated and the aqueous was extracted three times with DCM. The combined organic fractions were washed with sat $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue was subjected to flash silica gel column chromatography (DCM to ether to 9:1 ether/THF). The appropriate fractions were combined. The residue was taken up in ether and placed in the freezer. Crystallization occurred, yielding 0.55 g (29.3%) of 1-acetyl-2-(4-ethyl-1-methyl-1*H*-imidazol-2-yl)-2,3-dihydro-1*H*-indole (compound 132, mp. 105-106°C). The second set of fractions were combined. The residue was taken up in ether and placed in the freezer. Observed crystallization occurred, yielding 0.38 g of 1-acetyl-2-(4-ethyl-1-methyl-1*H*-imidazol-2-yl)-2,3-dihydro-1*H*-indole (compound 133, mp. 135-137°C).

Example B.14

Compound 80 (0.001 mole) was suspended in 1N NaOH (12 ml). The mixture was vigorously stirred and heated to 88°C under nitrogen for 1 hour. After stirring at room temperature for 3 hours, the mixture was cooled to 0°C, slowly neutralized with 1M HCl to precipitate some solid. The solid was filtered, rinsing with ice cold water. The aqueous phase was extracted twice, dried, filtered, concentrated and dried, yielding 0.140 g of 1,1-dimethylethyl 2-(4-carboxy-1*H*-imidazol-2-yl)-2,3-dihydro-1*H*-indole-1-carboxylate (compound 117).

Example B.15

1-Hydroxybenzotriazole hydrate (0.00036 mole), glycine methylester, hydrochloride (0.00047 mole), 4-methylmorpholine (0.00055 mole), and *N'*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine monohydrochloride (0.00047 mole) were added to compound 117 (0.00036 mole) dissolved in DCM (30 ml) at 0°C. The mixture was allowed to warm to room temperature under nitrogen, and stirred overnight. The mixture was extracted with water, saturated $NaHCO_3$, 2N citric acid, then saturated $NaHCO_3$, dried, filtered, and concentrated, yielding 0.100g (69%) of 1,1-dimethylethyl 2,3-dihydro-2-[4-[[(2-methoxy-2-oxoethyl)amino]carbonyl]-1*H*-imidazol-2-yl]- 1*H*-indole-1-carboxylate (compound 118).

Example B.16

Compound 61 (0.00028 mol) was treated with 3N NaOH (3 ml) and allowed to stir for 20 minutes at room temperature. The solution was then treated with 3 ml of 3 N HCl and extracted with chloroform. The material stayed in the aqueous layer. The aqueous layer was purified by preparative liquid chromatography, yielding 0.12 g of 2-[1-(aminoacetyl)-2,3-dihydro-1*H*-indol-2-yl]-1*H*-benzimidazole-5-carboxylic acid monohydrate trifluoroacetate (1:2) (compound 62, mp. 208-211°C).

Example B.17

Compound 102 (0.00238 mole) was dissolved in 40 ml of methanol and combined with 1N KOH (50 mL). The reaction was warmed to 40°C under argon overnight. The heat was increased to 55-60°C for an additional overnight heating. The reaction was then cooled to room temperature, filtered, and at 0°C slowly neutralized with 1N HCl. The sample was extracted 5 times with DCM, combined, and dried over Na_2SO_4. This organic solution was filtered and used in further synthesis without further purification, yielding 1,1-dimethylethyl 2-(4-carboxy-5-propyl-1*H*-imidazol-2-yl)-2,3-dihydro-1*H*-indole-1-carboxylate (compound 105).

Example B.18

1-Hydroxybenzotriazole hydrate (0.00318 mole) was added to a solution of compound 105 (0.00159 mole) in DCM (160 mL) at room temperture. *N*,*N*'-methane-tetrayl-biscyclohexanamine (0.00206 mole) was added neat at room temperature. After 60 minutes, NH_3 gas was bubbled in for 5 minutes, and a solid precipitated out. The mixture was allowed to sit over the weekend. The mixture was filtered, and the filtrate was extracted with saturated $NaHCO_3$. The organic phases were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by liquid chromatography, yielding 0.21 g of 1,1-dimethylethyl 2-[4-(aminocarbonyl)-5-propyl-1*H*-imidazol-2-yl]-2,3-dihydro-1*H*-indole-1-carboxylate (compound 106).

Example B.19

1-Hydroxybenzotriazole hydrate (0.00158 mole) was added to a solution of compound 105 (0.00079 mole) in DCM (80 ml). Glycine methylester hydrochloride (0.00103 mole), *N*'-(ethylcarbonimidoyl)-*N*,*N*-dimethyl-1,3 propanediamine monohydrochloride (0.00103 mole) and 4-methylmorpholine (0.00103 mole) were added. THF (25 mm) was added. The reaction was stirred at room temperature for 3 days. The mixture was extracted with water. The organic phase was washed with saturated $NaHCO_3$, 2N citric acid, saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated , yielding 0.20 g of 1,1-dimethylethyl 2,3-dihydro-2-[4-[[(2-methoxy-2-oxoethyl)amino]carbonyl]-5-propyl-1*H*-imidazol-2-yl]- 1*H*-indole-1-carboxylate (compound 109).

Example B.20

Compound 81 (0.0005 mole) was suspended in 1N NaOH (6 ml) under argon. The mixture was immediately heated to 80°C for 60 minutes. At room temperature, chloroform (6 ml) then (2-fluoro-2-oxoethyl)-1,1-dimethylethyl carbamic acid ester (0.001 mole) were added. The mixture was stirred overnight. The layers were separated. The aqueous phase was cooled, acidified, and extracted twice with chloroform. The latter organic phases were combined, dried, filtered, and concentrated. The sample was purified by prep HPLC, yielding 0.040 g of 2-[1-[[[(1,1-dimethylethoxy)carbonyl]-amino]acetyl]-2,3-dihydro-1*H*-indol-2-yl]- 1*H*-imidazole-4-carboxylic acid (compound 138).

Example B.21

To compound 145 (0.00097 mole), dissolved in ethanol (5 ml), was added several drops of 21% NaOEt in ethanol. The mixture was allowed to stir at room temperature under argon. An additional 2 drops of 21% NaOEt in ethanol were added after 30 minutes. An additional 2 drops of 21% NaOEt in ethanol were added after 16 hours. After 30

minutes the mixture was concentrated and partitioned between water and DCM. The aqueous layer was washed with additional DCM. The combined organics were washed with water, dried, and concentrated, yielding 0.193g (66%) of [2S-[1(R*),2R*]]-2,3-dihydro-α-methyl-β-oxo-2-(4-propyl-1*H*-imidazol-2-yl)-1*H*-indole-1-ethanol (compound 146).

Compound 148 was prepared analogously starting from compound 147.

Example B.22

To a suspension of compound 58 (0.0019 mole) in acetonitrile (15 ml) was added acetic acid, anhydride (0.074 mole). Stirred at room temperature under argon for 4 hours. An additional 1.0 ml of acetic acid, anhydride was added, and the reaction was stirred overnight. After stirring 6 hours more, the reaction was complete. The mixture was concentrated and the residue partitioned between saturated $NaHCO_3$ and chloroform. The organic layer was dried and concentrated. The residue was purified by column chromatography. The desired fractions were combined, triturated in ether and collected. yielding 0.37g of 1-[[1-[(4-chlorophenyl)acetyl]-4-(3-methoxyphenyl)-4-piperidinyl]methyl]-1,3-dihydro-2*H*-benzimidazol-2-one (compound 149).

Example B.23

A solution of compound 149 (0.0012 mole) and THF (200 ml) was placed inside of a photochemical reactor and irradiated with UV light for 14 hours. The mixture was then allowed to sit at room temperature under nitrogen for 2 days. The mixture was concentrated. The concentrate was purified on Biotage column, eluting with 1:9 THF in DCM, yielding 0.077 g of 1-[2-(1-acetyl-2,3-dihydro-1*H*-indol-2-yl)-5-propyl-1*H*-imidazol-4-yl]-ethanone (compound 150).

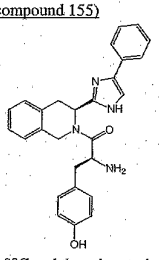
Example B.24

Compound 13 (0.00106 mole) dissolved in 10 ml of THF was treated at room temperature with BH_3.THF (19 ml), which was a solution in THF. The solution was then placed in an oil bath and heated to 60°C overnight. After cooling to 0°C, the solution was carefully treated with 15 ml of 3N HCl. The reaction was then warmed to room temperature and stirred for 4 hours. The mixture was then recooled to 0°C and basified with 12 ml of 3N NaOH, then completion of basification was done with solid Na_2CO_3. The layers were separated and the aqueous was rewashed with chloroform. The organics were combined, a small amount of aqueous separated, and the organic dried over Na_2SO_4. The mixture was filtered, and the filtrate concentrated under reduced pressure. The residue was submitted for preparative liquid chromatography,

yielding 0.33 g of [2S-[1(R*),2R*]]-2-(4-ethyl-1*H*-imidazol-2-yl)-2,3-dihydro-α-methyl-1*H*-indole-1-ethanamine trifluoroacetate (1:1) (compound 127).

Example B.25

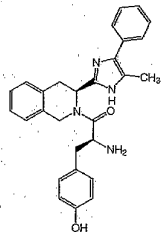
3-amino-4-(4-hydroxy-phenyl)-1-[3-(4-phenyl-1H-imidazol-2-yl)-3,4-dihydro-1-H-isoquinolin-2-yl]-butan-1-one (compound 155)



TFA (4mL) was cooled to about 0°C and then the product prepared in Example A.15 (1.10 g, 1.85 mmol) was added. The reaction mixture sat for about 0.5 hours. Excess TFA was then removed under a stream of N_2 to yield a brown oil. The oil was purified via preparative HPLC to yield the title compound as a white solid.
Measured MW (MH^+): 439

Example B.26

2-amino-3-(4-hydroxy-benzyl)-1-[3-(5-methyl-4-phenyl-imidazol-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-propan-1-one (compound 153)



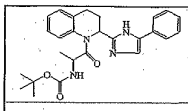
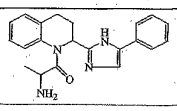
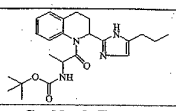
To a solution of TFA (4mL) cooled to about 0°C was added the compound prepared in Example A.18 (0.24 g, 0.4 mmol) and the reaction mixture stirred for about 20 minutes. The reaction mixture was then removed from the ice bath and allowed to warm to room

temperature. Excess TFA was removed under a stream of N_2 to yield crude product. This material was purified via preparative HPLC to yield the title compound as a white solid.

Measured MW (MH^+): 453

Table F-1 lists the compounds that were prepared according to one of the above Examples. The following abbreviations were used in the tables : $.C_2HF_3O_2$ stands for the trifluoroacetate salt, $.2C_2H_2O_4$ stands for the ethanedioate salt, and $.C_{10}H_8O_3S$ stands for the 2-naphthalenesulfonate salt. Said Table F-1 lists the structure of the compounds, the Example number according to which these compounds have been prepared, the salt form, the stereochemical designation and the melting point (if measured).

Table F-1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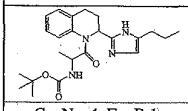
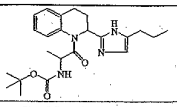
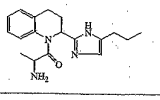
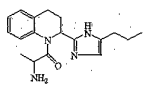
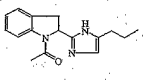
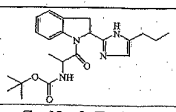
		
Co. No. 4; Ex. B.1; [1(S),2A]	Co. No. 5; Ex. B.1; [1(S),2B]	Co. No. 6, Ex. B.5; [1(S),2A]
		
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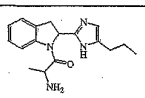	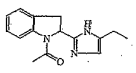	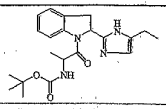
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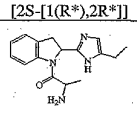
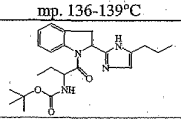
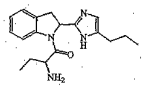
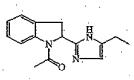
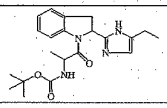
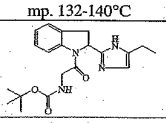
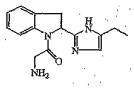
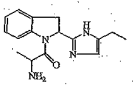
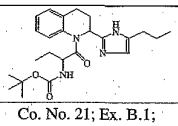
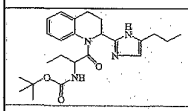
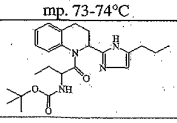
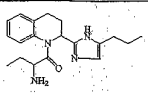
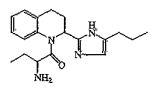
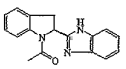
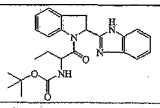
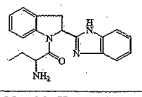
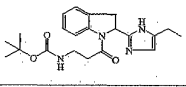
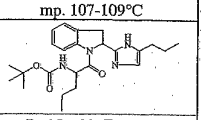
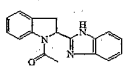
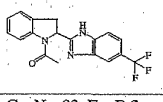
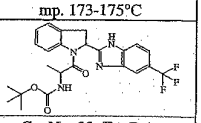
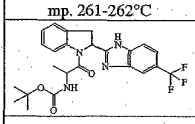
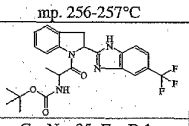
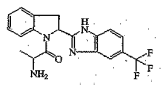
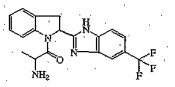
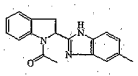
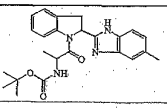
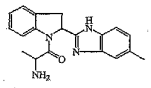
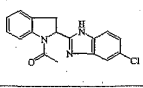
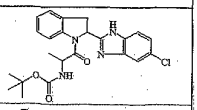
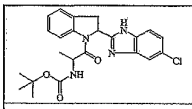
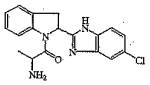
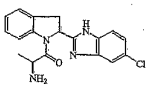
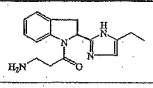
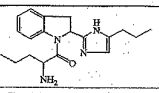
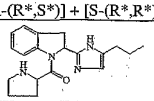
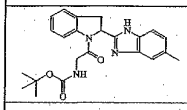
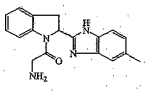
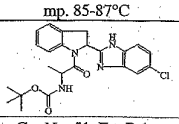
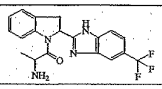
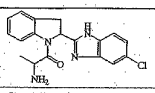
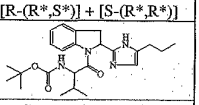
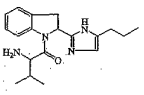
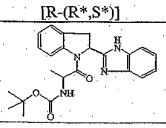
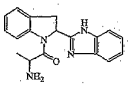
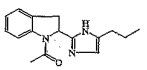
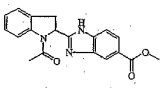
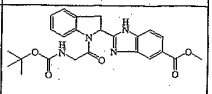
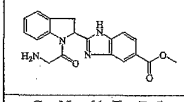
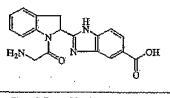
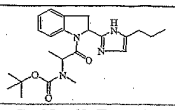
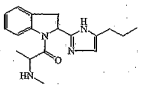
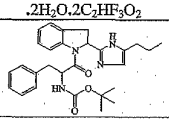
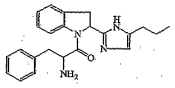
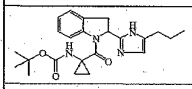
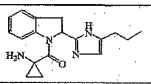
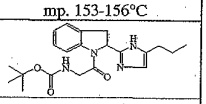
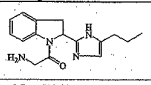
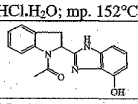
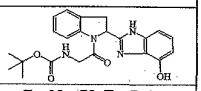
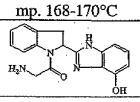
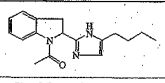
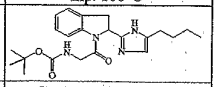
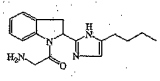
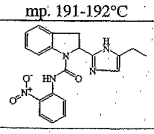
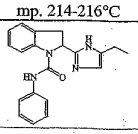
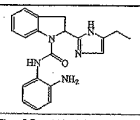
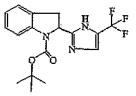
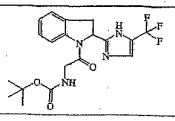
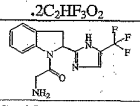
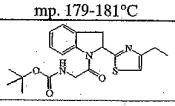
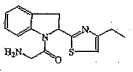
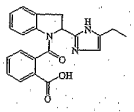
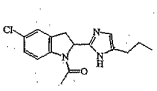
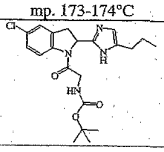
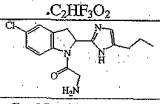
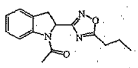
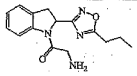
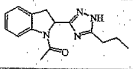
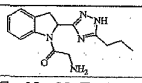
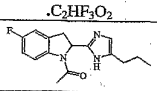
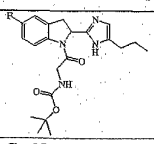
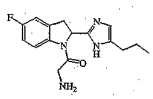
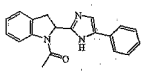
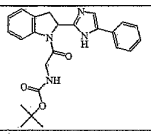
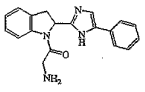
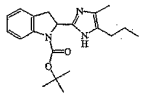
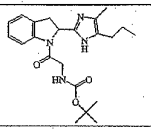
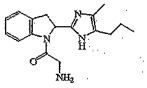
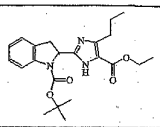
		
Co. No. 13; Ex. B.5; [2S-[1(R*),2R*]]; mp. 116-118°C	Co. No. 14; Ex. B.1; [2S-[1(R*),2R*]]	Co. No. 15; Ex. B.5; .2HCl.2H_2O [2S-[1(R*),2R*]]; mp. 132-140°C
		
Co. No. 16; Ex. B.2	Co. No. 17; Ex. B.1; [2R-[1(S*),2R*]]; mp. 76-79°C	Co. No. 18; Ex. B.1; mp. 198-199°C
		
Co. No. 19; Ex. B.5; mp. 184-186°C	Co. No. 20; Ex. B.5; .H_2O [2R-[1(S*),2R*]]; mp. 73-74°C	Co. No. 21; Ex. B.1; [2R-[1(S*),2R*]] + [2S-[1(R*),2R*]]
		
Co. No. 22; Ex. B.1; [1(S),2A]	Co. No. 23; Ex. B.1; [1(S),2B]	Co. No. 24; Ex. B.5; .2$C_2H_2O_4$; [1(S),2A]; mp. >90°C

		
Co. No. 25; Ex. B.5; .2HCl.2H$_2$O [1(S),2B]; mp. >100°C	Co. No. 26; Ex. B.2; (S); mp. 208-210°C	Co. No. 27; Ex. B.4; [S-[1(R*),R*]; mp. 107-109°C
		
Co. No. 28; Ex. B.5; .3HCl; [S-[1(R*),R*]; mp. 240-242°C	Co. No.29 ; Ex. B.4; mp. 170-171°C	Co. No. 30; Ex. B.4; .$C_2HF_3O_2$; [S-(R*,R*)]; mp. 173-175°C
		
Co. No. 31; Ex. B.2; mp. 261-262°C	Co. No. 32; Ex. B.2; mp. 256-257°C	Co. No. 33; Ex. B.1; .$C_2HF_3O_2$; [R-(R*,S*)]
		
Co. No. 34; Ex. B.1; .$C_2HF_3O_2$; [S-(R*,R*)]	Co. No. 35; Ex. B.1; .$C_2HF_3O_2$; [R-(R*,S*)] + [S-(R*,R*)]	Co. No. 36; Ex. B.5; .2$C_2HF_3O_2$; [S-(R*R*)]
		
Co. No. 37; Ex. B.5; .2$C_2HF_3O_2$; [R-(R*,S*)] + [S-(R*,R*)]	Co. No. 38; Ex. B.2; mp. 214-216°C	Co. No. 39; Ex. B.1; [1(S)]; mp. 137-138°C
		
Co. No. 40; Ex. B.5; [1(S)]; mp. 198-203°C	Co. No. 41; Ex. B.2; mp. 221-222°C	Co. No. 42; Ex. B.1; .2$C_2HF_3O_2$; [R-(R*,S*)]

		
Co. No. 43; Ex. B.1; .$C_2HF_3O_2$; [S-(R*,R*)]	Co. No. 44; Ex. B.5; .$3C_2HF_3O_2$; [S-(R*,R*)]	Co. No. 45; Ex. B.5; .$2C_2HF_3O_2$; [R-(R*,S*)] + [S-(R*,R*)]
		
Co. No.46 ; Ex. B.5; mp. 158-160°C	Co. No. 47; Ex. B.5; .$2C_2H_2O_4$; [S-(R*,R*)]; mp. 135-137°C	Co. No. 48; Ex. B.5; .2HCl.$3H_2O$; [S-(R*,R*)]; mp. 85-87°C
		
Co. No. 49; Ex. B.4; .$H_2O.C_2HF_3O_2$; mp.	Co. No. 50; Ex. B.5; mp. 116-118°C	Co. No. 51; Ex. B.1; .$C_2HF_3O_2$; [R-(R*,S*)] + [S-(R*,R*)]
		
Co. No. 52; Ex. B.5; .$2C_2HF_3O_2$; [R-(R*,S*)]	Co. No. 53; Ex. B.5; .$H_2O.2C_2HF_3O_2$; [R-(R*,S*)]	Co. No. 54; Ex. B.4; .$C_2HF_3O_2$; [S-(R*,R*)]; mp. 66-68°C
		
Co. No. 55; Ex. B.5; .$C_{10}H_8O_3S.H_2O$; [S-(R*,R*)]; mp. 195-197°C	Co. No. 56; Ex. B.1; [S-(R*,R*)]; mp. 76-78°C	Co. No. 57; Ex. B.5; [S-(R*,R*)]; mp. 141-143°C
		
Co. No. 58; Ex. B.2; mp. 173-174°C	Co. No. 59; Ex. B.2; mp. 220-222°C	Co. No. 60; Ex. B.1; .H_2O; mp. 183°C

		
Co. No. 61; Ex. B.5; mp. 122°C	Co. No. 62; Ex. B.16; .$2H_2O$.$2C_2HF_3O_2$	Co. No. 63; Ex. B.4; [S-(R*,R*)]; mp. 77-80°C
		
Co. No. 64; Ex. B.5; [S-(R*,R*)]; mp. 137-138°C	Co. No. 65; Ex. B.1; [2S-[1(R*),2R*]]	Co. No. 66; Ex. B.5; .$C_2H_2O_4$.$2H_2O$; [2S-[1(R*),2R*]]; mp. 153-156°C
		
Co. No. 67; Ex. B.1; mp. 100-104°C	Co. No. 68; Ex. B.5; .HCl.H_2O; mp. 152°C	Co. No. 69; Ex. B.1
		
Co. No. 70; Ex. B.5; .H_2O; mp. 168-170°C	Co. No. 71; Ex. B.2; .2KCl; mp. 189-191°C	Co. No. 72; Ex. B.1; mp. 168°C
		
Co. No. 73; Ex. B.5; .H_2O.$2C_2F_3O_2$; mp. >300°C	Co. No. 74; Ex. B.2; mp. 191-192°C	Co. No. 75; Ex. B.1; mp. 214-216°C
		
Co. No. 76; Ex. B.5; mp. 158-160°C	Co. No. 77; Ex. B.11	Co. No. 78; Ex. B.11

		
Co. No. 79; Ex. B.12; .2$C_2HF_3O_2$	Co. No. 80; Ex. B.3; mp. 179-181°C	Co. No. No. 81; Ex. B.1
		
Co. No. 82; Ex. B.5; mp. 186-188°C	Co. No. 83; Ex. B.1	Co. No. 84; Ex. B.5; .$C_4H_4O_4$; mp. 173-174°C
		
Co. No. 85; Ex. B.10; .$C_2HF_3O_2$	Co. No. 86; Ex. B.2; mp. 225-226°C	Co. No. 87; Ex. B.4;
		
Co. No. 88; Ex. B.5; mp. 193-195°C	Co. No. 89; Ex. B.8	Co. No. 90; Ex. B.9; .$C_2HF_3O_2$
		
Co. No. 91; Ex. B.6; mp.	Co. No. 92; Ex. B.7; .$C_2HF_3O_2$	Co. No. 93; Ex. B.2
		
Co. No. 94; Ex. B.1; .$C_2HF_3O_2$	Co. No. 95; Ex. B.5; .$C_2HF_3O_2$	Co. No. 96; Ex. B.2

		
Co. No. 97; Ex. B.4	Co. No. 98; Ex. B.5; mp. 214-215°C	Co. No. 99; Ex. B.3
		
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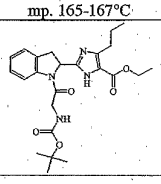
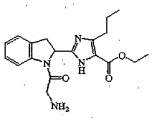
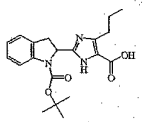
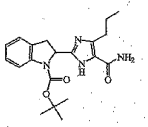
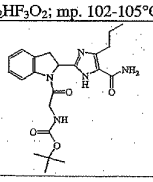
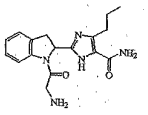
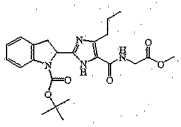
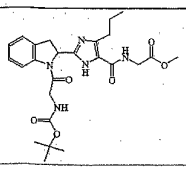
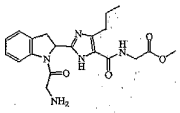
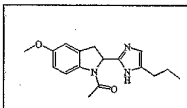
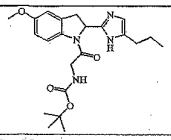
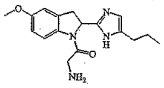
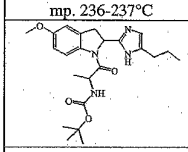
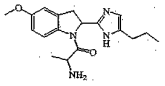
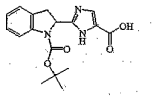
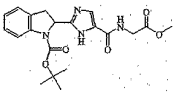
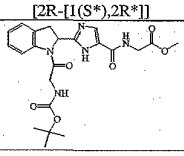
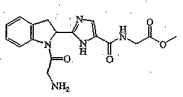
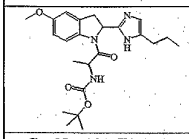
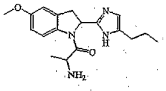
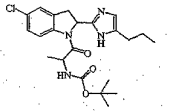
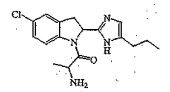
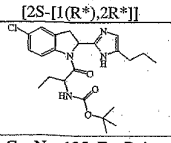
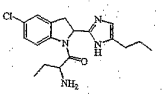
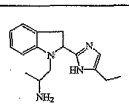
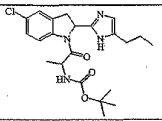
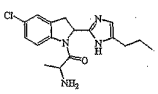
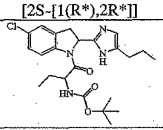
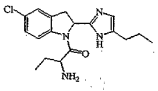
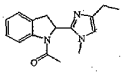
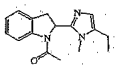
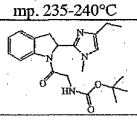
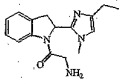
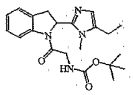
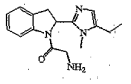
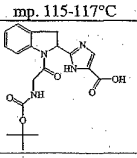
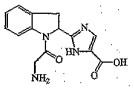
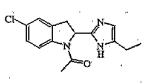
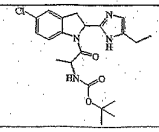
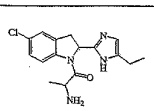
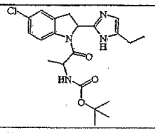
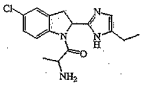
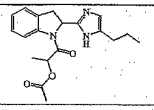
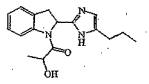
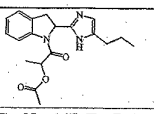
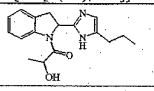
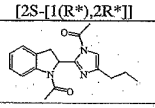
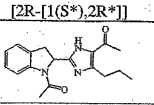
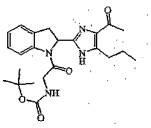
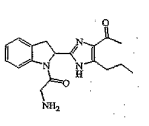
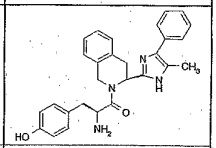
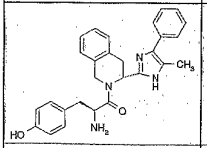
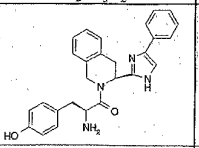
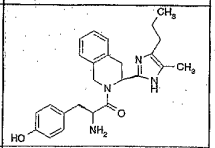
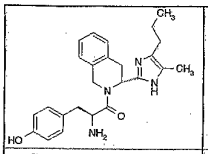
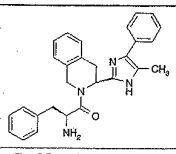
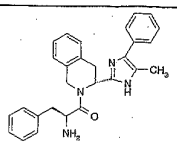
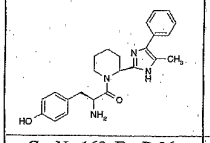
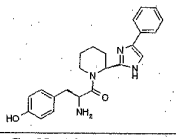
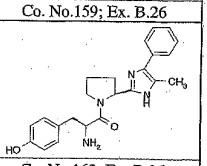
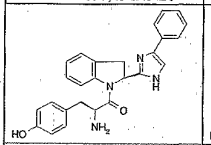
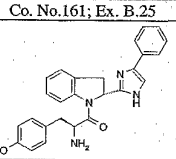
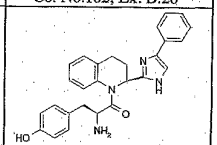
		
Co. No. 103; Ex. B.4	Co. No. 104; Ex. B.5; $.C_2HF_3O_2$; mp. 102-105°C	Co. No. 105; Ex. B.17
		
Co. No. 106; Ex. B.18	Co. No. 107; Ex. B.1	Co. No. 108; Ex. B.5; $.C_2HF_3O_2$; mp. 124-131°C
		
Co. No. 109; Ex. B.19	Co. No. 110; Ex. B.1	Co. No. 111; Ex. B.5; $.C_2HF_3O_2$; mp. 95-99°C

		
Co. No. 112; Ex. B.2; mp. 236-237°C	Co. No. 113; Ex. B.1; mp. 184-188°C	Co. No. 114; Ex. B.5; $.C_2HF_3O_2$
		
Co. No. 115; Ex. B.1; $.C_2HF_3O_2$ [2R-[1(S*),2R*]]	Co. No. 116; Ex. B.5; $.C_2HF_3O_2$ [2R-[1(S*),2R*]]	Co. No. 117; Ex. B.14
		
Co. No. 118; Ex. B.15	Co. No. 119; Ex. B.1	Co. No. 120; Ex. B.5; $.C_2HF_3O_2$
		
Co. No. 121; Ex. B.1; $.C_2HF_3O_2$ [2S-[1(R*),2R*]]	Co. No. 122; Ex. B.5; $.C_2HF_3O_2$ [2S-[1(R*),2R*]]	Co. No. 123; Ex. B.1; $.C_2HF_3O_2$ [2R-[1(S*),2R*]]
		
Co. No. 124; Ex. B.5; $.C_2HF_3O_2$ [2R-[1(S*),2R*]]	Co. No. 125; Ex. B.4; $.C_2HF_3O_2$ [2R-[1(S*),2R*]]	Co. No. 126; Ex. B.5; $.C_2HF_3O_2$ [2R-[1(S*),2R*]]

		
Co. No. 127; Ex. B.24; .$C_2HF_3O_2$; [2S-[1(R*),2R*]]	Co. No. 128; Ex. B.1; .$C_2HF_3O_2$; [2S-[1(R*),2R*]]	Co. No. 129; Ex. B.5; .$C_2HF_3O_2$; [2S-[1(R*),2R*]]
		
Co. No. 130; Ex. B.4; .$C_2HF_3O_2$; [2S-[1(R*),2R*]]	Co. No. 131; Ex. B.5; .HCl [2S-[1(R*),2R*]]; mp. 235-240°C	Co. No. 132; Ex. B.13
		
Co. No. 133; Ex. B.13	Co. No. No. 134; Ex. B.1	Co. No. 135; Ex. B.5; mp. 115-117°C
		
Co. No. 136; Ex. B.1	Co. No. 137; Ex. B.5; mp. 107-109°C	Co. No. 138; Ex. B.20
		
Co. No. 139; Ex. B.5; .$C_2HF_3O_2$	Co. No. 140; Ex. B.2	Co. No. 141; Ex. B.1; .$C_2HF_3O_2$; [2R-[1(S*),2R*]]

		
Co. No. 142; Ex. B.5; [2R-[1(S*),2R*]]	Co. No. 143; Ex. B.1; .$C_2HF_3O_2$; [2S-[1(R*),2R*]]	Co. No. 144; Ex. B.5; [2S-[1(R*),2R*]]
		
Co. No. 145; Ex. B.1; [2S-[1(R*),2R*]]	Co. No. 146; Ex. B.21; [2S-[1(R*),2R*]]	Co. No. 147; Ex. B.1; [2R-[1(S*),2R*]]
		
Co. No. 148; Ex. B.21; [2R-[1(S*),2R*]]	Co. No. 149; Ex. B.22	Co. No. 150; Ex. B.23
		
Co. No. 151; Ex. B.1	Co. No. 152; Ex. B.5; .$C_2HF_3O_2$	Co. No.153; Ex. B.26
		
Co. No.154; Ex. B.26	Co. No.155; Ex. B.25	Co. No.156; Ex. B.26

		
Co. No.157; Ex. B.26	Co. No.158; Ex. B.26	Co. No.159; Ex. B.26
		
Co. No.160; Ex. B.26	Co. No.161; Ex. B.25	Co. No.162; Ex. B.26
		
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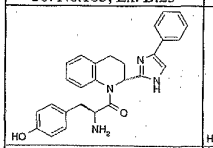	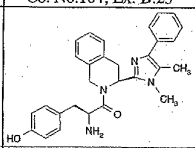	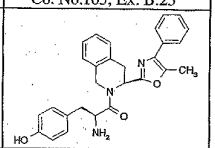
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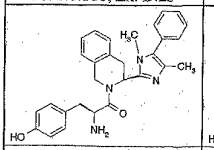	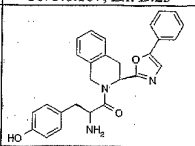	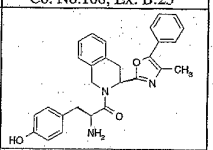
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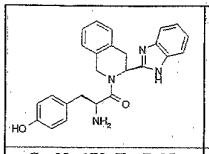	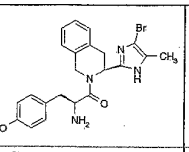	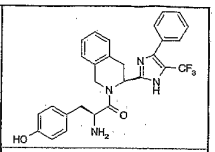
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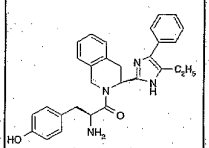	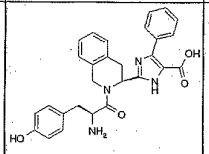	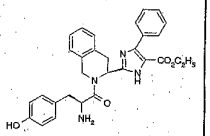
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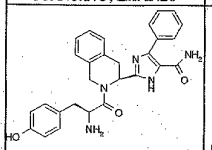	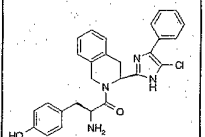	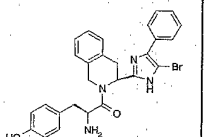
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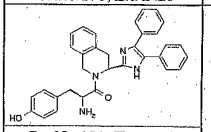
		
Co. No.181; Ex. B.26		

C. Pharmacological examples

C.1. Inhibition of tripeptidyl peptidase II (TPP II)

The inhibition of TPP II was measured using the procedure as described by C. Rose et al. in Nature, 380, 403-409 (1996).

TPPII activity was evaluated using 15 μM AAF-AMC as a substrate in a 50 mM Potassiumphosphate buffer pH 7.5 with 1 mM DTT and 1 mM EGTA. Compounds were added at a final DMSO concentration of 1%. Fluorescence was measured at 405 nm. The potency of the compounds of formula (I) was expressed as the IC_{50} value, *i.e.* the concentration needed to provide 50% inhibition.

Compounds 6, 10, 13, 15, 19, 22, 24, 28, 30, 44, 47, 48, 54, 55, 57, 61, 62, 66, 68, 70, 73, 76, 82, 84, 88, 90, 92, 95, 101, 104, 108, 111, 114, 116, 120, 122, 124, 126, 129, 131, 135, 142, and 144 have an IC_{50} value equal to or lower than 1.10^{-5} M.

C.2 Rat Brain δ-Opioid Receptor Binding Assay

Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, NY) are killed by cervical dislocation, and their brains removed and placed immediately in ice cold Tris HCl buffer (50 mM, pH 7.4). The forebrains are separated from the remainder of the brain by a coronal transection, beginning dorsally at the colliculi and passing ventrally through the midbrain-pontine junction. After dissection, the forebrains are homogenized in Tris buffer in a Teflon®-glass homogenizer. The homogenate is diluted to a concentration of 1 g of forebrain tissue per 100 mL Tris buffer and centrifuged at 39,000 X G for 10 min. The pellet is re-suspended in the same volume of Tris buffer with several brief pulses from a Polytron homogenizer. This particulate preparation is used for the δ-opioid binding assays. Following incubation with the δ-selective peptide ligand [^{3}H]DPDPE at 25°C, the tube contents are filtered through Whatman GF/B filter sheets on a Brandel cell harvester. The tubes and filters are rinsed three times with 4 mL of 10 mM HEPES (pH 7.4), and the radioactivity associated with the filter circles is determined using Formula 989 scintillation fluid (New England Nuclear, Boston, MA) in a scintillation counter.

The data are used to calculate either the % inhibition compared to control binding (when only a single concentration of test compound is evaluated) or a K_i value (when a range of concentrations is tested).

% Inhibition is calculated as follows:

$$\left(1 - \left[\frac{\text{(Test Compound dpm - Non-specific dpm)}}{\text{(Total dpm - Non-specific dpm)}}\right]\right) \text{ X } 100\%$$

K_i value is calculated using the LIGAND (Munson, P.J. and Rodbard, D., Anal. Biochem. 107: 220-239, 1980) data analysis program.

C.3 Rat Brain μ-Opioid Receptor Binding Assay

Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, NY) are killed by cervical dislocation and their brains removed and placed immediately in ice cold Tris HCl buffer (50 mM, pH 7.4). The forebrains are separated from the remainder of the brain by a coronal transection, beginning dorsally at the colliculi and passing ventrally

through the midbrain-pontine junction. After dissection, the forebrains are homogenized in Tris buffer in a Teflon®-glass homogenizer. The homogenate is diluted to a concentration of 1 g of forebrain tissue per 100 mL Tris buffer and centrifuged at 39,000 X G for 10 min. The pellet is re-suspended in the same volume of Tris buffer with several brief pulses from a Polytron homogenizer. This particulate preparation is used for the μ-opioid binding assays. Following incubation with the μ-selective peptide ligand [^{3}H]DAMGO at 25°C, the tube contents are filtered through Whatman GF/B filter sheets on a Brandel cell harvester. The tubes and filters are rinsed three times with 4 mL of 10 mM HEPES (pH 7.4) and the radioactivity associated with the filter circles is determined using Formula 989 scintillation fluid (New England Nuclear, Boston, MA) in a scintillation counter.

The data are used to calculate either the % inhibition compared to control binding (when only a single concentration of test compound is evaluated) or a K_i value (when a range of concentrations is tested).

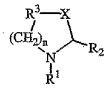
% Inhibition is calculated as follows:

$$\left(1 - \left[\frac{\text{(Test Compound dpm - Non-specific dpm)}}{\text{(Total dpm - Non-specific dpm)}}\right]\right) \text{ X 100\%}$$

K_i value was calculated using the LIGAND (Munson, P.J. and Rodbard, D., Anal. Biochem. 107: 220-239, 1980) data analysis program.

Claims

1. A compound of formula (I)



(I),

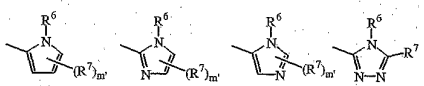
a stereochemically isomeric form thereof, or a pharmaceutically acceptable addition salt thereof, wherein

n is an integer 0 or 1;

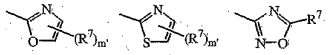
X represents O; S; or -(CR^{4}R^5)$_m$- wherein m is an integer 1 or 2; R^4 and R^5 are each independently from each other hydrogen or C_{1-4}alkyl;

R^1 is C_{1-6}alkylcarbonyl optionally substituted with hydroxy; C_{1-6}alkyloxycarbonyl; aminoC_{1-6}alkylcarbonyl wherein the C_{1-6}alkyl group is optionally substituted with C_{3-6}cycloalkyl; mono- and di(C_{1-4}alkyl)aminoC_{1-6}alkylcarbonyl; aminocarbonyl substituted with aryl; C_{1-6}alkylcarbonyloxyC_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonylaminoC_{1-6}alkylcarbonyl wherein the amino group is optionally substituted with C_{1-4}alkyl; an amino acid residue bound via the carbonyl group; C_{1-6}alkyl substituted with amino; or arylcarbonyl;

R^2 is a 5-membered heterocycle selected from



(a-1) (a-2) (a-3) (a-4)



(a-5) (a-6) (a-7)

wherein m' is an integer 1 to 2;

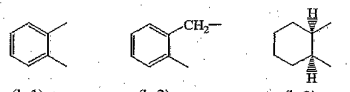
R^6 is hydrogen or C_{1-4}alkyl;

R^7 is independently from each other hydrogen; halo; amino; hydroxy; trifluoromethyl; C_{1-6}alkyl; C_{1-4}alkyl substituted with hydroxy, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, amino, or mono- or di(C_{1-4}alkyl)amino; phenyl; aminocarbonyl; hydroxycarbonyl; C_{1-4}alkyloxycarbonyl; C_{1-4}alkylcarbonyl; or C_{1-4}alkyloxycarbonylC_{1-4}alkylaminocarbonyl;

or R^2 is benzimidazole, or benzimidazole substituted with one or two substituents each independently selected from halo, trifluoromethyl, C_{1-4}alkyl, hydroxy, hydroxycarbonyl, or C_{1-4}alkyloxycarbonyl;

R^3 is a bivalent radical $-CH_2CH_2-$ optionally substituted with halo or phenylmethyl;

or R^3 is a bivalent radical of formula



(b-1) (b-2) (b-3)

wherein said (b-1), (b-2), or (b-3) optionally can be substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, nitro, amino, cyano, trifluoromethyl, phenyl, or phenyl substituted with one or two subsitutents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, nitro, cyano, and trifluoromethyl;

aryl is phenyl, or phenyl substituted with amino, nitro or hydroxycarbonyl.

2. A compound as claimed in claim 1 wherein n is 0 and R^3 is a radical of formula (b-1) optionally substituted with halo or methoxy.

3. A compound as claimed in claim 1 wherein n is 0, R^3 is a radical of formula (b-1) optionally substituted with halo or methoxy, and X represents $-CH_2-$ or $-CH_2CH_2-$.

4. A compound according to any of the preceding claims wherein (a-2), (a-4), (a-6), or (a-7).

5. A compound according to any of the preceding claims wherein R^1 is C_{1-6}alkylcarbonyl, aminoC_{1-6}alkylcarbonyl or an amino acid.

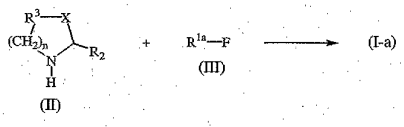
6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound as claimed in any of claims 1 to 5.

7. A process for preparing a pharmaceutical composition as claimed in claim 6 wherein a therapeutically active amount of a compound as claimed in any of claims 1 to 5 is intimately mixed with a pharmaceutically acceptable carrier.

8. A compound as claimed in any of claims 1 to 5 for use as a medicine.

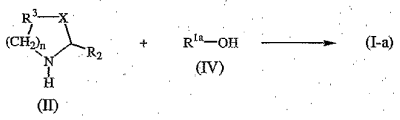
9. A process for preparing a compound of formula (I) wherein

a) an intermediate of formula (II) is reacted with an intermediate of formula (III) in a reaction-inert solvent and, optionally in the presence of a suitable base, thereby yielding compounds of formula (I-a), defined as compounds of formula (I) wherein R^{1a} represents all R^1 substituents other than C_{1-4}alkyl substituted with amino; or



(II) (III) (I-a)

b) an intermediate of formula (II) is reacted with an intermediate of formula (IV), thereby yielding a compound of formula (I-a);



(II) (IV) (I-a)

wherein in the above reaction schemes the radicals R^1, R^2, R^3, and the integer n, are as defined in claim 1;

c) or, compounds of formula (I) are converted into each other following art-known transformation reactions; or if desired; a compound of formula (I) is converted into an acid addition salt, or conversely, an acid addition salt of a compound of formula (I) is converted into a free base form with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

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Declarations under Rule 4.17:

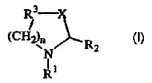
as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations

as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations

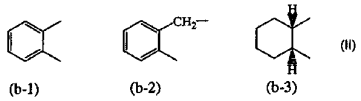
of inventorship (Rule 4.17(iv)) for US only

[Continued on next page]

(54) **Title:** TRIPEPTIDYL PEPTIDASE INHIBITORS



(I)



(b-1) (b-2) (b-3) (II)

(57) **Abstract:** The present invention is concerned with novel compounds of formula (I) which are inhibitors of a membrane tripeptidyl peptidase responsible for the inactivation of endogenous neuropeptides such as cholecystokinis (CCKs). The invention further relates to methods for preparing such compounds, pharmaceutical compositions comprising said compounds as well as the use as a medicine of said compounds. (I) wherein n is an integer (0) or (1); X represents O; S; or -(CR⁴R⁵)$_m$- wherein m is an integer (1) or (2); R^4 and R^5 are each independently from each other hydrogen or C_{1-4}alkyl; R^1 is C_{1-6}alkylcarbonyl optionally substituted with hydroxy; C_{1-6}alkyloxycarbonyl; aminoC_{1-6}alkylcarbonyl wherein the C_{1-6}alkyl group is optionally substituted with C_{3-6}cycloalkyl; mono- and di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl; aminocarbonyl substituted with aryl; C_{1-6}alkylcarbonyloxyC_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonylaminoC_{1-6}alkylcarbonyl wherein the amino group is optionally substituted with C_{1-4}alkyl; an amino acid; C_{1-6}alkyl substituted with amino; or arylcarbonyl; R^2 is an optionally substituted (5)-membered heterocycle, or R^2 is optionally substituted benzimidazole; R^3 is a bivalent radical -CH_2CH_2- optionally substituted with halo or phenylmethyl; or R^3 is a bivalent radical of formula (II).

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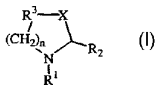
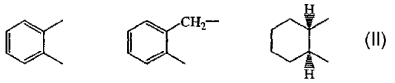
(54) **Title:** TRIPEPTIDYL PEPTIDASE INHIBITORS



(I)



(b-1) (b-2) (II) (b-3)

(57) **Abstract:** The present invention is concerned with novel compounds of formula (I) which are inhibitors of a membrane tripeptidyl peptidase responsible for the inactivation of endogenous neuropeptides such as cholecystokinis (CCKs). The invention further relates to methods for preparing such compounds, pharmaceutical compositions comprising said compounds as well as the use as a medicine of said compounds. (I) wherein n is an integer (0) or (1); X represents O; S; or -(CR⁴R⁵)$_m$- wherein m is an integer (1) or (2); R⁴ and R⁵ are each independently from each other hydrogen or C_{1-4}alkyl; R¹ is C_{1-4}alkylcarbonyl optionally substituted with hydroxy; C_{1-6}alkyloxycarbonyl; aminoC_{1-6}alkylcarbonyl wherein the C_{1-6}alkyl group is optionally substituted with C_{5-6}cycloalkyl; mono- and di(C_{1-4}alkyl)aminoC_{1-6}alkylcarbonyl; aminocarbonyl substituted with aryl; C_{1-6}alkylcarbonyloxyC_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonylaminoC_{1-6}alkylcarbonyl wherein the amino group is optionally substituted with C_{1-4}alkyl; an amino acid; C_{1-6}alkyl substituted with amino; or arylcarbonyl; R² is an optionally substituted (5)-membered heterocycle, or R² is optionally substituted benzimidazole; R³ is a bivalent radical -CH_2CH_2- optionally substituted with halo or phenylmethyl; or R² is a bivalent radical of formula (II).

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TRIPEPTIDYL PEPTIDASE INHIBITORS

The present invention is concerned with novel compounds of formula (I) which are inhibitors of a membrane tripeptidyl peptidase responsible for the inactivation of endogenous neuropeptides such as cholecystokinins (CCKs). The invention further relates to methods for preparing such compounds, pharmaceutical compositions comprising said compounds as well as the use as a medicine of said compounds.

Cholecystokinins (CCKs) are a family of hormonal and neuronal peptides which exert pleiotropic biological effects in the gut and brain. The actions of CCK are mediated by CCK_A and CCK_B receptors. CCK is known to have a physiological role in the control of food intake, which is enhanced by CCK_A agonists (Smith G.P. et al., *J. Ann. N.Y. Acad. Sci.*, 713, 236-241 (1994)), and the control of anxiety, which is decreased by CCK_B antagonists (Woodruff G. et al., *Rev. Pharmac.*, 31, 469-501 (1991)).

Tripeptidyl peptidase II (TPP II) is a CCK inactivating peptidase. TPP II is found in neurons responding to cholecystokinin as well as in non-neuronal cells. TPP II is considered to be a neuropeptidase responsible for CCK-8 inactivation (Rose C. et al., *Nature*, 380, 403-409, (1996)).

TPP II could be involved in CCK-8 inactivation in the gastrointestinal tract. Exogenous CCK reduces food intake and elicits other behavioural concomitants of satiation. Food intake is increased by systemic administration of CCK_A receptor agonists (Smith G.P. et al., *J. Ann. N.Y. Acad. Sci.*, 713, 236-241 (1994)). Endogenous CCK-controlling food intake seems to be of neuronal rather than hormonal origin and acts upon peripheral CCK_A receptors on vagal afferent fibres (Smith G.P. et al., *Am. J. Physiol.*, 249, R638-R641 (1985)).

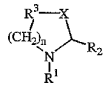
Inhibitors of TPP II are useful tools in investigating the functions of CCK neurons and may be useful drugs for the treatment of disorders such as over-eating, obesity, problems with gastrointestinal motility and psychotic syndromes.

WO-96/35805, published 14 November 1996, discloses inhibitors of a membrane tripeptidylpeptidase responsible for the inactivation of endogenous neuropeptides useful in treatment of gastrointestinal and mental disorders. WO-99/33801, published 8 July 1999, discloses CCK-inactivating tripeptidyl peptidase (TPP II) inhibiting compounds

useful in the treatment of eating disorders, obesity, psychotic syndromes and associated psychiatric disorders.

The compounds of the present invention differ from the cited art-known compounds structurally, by the nature of the R^2 substituent.

The present invention concerns compounds of formula (I)



(I),

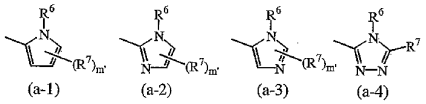
a stereochemically isomeric form thereof, or a pharmaceutically acceptable addition salt thereof, wherein

n is an integer 0 or 1;

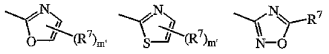
X represents O; S; or $-(CR^4R^5)_m-$ wherein m is an integer 1 or 2; R^4 and R^5 are each independently from each other hydrogen or C_{1-4}alkyl;

R^1 is C_{1-6}alkylcarbonyl optionally substituted with hydroxy; C_{1-6}alkyloxycarbonyl; aminoC_{1-6}alkylcarbonyl wherein the C_{1-6}alkyl group is optionally substituted with C_{3-6}cycloalkyl; mono- and di(C_{1-4}alkyl)aminoC_{1-6}alkylcarbonyl; aminocarbonyl substituted with aryl; C_{1-6}alkylcarbonyloxyC_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonylaminoC_{1-6}alkylcarbonyl wherein the amino group is optionally substituted with C_{1-4}alkyl; an amino acid residue bound via the carbonyl group; C_{1-6}alkyl substituted with amino; or arylcarbonyl;

R^2 is a 5-membered heterocycle selected from



(a-1) (a-2) (a-3) (a-4)



(a-5) (a-6) (a-7)

wherein m' is an integer 1 to 2;

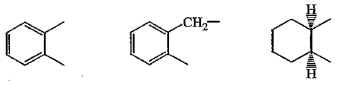
R^6 is hydrogen or C_{1-4}alkyl;

R^7 is independently from each other hydrogen; halo; amino; hydroxy; trifluoromethyl; C_{1-6}alkyl; C_{1-4}alkyl substituted with hydroxy,

hydroxycarbonyl, C_{1-4}alkyloxycarbonyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, amino, or mono- or di(C_{1-4}alkyl)amino; phenyl; aminocarbonyl; hydroxycarbonyl; C_{1-4}alkyloxycarbonyl; C_{1-4}alkylcarbonyl; or C_{1-4}alkyloxycarbonylC_{1-4}alkylaminocarbonyl;

or R^2 is benzimidazole, or benzimidazole substituted with one or two substituents each independently selected from halo, trifluoromethyl, C_{1-4}alkyl, hydroxy, hydroxycarbonyl, or C_{1-4}alkyloxycarbonyl;

R^3 is a bivalent radical $-CH_2CH_2-$ optionally substituted with halo or phenylmethyl; or R^3 is a bivalent radical of formula



(b-1) (b-2) (b-3)

wherein said (b-1), (b-2), or (b-3) optionally can be substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, nitro, amino, cyano, trifluoromethyl, phenyl, or phenyl substituted with one or two subsitutents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, nitro, cyano, and trifluoromethyl;

aryl is phenyl, or phenyl substituted with amino, nitro or hydroxycarbonyl.

The term "amino acid residues" as used herein are the glycine, alanine, valine, leucine, isoleucine, methionine, proline, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, esters of aspartic acid, glutamic acid, esters of glutamic acid, lysine, arginine, and histidine amino acid radicals which are bound via their carbonyl group to the nitrogen atom of the rest of the molecule and which can be generally represented by "R-CH(NH_2)-CO-".

As used in the foregoing definitions halo is generic to fluoro, chloro, bromo and iodo; C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methyl-ethyl, 2-methylpropyl and the like; C_{1-6}alkyl is meant to include C_{1-4}alkyl and the higher homologues thereof having 5 or 6 carbon atoms, such as, for example, 2-methyl-butyl, pentyl, hexyl and the like; C_{3-6}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; C_{3-6}alkenyl defines straight and branched chain unsaturated hydrocarbon radicals having from 3 to 6 carbon atoms, such as propenyl,

butenyl, pentenyl or hexenyl; C_{1-2}alkanediyl defines methylene or 1,2-ethanediyl; C_{1-5}alkanediyl defines bivalent straight or branched chain hydrocarbon radicals containing from 1 to 5 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, and the branched isomers thereof; C_{1-6}alkanediyl includes C_{1-5}alkanediyl and the higher homologues thereof having 6 carbon atoms such as, for example, 1,6-hexanediyl and the like. The term "CO" refers to a carbonyl group.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration. Compounds encompassing double bonds can have an E or Z-stereochemistry at said double bond. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

The pharmaceutically acceptable addition salts as mentioned hereinabove include pharmaceutically acceptable acid addition salts and are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (*i.e.* ethanedioic), malonic, succinic (*i.e.* butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable base addition salts are possible which include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and base addition salts formed with suitable organic ligands, e.g., primary, secondary, tertiary or quaternary ammonium salts, such as morpholinyl, tert-butylamino, and the like.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

Interesting compounds are those compounds of formula (I) wherein one or more of the following restrictions apply :

a) n is 0;
b) R^3 is a radical of formula (b-1) optionally substituted with halo or methoxy;
c) X represents $-CH_2-$ or $-CH_2CH_2-$;
d) R^2 is a radical of formula (a-2) wherein R^6 is hydrogen;
e) R^2 is a radical of formula (a-2), (a-4), (a-6), or (a-7);
f) R^2 is benzimidazole optionally substituted with methyl, hydroxy, halo, trifluoromethyl, methyloxycarbonyl, or hydroxycarbonyl;
g) R^1 is C_{1-6}alkylcarbonyl, aminoC_{1-6}alkylcarbonyl or an amino acid.

Particular compounds are those compounds of formula (I) wherein n is 0 and R^3 is a radical of formula (b-1) optionally substituted with halo or methoxy.

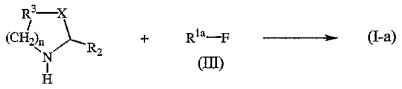
Preferred compounds are those compounds of formula (I) wherein n is 0, R^3 is a radical of formula (b-1) optionally substituted with halo or methoxy, and X represents $-CH_2-$.

Other preferred compounds are those compounds of formula (I) wherein n is 0, R^3 is a radical of formula (b-1) optionally substituted with halo or methoxy, and X represents $-CH_2CH_2-$.

Still other preferred compounds are those compounds of formula (I) wherein R^1 is C_{1-6}alkylcarbonyl, aminoC_{1-6}alkylcarbonyl or an amino acid.

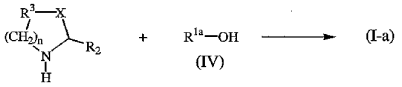
Compounds of formula (I-a), defined as compounds of formula (I) wherein R^{1a} represents all R^1 substituents other than C_{1-4}alkyl substituted with amino, can be prepared by reacting an intermediate of formula (II) with an intermediate of formula (III) in the presence of 4-methyl-morpholine, in a reaction-inert solvent such as, e.g. dichloromethane of chloroform. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried out at a temperature ranging between room temperature and the reflux temperature of the reaction mixture and, if desired, the reaction may be carried out in an autoclave at an increased pressure. Optionally said

reaction is followed by an acid hydrolysis step to remove acid labile protecting groups, such as a *tert*-butyloxycarbonyl.



(II) (III) (I-a)

Alternatively, compounds of formula (I-a) can also be prepared by reacting an intermediate of formula (II) with an intermediate of formula (IV) in the presence of an appropriate activating agent, such as e.g. isobutyl chloroformate, in a reaction-inert solvent such as, e.g. dichloromethane, in the presence of a suitable base such as, e.g. triethylamine. Optionally said reaction is followed by an acid hydrolysis step to remove acid labile protecting groups, such as a *tert*-butyloxycarbonyl.

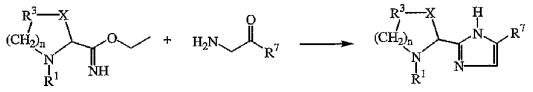


(II) (IV) (I-a)

Compounds of formula (I-b), defined as compounds of formula (I) wherein R^1 represents C_{1-6}alkyl substituted with amino, can conveniently be prepared by submitting the corresponding starting compounds (I-b') wherein R^1 represents aminoC_{1-5}alkylcarbonyl to an appropriate reduction reaction. Appropriate reduction reactions can be e.g. treatment with borane-tetahydrofuran complex.

(I-b') (I-b)

Compounds of formula (I-c), defined as compounds of formula (I) wherein R^2 represents a radical (a-2) wherein R^6 is hydrogen and R^7 is located at the 3-position of the imidazole moiety, can be prepared by reacting an intermediate of formula (V) with an intermediate of formula (VI) in the presents of potassium acetate in a suitable solvent such as methanol.



(V) (VI) (I-c)

The compounds of formula (I) may further be prepared by converting compounds of formula (I) into each other according to art-known group transformation reactions.

The starting materials and some of the intermediates, such as e.g. intermediates of formula (III), (IV) and (VI), are known compounds and are commercially available or may be prepared according to conventional reaction procedures generally known in the art.

Compounds of formula (I) and some of the intermediates may have one or more stereogenic centers in their structure, present in a R or a S configuration, such as, e.g. the carbon atom bearing the R^2 substituent.

Following CAS nomenclature conventions, when two stereogenic centers of known absolute configuration are present in a molecule, an *R* or *S* descriptor is assigned (based on Cahn-Ingold-Prelog sequence rule) to the lowest-numbered chiral center, the reference center. The configuration of the second stereogenic center is indicated using relative descriptors [*R*,R*]* or [*R*,S*]*, where R* is always specified as the reference center and [*R*,R**] indicates centers with the same chirality and [*R*,S**] indicates centers of unlike chirality. For example, if the lowest-numbered chiral center in the molecule has an *S* configuration and the second center is *R*, the stereo descriptor would be specified as *S*-[*R*,S**].

The compounds of formula (I) as prepared in the hereinabove described processes may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from

the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (I), the pharmaceutically acceptable salts and stereoisomeric forms thereof are inhibitors of a membrane tripeptidyl peptidase responsible for the inactivation of endogenous neuropeptides such as cholecystokinis (CCKs) as evidenced in pharmacological example C-1.

In view of their TPP II inhibiting properties the compounds of the present invention are useful in treatment of conditions or disorders associated with TPP II activity such as, e.g. eating disorders, obesity, psychotic syndromes and associated psychiatric disorders.

In view of the utility of the compounds of formula (I), it follows that the present invention also provides a method of treating warm-blooded animals, including humans, (generally called herein patients) suffering from eating disorders, obesity, psychotic syndromes and associated psychiatric disorders Consequently a method of treatment is provided for inhibiting the activity of TPP II and/or relieving patients suffering from conditions, such as, for example, eating disorders, obesity, psychotic syndromes and associated psychiatric disorders.

Hence, the use of a compound of formula (I) as medicine is provided acting as an inhibitor of the CCK-inactivating peptidase tripeptidyl peptidase (TPP II) and/or for the treatment of eating disorders, especially obesity and/or for the treatment of psychotic syndromes and associated psychiatric disorders, which comprises a therepautically effective amount of a compound of formula (I). Also provided is the use of a compound of formula (I) for the manufacture of a medicine for inhibiting the activity of TPP II and/or treating eating disorders, obesity, psychotic syndromes and associated psychiatric disorders. Both prophylactic and therapeutic treatment are envisaged.

It is believed that some of the compounds of the present invention, in particular compounds (153) to (181), may also have opioid activity such as delta-opioid (δ), mu-opioid (μ) and/or kappa-opioid (κ) activity. Opioid activity can be measured using the assays as described in pharmacological examples C.2 and C.3.

To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. Acid addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

For oral administration, the pharmaceutical compositions may take the form of solid dose forms, for example, tablets (both swallowable-only and chewable forms), capsules or gelcaps, prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art.

Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means, optionally with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methylcellulose, hydroxypropyl methylcellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid).

Pharmaceutically acceptable sweeteners comprise preferably at least one intense sweetener such as saccharin, sodium or calcium saccharin, aspartame, acesulfame potassium, sodium cyclamate, alitame, a dihydrochalcone sweetener, monellin, stevioside or sucralose (4,1',6'-trichloro-4,1',6'-trideoxy*galacto*sucrose), preferably saccharin, sodium or calcium saccharin, and optionally a bulk sweetener such as sorbitol, mannitol, fructose, sucrose, maltose, isomalt, glucose, hydrogenated glucose syrup, xylitol, caramel or honey.

Intense sweeteners are conveniently employed in low concentrations. For example, in the case of sodium saccharin, the concentration may range from 0.04% to 0.1% (w/v) based on the total volume of the final formulation, and preferably is about 0.06% in the low-dosage formulations and about 0.08% in the high-dosage ones. The bulk sweetener can effectively be used in larger quantities ranging from about 10% to about 35%, preferably from about 10% to 15% (w/v).

The pharmaceutically acceptable flavours which can mask the bitter tasting ingredients in the low-dosage formulations are preferably fruit flavours such as cherry, raspberry, black currant or strawberry flavour. A combination of two flavours may yield very

good results. In the high-dosage formulations stronger flavours may be required such as Caramel Chocolate flavour, Mint Cool flavour, Fantasy flavour and the like pharmaceutically acceptable strong flavours. Each flavour may be present in the final composition in a concentration ranging from 0.05% to 1% (w/v). Combinations of said strong flavours are advantageously used. Preferably a flavour is used that does not undergo any change or loss of taste and colour under the acidic conditions of the formulation.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example as a sparingly soluble salt.

The compounds of the invention may be formulated for parenteral administration by injection, conveniently intravenous, intramuscular or subcutaneous injection, for example by bolus injection or continuous intravenous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multidose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as isotonizing, suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration the compounds of the invention may be used, for example, as a liquid spray, as a powder or in the form of drops.

Experimental part

In the procedures described hereinafter the following abbreviations were used : "ACN" stands for acetonitrile; "THF", which stands for tetrahydrofuran; "DCM" stands for dichloromethane; and "MIK" stands for methyl isobutyl ketone.

For some chemicals the chemical formula was used, e.g. CH_2Cl_2 for dichloromethane, CH_3OH for methanol, NH_3 for ammonia, HCl for hydrochloric acid, NaOH for sodium hydroxide, $NaHCO_3$ for sodium hydrogen carbonate, and Na_2CO_3 sodium carbonate.

In those cases the stereochemically isomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration.

Preparative liquid chromatography was performed on a semi-preparative HPLC unit using a YMC ODS-A column (30 x 100 mm, 5 micron, temperature : ambient, flow rate : 35 mL/min, mobile phase : a) 10/90 acetonitrile/ water with 0.1% trifluoroacetic acid, b) 90/10 acetonitrile/ water with 0.1% trifluoroacetic acid, gradient : linear gradient from A to B over 9 minutes, UV detection at 254 nm.

A. Preparation of the intermediates

Example A.1

a) 2,3-Dihydroxy-1*H*-indole-2-carboxamide (0.030 mol) was suspended in trichloromethane (400 ml). The mixture was cooled to 0°C. Triethylamine (0.045 mol) was added. Acetyl chloride (0.045 mol) was added over 2 minutes. After 30 minutes, TLC showed the reaction was incomplete. While the flask was still cool, more Triethylamine (6.26 ml) was added, followed 15 minutes later with more acetyl chloride (3.21 ml). TLC showed the reaction was still incomplete. The reaction was continued to allow to stir, cooled to 0°C, and more triethylamine (6.26 ml) was added. Over 2 minutes, more acetyl chloride (3.21 ml) was added neat. TLC showed 80% completion after 60 minutes, and no progress after 30 more minutes. A third portion of acetyl chloride and triethylamine was added. After an additional 15 minutes, ice cold water (200 ml) was added. The mixture was stirred for 10 minutes, filtered, and rinsed with water (3 x 100 ml) and trichloromethane (2 x 75 ml). The sample was allowed to dry overnight, yielding 4.71 g of (S)-1-acetyl-2,3-dihydro-1*H*-indole-2-carboxamide (intermediate 1, mp. >260°C).

b) Intermediate (1) (0.02022 mol) was suspended in DCM (175 ml). The mixture was cooled to 0°C. Triethylamine (0.06066 mol) was added neat. Trichloroacetyl chloride (0.03033 mol) in DCM (20 ml) was added dropwise over 20 minutes. After 2 hours, ice water (200 ml) was added, the phases separated and the organic phase reextracted with 3 N HCl and then with a saturated aqueous $NaHCO_3$ solution. The organic phase was dried, filtered, and stripped to leave 4.61 g brown solid. The solid was triturated with ice cold diethylether (30 ml), filtered, and rinsed with ice cold diethylether (twice),

yielding 3.12g (83%) of (S)-1-acetyl-2,3-dihydro-1*H*-indole-2-carbonitrile (intermediate 2, mp. 134-135°C).

c) Intermediate (2) (0.0151 mol) was suspended in diethylether (200 ml). Ethanol (0.0214 mol) was added, and the mixture was cooled to 0°C. HCl (gas) was bubbled in for 45 minutes. The mixture was removed from the ice bath and stirred. After 20 minutes, a residue collected on the wall sides. The walls were scratched, and a white solid precipitated out. After 1 hour the sample was filtered, rinsed with diethylether, air dried quickly, yielding 3.99 g of (S)-ethyl 1-acetyl-2,3-dihydro-1*H*-indole-2-carboximidate monohydrochloride (intermediate 3).

In analogy, ethyl 1-acetyl-2,3-dihydro-1*H*-indole-2-carboximidate monohydrochloride (intermediate 6) was prepared starting from 1-acetyl-2,3-dihydro-1*H*-indole-2-carbonitrile.

Example A.2

a) 5-chloro-2,3-dihydroxy-1*H*-indole-2-carboxylic acid, methyl ester (0.00761 mole) was dissolved in methanol (25 ml) and cooled to 0°C. NH_3 was bubbled in for 10 minutes. The flask was stoppered and allowed to warm to room temperature. The mixture was stirred overnight. TLC showed the reaction was mostly complete. The sample was concentrated to ± 1/3 volume, cooled, and filtered, rinsing resulting solid with ice cold methanol (2 ml) and then dried ion the air, yielding 0.74 g of 5-chloro-2,3-dihydro-1*H*-indole-2-carboxamide (intermediate 7, mp. 151-152°C).

b) Triethylamine (0.02080 mole) was added to intermediate (7) (0.09632 mole) dissolved in trichloromethane (700 ml). The mixture was cooled to 5°C. Acetyl chloride (0.2480 mole) was added over 2 minutes with stirring. After 5 minutes, a precipitate formed. The ice bath was removed, and the container allowed to sit for 15 minutes. Ice water (250 ml) was added, and the mixtture was stirred for 10 minutes. The sample was filtered, rinsed with water and trichloromethane. The solid was suspended in water (200 ml), and swirled for 10 minutes. Trichloromethane (200 ml) was added and the mixture was stirred, then filtered and rinsed with water and trichloromethane, and then dried to the air overnight, yielding 19.71 g of 1-acetyl-5-chloro-2,3-dihydro-1*H*-indole-2-carboxamide (intermediate 8).

c) Triethylamine (0.41291 mole) was added to intermediate (8) (0.08258 mole) suspended in dichloromethane (500 ml) at 0°C. Trichloroacetyl chloride (0.20645 mole) was added over 10 minutes. When the reaction appeared sluggish, an additional portion of triethylamine (20 ml) and then more trichloroacetyl chloride (7.6 ml) were added, and the mixture was stirred for 2 hours at low temperature. The ice bath was removed, and the mixture was allowed to sit for 2 hours. This resulted in a darker

colored reaction, which was re-cooled to 0°C. Ice cold water (150 ml) was slowly added, and the mixture was stirred for 5 minutes. The layers were separated, and the organic phase was washed (ice cold 3N HCl, saturated $NaHCO_3$), dried, filtered, and concentrated . The residue was triturated in ice cold diethylether (40 ml). Filtration, rinsing with ice cold diethylether (10 ml), yielding 15.13 g of 1-acetyl-5-chloro-2,3-dihydro-1*H*-indole-2-carbonitrile (intermediate 9, mp. 140-142°C).

d) HCl (as a 2 M solution) was added slowly to intermediate (9) until gas evolution was noted. Then stopped adding the prepared HCl (2N in diethylether), and suspended HCl in diethylether (150 ml) and then ethanol (0.042 mole) was added. The mixture was cooled to 0°C and HCl (gas) was added over an hour, with an oil precipitating out. The reaction was diluted to 1 l with diethylether. More oil precipitates, and no solid formed after sitting for 1 hour. The diethylether was decanted off. The residue was diluted (diethylether, 500 ml). The solid begins to form, and the mixture was stirred for 2 hours. The sample was filtered, rinsing with diethylether. The sample was placed under vacuum, yielding 6.41g of ethyl 1-acetyl-5-chloro-2,3-dihydro-1*H*-indole-2-carboximidate monohydrochloride (intermediate 10).

Example A.3

a) Bis (1,1-dimethylethyl)ester dicarbonic acid (0.07615 mol) in DCM (50 ml) was added over 5 minutes to 2,3-dihydro-1*H*-indole-2-methanol (0.07615 mol) in DCM (150 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was concentrated under reduced pressure and submitted to a Kogel Rohr distillation, yielding 11.98 g of 1,1-dimethylethyl 2,3-dihydro-2-(hydroxymethyl)-1*H*-indole-1-carboxylate (intermediate 11).

b) Dess-Martin Reagent (0.011 mol) was added neat over 1 minutes to intermediate (11) (0.010 mol) dissolved in DCM (35 ml). After 15 minutes, the ice bath was removed, and the mixture was allowed to warm to room temperature. More Dess-Martin Reagent (0.33 g) was added, and the mixture was stirred for 30 minutes more. The mixture was re-cooled to 0°C and treated slowly with a partial suspension/solution of $Na_2S_2O_3$ (25 g) which had attempted to dissolve in a saturated aqueous $NaHCO_3$ (100 ml) solution. After 10 minutes, the mixture was removed from ice, and the layers were separated. More DCM was added, and the mixture was filtered. The organic was separated from the filtrate, and the combined organic phases were dried, filtered, concentrated and purified through flash column chromatography (eluent : 10% ethyl acetate: hexane, dissolving the sample in 3:1 ethyl acetate: hexane (5 ml)), yielding 1,1-dimethylethyl 2-formyl-2,3-dihydro-1*H*-indole-1-carboxylate (intermediate 12, mp. 85-87°C).

Example A.4

A solution of 1-acetyl-2,3-dihydro-1*H*-indole-2-carbonitrile (0.00988 mol) and Triethylamine (0.0197 mol) in pyridine (50 ml) was treated with hydrogen sulfide (gas) at room temperature via a bubbler for 2 hours and the resultant saturated reaction mixture was closed and allowed to set for 16 hours. The reaction mixture was poured into 200 ml of an ice water slurry. A voluminous precipitate formed. The mixture was recooled in an ice bath and the precipitate was collected by suction filtration, washed with cold water, and air dried, yielding 1.62 g of 1-acetyl-2,3-dihydro-1*H*-indole-2-carbothioamide (intermediate 13, mp. 194-195°C).

Example A.5

1-acetyl-2,3-dihydro-1*H*-indole-2-carbonitrile (0.0132 mole) was treated with water (54 ml) and the resulting suspension was treated sequentially with Na_2CO_3 (0.00726 mole) and $NH_2OH.HCl$ 0.0145 mole). The mixture was treated with ethanol (26 ml) and heated to 80-90°C. Upon achieving reaction temperature, the mixture was still a suspension. Added another 26 ml of ethanol which afforded a clear solution. The reaction was heated for 2.5 hours and cooled to room temperature with stirring. A voluminous precipitate formed which was collected by suction filtration, washed with cold distilled water, and air dried, yielding 2.23 g of 1-acetyl-2,3-dihydro-*N*'-hydroxy-1*H*-indole-2-carboximidamide (intermediate 14, mp. 204-205°C).

Example A.6

1-acetyl-2-(4-ethyl-1*H*-imidazol-2-yl)-2,3-dihydro-1*H*-indole (0.0035 mol) and HCl, 6N (50 ml) were combined under nitrogen atmosphere. The reaction mixture was heated immediately and the heating was continued for 3.5 hours. The mixture was allowed to cool to room temperature, then extracted with diethylether (2 x 75 ml), cooled to 0°C, alkalized (with cooled 3 N NaOH), then extracted with chloroform (3 x 60 ml). The combined organic layers were dried, filtered and the solvent was evaporated, yielding 0.79 g of 2-(4-ethyl-1*H*-imidazol-2-yl)-2,3-dihydro-1*H*-indole (intermediate 15).

Example A.7

a) To a suspension of 5-fluoro-1*H*-indole-2-carboxylic acid, ethyl ester (0.121 mole) in methanol (600 ml) was added Mg (0.36 mole). The mixture was in a 3-neck round bottom flask under argon at room temperature. The temperature of the reaction was monitored closely. After about 10 minutes, the mixture began to bubble, slowly at first and then more vigorously. The reaction temperature was maintained between 15 and

25°C with intermittent applications of an ice bath. After 30 minutes, the bubbling had slowed. The mixture was allowed to stir at room temperature for three days. The mixture was partitioned between 600 ml of chloroform and 500 ml of saturated NH_4Cl solution. The organic layer was dried over $MgSO_4$ and concentrated to a brown oil. The oil was dissolved in ether and extracted with 3N HCl. The aqueous layer was washed with ether, basified with 3N NaOH, and extracted with chloroform. The extract was dried over $MgSO_4$ and concentrated, yielding 13.91 g of methyl 5-fluoro-2,3-dihydro-1*H*-indole-2-carboxylate (intermediate 16).

b) To 2M NH_3 in methanol (0.6 mol), cooled in an ice bath under Ar, was added intermediate (16) (0.0574 mol) dissolved in methanol (150 ml). The mixture was allowed to warm to room temperature and stir under argon for 6 hours. The reaction was concentrated to 150 ml and filtered. The solid was rinsed with a small amount of cold methanol and allowed to dry, yielding 2.33 g of 5-fluoro-2,3-dihydro-1*H*-indole-2-carboxamide (intermediate 17, mp. 197-199°C).

c) To a mixture of intermediate (17) (0.0094 mole) in DCM (30 ml), cooled in an ice bath under argon, was added triethylamine (0.031 mole) followed by acetyl chloride (0.031 mole). The resulting mixture was allowed to return to room temperature. After stirring for 6 hours, the mixture was cooled in an ice bath and 50 ml of water was added. The mixture was allowed to stir about 20 minutes, was filtered and the solid was allowed to dry to obtain 1.58 g of 1-acetyl-5-fluoro-2,3-dihydro-1*H*-indole-2-carboxamide (intermediate 18, mp. 232-235°C).

d) To a suspension of intermediate (18) (0.0076 mole) in DCM (30 ml), cooled in an ice bath under argon, was added triethylamine (0.0228 mole) followed by trichloroacetyl chloride (0.0115 mole). The mixture was allowed to warm to room temperature and stir for 2 hours. The mixture was washed with water, 2N HCl, and saturated $NaHCO_3$. The organic layer was dried and concentrated. The concentrate was triturated in ether and purified on silica gel column, eluting with 50% ethyl acetate in hexane. The desired fractions were combined and concentrated. The residue was triturated in ether and the solid collected by filtration and allowed to dry, yielding 0.30g of 1-acetyl-5-fluoro-2,3-dihydro-1*H*-indole-2-carbonitrile (intermediate 19, mp. 93-95°C).

e) A solution of intermediate (19) (0.004 mole) and HCl/diethylether (60 mL) was cooled in an ice bath under argon. Ethanol (0.0075 mole) was added. HCl was bubbled into the solution for 50 minutes until the mixture became homogeneous. The mixture was allowed to slowly warm to room temperature and stir for 4 hours. The ether was decanted off and dissolved in methanol. The methanol solution was concentrated in

vacuum and the residue was used as is for the next step, yielding ethyl 1-acetyl-5-fluoro-2,3-dihydro-1*H*-indole-2-carboximidate monohydrochloride (intermediate 20).

Example A.8

a) 2,3-dihydro-5-methoxy-1*H*-indole-2-carboxylic acid methyl ester (0.084 mole) and 2M NH_3 in methanol (500 ml) were combined and stirred at room temperature under argon over the weekend. The solution was concentrated to 100 ml, cooled in an ice bath, and filtered. The solid was rinsed with a small amount of cold methanol and dried.The residue was triturated in methanol/ACN and filtered, yielding 4.56 g of 2,3-dihydro-5-methoxy-1*H*-indole-2-carboxamide (intermediate 21, mp. 228-229°C).

b) Triethylamine (0.0106 mole) then acetyl chloride (0.0106 mole) were added to a solution of intermediate (21) (0.0032 mole) in DCM (40 ml) cooled in an ice bath under argon. The mixture was allowed to slowly warm to room temperature and stir overnight. The mixture was cooled in an ice bath and ice cold water (30 ml) was added. After stirring for 10 minutes, the mixture was filtered, and the solid was allowed to dry overnight. The residue was suspended in 50 ml water. The suspension was allowed to stir for 30 minutes, filtered, and dried overnight, yielding 0.40 g of 1-acetyl-2,3-dihydro-5-methoxy-1*H*-indole-2-carboxamide (intermediate 22, mp. 196-197°C).

c) To a suspension of intermediate (22) (0.022 mole) in DCM (150 ml), cooled in an ice bath under argon, was added triethylamine (0.066 mole) then trichloroacetyl chloride (0.033 mole). The mixture was allowed to slowly warmed to room temperature overnight. The mixture was washed with water, 2N HCl, and saturated $NaHCO_3$. The organic phase was dried, concentrated and triturated in ether and the solid collected, yielding 1-acetyl-2,3-dihydro-5-methoxy-1*H*-indole-2-carbonitrile (intermediate 23, mp. 108-110°C).

d) To a solution of intermediate (23) (0.0154 mole) and ethanol (0.0231 mole) in 1M HCl/diethylether (200 ml), cooled in an ice bath was bubbled HCl (gas) for 60 minutes. The ice bath was maintained for 45 minutes, and the mixture was concentrated at room temperature under vacuum to 200 ml of an oily precipitate. The residue was triturated to a brown solid that became an oil after decanting off the diethylether. The residue was washed with diethylether twice, dissolved in methanol, and used without further purification for further synthesis, yielding ethyl 1-acetyl-2,3-dihydro-5-methoxy-1*H*-indole-2-carboximidate monohydrochloride (intermediate 24).

Example A.9

(S)-2-(Tert-butoxycarbonylamino)butyric acid (0.010 mol) dissolved in DCM (25 ml) was placed in a cooling bath at -10 °C. Pyridine (0.010 mol) was added, followed by

2,4,6-trifluoro-1,3,5-triazine (0.0345 mol). The mixture was stirred under nitrogen. After one hour, ice cold water (75 ml) was added. More DCM (45 ml) was added, and the mixture was shaken. The organic phase was separated, washed with ice cold water again (100 ml), then the organic phase dried, filtered, and concentrated to yield 2.29g of (S)-1,1-dimethylethyl [1-(fluorocarbonyl)propyl]-carbamate (intermediate 25).

Example A.10

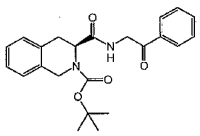
Compound (8) (0.00170 mol) was dissolved in HCl, 6N (20 ml), and immediately warmed in an oil bath at 100°C under nitrogen for 200 minutes. The heat was turned off, and the sample was cooled to 0°C. 3 N NaOH (35 ml) was slowly added. Basification was completed with saturated $NaHCO_3$. The sample was extracted with chloroform. The combined organic phases were dried, filtered, and the resulting solution was used without further purification in further synthesis, yielding (S)-2,3-dihydro-2-(4-propyl-1*H*-imidazol-2-yl)-1*H*-indole (intermediate 5).

Example A.11

A mixture of intermediate (13) (0.00844 mol) in ethanol (180 ml) was treated with 1-bromo-2-butanone (0.0085 mol) in one portion and heated to reflux for 16 hours. The reaction mixture was cooled to room temperature and extracted between ether and cold 1 M NaOH (aqueous). The organic fraction was dried over MgSO4 and concentrated in vacuo to afford a dark solid which was subjected to silica gel flash column chromatography (eluent 100% DCM to 97:3 DCM / diethyl ether), yielding 0.91 g of 2-(4-ethyl-2-thiazolyl)-2,3-dihydro-1*H*-indole (intermediate 4).

Example A.12

3-(2-oxo-2-phenyl-ethylcarbamoyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid tert butyl ester

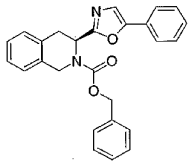


3,4-Dihydro-1*H*-isoquinoline-2,3-dicarboxylic acid-2-tertbutyl ester (2.77 g, 10 mmol) and 2-amino-1phenyl-ethanone (1.71 g, 10 mmol), and HOBT (1-hydroxybenzo-triazole) (2.70 g, 20 mmol) were dissolved in dichloromethane (100 ml). The solution was cooled to 0°C and then (4-dimethylamino-butyl)-ethyl-carbodiimide (2.29 g, 12 mmol) was added followed by NMM (N-methyl-morpholine) (1.31 g, 13 mmol).

The reaction mixture was then warmed to room temperature. After 72 hours the reaction mixture was extracted with water, and the organic phase extracted consecutively with saturated $NaHCO_3$, 2N citric acid and $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to yield the title product as a yellow foam. Liquid chromatography (LC) indicated the compound was 86% pure (214 nm), and was used without further purification.

Example A.12a

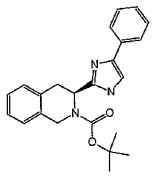
Dehydration of 3-(2-oxo-2-phenyl-ethylcarbamoyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid benzyl ester (prepared in a similar manner as 3-(2-oxo-2-phenyl-ethylcarbamoyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid tert butyl ester of Example A.12) with $POCl_3$ yields the following intermediate compound :



The CBZ group is readily removed from the resulting oxazole by treatment with iodotrimethylsilane. The resulting nor-amine oxazole intermediate can be carried on to compound 170 following similar procedures as described for its analogous imidazole intermediates.

Example A.13

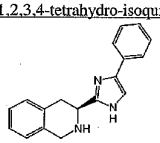
3-(4-phenyl-1H-imidazol-2-yl)-3,4,-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester



The product prepared in Example A.12 above (3.55g, 9mmol), NH_4OAc (ammonium acetate) (20.8g, 270 mmol) and AcOH (acetic acid) (30 mL) were combined at room

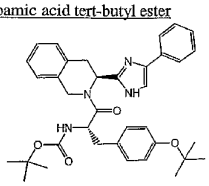
temperature and the reaction mixture was warmed on a steam bath for about 3 hours. The reaction mixture was then cooled to room temperature and poured into an ice slurry mix (400 g). To this mixture was added concentrated ammonium hydroxide (50 mL) and ethyl ether. The layers were separated, and the aqueous phase washed with a second portion of ethyl ether. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a brown foam. This sample was purified by preparative HPLC to yield the purified title compound as a white powder. LC indicated the sample was 96% pure at 214nm.
Measured MW (MH^+): 376

Example A.14
3-(4-phenyl-1H-imidazol-2-yl)-1,2,3,4-tetrahydro-isoquinoline



Triflouroacetic acid (TFA) (4mL) was cooled in a test tube to about 0°C. To the cool solvent was then added the product prepared in Example A.13 (0.75 g, 2 mmol) above. The reaction mixture was allowed to warm to room temperature over about 45 minutes. Excess TFA was removed under a stream of N_2 gas. The residue was partitioned between dichloromethane (15 mL) and saturated $NaHCO_3$. The aqueous phase was then re-extracted with a second portion of dichloromethane and the organic phases combined, dried over $MgSO_4$ and filtered, to yield the title compound in dichloromethane solution. The filtrate was used in the next step (Example A.15) without further purification or isolation.
Measured MW (MH^+): 276

Example A.15
[1-(4-tert-butoxy-benzyl)-2-oxo-2-[3-(4-phenyl-1H-imidazol-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-ethyl]-carbamic acid tert-butyl ester



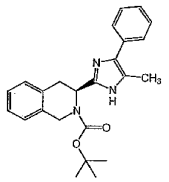
2-Tert-butoxycarbonylamino-3-(4-tert-butoxy-phenyl)-propionic acid (0.74 g, 2.2 mmol) was dissolved in dichloromethane (40 mL) and the reaction mixture cooled to about 0°C. To the solution was then added NMM (0.21 g, 2.1 mmol) followed by isobutyl chloroformate (0.27 g, 2 mmol, 0.26 mL) and the solution was allowed to stand for about 1.25 hours. To the reaction mixture was then added the product prepared in Example A.14 (0.55 g, 2 mmol) and the reaction mixture stirred for about 16 hours. The reaction mixture was then extracted with water, saturated $NaHCO_3$, 2N citric acid, saturated $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to yield the title product as a foam. Measured MW (MH^+): 595.

A bromine can be introduced at the 5-position of the imidazole moiety of this intermediate compound by reacting said intermediate compound with 1 equivalent of Br_2 at 0°C in chloroform.

A chlorine can be introduced at the 5-position of the imidazole moiety of this intermediate compound by reacting said intermediate compound with *N*-chloro-succinimide.

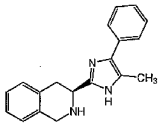
Example A.16

3-(5-methyl-4-phenyl-1H-imidazol-2-yl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester



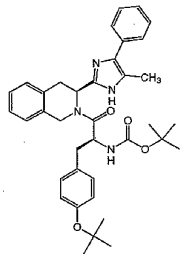
3-Formyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (1.83 g, 7 mmol) was combined with AcOH (25 mL) to which was immediately added 1-phenyl-propane-1,2-dione (3.11 g, 21 mmol) and NH_4OAc (13.49 g, 175 mmol). The reaction mixture was then placed on a steam bath and heated under an argon atmosphere for 20 minutes. The reaction mixture was cooled in an ice bath and then added to an ice slurry (44 g). The resulting mixture was basified by addition of concentrated NH_4OH (50 mL) and then extracted twice with diethyl ether (150 mL each). The combined organic phases were dried over MgSO4, filtered and concentrated to yield crude product. This material was purified by preparative HPLC to yield the title compound as a white solid. Measured MW (MH^+): 390

Example A.17
3-(5-methyl-4-phenyl-1H-imidazol-2-yl)-3,4,-dihydro-1H-isoquinoline



To a solution of TFA (5mL) cooled to about 0°C was added the compound prepared in Example A.16 (1.10 g, 2.82 mmol) and the reaction mixture stirred for about 30 minutes. The reaction mixture was then removed from the ice bath and allowed to warm to room temperature. Excess TFA was removed under a stream of N_2. The residue was partitioned between saturated $NaHCO_3$ and dichloromethane. The aqueous phase was washed with a second portion of dichloromethane and the organic phases combined. The combined organic phase was dried over Na_2SO_4, then filtered to yield the title product as a solution in dichloromethane, which was used without further purification or isolation.

Example A.18
[1-(4-tert-butoxy-benzyl)-2-[3-(5-methyl-4-phenyl-1H-imidazol-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-2-oxo-ethyl]-carbamic acid tert-butyl ester



2-Tert-butoxycarbonylamino-3-(4-tert-butoxy-phenyl)-propionic acid (0.74 g, 2.2 mmol) was dissolved in dichloromethane (60 mL), cooled to about 0°C. To the reaction mixture was then added NMM (0.30 g, 2.97 mmol), followed by isobutyl chloroformate (0.39 g, 2.82 mmol, 0.37 mL). The solution was allowed to stand at 0°C for about 90 minutes. To the reaction mixture was then added the product prepared in

Example A.17 (2.82 mmol) as a solution in dichloromethane. The reaction mixture was then warmed to room temperature. After 16 h the reaction mixture was extracted sequentially with water, saturated $NaHCO_3$, 2N citric acid, saturated $NaHCO_3$, then dried over $MgSO_4$, filtered and concentrated to yield crude product. This material was purified via preparative HPLC to yield the title product as a whitish foam.
Measured MW (MH^+): 609

B. Preparation of the final compounds

Example B.1

4-Methylmorpholine (0.003 mol) was added to intermediate (5) (0.003 mol) dissolved in chloroform (80 ml). After cooling to 0°C, intermediate (25) (0.003 mol) was added neat as an oil. After 27 minutes, the reaction mixture was washed with water, saturated $NaHCO_3$, and brine, dried, filtered, and concentrated, yielding [2S-[1(R*),2R*]]-1,1-dimethylethyl [1-[[2,3-dihydro-2-(4-propyl-1*H*-imidazol-2-yl)-1*H*-indol-1-yl]-carbonyl]propyl]-carbamate (compound 14).

Example B.2

To intermediate (3) (0.047 mole) in methanol (200 ml) was added potassium acetate (0.199 mole). The mixture was heated to reflux under argon. To this was slowly added a solution of 1-amino-2-pentanone hydrochloride (0.094 mole) in methanol (95 ml) over 45 minutes. After the addition was complete, the mixture was allowed to stir overnight at reflux, then concentrated. The concentrate was taken up in DCM and washed with saturated $NaHCO_3$. The aqueous layer was extracted with DCM. The combined organic extracts were dried and concentrated to a solid residue. The residue was purified by trituration with diethyl ether and ACN and optionally further purified by column chromatography, yielding 5.83 g of (S)-1-acetyl-2,3-dihydro-2-(4-propyl-1*H*-imidazol-2-yl)-1*H*-indole (compound 8, mp. 174-175°C).

Example B.3

Intermediate (12) (0.00101 mole), 2-3-hexanedione (0.004 mole), and ammonium acetate (0.025 mole) were combined in acetic acid (4 ml), and immediately placed on a steam bath for 15 minutes. After 2 hours at room temperature, the reaction was poured into ice water (100 ml), basified with 3N NaOH, and extracted with diethylether (twice). The organic phases were combined, dried, filtered, and concentrated. The residue was taken up in diethylether, concentrated and then purified by prep LC, yielding 0.440 g of 1,1-dimethylethyl 2,3-dihydro-2-(5-methyl-4-propyl-1*H*-imidazol-2-yl)- 1*H*-indole-1-carboxylate (compound 99).

Analogously, compound (80) was prepared by reacting intermediate (12) with the respective aldehyde of 1,1,1-trifluoro-3,3-dibromoacetone.

Example B.4

N-[(1,1-dimethylethoxy)carbonyl]-*N*-methyl- L-alanine (0.00181 mol) was dissolved in DCM and cooled to 0°C. Triethylamine (0.00181 mol), then isobutyl chloroformate (0.00181 mol) were added, and the mixture was stirred at 0°C for 70 minutes. Intermediate (5) (0.00181 mol) in DCM (6 ml) was added. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was extracted (water, saturated $NaHCO_3$), dried, filtered, and concentrated. The residue was purified by HPLC. The pure fractions were collected and the solvent was evaporated, yielding 0.380 g of [2S-[1(R*),2R*]]-1,1-dimethylethyl [2-[2,3-dihydro-2-(4-propyl-1*H*-imidazol-2-yl)-1*H*-indol-1-yl]-1-methyl-2-oxoethyl]methyl-carbamate (compound 63, mp. 77-80°C).

Example B.5

Compound 14 (0.0073 mole) and trifluoroacetic acid (5 ml), both precooled in an ice bath, were combined and allowed to slowly return to room temperature under nitrogen. After 1 hour, the mixture was concentrated. The concentrate was dissolved in water and extracted with diethylether. The aqueous layer was basified with saturated $NaHCO_3$ and extracted twice with chloroform. The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was dissolved in ether and treated with 3 ml of 1M HCl in ether. The precipitate was filtered and dried under vacuum. The residue was partitioned between saturated $NaHCO_3$ and chloroform. The organic layer was dried over $MgSO_4$ and concentrated. The concentrate was purified on a Biotage column, eluting with 5% MeOH in chloroform. The residue was dissolved in ether and treated with ±2 ml of 1M HCl in diethyl ether. The solid was collected by filtration under nitrogen and dried under vacuum overnight, yielding 0.364 g of [2S-[1(R*),2R*]]-α-ethyl-2,3-dihydro-β-oxo-2-(4-propyl-1*H*-imidazol-2-yl)-1*H*-indole-1-ethanamine dihydrochloride dihydrate (compound 15, mp. 132-140°C).

Example B.6

A suspension of intermediate (13) (0.0102 mole) in n-butanol (200 ml) was treated with butanoic acid hydazide (0.0254 mole), stirred for 10 minutes, and then heated to reflux for 10 days. The reaction was cooled, concentrated *in vacuo*, distributed between DCM and distilled water. The concentrated organic phase was subjected to reverse phase preparatory column chromatography to give 1-acetyl-2,3-dihydro-2-(5-propyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (compound 91).

Example B.7

a) A solution of the compound 91 (0.42g) in ethanol (25 ml) was treated with an aqueous NaOH solution (3 M, 25 mL) and the reaction mix was refluxed for 24 hours. The reaction was cooled, diluted with ethyl acetate, and treated with cold distilled water. The layers were separated and the aqueous fraction was extracted 5 times with ethyl acetate and the combined organic fractions were dried, concentrated and purified by preparatory column chromatography yielding 2,3-dihydro-2-(5-propyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole.

b) A solution of 2,3-dihydro-2-(5-propyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole (0.00017 mole) in DCM (5 ml) was treated with *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (0.00072 mole) then (2-fluoro-2-oxoethyl)-9*H*-fluoren-9-yl-carbamic acid methyl ester (0.00070 mole). The reaction was stirred at room temperature for 15 hours. The reaction was diluted with DCM, treated twice with saturated $NaHCO_3$, and dried over Na_2SO_4 and concentrated. The residue was subjected to reverse phase prep column chromatography to obtain 0.02 g of the desired mono-adduct and 0.02g of a bis-adduct that was completely converted to the desired mono-adduct by treatment with the prep chromatography eluent (0.1% trifluoroacetic acid in water / acetonitrile). These were combined, yielding 0.03 g of *H*-fluoren-9-ylmethyl [2-[2,3-dihydro-2-(5-propyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl]-2-oxoethyl]-carbamate.

c) A solution of *H*-fluoren-9-ylmethyl [2-[2,3-dihydro-2-(5-propyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indol-1-yl]-2-oxoethyl]-carbamate (0.00006 mole) in DCM (10 ml) was treated with piperidine (0.010 mole) and stirred at room temperature for 1 hour. The completed reaction was concentrated in vacuo and subjected to reverse phase prep column chromatography, yielding 0.02 g of 2,3-dihydro-β-oxo-2-(5-propyl-1*H*-1,2,4-triazol-3-yl)-1*H*-indole-1-ethanamine trifluoroacetate (1:1) (compound 92).

Example B.8

A mixture of intermediate (14) (0.00898 mole) and butanoyl chloride (0.0094 mole) in pyridine (140 ml) was stirred at room temperature for 40 hours and then heated to reflux. After 21 hours the reaction was cooled and concentrated in vacuo. The residue was extracted between DCM and saturated aqueous $NaHCO_3$ and the organic fraction was dried over Na_2SO_4, filtered, and concentrated.The residue was subjected to silica gel flash column chromatography (eluent 100% CH_2Cl_2 to 95/5 CH_2Cl_2 / ether), yielding 1-acetyl-2,3-dihydro-2-(5-propyl-1,2,4-oxadiazol-3-yl)-1*H*-indole (compound 89, mp. 93-94°C).

Example B.9

a) A solution of compound 89 (0.0035 mole) in ethanol (60 ml) was treated with 3M NaOH (60 ml), and the reaction mix was heated to 55 - 60°C for 5.5 hours. The reaction was rapidly cooled in an ice bath, diluted with DCM, and treated with cold distilled water. The layers were separated and the aqueous fraction was extracted three times with DCM. The organic fractions were combined, washed once with 1M NaOH, and dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by prep column chromatography, yielding 0.45g of 2,3-dihydro-2-(5-propyl-1,2,4-oxadiazol-3-yl)-1*H*-indole.

b) A solution of 2,3-dihydro-2-(5-propyl-1,2,4-oxadiazol-3-yl)-1*H*-indole (0.0011 mole) in DCM (10 ml)was treated with *N*-methyl-*N*-(1-methylethyl)-2-propanamine (0.40 mL) then (2-fluoro-2-oxoethyl)-9*H*-fluoren-9-yl carbamic acid methyl ester (0.67 g). The reaction was stirred at room temperature for 40 hours and treated with another portion each of *N*-methyl-*N*-(1-methylethyl)-2-propanamine then (2-fluoro-2-oxoethyl)-9*H*-fluoren-9-yl carbamic acid methyl ester and stirred at room temperature for two days. The reaction was diluted with DCM, treated twice with saturated $NaHCO_3$, and dried over Na_2SO_4. and concentrated. The residue was subjected to reverse phase prep column chromatography, yielding 0.35 g of 9*H*-fluoren-9-ylmethyl [2-[2,3-dihydro-2-(5-propyl-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]-2-oxoethyl]-carbamate.

c) 9*H*-fluoren-9-ylmethyl [2-[2,3-dihydro-2-(5-propyl-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]-2-oxoethyl]-carbamate (0.35 g) was dissolved in DCM (40 ml), treated with piperidine (0.50 ml), and stirred at room temperature for 18 hours. The completed reaction was concentrated *in vacuo* and subjected to reverse phase prep column chromatograph, yielding 0.13 g of 2,3-dihydro-β-oxo-2-(5-propyl-1,2,4-oxadiazol-3-yl)-1*H*-indole-1-ethanamine trifluoroacetate (1:1) (compound 90, mp. 160-162°C).

Example B.10

2,3-dihydro-2-(4-propyl-1*H*-imidazol-2-yl)-1*H*-indole (0.0024 mol) and 1,3-isobenzofurandione (0.0026 mol) were heated to 100°C in a 25 ml pear shaped flask under argon for 2 hours. The mixture was dissolved in methanol and heated to reflux for 15 hours. The reaction mixture was concentrated and taken up in DCM, washed with water and 3 N NaOH. The basic aqueous extract was acidified with 6 N HCl and extracted with DCM. This organic extract was dried over $MgSO_4$ and concentrated. The concentrate was triturated in ether and collected. This was further purified, together with the acidic aqueous solution, by prep liquid chromatography, yielding 0.23 g of 2-[[2-(4-ethyl-1*H*-imidazol-2-yl)-2,3-dihydro-1*H*-indol-1-yl]carbonyl]- benzoic acid trifluoroacetate (1:1) (compound 85, mp. 98-103°C).

Example B.11

1-Isocyanato-2-nitro-benzene (0.002 mol) was added to a solution of intermediate (15) (0.016 mol) in THF (10 ml). The mixture was stirred at room temperature under argon for 5 hours. The mixture was diluted with hexanes, filtered, and allowed to dry, yielding 0.34 g of 2-(4-ethyl-1*H*-imidazol-2-yl)-2,3-dihydro-*N*-(2-nitrophenyl)-1*H*-indole-1-carboxamide (compound 77, mp. 208-209°C).

Example B.12

To a mixture of compound 77 (0.0006 mol), Raney Nickel (0.02 g; 50% slurry in water), and methanol (20 ml) was added hydrazin. Water (0.003 mol). The resulting mixture was heated to reflux for 2 hours. After cooling to room temperature, the mixture was carefully filtered through celite and the filtrate was concentrated. The residue was triturated in ether and filtered. The residue was purified by prep liquid chromatography, yielding 0.24 g of *N*-(2-aminophenyl)-2-(4-ethyl-1*H*-imidazol-2-yl)-2,3-dihydro-1*H*-indole-1-carboxamide trifluoroacetate (1:2) (compound 79, mp. 106-108°C).

Example B.13

A mixture of compound 16 (0.00697 mole) in THF (70 ml) was treated with of sodium hydride (0.007 mole) in one portion and stirred at ambient temperature for 16 hours. Iodomethane (0.0071 mole) was introduced in one portion. After stirring at ambient temperature for 24 hours, more sodium hydride (0.007 mole) was added in one portion under an argon atmosphere. The flask was restoppered after effervescence had subsided, and stirred for 16 hours. The completed reaction was cooled in an ice bath, poured into DCM, and treated with cold water. The layers were separated and the aqueous was extracted three times with DCM. The combined organic fractions were washed with sat $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue was subjected to flash silica gel column chromatography (DCM to ether to 9:1 ether/THF). The appropriate fractions were combined. The residue was taken up in ether and placed in the freezer. Crystallization occurred, yielding 0.55 g (29.3%) of 1-acetyl-2-(4-ethyl-1-methyl-1*H*-imidazol-2-yl)-2,3-dihydro-1*H*-indole (compound 132, mp. 105-106°C). The second set of fractions were combined. The residue was taken up in ether and placed in the freezer. Observed crystallization occurred, yielding 0.38 g of 1-acetyl-2-(4-ethyl-1-methyl-1*H*-imidazol-2-yl)-2,3-dihydro-1*H*-indole (compound 133, mp. 135-137°C).

Example B.14

Compound 80 (0.001 mole) was suspended in 1N NaOH (12 ml). The mixture was vigorously stirred and heated to 88°C under nitrogen for 1 hour. After stirring at room temperature for 3 hours, the mixture was cooled to 0°C, slowly neutralized with 1M HCl to precipitate some solid. The solid was filtered, rinsing with ice cold water. The aqueous phase was extracted twice, dried, filtered, concentrated and dried, yielding 0.140 g of 1,1-dimethylethyl 2-(4-carboxy-1*H*-imidazol-2-yl)-2,3-dihydro-1*H*-indole-1-carboxylate (compound 117).

Example B.15

1-Hydroxybenzotriazole hydrate (0.00036 mole), glycine methylester, hydrochloride (0.00047 mole), 4-methylmorpholine (0.00055 mole), and *N'*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine monohydrochloride (0.00047 mole) were added to compound 117 (0.00036 mole) dissolved in DCM (30 ml) at 0°C. The mixture was allowed to warm to room temperature under nitrogen, and stirred overnight. The mixture was extracted with water, saturated $NaHCO_3$, 2N citric acid, then saturated $NaHCO_3$, dried, filtered, and concentrated, yielding 0.100g (69%) of 1,1-dimethylethyl 2,3-dihydro-2-[4-[[(2-methoxy-2-oxoethyl)amino]carbonyl]-1*H*-imidazol-2-yl]- 1*H*-indole-1-carboxylate (compound 118).

Example B.16

Compound 61 (0.00028 mol) was treated with 3N NaOH (3 ml) and allowed to stir for 20 minutes at room temperature. The solution was then treated with 3 ml of 3 N HCl and extracted with chloroform. The material stayed in the aqueous layer. The aqueous layer was purified by preparative liquid chromatography, yielding 0.12 g of 2-[1-(aminoacetyl)-2,3-dihydro-1*H*-indol-2-yl]-1*H*-benzimidazole-5-carboxylic acid monohydrate trifluoroacetate (1:2) (compound 62, mp. 208-211°C).

Example B.17

Compound 102 (0.00238 mole) was dissolved in 40 ml of methanol and combined with 1N KOH (50 mL). The reaction was warmed to 40°C under argon overnight. The heat was increased to 55-60°C for an additional overnight heating. The reaction was then cooled to room temperature, filtered, and at 0°C slowly neutralized with 1N HCl. The sample was extracted 5 times with DCM, combined, and dried over Na_2SO_4. This organic solution was filtered and used in further synthesis without further purification, yielding 1,1-dimethylethyl 2-(4-carboxy-5-propyl-1*H*-imidazol-2-yl)-2,3-dihydro-1*H*-indole-1-carboxylate (compound 105).

Example B.18

1-Hydroxybenzotriazole hydrate (0.00318 mole) was added to a solution of compound 105 (0.00159 mole) in DCM (160 mL) at room temperture. *N,N'*-methane-tetrayl-biscyclohexanamine (0.00206 mole) was added neat at room temperature. After 60 minutes, NH_3 gas was bubbled in for 5 minutes, and a solid precipitated out. The mixture was allowed to sit over the weekend. The mixture was filtered, and the filtrate was extracted with saturated $NaHCO_3$. The organic phases were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by liquid chromatography, yielding 0.21 g of 1,1-dimethylethyl 2-[4-(aminocarbonyl)-5-propyl-1*H*-imidazol-2-yl]-2,3-dihydro-1*H*-indole-1-carboxylate (compound 106).

Example B.19

1-Hydroxybenzotriazole hydrate (0.00158 mole) was added to a solution of compound 105 (0.00079 mole) in DCM (80 ml). Glycine methylester hydrochloride (0.00103 mole), *N'*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3 propanediamine monohydrochloride (0.00103 mole) and 4-methylmorpholine (0.00103 mole) were added. THF (25 mm) was added. The reaction was stirred at room temperature for 3 days. The mixture was extracted with water. The organic phase was washed with saturated $NaHCO_3$, 2N citric acid, saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated , yielding 0.20 g of 1,1-dimethylethyl 2,3-dihydro-2-[4-[[(2-methoxy-2-oxoethyl)amino]carbonyl]-5-propyl-1*H*-imidazol-2-yl]- 1*H*-indole-1-carboxylate (compound 109).

Example B.20

Compound 81 (0.0005 mole) was suspended in 1N NaOH (6 ml) under argon. The mixture was immediately heated to 80°C for 60 minutes. At room temperature, chloroform (6 ml) then (2-fluoro-2-oxoethyl)-1,1-dimethylethyl carbamic acid ester (0.001 mole) were added. The mixture was stirred overnight. The layers were separated. The aqueous phase was cooled, acidified, and extracted twice with chloroform. The latter organic phases were combined, dried, filtered, and concentrated. The sample was purified by prep HPLC, yielding 0.040 g of 2-[1-[[[(1,1-dimethylethoxy)carbonyl]-amino]acetyl]-2,3-dihydro-1*H*-indol-2-yl]- 1*H*-imidazole-4-carboxylic acid (compound 138).

Example B.21

To compound 145 (0.00097 mole), dissolved in ethanol (5 ml), was added several drops of 21% NaOEt in ethanol. The mixture was allowed to stir at room temperature under argon. An additional 2 drops of 21% NaOEt in ethanol were added after 30 minutes. An additional 2 drops of 21% NaOEt in ethanol were added after 16 hours. After 30

minutes the mixture was concentrated and partitioned between water and DCM. The aqueous layer was washed with additional DCM. The combined organics were washed with water, dried, and concentrated, yielding 0.193g (66%) of [2S-[1(R*),2R*]]-2,3-dihydro-α-methyl-β-oxo-2-(4-propyl-1*H*-imidazol-2-yl)-1*H*-indole-1-ethanol (compound 146).

Compound 148 was prepared analogously starting from compound 147.

Example B.22

To a suspension of compound 58 (0.0019 mole) in acetonitrile (15 ml) was added acetic acid, anhydride (0.074 mole). Stirred at room temperature under argon for 4 hours. An additional 1.0 ml of acetic acid, anhydride was added, and the reaction was stirred overnight. After stirring 6 hours more, the reaction was complete. The mixture was concentrated and the residue partitioned between saturated $NaHCO_3$ and chloroform. The organic layer was dried and concentrated. The residue was purified by column chromatography. The desired fractions were combined, triturated in ether and collected. yielding 0.37g of 1-[[1-[(4-chlorophenyl)acetyl]-4-(3-methoxyphenyl)-4-piperidinyl]methyl]-1,3-dihydro-2*H*-benzimidazol-2-one (compound 149).

Example B.23

A solution of compound 149 (0.0012 mole) and THF (200 ml) was placed inside of a photochemical reactor and irradiated with UV light for 14 hours. The mixture was then allowed to sit at room temperature under nitrogen for 2 days. The mixture was concentrated. The concentrate was purified on Biotage column, eluting with 1:9 THF in DCM, yielding 0.077 g of 1-[2-(1-acetyl-2,3-dihydro-1*H*-indol-2-yl)-5-propyl-1*H*-imidazol-4-yl]-ethanone (compound 150).

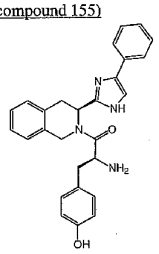
Example B.24

Compound 13 (0.00106 mole) dissolved in 10 ml of THF was treated at room temperature with BH_3.THF (19 ml), which was a solution in THF. The solution was then placed in an oil bath and heated to 60°C overnight. After cooling to 0°C, the solution was carefully treated with 15 ml of 3N HCl. The reaction was then warmed to room temperature and stirred for 4 hours. The mixture was then recooled to 0°C and basified with 12 ml of 3N NaOH, then completion of basification was done with solid Na_2CO_3. The layers were separated and the aqueous was rewashed with chloroform. The organics were combined, a small amount of aqueous separated, and the organic dried over Na_2SO_4. The mixture was filtered, and the filtrate concentrated under reduced pressure. The residue was submitted for preparative liquid chromatography,

yielding 0.33 g of [2S-[1(R*),2R*]]-2-(4-ethyl-1*H*-imidazol-2-yl)-2,3-dihydro-α-methyl-1*H*-indole-1-ethanamine trifluoroacetate (1:1) (compound 127).

Example B.25

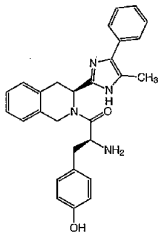
3-amino-4-(4-hydroxy-phenyl)-1-[3-(4-phenyl-1H-imidazol-2-yl)-3,4-dihydro-1-H-isoquinolin-2-yl]-butan-1-one (compound 155)



TFA (4mL) was cooled to about 0°C and then the product prepared in Example A.15 (1.10 g, 1.85 mmol) was added. The reaction mixture sat for about 0.5 hours. Excess TFA was then removed under a stream of N_2 to yield a brown oil. The oil was purified via preparative HPLC to yield the title compound as a white solid.
Measured MW (MH^+): 439

Example B.26

2-amino-3-(4-hydroxy-benzyl)-1-[3-(5-methyl-4-phenyl-imidazol-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-propan-1-one (compound 153)



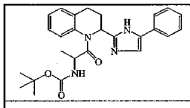
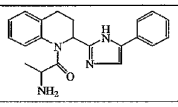
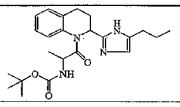
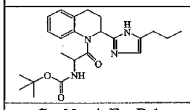
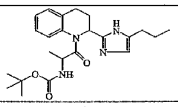
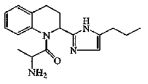
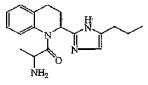
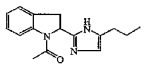
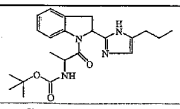
To a solution of TFA (4mL) cooled to about 0°C was added the compound prepared in Example A.18 (0.24 g, 0.4 mmol) and the reaction mixture stirred for about 20 minutes. The reaction mixture was then removed from the ice bath and allowed to warm to room

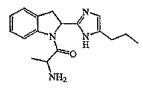
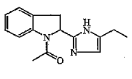
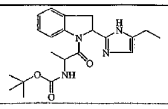
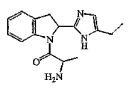
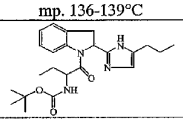
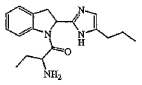
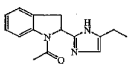
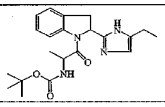
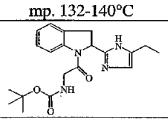
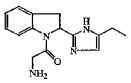
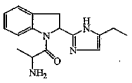
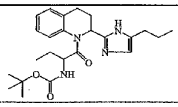
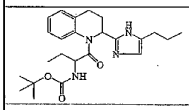
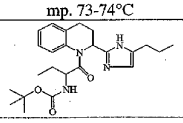
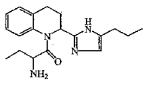
temperature. Excess TFA was removed under a stream of N_2 to yield crude product. This material was purified via preparative HPLC to yield the title compound as a white solid.

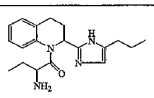
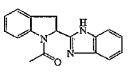
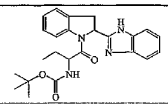
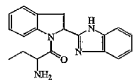
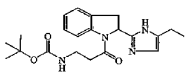
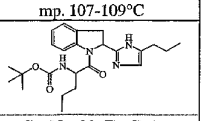
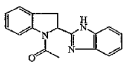
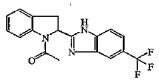
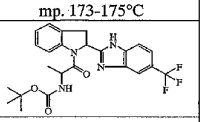
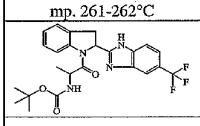
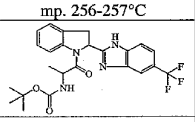
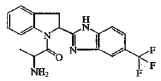
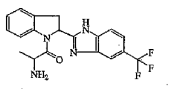
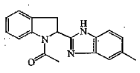
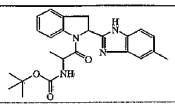
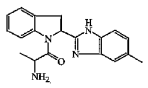
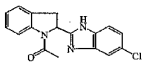
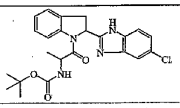
Measured MW (MH^+): 453

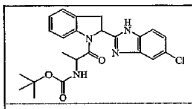
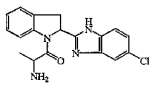
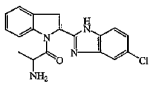
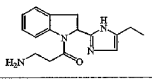
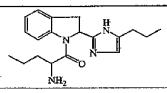
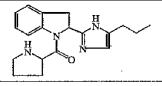
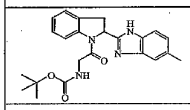
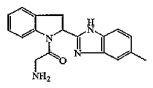
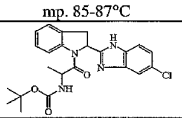
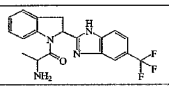
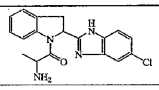
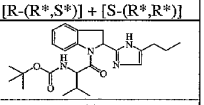
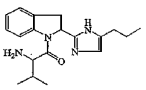
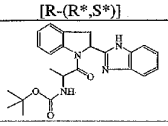
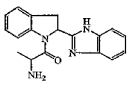
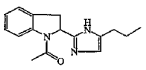
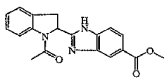
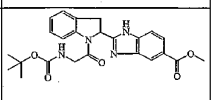
Table F-1 lists the compounds that were prepared according to one of the above Examples. The following abbreviations were used in the tables : $.C_2HF_3O_2$ stands for the trifluoroacetate salt, $.2C_2H_2O_4$ stands for the ethanedioate salt, and $.C_{10}H_8O_3S$ stands for the 2-naphthalenesulfonate salt. Said Table F-1 lists the structure of the compounds, the Example number according to which these compounds have been prepared, the salt form, the stereochemical designation and the melting point (if measured).

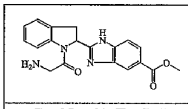
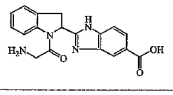
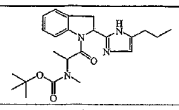
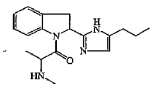
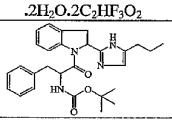
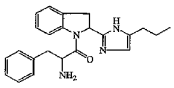
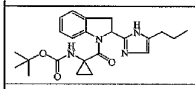
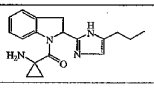
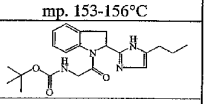
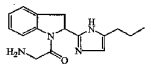
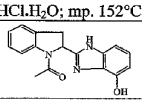
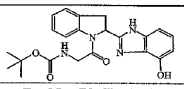
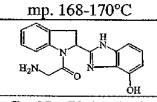
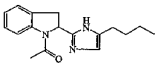
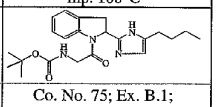
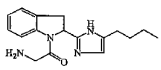
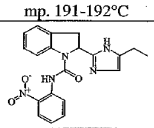
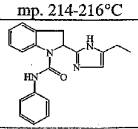
Table F-1

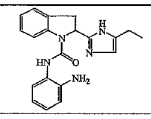
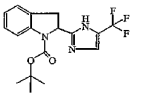
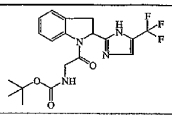
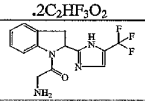
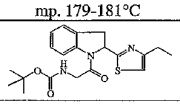
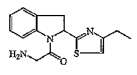
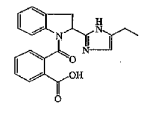
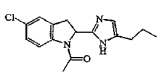
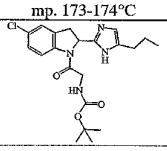
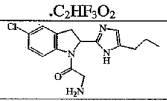
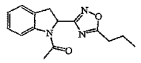
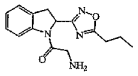
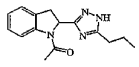
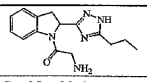
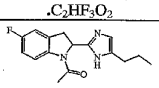
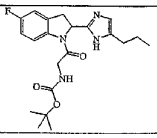
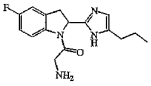
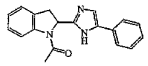
		
Co. No. 1; Ex. B.1	Co. No. 2; Ex. B.5	Co. No. 3; Ex. B.1; [2R-[1(S*),2R*]] + [2S-(1(R*),2R*]]
		
Co. No. 4; Ex. B.1; [1(S),2A]	Co. No. 5; Ex. B.I; [1(S),2B]	Co. No. 6, Ex. B.5; [1(S),2A]
		
Co. No. 7; Ex. B.5; [1(S),2B]	Co. No. 8; Ex. B.2; (S); mp. 174-175°C	Co. No. 9; Ex. B.1; [2S-[1(R*),2R*]]

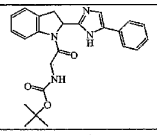
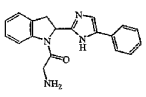
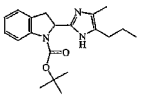
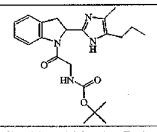
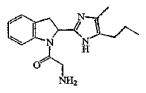
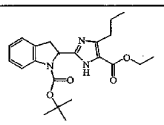
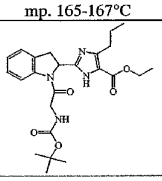
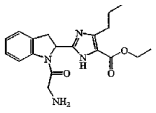
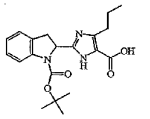
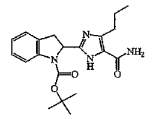
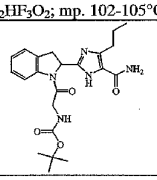
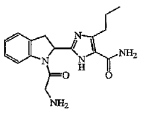
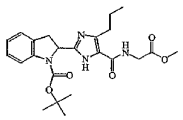
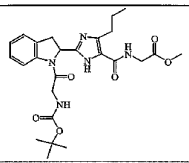
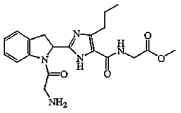
		
Co. No. 10; Ex. B.5; [2S-[1(R*),2R*]]	Co. No. 11; Ex. B.2; (S); mp. 136-139°C	Co. No. 12; Ex. B.1; [2S-[1(R*),2R*]]
		
Co. No. 13; Ex. B.5; [2S-[1(R*),2R*]]; mp. 116-118°C	Co. No. 14; Ex. B.1; [2S-[1(R*),2R*]]	Co. No. 15; Ex. B.5; .2HCl.2H$_2$O [2S-[1(R*),2R*]]; mp. 132-140°C
		
Co. No. 16; Ex. B.2	Co. No. 17; Ex. B.1; [2R-[1(S*),2R*]]; mp. 76-79°C	Co. No. 18; Ex. B.1; mp. 198-199°C
		
Co. No. 19; Ex. B.5; mp. 184-186°C	Co. No. 20; Ex. B.5; .H$_2$O [2R-[1(S*),2R*]]; mp. 73-74°C	Co. No. 21; Ex. B.1; [2R-[1(S*),2R*]] + [2S-[1(R*),2R*]]
		
Co. No. 22; Ex. B.1; [1(S),2A]	Co. No. 23; Ex. B.1; [1(S),2B]	Co. No. 24; Ex. B.5; .2C$_2$H$_2$O$_4$; [1(S),2A]; mp. >90°C

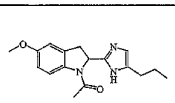
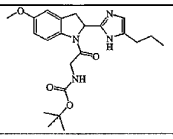
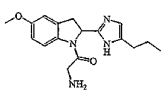
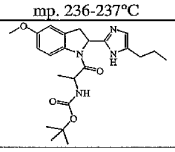
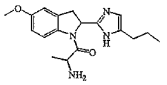
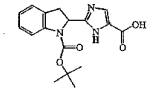
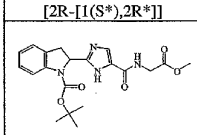
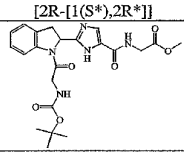
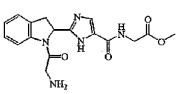
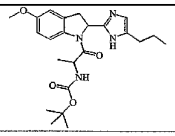
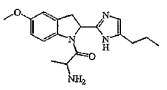
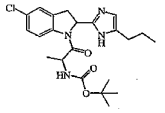
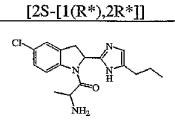
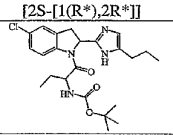
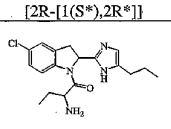
		
Co. No. 25; Ex. B.5; .2HCl.2H$_2$O [1(S),2B]; mp. >100°C	Co. No. 26; Ex. B.2; (S); mp. 208-210°C	Co. No. 27; Ex. B.4; [S-[1(R*),R*]; mp. 107-109°C
		
Co. No. 28; Ex. B.5; .3HCl; [S-[1(R*),R*]; mp. 240-242°C	Co. No.29 ; Ex. B.4; mp. 170-171°C	Co. No. 30; Ex. B.4; .$C_2HF_3O_2$; [S-(R*,R*)]; mp. 173-175°C
		
Co. No. 31; Ex. B.2; mp. 261-262°C	Co. No. 32; Ex. B.2; mp. 256-257°C	Co. No. 33; Ex. B.1; .$C_2HF_3O_2$; [R-(R*,S*)]
		
Co. No. 34; Ex. B.1; .$C_2HF_3O_2$; [S-(R*,R*)]	Co. No. 35; Ex. B.1; .$C_2HF_3O_2$; [R-(R*,S*)] + [S-(R*,R*]]	Co. No. 36; Ex. B.5; .2$C_2HF_3O_2$; [S-(R*R*)]
		
Co. No. 37; Ex. B.5; .2$C_2HF_3O_2$; [R-(R*,S*)] + [S-(R*,R*)]	Co. No. 38; Ex. B.2; mp. 214-216°C	Co. No. 39; Ex. B.1; [1(S)]; mp. 137-138°C
		
Co. No. 40; Ex. B.5; [1(S)]; mp. 198-203°C	Co. No. 41; Ex. B.2; mp. 221-222°C	Co. No. 42; Ex. B.1; .2$C_2HF_3O_2$; [R-(R*,S*)]

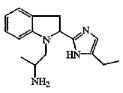
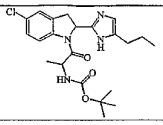
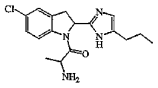
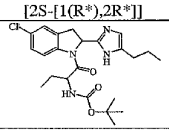
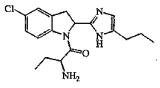
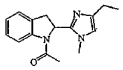
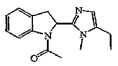
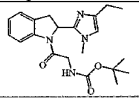
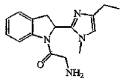
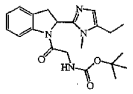
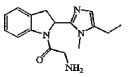
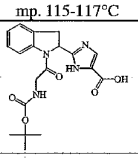
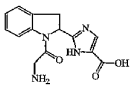
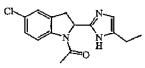
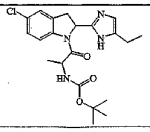
		
Co. No. 43; Ex. B.1; .$C_2HF_3O_2$; [S-(R*,R*)]	Co. No. 44; Ex. B.5; .$3C_2HF_3O_2$; [S-(R*,R*)]	Co. No. 45; Ex. B.5; .$2C_2HF_3O_2$; [R-(R*,S*)] + [S-(R*,R*)]
		
Co. No.46 ; Ex. B.5; mp. 158-160°C	Co. No. 47; Ex. B.5; .$2C_2H_2O_4$; [S-(R*,R*)]; mp. 135-137°C	Co. No. 48; Ex. B.5; .$2HCl.3H_2O$; [S-(R*,R*)]; mp. 85-87°C
		
Co. No. 49; Ex. B.4; .$H_2O.C_2HF_3O_2$; mp.	Co. No. 50; Ex. B.5; mp. 116-118°C	Co. No. 51; Ex. B.1; .$C_2HF_3O_2$; [R-(R*,S*)] + [S-(R*,R*)]
		
Co. No. 52; Ex. B.5; .$2C_2HF_3O_2$; [R-(R*,S*)]	Co. No. 53; Ex. B.5; .$H_2O.2C_2HF_3O_2$; [R-(R*,S*)]	Co. No. 54; Ex. B.4; .$C_2HF_3O_2$; [S-(R*,R*)]; mp. 66-68°C
		
Co. No. 55; Ex. B.5; .$C_{10}H_8O_3S.H_2O$; [S-(R*,R*)]; mp. 195-197°C	Co. No. 56; Ex. B.1; [S-(R*,R*)]; mp. 76-78°C	Co. No. 57; Ex. B.5; [S-(R*,R*)]; mp. 141-143°C
		
Co. No. 58; Ex. B.2; mp. 173-174°C	Co. No. 59; Ex. B.2; mp. 220-222°C	Co. No. 60; Ex. B.1; .H_2O; mp. 183°C

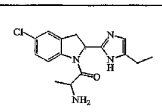
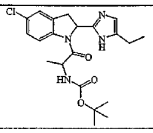
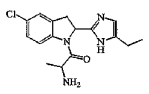
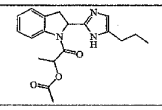
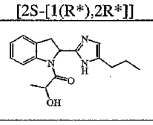
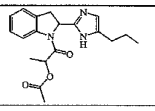
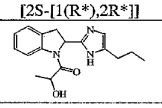
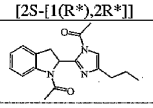
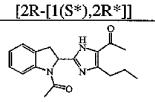
		
Co. No. 61; Ex. B.5; mp. 122°C	Co. No. 62; Ex. B.16; $.2H_2O.2C_2HF_3O_2$	Co. No. 63; Ex. B.4; [S-(R*,R*)]; mp. 77-80°C
		
Co. No. 64; Ex. B.5; [S-(R*,R*)]; mp. 137-138°C	Co. No. 65; Ex. B.1; [2S-[1(R*),2R*]]	Co. No. 66; Ex. B.5; $.C_2H_2O_4.2H_2O$; [2S-[1(R*),2R*]]; mp. 153-156°C
		
Co. No. 67; Ex. B.1; mp. 100-104°C	Co. No. 68; Ex. B.5; $.HCl.H_2O$; mp. 152°C	Co. No. 69; Ex. B.1
		
Co. No. 70; Ex. B.5; $.H_2O$; mp. 168-170°C	Co. No. 71; Ex. B.2; .2KCl; mp. 189-191°C	Co. No. 72; Ex. B.1; mp. 168°C
		
Co. No. 73; Ex. B.5; $.H_2O.2C_2F_3O_2$; mp. >300°C	Co. No. 74; Ex. B.2; mp. 191-192°C	Co. No. 75; Ex. B.1; mp. 214-216°C
		
Co. No. 76; Ex. B.5; mp. 158-160°C	Co. No. 77; Ex. B.11	Co. No. 78; Ex. B.11

		
Co. No. 79; Ex. B.12; .$2C_2HF_3O_2$	Co. No. 80; Ex. B.3; mp. 179-181°C	Co. No. 81; Ex. B.1
		
Co. No. 82; Ex. B.5; mp. 186-188°C	Co. No. 83; Ex. B.1	Co. No. 84; Ex. B.5; .$C_4H_4O_4$; mp. 173-174°C
		
Co. No. 85; Ex. B.10; .$C_2HF_3O_2$	Co. No. 86; Ex. B.2; mp. 225-226°C	Co. No. 87; Ex. B.4;
		
Co. No. 88; Ex. B.5; mp. 193-195°C	Co. No. 89; Ex. B.8	Co. No. 90; Ex. B.9; .$C_2HF_3O_2$
		
Co. No. 91; Ex. B.6; mp.	Co. No. 92; Ex. B.7; .$C_2HF_3O_2$	Co. No. 93; Ex. B.2
		
Co. No. 94; Ex. B.1; .$C_2HF_3O_2$	Co. No. 95; Ex. B.5; .$C_2HF_3O_2$	Co. No. 96; Ex. B.2

		
Co. No. 97; Ex. B.4	Co. No. 98; Ex. B.5; mp. 214-215°C	Co. No. 99; Ex. B.3
		
Co. No. 100; Ex. B.1; mp. 165-167°C	Co. No. 101; Ex. B.5; mp. 197-198°C	Co. No. 102; Ex. B.3
		
Co. No. 103; Ex. B.4	Co. No. 104; Ex. B.5; $.C_2HF_3O_2$; mp. 102-105°C	Co. No. 105; Ex. B.17
		
Co. No. 106; Ex. B.18	Co. No. 107; Ex. B.1	Co. No. 108; Ex. B.5; $.C_2HF_3O_2$; mp. 124-131°C
		
Co. No. 109; Ex. B.19	Co. No. 110; Ex. B.1	Co. No. 111; Ex. B.5; $.C_2HF_3O_2$; mp. 95-99°C

		
Co. No. 112; Ex. B.2; mp. 236-237°C	Co. No. 113; Ex. B.1; mp. 184-188°C	Co. No. 114; Ex. B.5; $.C_2HF_3O_2$
		
Co. No. 115; Ex. B.1; $.C_2HF_3O_2$ [2R-[1(S*),2R*]]	Co. No. 116; Ex. B.5; $.C_2HF_3O_2$ [2R-[1(S*),2R*]]	Co. No. 117; Ex. B.14
		
Co. No. 118; Ex. B.15	Co. No. 119; Ex. B.1	Co. No. 120; Ex. B.5; $.C_2HF_3O_2$
		
Co. No. 121; Ex. B.1; $.C_2HF_3O_2$ [2S-[1(R*),2R*]]	Co. No. 122; Ex. B.5; $.C_2HF_3O_2$ [2S-[1(R*),2R*]]	Co. No. 123; Ex. B.1; $.C_2HF_3O_2$ [2R-[1(S*),2R*]]
		
Co. No. 124; Ex. B.5; $.C_2HF_3O_2$ [2R-[1(S*),2R*]]	Co. No. 125; Ex. B.4; $.C_2HF_3O_2$ [2R-[1(S*),2R*]]	Co. No. 126; Ex. B.5; $.C_2HF_3O_2$ [2R-[1(S*),2R*]]

		
Co. No. 127; Ex. B.24; .$C_2HF_3O_2$; [2S-[1(R*),2R*]]	Co. No. 128; Ex. B.1; .$C_2HF_3O_2$; [2S-[1(R*),2R*]]	Co. No. 129; Ex. B.5; .$C_2HF_3O_2$; [2S-[1(R*),2R*]]
		
Co. No. 130; Ex. B.4; .$C_2HF_3O_2$; [2S-[1(R*),2R*]]	Co. No. 131; Ex. B.5; .HCl [2S-[1(R*),2R*]]; mp. 235-240°C	Co. No. 132; Ex. B.13
		
Co. No. 133; Ex. B.13	Co. No. 134; Ex. B.1	Co. No. 135; Ex. B.5; mp. 115-117°C
		
Co. No. 136; Ex. B.1	Co. No. 137; Ex. B.5; mp. 107-109°C	Co. No. 138; Ex. B.20
		
Co. No. 139; Ex. B.5; .$C_2HF_3O_2$	Co. No. 140; Ex. B.2	Co. No. 141; Ex. B.1; .$C_2HF_3O_2$; [2R-[1(S*),2R*]]

		
Co. No. 142; Ex. B.5; [2R-[1(S*),2R*]]	Co. No. 143; Ex. B.1; .$C_2HF_3O_2$; [2S-[1(R*),2R*]]	Co. No. 144; Ex. B.5; [2S-[1(R*),2R*]]
		
Co. No. 145; Ex. B.1; [2S-[1(R*),2R*]]	Co. No. 146; Ex. B.21; [2S-[1(R*),2R*]]	Co. No. 147; Ex. B.1; [2R-[1(S*),2R*]]
		
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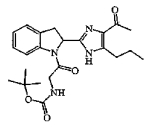	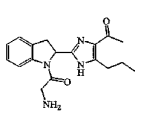	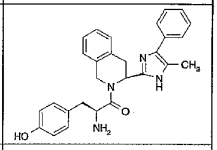
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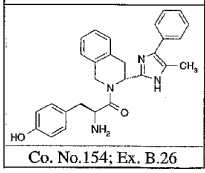	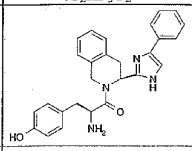	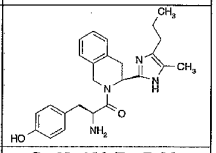
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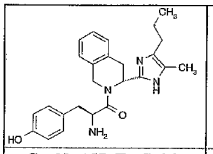	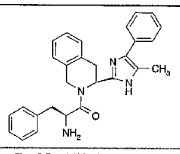	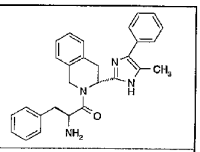
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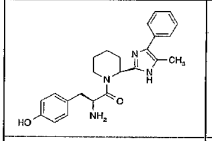	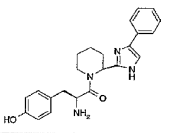	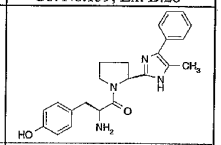
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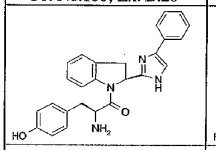	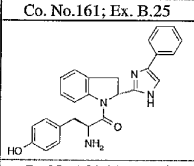	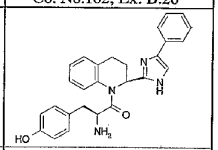
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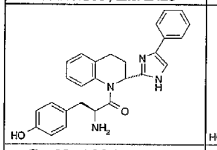	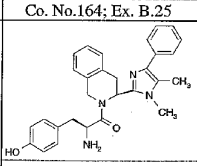	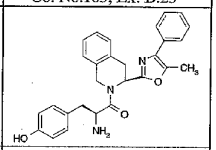
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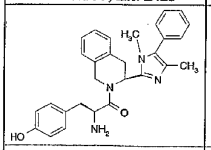	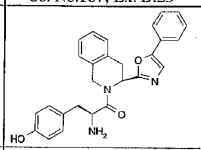	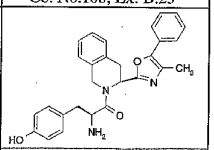
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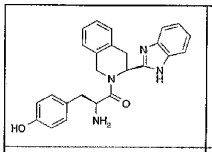	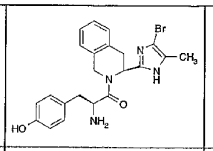	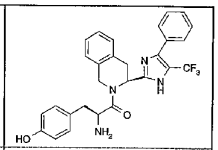
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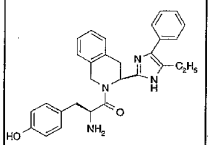	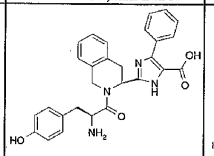	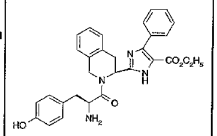
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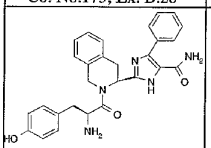	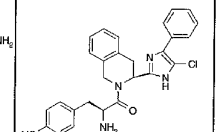	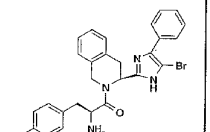
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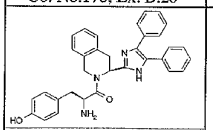
		
Co. No.181; Ex. B.26		

C. Pharmacological examples

C.1. Inhibition of tripeptidyl peptidase II (TPP II)

The inhibition of TPP II was measured using the procedure as described by C. Rose et al. in Nature, 380, 403-409 (1996).

TPPII activity was evaluated using 15 μM AAF-AMC as a substrate in a 50 mM Potassiumphosphate buffer pH 7.5 with 1 mM DTT and 1 mM EGTA. Compounds were added at a final DMSO concentration of 1%. Fluorescence was measured at 405 nm. The potency of the compounds of formula (I) was expressed as the IC_{50} value, *i.e.* the concentration needed to provide 50% inhibition.

Compounds 6, 10, 13, 15, 19, 22, 24, 28, 30, 44, 47, 48, 54, 55, 57, 61, 62, 66, 68, 70, 73, 76, 82, 84, 88, 90, 92, 95, 101, 104, 108, 111, 114, 116, 120, 122, 124, 126, 129, 131, 135, 142, and 144 have an IC_{50} value equal to or lower than 1.10^{-5} M.

C.2 Rat Brain δ-Opioid Receptor Binding Assay

Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, NY) are killed by cervical dislocation, and their brains removed and placed immediately in ice cold Tris HCl buffer (50 mM, pH 7.4). The forebrains are separated from the remainder of the brain by a coronal transection, beginning dorsally at the colliculi and passing ventrally through the midbrain-pontine junction. After dissection, the forebrains are homogenized in Tris buffer in a Teflon®-glass homogenizer. The homogenate is diluted to a concentration of 1 g of forebrain tissue per 100 mL Tris buffer and centrifuged at 39,000 X G for 10 min. The pellet is re-suspended in the same volume of Tris buffer with several brief pulses from a Polytron homogenizer. This particulate preparation is used for the δ-opioid binding assays. Following incubation with the δ-selective peptide ligand [^{3}H]DPDPE at 25°C, the tube contents are filtered through Whatman GF/B filter sheets on a Brandel cell harvester. The tubes and filters are rinsed three times with 4 mL of 10 mM HEPES (pH 7.4), and the radioactivity associated with the filter circles is determined using Formula 989 scintillation fluid (New England Nuclear, Boston, MA) in a scintillation counter.

The data are used to calculate either the % inhibition compared to control binding (when only a single concentration of test compound is evaluated) or a K_i value (when a range of concentrations is tested).

% Inhibition is calculated as follows:

$$\left(1 - \left[\frac{\text{(Test Compound dpm - Non-specific dpm)}}{\text{(Total dpm - Non-specific dpm)}}\right]\right) \text{ X } 100\%$$

K_i value is calculated using the LIGAND (Munson, P.J. and Rodbard, D., Anal. Biochem. 107: 220-239, 1980) data analysis program.

C.3 Rat Brain μ-Opioid Receptor Binding Assay

Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, NY) are killed by cervical dislocation and their brains removed and placed immediately in ice cold Tris HCl buffer (50 mM, pH 7.4). The forebrains are separated from the remainder of the brain by a coronal transection, beginning dorsally at the colliculi and passing ventrally

through the midbrain-pontine junction. After dissection, the forebrains are homogenized in Tris buffer in a Teflon®-glass homogenizer. The homogenate is diluted to a concentration of 1 g of forebrain tissue per 100 mL Tris buffer and centrifuged at 39,000 X G for 10 min. The pellet is re-suspended in the same volume of Tris buffer with several brief pulses from a Polytron homogenizer. This particulate preparation is used for the μ-opioid binding assays. Following incubation with the μ-selective peptide ligand [^{3}H]DAMGO at 25°C, the tube contents are filtered through Whatman GF/B filter sheets on a Brandel cell harvester. The tubes and filters are rinsed three times with 4 mL of 10 mM HEPES (pH 7.4) and the radioactivity associated with the filter circles is determined using Formula 989 scintillation fluid (New England Nuclear, Boston, MA) in a scintillation counter.

The data are used to calculate either the % inhibition compared to control binding (when only a single concentration of test compound is evaluated) or a K_i value (when a range of concentrations is tested).

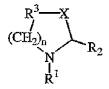
% Inhibition is calculated as follows:

$$\left(1 - \left[\frac{\text{(Test Compound dpm - Non-specific dpm)}}{\text{(Total dpm - Non-specific dpm)}}\right]\right) \text{ X 100\%}$$

K_i value was calculated using the LIGAND (Munson, P.J. and Rodbard, D., Anal. Biochem. 107: 220-239, 1980) data analysis program.

Claims

1. A compound of formula (I)



(I),

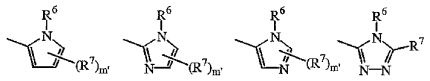
a stereochemically isomeric form thereof, or a pharmaceutically acceptable addition salt thereof, wherein

n is an integer 0 or 1;

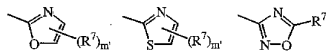
X represents O; S; or -$(CR^4R^5)_m$- wherein m is an integer 1 or 2; R^4 and R^5 are each independently from each other hydrogen or C_{1-4}alkyl;

R^1 is C_{1-6}alkylcarbonyl optionally substituted with hydroxy; C_{1-6}alkyloxycarbonyl; aminoC_{1-6}alkylcarbonyl wherein the C_{1-6}alkyl group is optionally substituted with C_{3-6}cycloalkyl; mono- and di(C_{1-4}alkyl)aminoC_{1-6}alkylcarbonyl; aminocarbonyl substituted with aryl; C_{1-6}alkylcarbonyloxyC_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonylaminoC_{1-6}alkylcarbonyl wherein the amino group is optionally substituted with C_{1-4}alkyl; an amino acid residue bound via the carbonyl group; C_{1-6}alkyl substituted with amino; or arylcarbonyl;

R^2 is a 5-membered heterocycle selected from



(a-1) (a-2) (a-3) (a-4)



(a-5) (a-6) (a-7)

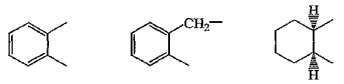
wherein m' is an integer 1 to 2;

R^6 is hydrogen or C_{1-4}alkyl;

R^7 is independently from each other hydrogen; halo; amino; hydroxy; trifluoromethyl; C_{1-6}alkyl; C_{1-4}alkyl substituted with hydroxy, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, amino, or mono- or di(C_{1-4}alkyl)amino; phenyl; aminocarbonyl; hydroxycarbonyl; C_{1-4}alkyloxycarbonyl; C_{1-4}alkylcarbonyl; or C_{1-4}alkyloxycarbonylC_{1-4}alkylaminocarbonyl;

or R^2 is benzimidazole, or benzimidazole substituted with one or two substituents each independently selected from halo, trifluoromethyl, C_{1-4}alkyl, hydroxy, hydroxycarbonyl, or C_{1-4}alkyloxycarbonyl;

R^3 is a bivalent radical $-CH_2CH_2-$ optionally substituted with halo or phenylmethyl; or R^3 is a bivalent radical of formula



(b-1) (b-2) (b-3)

wherein said (b-1), (b-2), or (b-3) optionally can be substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, nitro, amino, cyano, trifluoromethyl, phenyl, or phenyl substituted with one or two subsitutents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, nitro, cyano, and trifluoromethyl;

aryl is phenyl, or phenyl substituted with amino, nitro or hydroxycarbonyl.

2. A compound as claimed in claim 1 wherein n is 0 and R^3 is a radical of formula (b-1) optionally substituted with halo or methoxy.

3. A compound as claimed in claim 1 wherein n is 0, R^3 is a radical of formula (b-1) optionally substituted with halo or methoxy, and X represents $-CH_2-$ or $-CH_2CH_2-$.

4. A compound according to any of the preceding claims wherein (a-2), (a-4), (a-6), or (a-7).

5. A compound according to any of the preceding claims wherein R^1 is C_{1-6}alkylcarbonyl, aminoC_{1-6}alkylcarbonyl or an amino acid.

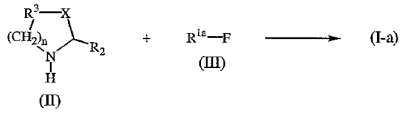
6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound as claimed in any of claims 1 to 5.

7. A process for preparing a pharmaceutical composition as claimed in claim 6 wherein a therapeutically active amount of a compound as claimed in any of claims 1 to 5 is intimately mixed with a pharmaceutically acceptable carrier.

8. A compound as claimed in any of claims 1 to 5 for use as a medicine.

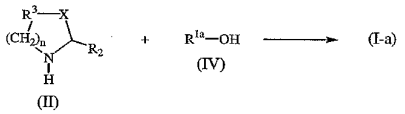
9. A process for preparing a compound of formula (I) wherein

a) an intermediate of formula (II) is reacted with an intermediate of formula (III) in a reaction-inert solvent and, optionally in the presence of a suitable base, thereby yielding compounds of formula (I-a), defined as compounds of formula (I) wherein R^{1a} represents all R^1 substituents other than C_{1-4}alkyl substituted with amino; or



(II) (III) (I-a)

b) an intermediate of formula (II) is reacted with an intermediate of formula (IV), thereby yielding a compound of formula (I-a);



(II) (IV) (I-a)

wherein in the above reaction schemes the radicals R^1, R^2, R^3, and the integer n, are as defined in claim 1;

c) or, compounds of formula (I) are converted into each other following art-known transformation reactions; or if desired; a compound of formula (I) is converted into an acid addition salt, or conversely, an acid addition salt of a compound of formula (I) is converted into a free base form with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

【国際調査報告】

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/12388

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/404 A61K31/422 A61K31/47 C07D403/04 C07D417/04
C07D413/04 C07D233/64 A61P1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, PAJ, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 735 776 A (SYNTHELABO) 27 December 1996 (1996-12-27) *compound No 27, 29, 30 on page 16* page 17, line 34 ---	1-9
A	WO 99 55679 A (TREGA BIOSCIENCES INC) 4 November 1999 (1999-11-04) page 67, last paragraph -page 68, paragraph 1; claim 1 ---	1-9
A	WO 99 33801 A (INST NAT SANTE RECH MED ;SCHWARTZ JEAN CHARLES (FR); ROSE CHRISTIA) 8 July 1999 (1999-07-08) page 1, paragraph 1; claim 1 --- -/--	1-9

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex

* Special categories of cited documents :
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2002	28/06/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Härtinger, S

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/12388

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A	ROSE C ET AL: "CHARACTERIZATION AND INHIBITION OF A CHOLECYSTOKININ-INACTIVATING SERINE PEPTIDASE" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 380, no. 6573, 4 April 1996 (1996-04-04), pages 403-409, XP002068304 ISSN: 0028-0836 page 406, right-hand column -page 407, left-hand column; figure 4 ---	1-9
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/12388

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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X	WIPF P ET AL: "Total Synthesis of (-)-Muscoride A" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 61, 1996, pages 6517-6522, XP002199739 ISSN: 0022-3263 example 8 ---	1,5
X	BORG S ET AL: "SYNTHESIS OF 1,2,4-OXADIAZOLE-, 1,3,4-OXADIAZOLE-, AND 1,2,4-TRIAZOLE-DERIVED DIPEPTIDOMIMETICS" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 60, no. 10, 19 May 1995 (1995-05-19), pages 3112-3120, XP000973994 ISSN: 0022-3263 page 3113, left-hand column; example 7F -----	1,4,5

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
PCT/EP 01/12388

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			EP 1076649	A1	21-02-2001
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			ZA 9205128	A	28-04-1993

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(51)Int.Cl.[7]	FI		テーマコード（参考）
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Ａ６１Ｋ 31/454	Ａ６１Ｋ 31/454		
Ａ６１Ｋ 31/4709	Ａ６１Ｋ 31/4709		
Ａ６１Ｋ 31/4725	Ａ６１Ｋ 31/4725		
Ａ６１Ｐ 1/00	Ａ６１Ｐ 1/00		
Ａ６１Ｐ 3/04	Ａ６１Ｐ 3/04		
Ａ６１Ｐ 25/18	Ａ６１Ｐ 25/18		
Ａ６１Ｐ 43/00	Ａ６１Ｐ 43/00	１１１	
Ｃ０７Ｄ 403/04	Ｃ０７Ｄ 403/04		
Ｃ０７Ｄ 403/14	Ｃ０７Ｄ 403/14		
Ｃ０７Ｄ 413/04	Ｃ０７Ｄ 413/04		
Ｃ０７Ｄ 417/04	Ｃ０７Ｄ 417/04		
// Ｃ０７Ｍ 7:00	Ｃ０７Ｍ 7:00		

(81)指定国 AP(GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZW),EA(AM,AZ,BY,KG,KZ,MD,RU,TJ,TM),EP(AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR),OA(BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG),AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EC,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,PH,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,US,UZ,VN,YU,ZA,ZW

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Ｆターム(参考) 4C063 AA01 AA03 BB01 CC25 CC26 CC41 CC52 CC58 CC62 DD03
DD06 DD10 DD14 DD15 EE01
4C086 AA01 AA02 AA03 AA04 BC38 BC39 BC60 BC69 BC71 BC82
GA07 GA09 GA10 MA01 MA04 NA14 ZA18 ZA66 ZA70 ZC20

【要約の続き】
ルボニル；アミノC_{1-6}アルキルカルボニル［式中、C_{1-6}アルキル基はC_{3-6}シクロアルキルにより場合によっては置換されている］；モノ－およびジ（C_{1-4}アルキル）アミノC_{1-6}アルキルカルボニル；アリールにより置換されているアミノカルボニル；C_{1-6}アルキルカルボニルオキシC_{1-6}アルキルカルボニル；C_{1-6}アルキルオキシカルボニルアミノC_{1-6}アルキルカルボニル［式中、アミノ基はC_{1-4}アルキルにより場合によっては置換されている］；アミノ酸；アミノにより置換されているC_{1-6}アルキル；またはアリールカルボニルであり；R^2は、場合によっては置換されている（５）員の複素環であるか、あるいはR^2は、場合によっては置換されているベンズイミダゾールであり；R^3は、ハロもしくはフェニルメチルにより場合によっては置換されている二価の基－CH_2 CH_2－であるか；あるいはR^3は、式（ＩＩ）の二価の基である。