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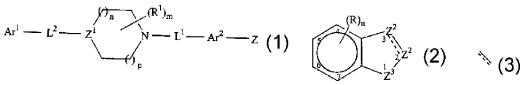
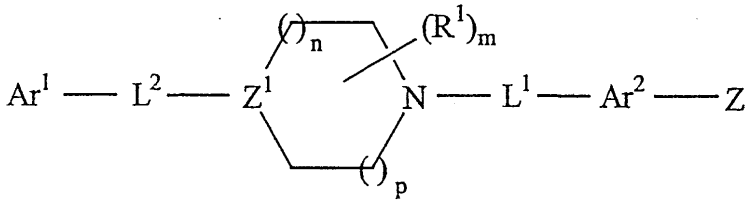
(54)【発明の名称】ｐ３８キナーゼのピペリジン／ピペラジン型阻害剤

(57)【要約】
本発明は、式（Ｉ）の化合物およびその薬学的に許容される塩、又は、その薬学的組成物を使用してｐ３８－αキナーゼを阻害する方法に関し、Ar^1が、０～５個の非妨害性置換基で置換されたアリール基であり、ここで隣接した２つの非妨害性置換基が、縮合した芳香族または非芳香族環を形成し得、L^1およびL^2がリンカーであり、各R^1が、独立して、非妨害性置換基であり、Z^1がCR^2またはNであり、ここでR^2が水素または非妨害性置換基であり、ｍが０～４であり、ｎおよびｐの各々が、０～２の整数であり、ここでｎおよびｐの和が０～３であり、Ar^2が、１つまたはそれ以上の選択的な環構成ヘテロ原子を有する、実質的に平面、単環、または、多環式芳香族部分であって、該部分が、１つまたはそれ以上の選択的な環構成ヘテロ原子で選択的に置換され、該部分が１つまたはそれ以上の非妨害性置換基で選択的に置換され、その２つまたはそれ以上で縮合環を形成し得、Ｚが$-W_i-COX_j$ Ｙであり、ここでＹがCOR^3またはその等配電子体であり、R^3が非妨害性置換基であり、ＷおよびＸの各々が、２～６Åのスペー

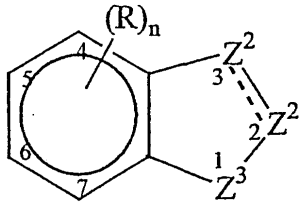

(1)

(2)
(3)

【特許請求の範囲】
【請求項１】
式
【化１】



の化合物およびその薬学的に許容される塩、または、その薬学的組成物であって、
Ａｒ[1]が、０～５個の非妨害性置換基で置換されたアリール基であり、ここで隣接した２つの非妨害性置換基が、縮合した芳香族または非芳香族環を形成し得；
Ｌ[1]およびＬ[2]がリンカーであり；
各Ｒ[1]が、独立して、非妨害性置換基であり；
Ｚ[1]がＣＲ[2]またはＮであり、ここでＲ[2]が水素または非妨害性置換基であり；
ｍが０～４であり；
ｎおよびｐの各々が、０～２の整数であり、ここでｎおよびｐの和が０～３であり；
Ａｒ[2]が、１つまたはそれ以上の選択的な環構成ヘテロ原子を有する、実質的に平面、単環、または、多環式芳香族部分であって、前記部分が、１つまたはそれ以上の非妨害性置換基で選択的に置換されていて、その２つまたはそれ以上で縮合環を形成し得；
Ｚが－Ｗ$_i$－ＣＯＸ$_j$Ｙであり、ここでＹがＣＯＲ[3]またはその等配電子体であり；Ｒ[3]が非妨害性置換基であり、ＷおよびＸの各々が、２～６Åのスペーサーであり、かつ、ｉおよびｊの各々が独立して０または１であり；
ここで、Ｌ[2]に結合したＡｒ[1]の原子とＬ[1]に結合したＡｒ[2]の原子を隔てている化合物内の共有結合の数の最小値が少なくとも６であり、結合の各々の結合距離が１．２Åないし２．０Åであり；および／またはＬ[2]に結合したＡｒ[1]の原子とＬ[1]に結合したＡｒ[2]の原子の間の空間の距離が４．５～２４Åであり；
Ａｒ[2]－Ｚで示される化合物の部分が
【化２】



でないという条件の化合物であって、
ここで

が単結合または二重結合を示し；ｎが０～３であり；１つのＺ[2]がＣＡまたはＣＲＡであり、かつその他のＺ[2]がＣＲ、ＣＲ$_2$、ＮＲまたはＮであり；Ａが－Ｗ$_i$－ＣＯＸ$_j$Ｙであり、ここでＹがＣＯＲまたはその等配電子体であり、ＷおよびＸの各々が２～６Åのスペーサーであり、かつ、ｉおよびｊの各々が独立して０または１であり；Ｚ[3]がＮＲまたはＯであり；各Ｒが独立して、水素または非妨害性置換基である、化合物。
【請求項２】
結合の数の最小値が６～１２である、請求項１に記載の化合物。
【請求項３】
請求項１に記載の化合物であって、ＺがＣＯＸ$_j$ＣＯＲ[3]であり、かつ、
ここでＲ[3]がＨであるか、または、直鎖もしくは分岐鎖アルキル、アルケニル、アルキニ

ル、アリール、アリールアルキル、ヘテロアルキル、ヘテロアリール、またはヘテロアリールアルキルであり、各々ハロ、アルキル、ヘテロアルキル、ＳＲ、ＳＯＲ、SO_2R、SO_2NR_2、ＯＲ、NR_2、ＯＣＯＲ、ＮＲＣＯＲ、$NRCONR_2$、$NRSO_2R$、$NRSO_2NR_2$、$OCONR_2$、ＣＮ、ＣＯＯＲ、$CONR_2$、ＣＯＲ、または、R_3Siで選択的に置換され、ここで各Ｒが独立してＨ、アルキル、アルケニルまたはアリール、または、そのヘテロ原子含有形態であるか、または、
ここでR^3が、ＯＲ、NR_2、ＳＲ、$NRCONR_2$、$OCONR_2$、または、$NRSO_2NR_2$であり、ここで各Ｒが、独立してＨ、アルキル、アルケニルまたはアリール、または、そのヘテロ原子含有形態であり、ここで同じ原子に結合した２つのＲが３～８員を含む炭素環またはヘテロ環を形成し得、かつ、ここで環がアルキル、アルケニル、アルキニル、アリール、アリールアルキル、ヘテロアルキル、ヘテロアリール、ヘテロアリールアルキルで更に置換し得、その各々が、ハロ、ＳＲ、ＯＲ、NR_2、ＯＣＯＲ、ＮＲＣＯＲ、$NRCONR_2$、$NRSO_2R$、$NRSO_2NR_2$、$OCONR_2$、または、R_3Siで選択的に置換され、ここで各Ｒが独立して、Ｈ、アルキル、アルケニルまたはアリール、またはそのヘテロ原子含有形態であり、ここで同じ原子に結合した２つのＲが、前記定義と同様に選択的に置換された３～８員環を形成し得；かつ
Ｘが、存在する場合、CR_2であり、Ｒが前記定義のとおりである、化合物。

【請求項４】
ＹがCOR^3の等配電子体である、請求項１に記載の化合物。

【請求項５】
Ｙがテトラゾール、１，２，３－トリアゾール、１，２，４－トリアゾール、または、イミダゾールである、請求項４に記載の化合物。

【請求項６】
ｉおよびｊの各々が０である、請求項１に記載の化合物。

【請求項７】
ｊが０である、請求項３に記載の化合物。

【請求項８】
請求項１に記載の化合物であって、$-Ar^2-$が、選択的に置換された単環または多環式芳香核からなり、ここで芳香核が、（ｉ）５員ヘテロ環または炭素環、（ｉｉ）６員炭素環またはヘテロ環、（ｉｉｉ）別の５員炭素環またはヘテロ環に縮合した５員炭素環またはヘテロ環、（ｉｖ）別の６員炭素環またはヘテロ環に縮合した６員炭素環またはヘテロ環、および（ｖ）６員炭素環またはヘテロ環に縮合した５員ヘテロ環または炭素環、から選択される炭素環またはヘテロ環からなる、化合物。

【請求項９】
請求項８に記載の化合物であって、Ar^2が、下記の

【化３】


【化４】


【化５】


【化６】


【化７】


【化８】

【化９】

【化１０】

【化１１】

【化１２】

【化１３】

【化１４】

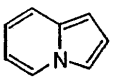
【化１５】

【化１６】

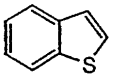
【化１７】

【化１８】

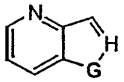
【化１９】



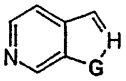
【化２０】



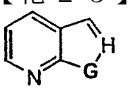
【化２１】



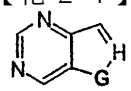
【化２２】



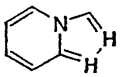
【化２３】



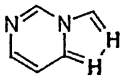
【化２４】



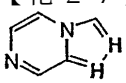
【化２５】



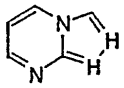
【化２６】



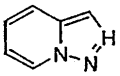
【化２７】



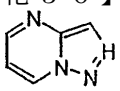
【化２８】



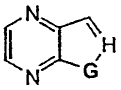
【化２９】



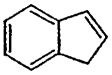
【化３０】



【化３１】



【化３２】



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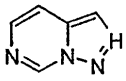

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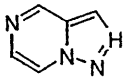
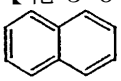


【化３５】

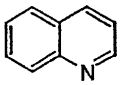
G＝CR_2, NR, O または S

H＝N または CR

【化３６】



【化３７】



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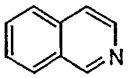

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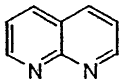

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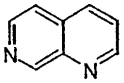
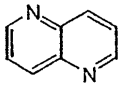
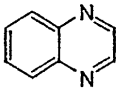


【化４１】



【化４２】



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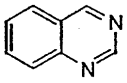

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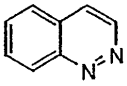
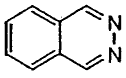
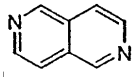
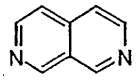
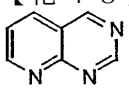


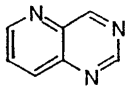
【化４５】

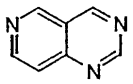


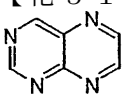
【化４６】

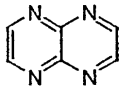


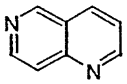
【化４７】

【化４８】


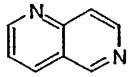
【化４９】


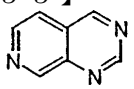
【化５０】


【化５１】


【化５２】


【化５３】


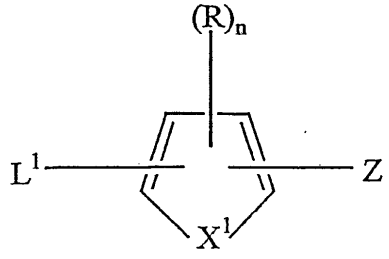
【化５４】


【化５５】
および 

から選択され、Ｒが非妨害性置換基である、化合物。

【請求項１０】

請求項８に記載の化合物であって、Ｌ^{1}－Ａｒ^{2}－Ｚで示される前記化合物の部分が、下記に示す

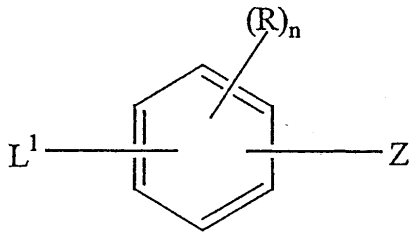
【化５６】


(I)

ここで、ｎが０、１または２であり；Ｘ^{1}がＮＲ、ＣＲ$_{2}$、ＯまたはＳであり；

各Ｒが独立してＨまたは非妨害性置換基であり；かつ、２つまたはそれ以上のＲ基が縮合環を形成し得；

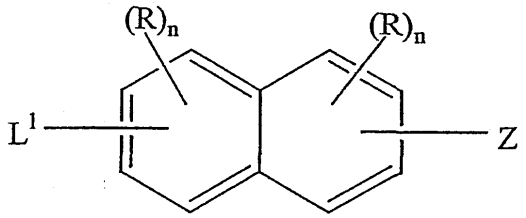
【化５７】



(II)

ここでｎが０～４であり；Ｒが、Ｈまたは非妨害性置換基であり、２つまたはそれ以上のＲ基が、縮合環を形成し得；かつ、環の１つまたはそれ以上の炭素が選択的に窒素に置き換えてもよく；

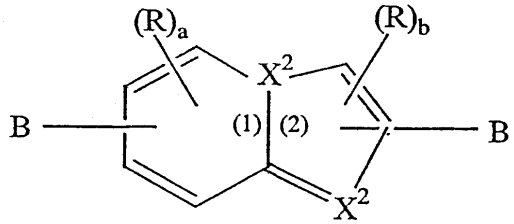
【化５８】



(III)

ここで、各ｎが独立して０ないし３であり；Ｒが、Ｈまたは非妨害性置換基であり、２つまたはそれ以上のＲ基が縮合環を形成し得；かつ、環の１つまたはそれ以上の炭素が選択的に窒素に置き換えてもよく；

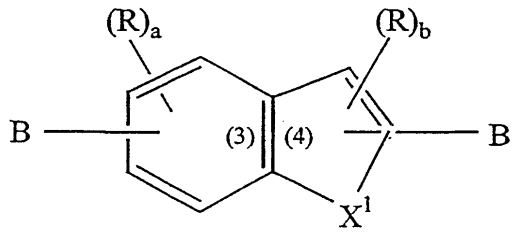
【化５９】



(IV-a)

および

【化６０】

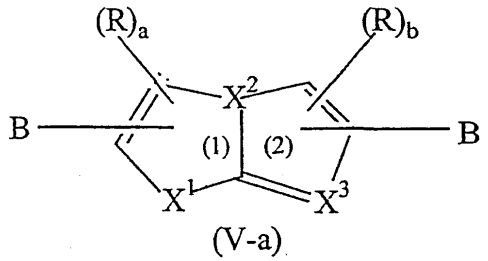


(IV-b)

ここで、請求項１の条件に従い、１つのＢがＬ^{1}であり、かつその他のＢがＺであり；ここでａが０ないし４であるため、６員環（１）および（３）において（Ｒ）$_{a}$が結合する位置が、Ｘ^{2}がＣの場合、Ｘ^{2}を含み得；ｂが０～３であるため、５員環（２）および（４）において（Ｒ）$_{b}$が結合する位置が、Ｘ^{2}がＣであり、Ｘ^{1}がＮまたはＣである場合

、X^2およびX^1を含み得；各X^2が、独立してＮまたはＣＲであり；X^1が、ＮＲ、CR_2、ＯまたはＳであり；各ＲがＨまたは非妨害性置換基であり、２つまたはそれ以上のＲ基が縮合環を形成し得；ここで、X^2またはX^1以外の位置の１つまたはそれ以上の環構成炭素であり、かつＢに結合していないものが、選択的にＮに置換でき；

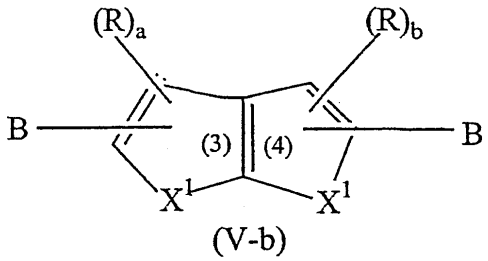
【化６１】



(V-a)

および

【化６２】



(V-b)

ここで、１つのＢがL^1であり、かつ、その他のＢがＺであり；ａが０～４であるため、環（１）および（３）において$(R)_a$が結合し得る位置が、X^2およびX^1を含み、ここで、X^2がＣであり、かつX^1がＣまたはＮであり；ｂが０または３であるため、環（２）および（４）において$(R)_b$が結合し得る位置が、X^1がＣまたはＮ、かつ、X^2および／またはX^3がＣの場合、X^1、X^2およびX^3を含み；各X^1が独立してＮＲ、$C(R)_2$、ＯまたはＳであり；X^2およびX^3が独立してＮまたはＣＲであり；各Ｒが、独立してＨまたは非妨害性置換基であり、２つまたはそれ以上のＲ基が選択的に縮合環を形成し得；ここで、X^1、X^2またはX^3以外の位置にあり、かつ、Ｂに結合していない１つまたはそれ以上の環構成炭素が、選択的にＮに置換し得るものから選択される、化合物。

【請求項１１】

L^1-Ar^2-Zが構造（Ｉ）である、請求項１０に記載の化合物。

【請求項１２】

構造（Ｉ）においてX^1がＮＲである、請求項１１に記載の化合物。

【請求項１３】

構造（Ｉ）においてX^1がＮＨである、請求項１２に記載の化合物。

【請求項１４】

Ｒがメチルである、請求項１３に記載の化合物。

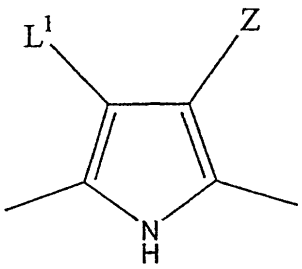
【請求項１５】

ｎが２である、請求項１４に記載の化合物。

【請求項１６】

構造（Ｉ）が

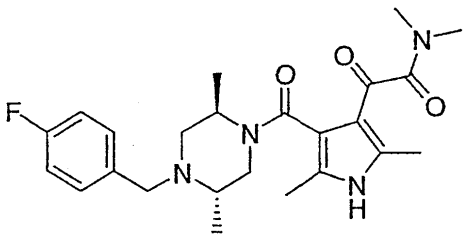
【化６３】



である、請求項１５に記載の化合物。

【請求項１７】

【化６４】



である、請求項１６に記載の化合物。

【請求項１８】

Ｌ^{1}－Ａｒ^{2}－Ｚが構造（ＩＩ）である、請求項１０に記載の化合物。

【請求項１９】

構造（ＩＩ）においてＲがメトキシである、請求項１８に記載の化合物。

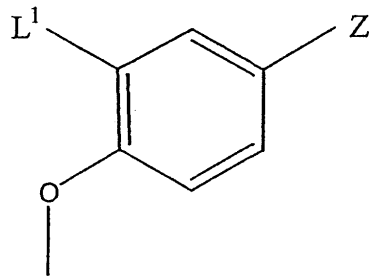
【請求項２０】

構造（ＩＩ）においてｎが１である、請求項１９に記載の化合物。

【請求項２１】

構造（ＩＩ）が

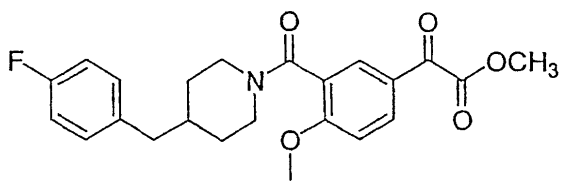
【化６５】



である、請求項２０に記載の化合物。

【請求項２２】

【化６６】



である、請求項２１に記載の化合物。

【請求項２３】

Ｌ^{1}－Ａｒ^{2}－Ｚが構造（ＩＩＩ）である、請求項１０に記載の化合物。

【請求項２４】

L^1-Ar^2-Zが構造（ＩＶ－ａ）または（ＩＶ－ｂ）である、請求項１０に記載の化合物。

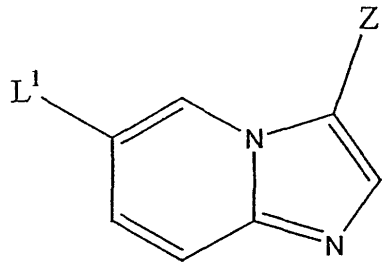
【請求項２５】

L^1-Ar^2-Zが（ＩＶ－ａ）であり、構造（ＩＶ－ａ）の両方のX^2が窒素である、請求項２４に記載の化合物。

【請求項２６】

構造（ＩＶ）が

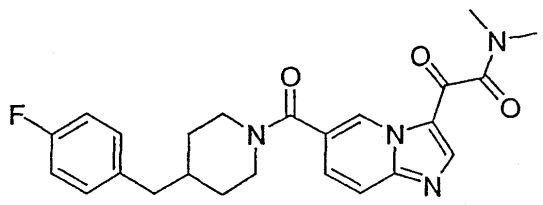
【化６７】



である、請求項２５に記載の化合物。

【請求項２７】

【化６８】



である、請求項２６に記載の化合物。

【請求項２８】

L^1-Ar^2-Zが構造（Ｖ－ａ）または（Ｖ－ｂ）である、請求項８に記載の化合物。

【請求項２９】

L^1-Ar^2-Zが構造（Ｖ－ａ）であり、構造（Ｖ－ａ）においてX^2およびX^3が窒素である、請求項２８に記載の化合物。

【請求項３０】

構造（Ｖ）において少なくとも１つのＲがメチルである、請求項２９に記載の化合物。

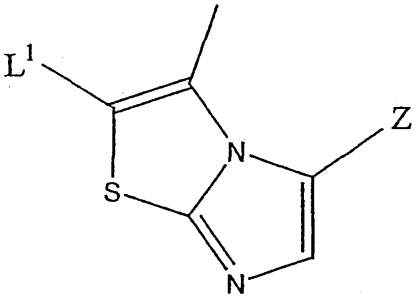
【請求項３１】

構造（Ｖ）においてX^1が硫黄である、請求項２９に記載の化合物。

【請求項３２】

構造（Ｖ）が

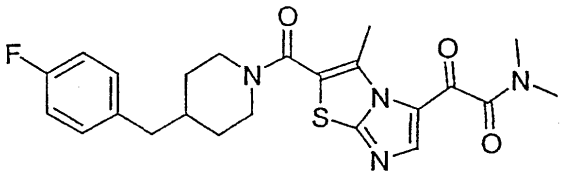
【化６９】



である、請求項３１に記載の化合物。

【請求項３３】

【化７０】



である、請求項３２に記載の化合物。

【請求項３４】

ｎおよびｐの両方が１である、請求項１に記載の化合物。

【請求項３５】

L^1がＣＯ、ＣＨＯＨまたはCH_2である、請求項１に記載の化合物。

【請求項３６】

L^1がＣＯである、請求項３５に記載の化合物。

【請求項３７】

Z^1が窒素である、請求項１に記載の化合物。

【請求項３８】

Z^1がCR^2であり、R^2が、水素、ＯＲ、NR_2、ＳＲまたはハロであり、ここで各Ｒが独立して、水素、アルキル、アルケニルまたはアリール、または、そのヘテロ原子含有形態である、請求項１に記載の化合物。

【請求項３９】

請求項１に記載の化合物であって、L^2がアルキル、アルケニル、アルキニル、アリール、アリールアルキル、アシル、アロイル、ヘテロアリール、ヘテロアルキル、ヘテロアルケニル、ヘテロアルキニル、ヘテロアルキルアリール、ＮＨ－アロイル、ハロ、ＯＲ、NR_2、ＳＲ、ＳＯＲ、SO_2R、ＯＣＯＲ、ＮＲＣＯＲ、$NRCONR_2$、ＮＲＣＯＯＲ、$OCONR_2$、ＲＣＯ、ＣＯＯＲ、アルキル－ＯＯＲ、SO_3R、$CONR_2$、SO_2NR_2、$NRSO_2NR_2$、ＣＮ、CF_3、R_3SiおよびNO_2からなる群より選択される部分で選択的に置換されたアルキレン（１－４Ｃ）またはアルケニレン（１－４Ｃ）であり、ここで各Ｒが独立して、水素、アルキル、アルケニルまたはアリール、またはそのヘテロ形態であり、ここでL^2上の２つの置換基を連結し、０～３個のＯ、Ｓ、及び／又は、Ｎのヘテロ原子を含み、３～８員を含む非芳香族飽和または不飽和環を形成でき、２つの置換基を連結しカルボニル部分又はカルボニル部分のオキシム、オキシムエーテル、オキシムエステル、又は、ケタールを形成できる、化合物。

【請求項４０】

L^2が置換されていないアルキレンである、請求項３９に記載の化合物。

【請求項４１】

L^2が置換されていないメチレン、アルキルで置換されたメチレン、または、－ＣＨ＝である、請求項３９に記載の化合物。

【請求項４２】

請求項１に記載の化合物であって、Ar^1がアルキル、アルケニル、アルキニル、アリール、アリールアルキル、アシル、アロイル、ヘテロアリール、ヘテロアルキル、ヘテロアルケニル、ヘテロアルキニル、ヘテロアルキルアリール、ＮＨ－アロイル、ハロ、ＯＲ、NR_2、ＳＲ、ＳＯＲ、SO_2R、ＯＣＯＲ、ＮＲＣＯＲ、$NRCONR_2$、ＮＲＣＯＯＲ、$OCONR_2$、ＲＣＯ、ＣＯＯＲ、アルキル－ＯＯＲ、SO_3R、$CONR_2$、SO_2NR_2、$NRSO_2NR_2$、ＣＮ、CF_3、R_3SiおよびNO_2からなる群より選択される０～５個の置換基で選択的に置換され、ここで各Ｒが独立して、水素、アルキル、アルケニルまたはアリール、またはそのヘテロ形態であり、かつ、ここで隣接する位置の２つの選択的な置換基が連結されて、３～８員を含み、縮合した、選択的に置換された、芳香族または非芳香族、飽和または不飽和環を形成し得る、化合物。

【請求項４３】

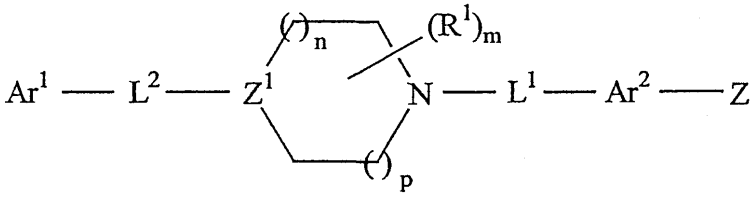
Ar^1が選択的に置換されたフェニルである、請求項４２に記載の化合物。
【請求項４４】
前記選択的な置換がハロ、ＯＲまたはアルキルによるものである、請求項４３に記載の化合物。
【請求項４５】
前記フェニルが置換されていないか、または、１つの置換基を有する、請求項４４に記載の化合物。
【請求項４６】
請求項１に記載の化合物であって、R^1がアルキル、アルケニル、アルキニル、アリール、アリールアルキル、アシル、アロイル、ヘテロアリール、ヘテロアルキル、ヘテロアルケニル、ヘテロアルキニル、ヘテロアルキルアリール、ＮＨ－アロイル、ハロ、ＯＲ、NR_2、ＳＲ、ＳＯＲ、SO_2R、ＯＣＯＲ、ＮＲＣＯＲ、$NRCONR_2$、ＮＲＣＯＯＲ、$OCONR_2$、ＲＣＯ、ＣＯＯＲ、アルキル－ＯＯＲ、SO_3R、$CONR_2$、SO_2NR_2、$NRSO_2NR_2$、ＣＮ、CF_3、R_3SiおよびNO_2からなる群より選択され、ここで各Ｒが独立して、水素、アルキル、アルケニルまたはアリール、またはそのヘテロ形態であり、かつ、ここで隣接する位置の２つのR^4が連結されて、３～８員を含み、縮合した、選択的に置換された、芳香族もしくは非芳香族、飽和または不飽和環を形成し得、またはR^4が＝Ｏ、もしくは、そのオキシム、オキシムエーテル、オキシムエステル、又は、ケタールを形成できる、化合物。
【請求項４７】
R^1がハロ、ＯＲまたはアルキルである、請求項４６に記載の化合物。
【請求項４８】
ｍが０、１、または、２である、請求項４７の化合物。
【請求項４９】
ｍが２であり、両方のR^1がアルキルである、請求項４８に記載の化合物。
【請求項５０】
請求項１０に記載の化合物であって、非妨害性置換基Ｒの各々が、環構成炭素原子に結合している場合、
（ａ）水素、アルキル、アルケニル、アルキニル、アリール、アリールアルキル、アシル、アロイル、ヘテロアリール、ヘテロアルキル、ヘテロアルケニル、ヘテロアルキニル、ヘテロアルキルアリール、ＮＨ－アロイルおよびハロ；または（ｂ）ＯＲ、NR_2、ＳＲ、ＳＯＲ、SO_2R、ＯＣＯＲ、ＮＲＣＯＲ、$NRCONR_2$、ＮＲＣＯＯＲ、$OCONR_2$、ＲＣＯ、ＣＯＯＲ、アルキル－ＯＯＲ、SO_3R、$CONR_2$、SO_2NR_2、$NRSO_2NR_2$、ＣＮ、CF_3、R_3SiおよびNO_2、ここで前記（ｂ）の選択肢のＲの各々が、独立して、水素、アルキル、アルケニルまたはアリール、またはそのヘテロ形態であるものからなる群より選択され、かつ、ここで、２つの非妨害性置換基Ｒが連結されて、３～８員を含み、縮合した、選択的に置換された、芳香族または非芳香族、飽和または不飽和環を形成し得る、化合物。
【請求項５１】
請求項５０に記載の化合物であって、非妨害性置換基Ｒが水素、アルキル、アシル、アリール、アリールアルキル、ヘテロアルキル、ヘテロアリール、ハロ、ＯＲ、NR_2、ＳＲ、ＮＲＣＯＲ、アルキル－ＯＯＲ、ＲＣＯ、ＣＯＯＲ、および、ＣＮからなる群より独立して選択され、ここで各Ｒが独立して、水素、アルキルまたはアリール、または、そのヘテロ形態である、化合物。
【請求項５２】
請求項１０に記載の化合物であって、非妨害性置換基Ｒが、環構成窒素原子に結合している場合、
（ａ）水素、または、アルキル、アルケニル、アルキニル、アリール、アリールアルキル、アシル、アロイル、ヘテロアリール、ヘテロアルキル、ヘテロアルケニル、ヘテロアルキニル、ヘテロアルキルアリール；および

（ｂ）ＳＯＲ、SO_2R、ＲＣＯ、ＣＯＯＲ、アルキル－ＣＯＲ、SO_3R、$CONR_2$、SO_2NR_2、ＣＮ、CF_3、または、R_3Si、ここで前記（ｂ）の選択肢のＲの各々が、独立して、水素、アルキル、アルケニルまたはアリール、またはそのヘテロ形態であるものからなる群より選択される、化合物。

【請求項５３】

増強したｐ３８－α活性により特徴付けられる状態を治療するための薬学的組成物であって、式

【化７１】



の化合物およびその薬学的に許容される塩、または、その薬学的組成物の治療上有効な量を含む組成物であって、

Ar^1が、０～５個の非妨害性置換基で置換されたアリール基であり、ここで隣接した２つの非妨害性置換基が、縮合した芳香族または非芳香族環を形成し得；

L^1およびL^2がリンカーであり；

各R^1が、独立して、非妨害性置換基であり；

Z^1がCR^2またはＮであり、ここでR^2が水素または非妨害性置換基であり；

ｍが０～４であり；

ｎおよびｐの各々が、０～２の整数であり、ここでｎおよびｐの和が０～３であり；

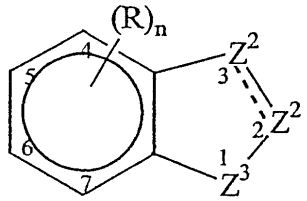
Ar^2が、１つまたはそれ以上の選択的な環構成ヘテロ原子を有する、実質的に平面、単環、または、多環式芳香族部分であって、前記部分が、１つまたはそれ以上の非妨害性置換基で選択的に置換されていて、その２つまたはそれ以上で縮合環を形成し得；

Ｚが$-W_i-COX_j$Ｙであり、ここでＹがCOR^3またはその等配電子体であり；R^3が非妨害性置換基であり、ＷおよびＸの各々が、２～６Åのスペーサーであり、かつ、ｉおよびｊの各々が独立して０または１であり；

ここで、L^2に結合したAr^1の原子とL^1に結合したAr^2の原子を隔てている化合物内の共有結合の数の最小値が少なくとも６であり、結合の各々の結合距離が１．２Åないし２．０Åであり；および／またはL^2に結合したAr^1の原子とL^1に結合したAr^2の原子の間の空間の距離が４．５～２４Åであり；

Ar^2-Zで示される化合物の部分が

【化７２】

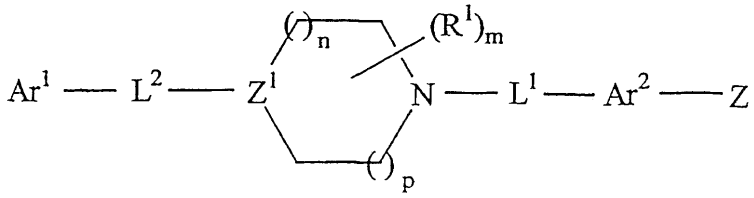


でないという条件の組成物であって、

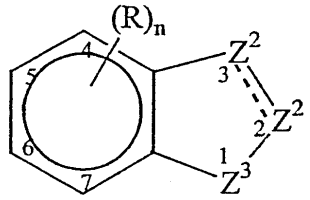
ここで

が単結合または二重結合を示し；ｎが０～３であり；１つのZ^2がCAまたはCRAであり、かつその他のZ^2がCR、CR_2、ＮＲまたはＮであり；Ａが$-W_i-COX_j$Ｙであり、ここでＹがＣＯＲまたはその等配電子体であり、ＷおよびＸの各々が２～６Åのスペーサーであり、かつ、ｉおよびｊの各々が独立して０または１であり；Z^3がＮＲまたはＯであり；各Ｒが独立して、水素または非妨害性置換基である、組成物。

【請求項５４】
結合の数の最小値が６～１２である、請求項５３に記載の薬学的組成物。
【請求項５５】
追加の治療薬を更に含む、請求項５３に記載の組成物。
【請求項５６】
追加の治療薬がコルチコステロイド、モノクローナル抗体、または、細胞分裂の阻害剤である、請求項５５に記載の組成物。
【請求項５７】
ｐ３８－αキナーゼにより媒介される状態を治療するための方法であって、式
【化７３】



の化合物およびその薬学的に許容される塩、または、その薬学的組成物を、このような治療を必要とする被験者に投与する工程を含む方法であって、ここで、
Ar^1が、０～５個の非妨害性置換基で置換されたアリール基であり、ここで隣接した２つの非妨害性置換基が、縮合した芳香族または非芳香族環を形成し得；
L^1およびL^2がリンカーであり；
各R^1が、独立して、非妨害性置換基であり；
Z^1がCR^2またはＮであり、ここでR^2が水素または非妨害性置換基であり；
ｍが０～４であり；
ｎおよびｐの各々が、０～２の整数であり、ここでｎおよびｐの和が０～３であり；
Ar^2が、１つまたはそれ以上の選択的な環構成ヘテロ原子を有する、実質的に平面、単環、または、多環式芳香族部分であって、前記部分が、１つまたはそれ以上の非妨害性置換基で選択的に置換されていて、その２つまたはそれ以上で縮合環を形成し得；
Ｚが$-W_i-COX_j$Ｙであり、ここでＹがCOR^3またはその等配電子体であり；R^3が非妨害性置換基であり、ＷおよびＸの各々が、２～６Åのスペーサーであり、かつ、ｉおよびｊの各々が独立して０または１であり；
ここで、L^2に結合したAr^1の原子とL^1に結合したAr^2の原子を隔てている化合物内の共有結合の数の最小値が少なくとも６であり、結合の各々の結合距離が１．２Åないし２．０Åであり；および／またはL^2に結合したAr^1の原子とL^1に結合したAr^2の原子の間の空間の距離が４．５～２４Åであり；
Ar^2-Zで示される化合物の部分が
【化７４】

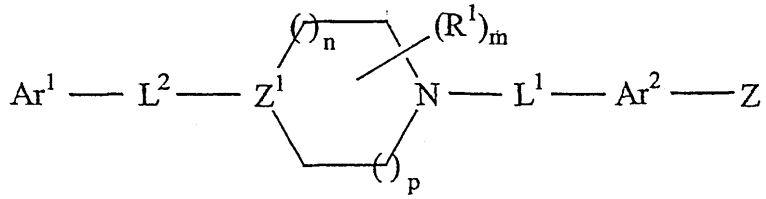


でないという条件の方法であって、
ここで

が単結合または二重結合を示し；ｎが０～３であり；１つのZ^2がＣＡまたはＣＲＡであり、かつその他のZ^2がＣＲ、CR_2、ＮＲまたはＮであり；Ａが$-W_i-COX_j$Ｙであり、ここでＹがＣＯＲまたはその等配電子体であり、ＷおよびＸの各々が２～６Åのス

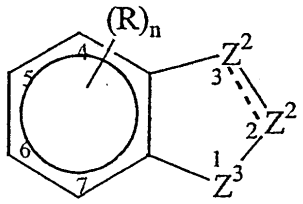
ペーサーであり、かつ、ｉおよびｊの各々が独立して０または１であり；Z^3がＮＲまたはＯであり；各Ｒが独立して、水素または非妨害性置換基である、方法。
【請求項５８】
結合の数の最小値が６～１２である、請求項５７に記載の方法。
【請求項５９】
状態が炎症誘発応答である、請求項５７に記載の方法。
【請求項６０】
炎症誘発応答が多発性硬化症、ＩＢＤ、関節リウマチ、リウマチ様脊椎炎、変形性関節症、痛風性関節炎、その他の関節炎状態、敗血症、敗血性ショック、内毒素性ショック、グラム陰性敗血症、毒素ショック症候群、喘息、成人呼吸窮迫症候群、発作、再灌流傷害、ＣＮＳ障害、乾癬、再狭窄、脳性マラリア、慢性肺炎症疾患、珪肺症、肺サルコーシス、骨吸収疾患、移植片対宿主反応、クローン病、潰瘍性大腸炎、アルツハイマー病、発熱、または、心臓病である、請求項５９に記載の方法。
【発明の詳細な説明】
【０００１】
技術分野
本発明は、ｐ３８－αキナーゼの増強した活性に関連する様々な疾患の治療法に関する。より具体的には、これらの方法において有用なピペリジンおよびピペラジン誘導体に関する。
【０００２】
背景技術
多数の慢性および急性の状態は、炎症反応の撹乱と関連していることが確認されている。ＩＬ－１、ＩＬ－６、ＩＬ－８およびＴＮＦを含む多数のサイトカインがこの応答に関与している。炎症の制御におけるこれらのサイトカインの作用は、ＭＡＰキナーゼファミリーの一員であり一般的にｐ３８として知られるか、もしくは、ＣＳＢＰおよびＲＫとして知られる細胞シグナル伝達経路上の酵素の活性化に少なくとも部分的に依存していると見られる。このキナーゼは、生理化学的負荷による刺激の後、二重リン酸化し、リポ多糖、もしくは、ＩＬ－１およびＴＮＦ等の炎症誘発性（ｐｒｏｉｎｆｌａｍｍａｔｏｒｙ）サイトカインで処理することにより活性化される。従って、ｐ３８のキナーゼ活性の阻害剤は、有用な抗炎症薬である。
【０００３】
繊維増殖状態に関連する眼病としては、増殖性硝子体網膜症を伴う網膜再付着手術、眼内レンズ移植を伴う白内障摘出、緑内障後ドレナージ手術等が挙げられる。
【０００４】
国際公開公報第９８／０６７１５号、国際公開公報第９８／０７４２５号、および、国際公開公報第９６／４０１４３号は、いずれも参照として本明細書に組み入れられ、ｐ３８キナーゼ阻害剤と様々な病態との関係を説明する。これらの本願に記載のとおり、ｐ３８キナーゼの阻害剤は、慢性の炎症に関連する様々な疾患を治療するのに有用である。これらの出願は、関節リウマチ、リウマチ様脊椎炎、変形性関節症、痛風性関節炎およびその他の関節炎状態、敗血症、敗血性ショック、内毒素性ショック、グラム陰性敗血症、毒素ショック症候群、喘息、成人呼吸窮迫症候群、発作、再灌流傷害、神経性外傷および虚血等のＣＮＳ障害、乾癬、再狭窄、脳性マラリア、慢性肺炎症疾患、珪肺症、肺サルコーシス、骨粗鬆症等の骨吸収疾患、移植片対宿主反応、クローン病、炎症性腸疾患（ＩＢＤ）を含む潰瘍性大腸炎、および発熱を列挙する。
【０００５】
上記で引用したＰＣＴ出願は、これらの病態を治療するために有用とされているｐ３８キナーゼ阻害剤である化合物を開示する。これらの化合物は、イミダゾールまたはインドールであり、３位もしくは４位がカルボキサミド結合を介して連結したピペラジン環で置換されている。ピペラジンとインドールの複合物である更なる化合物は、参照として本明細書に組み入れられる国際公開公報第９７／２６２５２号に殺虫剤として記載されている。

【０００６】
ｐ３８－αキナーゼを阻害するアロイル／フェニル置換された特定のピペラジンおよびピペリジンは、２０００年３月９日に公開された国際公開公報第００／１２０７４号に記載されている。更に、この酵素を阻害するインドリル置換されたピペリジンおよびピペラジンは、１９９９年１２月２日に公開された国際公開公報第９９／６１４２６号に記載されている。ｐ３８－α阻害剤としてのピペリジンおよびピペラジンのカルボレン誘導体は、２０００年３月２４日に出願された国際特許出願番号ＰＣＴ／ＵＳ００／０７９３４に記載されている。
【０００７】
ｐ３８－αを特異的に阻害する本明細書に記載のピペラジン誘導体は、前述のいずれの特許にも記載されていない。
【０００８】
発明の概要
本発明は、増加したｐ３８－α活性により特徴付けられる状態を治療する際に有用な方法及び化合物に関する。以下に更に説明するとおり、これらの状態としては、炎症、増殖性疾患、および、心臓血管傷害等、並びに、アルツハイマー病が挙げられる。
【０００９】
本発明の化合物は、ｐ３８キナーゼ、特にα－イソ型を阻害し、従って、特にこれらの活性により媒介される疾患を治療する際に有用である。本発明の化合物は、式（１）
【化７５】



(1)

およびその薬学的に許容される塩、もしくは、その薬学的組成物であって、
ここで、
Ａｒ[1]は、０～５個の非妨害性置換基で置換されたアリール基であり、ここで隣接した２つの非妨害性置換基は、縮合した芳香族または非芳香族環を形成し得；
Ｌ[1]およびＬ[2]はリンカーであり；
各Ｒ[1]は、独立して、非妨害性置換基であり；
Ｚ[1]はＣＲ[2]またはＮであり、ここでＲ[2]は水素または非妨害性置換基であり；
ｍは０～４であり；
ｎおよびｐの各々は、０～２の整数であり、ここでｎおよびｐの和は０～３であり；
Ａｒ[2]は、１つまたはそれ以上の選択的な環構成ヘテロ原子を有する、実質的に平面、単環、または、多環式芳香族部分であって、該部分は、１つまたはそれ以上の非妨害性置換基で選択的に置換されていて、その２つまたはそれ以上で縮合環を形成し得；
Ｚは－Ｗ$_i$－ＣＯＸ$_j$Ｙであり、ここでＹはＣＯＲ[3]またはその等配電子体であり；Ｒ[3]は非妨害性置換基であり、ＷおよびＸの各々は、２～６Åのスペーサーであり、かつ、ｉおよびｊの各々は独立して０または１であり；
ここで、Ｌ[2]に結合したＡｒ[1]の原子とＬ[1]に結合したＡｒ[2]の原子を隔てている化合物内の共有結合の数の最小値が少なくとも６であり、該結合の各々の結合距離が１．２Åないし２．０Åであり；および／またはＬ[2]に結合したＡｒ[1]の原子とＬ[1]に結合したＡｒ[2]の原子の間の空間の距離が４．５～２４Åであり；
Ａｒ[2]－Ｚで示される化合物の部分が
【化７６】



ではないという条件の化合物であって、
ここで

は単結合または二重結合を示し；ｎは０～３であり；１つのＺ^{2}はＣＡまたはＣＲＡであり、かつその他のＺ^{2}はＣＲ、ＣＲ$_{2}$、ＮＲまたはＮであり；Ａは－Ｗ$_{i}$－ＣＯＸ$_{j}$Ｙであり、ここでＹはＣＯＲまたはその等配電子体であり、ＷおよびＸの各々は２～６Åのスペーサーであり、かつ、ｉおよびｊの各々は独立して０または１であり；Ｚ^{3}はＮＲまたはＯであり；各Ｒは独立して、水素または非妨害性置換基である。

【００１０】

更に、本発明は、これらの化合物を使用して炎症または増殖状態を治療する方法に関する。また、本発明は、本発明の化合物を使用して、心不全およびアルツハイマー病に関連する状態を治療することに関する。

【００１１】

詳細な説明

式（１）で表される化合物は、ｐ３８キナーゼ、特にα－イソ型の過度の活性に特徴付けられる状態の治療に有用である。「増加したｐ３８－α活性に特徴付けられる」状態とは、酵素が増加した量存在するか、もしくは、固有の活性が増加するように酵素が改変されているか、または、その両方を含む状態である。従って、「増加した活性」とは、原因に関係無く、これらのタンパク質の効果が望ましくない程高い、如何なる状態も意味する。

【００１２】

本発明の化合物は、ｐ３８－αキナーゼが増加した活性を示す状態において有用である。これらの状態は、線維症および臓器硬化症が炎症、酸化障害、低酸素症、温度変化もしくは細胞外浸透圧の変化、細胞ストレスを引起す状態、アポトーシスもしくは壊死により引き起こされる、もしくは、これらを伴う状態である。これらの状態としては、虚血性再灌流傷害、うっ血性心不全、進行性肺および気管支線維症、肝炎、関節炎、炎症性腸疾患、糸球体硬化症、間質性腎線維症、眼、膀胱および生殖器官の慢性瘢痕疾患、骨髄異形成症、慢性感染症もしくは自己免疫疾患、脊髄損傷、および、外傷もしくは外科的創傷等が挙げられる。当然これらの状態は、ｐ３８－αを阻害する化合物により改善される。本発明の化合物による治療方法を更に以下に説明する。

【００１３】

本発明において有用な化合物は、芳香族部分Ａｒ^{2}に結合した必須の置換基Ｚを含むピペリジン／ピペラジン型化合物の誘導体である。芳香族部分は、１つまたはそれ以上の選択的な環構成ヘテロ原子を有する、実質的に平面、単環、または、多環式芳香族部分である。芳香族部分は、１つまたはそれ以上の非妨害性置換基で選択的に置換し得、該部分の２つまたはそれ以上で縮合環を形成し得る。

【００１４】

より具体的に、芳香族部分Ａｒ^{2}は、選択的に置換された単環または多環式芳香核からなり、ここで芳香核は、（ｉ）５員ヘテロ環または炭素環、（ｉｉ）６員炭素環またはヘテロ環、（ｉｉｉ）別の５員炭素環またはヘテロ環に縮合した５員炭素環またはヘテロ環、（ｉｖ）別の６員炭素環またはヘテロ環に縮合した６員炭素環またはヘテロ環、および（ｖ）６員炭素環またはヘテロ環に縮合した５員ヘテロ環または炭素環から選択される炭素環またはヘテロ環からなる。前記のものとしては、例えば、下記の芳香族部分：

【化７７】

【化７８】

【化７９】

【化８０】

【化８１】

【化８２】

【化８３】

【化８４】

【化８５】

【化８６】

【化８７】

【化８８】

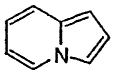
【化８９】

【化９０】

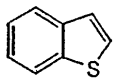
【化９１】

【化９２】

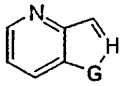
【化９３】



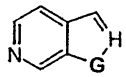
【化９４】



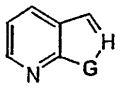
【化９５】



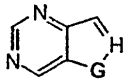
【化９６】



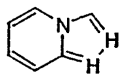
【化９７】



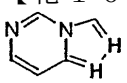
【化９８】



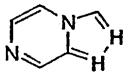
【化９９】



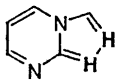
【化１００】



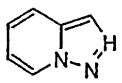
【化１０１】



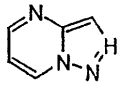
【化１０２】



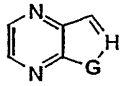
【化１０３】



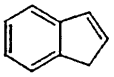
【化１０４】



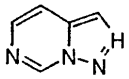
【化１０５】



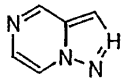
【化１０６】



【化１０７】



【化１０８】

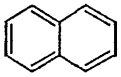


【化１０９】

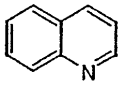
G＝CR_2, NR, O または S

H＝N または CR

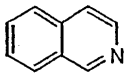
【化１１０】



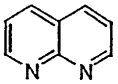
【化１１１】



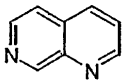
【化１１２】



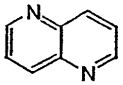
【化１１３】



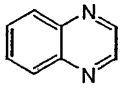
【化１１４】



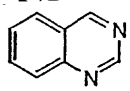
【化１１５】



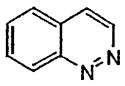
【化１１６】



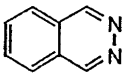
【化１１７】



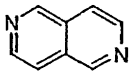
【化１１８】



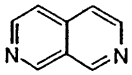
【化１１９】



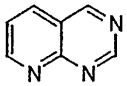
【化１２０】



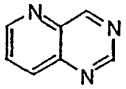
【化１２１】



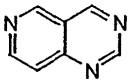
【化１２２】



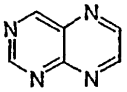
【化１２３】



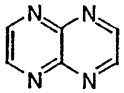
【化１２４】



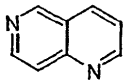
【化１２５】



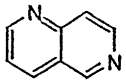
【化１２６】



【化１２７】

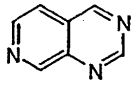


【化１２８】



および

【化１２９】



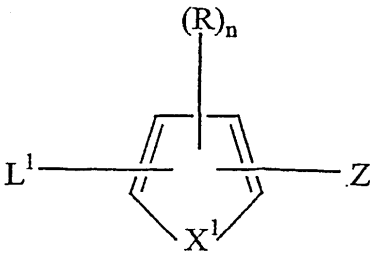
が含まれ、

ここで、Ｒは非妨害性置換基である。

【００１５】

式（１）中のＡｒ^{2}の具体的な例としては、Ｌ^{1}－Ａｒ^{2}－Ｚで示される化合物（１）の部分が下記に示す

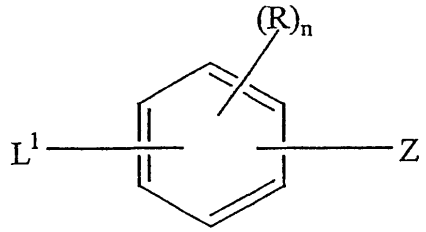
【化１３０】



(I)

ここで、ｎは０、１または２であり；X^1はＮＲ、CR_2、ＯまたはＳであり；かつ、各Ｒは独立してＨまたは非妨害性置換基であり；２つまたはそれ以上のＲ基は縮合環を形成し得；

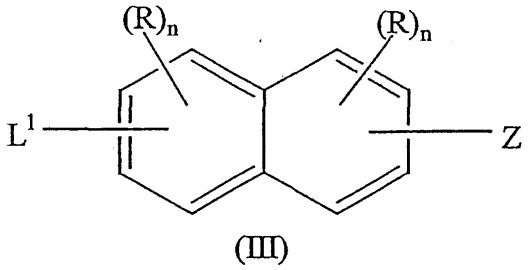
【化１３１】



(II)

ここで、ｎは０～４であり；ＲはＨまたは非妨害性置換基であって、２つまたはそれ以上のＲ基は縮合環を形成し得；かつ、環の１つまたはそれ以上の炭素は選択的に窒素に置換され得；

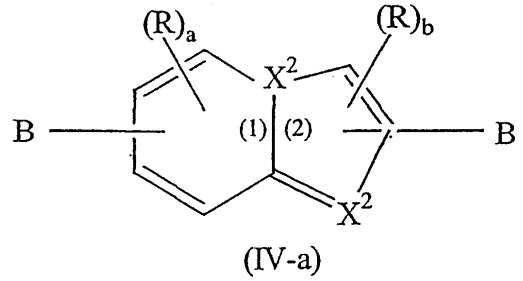
【化１３２】



(III)

ここで、各ｎは独立して０ないし３であり；ＲはＨまたは非妨害性置換基であり、２つまたはそれ以上のＲ基は縮合環を形成し得；かつ、１つまたはそれ以上の環構成炭素は選択的に窒素に置換され得；

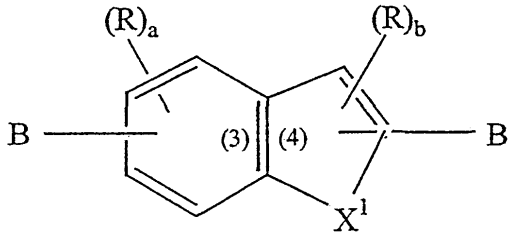
【化１３３】



(IV-a)

および

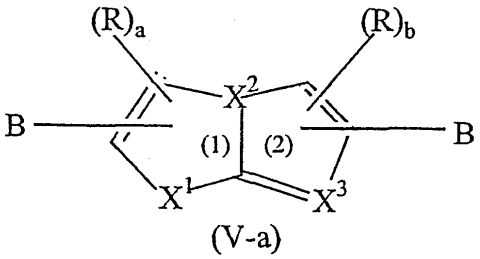
【化１３４】



(IV-b)

ここで、式（１）に対して上記で設定した条件下、１つのＢは、L^1であり、かつ、その他のＢはＺであり；ここで、ａは０ないし４であるため、６員環（１）および（３）において$(R)_a$が結合する位置は、X^2がＣの場合、X^2を含み得；ｂは０～３であるため、５員環（２）および（４）において$(R)_b$が結合する位置は、X^2がＣであり、X^1がＮまたはＣである場合、X^2およびX^1を含み得；各X^2は、独立してＮまたはＣＲであり；X^1は、ＮＲ、CR_2、ＯまたはＳであり；各ＲはＨまたは非妨害性置換基であり、２つまたはそれ以上のＲ基は縮合環を形成し得；ここで、X^2またはX^1以外の位置の１つまたはそれ以上の環構成炭素であり、かつ、Ｂに結合していないものは、選択的にＮに置換でき；

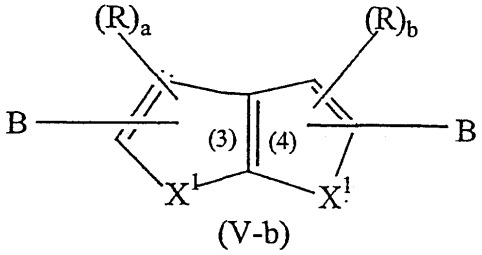
【化１３５】



(V-a)

および

【化１３６】



(V-b)

ここで、１つのＢはL^1であり、かつ、その他のＢはＺであり；ａは０～４であるため、環（１）および（３）において$(R)_a$が結合し得る位置は、X^2およびX^1を含み、ここでX^2はＣであり、かつX^1はＣまたはＮであり；ｂは０または３であるため、環（２）および（４）において$(R)_b$が結合し得る位置は、X^1がＣまたはＮ、かつ、X^2および／またはX^3がＣの場合、X^1、X^2およびX^3を含み；各X^1は独立してＮＲ、$C(R)_2$、ＯまたはＳであり；X^2およびX^3は独立してＮまたはＣＲであり；各Ｒは、独立してＨまたは非妨害性置換基であり、２つまたはそれ以上のＲ基は選択的に縮合環を形成し得；ここで、X^1、X^2またはX^3以外の位置にあり、かつ、Ｂに結合していない１つまたはそれ以上の環構成炭素は、選択的にＮで置換し得るものから選択されるものである。

【００１６】

式Ｉの分子の特定の位置は、「非妨害性置換基」を許容すると記載されている。これらの位置の置換基は一般的に分子全体の本質的な活性に関連していないため、この用語が使用されている。これらの位置には多様な置換基を用いることができ、特定の任意の置換基が

「非妨害性」であるかどうかは、当技術分野において容易に判断できる。

【００１７】

本明細書で用いられる「非妨害性置換基」とは、式（１）の化合物のｐ３８－α活性阻害能力を定性的に損なわれないようにする置換基のことである。従って、該置換基は、ｐ３８－αの阻害の程度を変化し得る。しかしながら、式（１）の化合物がｐ３８－α活性を阻害する能力を保持する限り、置換基は「非妨害性」であると分類される。化合物のｐ３８－α活性を阻害する能力を判定する数々のアッセイ法が当技術分野において使用できる。この評価のための全血アッセイ法を以下に説明する。ｐ３８－αの遺伝子はクローニングされ、タンパク質は組換え技術により調製でき、その活性の評価が可能であり、選択的に選択した化合物のこの活性を妨害する能力の評価も可能である。分子の本質的な特徴はしっかりと定義されている。「非妨害性置換基」により占有されている位置は、当技術分野において一般的な有機部分により置換できる。このような置換の限界を検査することは、本発明には無関係なことである。化合物の本質的な特徴を本明細書に具体的に説明する。

【００１８】

更に、L^1およびL^2は、リンカーとして本明細書に記載されている。このようなリンカーの性質は、これらが分子の部分の間に与える距離ほど重要ではない。典型的なリンカーとしては、アルキレン、即ち、$(CH_2)_n$－Ｒ；アルケニレン、即ち、末端に二重結合を含む二重結合を有するアルキレン部分が挙げられる。その他の適切なリンカーとしては、置換されたアルキレンもしくはアルケニレン、カルボニル部分等が挙げられる。

【００１９】

本明細書で「ヒドロカルビル残基」とは、炭素および水素のみを含む残基を意味する。該残基は、脂肪族もしくは芳香族、直鎖、環状、分岐、飽和、もしくは、不飽和であり得る。しかしながら、ヒドロカルビル残基と記した場合は、置換残基を構成する炭素および水素の他にヘテロ原子を含んでもよい。従って、このようなヘテロ原子が含まれていることが具体的に明記されている場合、ヒドロカルビル残基は、カルボニル基、アミノ基、水酸基等を含んでもよく、もしくは、ヒドロカルビル残基の「主鎖」の中にヘテロ原子を含んでもよい。

【００２０】

本明細書で「無機残基」とは、炭素を含まない残基を意味する。例としては、ハロ、ヒドロキシ、NO_2、もしくはNH_2等が含まれるが、これらに限定されない。

【００２１】

本明細書で「アルキル」、「アルケニル」および「アルキニル」という用語には、直鎖および分枝鎖、並びに、環状で一価の置換基が含まれる。例としては、メチル、エチル、イソブチル、シクロヘキシル、シクロペンチルエチル、２－プロペニル、３－ブチニル等が含まれる。典型的にはアルキル、アルケニル、およびアルキニル置換基は、１～１０個のＣ（アルキル）もしくは２～１０個のＣ（アルケニルもしくはアルキニル）を含む。これらは、好ましくは、１～６個のＣ（アルキル）もしくは２～６個のＣ（アルケニルもしくはアルキニル）を含む。ヘテロアルキル、ヘテロアルケニル、および、ヘテロアルキニルは同様に定義されるが、１～２個のＯ、Ｓ、もしくは、Ｎヘテロ原子、もしくは、それの組合せを主鎖残基の中に含んでもよい。

【００２２】

本明細書で「アシル」とは、カルボニル基を介して追加の残基に結合したアルキル、アルケニル、アルキニル、および、関連するヘテロ形態を意味するものを含む。

【００２３】

Ar^1において「芳香族」とは、フェニルまたはナフチル等の単環または縮合二環系部分であり；「ヘテロ芳香族」は、Ｏ、ＳおよびＮから選択される１つまたはそれ以上のヘテロ原子を含む単環または縮合二環系を意味する。ヘテロ原子が含まれることにより、５員環並びに６員環を含むことも許可される。したがって、典型的な芳香族系としては、ピリジル、ピリミジル、インドリル、ベンズイミダゾリル、ベンゾトリアゾリル、イソキノリ

ル、キノリル、ベンゾチアゾリル、ベンゾフラニル、チエニル、フリル、ピロリル、チアゾリル、オキサゾリル、および、イミダゾリル等が含まれる。環状系全体の電子分布において芳香族性の特徴を有する、いかなる単環または縮合二環系もこの定義に含まれる。環状系は、典型的には、５～１２個の環構成原子を含む。

【００２４】

同様に、「アリールアルキル」および「ヘテロアルキル」とは、置換されていてもよく、飽和していてもよく、典型的には１～６個の炭素を含む炭素鎖を介して他の残基と結合した芳香族系、及び、複素芳香族系を意味する。これらの炭素鎖は、カルボニル基も含んでもよいため、アシル部分等の置換基を提供することが可能となる。

【００２５】

式（１）の化合物が１つまたはそれ以上のキラル中心を含む場合、本発明は、光学的に純粋な形態、並びに、立体異性体もしくは鏡像異性体の混合物を含む。

【００２６】

該化合物のAr^1とAr^2の間の部分において、リンカーL^2とL^1およびピペリジン／ピペラジン環は一緒になって、L^2に結合したAr^1の原子からL^1に結合したAr^2の原子までの間隔を提供し、その距離は、空間中の直線距離の長さとは対照的に、化合物の端から端までの共有結合の結合距離と数の最小値として定義される。より具体的には、L^2に結合したAr^1の原子からL^1に結合したAr^2の原子までを隔てる、化合物の端から端までの結合の数の最小値が少なくとも５であり、好ましくは６ないし１２であり、ここで、これらの結合の各々の長さは、１．２Åないし２．０Åである。空間中の直線距離においては、L^2に結合したAr^1の原子からL^1に結合したAr^2の原子までを測定した空間中の直線距離は４．５Å～２４Åであり、好ましくは６Å～２０Åであり、より好ましくは７．５Å～１０Åである。

【００２７】

典型的なL^1およびL^2の態様は、ＣＯおよびその等配電子体、または、選択的に置換された等配電子体、または、それより長鎖の形態であるが、これらに限定されない。具体的には、L^2は、非妨害性置換基で選択的に置換されたアルキレンもしくはアルケニレンであるか、または、L^1もしくはL^2は、Ｎ、ＳまたはＯ等のヘテロ原子であり得るか、または、ヘテロ原子を含み得る。このような置換基としては、アルキル、アルケニル、アルキニル、アリール、アリールアルキル、アシル、アロイル、ヘテロアリール、ヘテロアルキル、ヘテロアルケニル、ヘテロアルキニル、ヘテロアルキルアリール、ＮＨ－アロイル、ハロ、ＯＲ、NR_2、ＳＲ、ＳＯＲ、SO_2R、ＯＣＯＲ、ＮＲＣＯＲ、$NRCONR_2$、ＮＲＣＯＯＲ、$OCONR_2$、ＲＣＯ、ＣＯＯＲ、アルキル－ＯＯＲ、SO_3R、$CONR_2$、SO_2NR_2、$NRSO_2NR_2$、ＣＮ、CF_3、R_3Si、および、NO_2からなる群より選択される部分を含み、ここで各Ｒは独立してＨ、アルキル、アルケニル、または、アリールもしくはそのヘテロ形態であり、かつ、ここでL^2上の２つの置換基を連結することにより０～３個のＯ、Ｓ、及び／又は、Ｎのヘテロ原子を含み、３～８員を含む非芳香族の飽和または不飽和環を形成できるか、または、２つの置換基を連結しカルボニル部分、又は、該カルボニル部分のオキシム、オキシムエーテル、オキシムエステル又はケタールを形成できるが、これらに限定されない。

【００２８】

ＣＯおよびCH_2の等配電子体としては、ＳＯ、SO_2、もしくは、ＣＨＯＨが含まれる。ＣＯおよびCH_2が好ましい。従って、L^2は０～２個の置換基で置換される。適切な場合、L^2上の２つの選択的な置換基を結合し、０～３個のＯ、Ｓ、及び／もしくは、Ｎ等のヘテロ原子を含み３～８員を含む非芳香族飽和もしくは不飽和ヒドロカルビル環を形成できる。L^2上の２つの選択的な置換基は結合し、カルボニル部分を形成でき、その後それはオキシム、オキシムエーテル、オキシムエステル、もしくは、ケタールに変換できる。

【００２９】

Ar^1は、選択的に置換できるアリール、６～５員の縮合ヘテロアリールを含むヘテロア

リール、環状脂肪族、もしくは、環状複素脂肪族である。Ａｒは、好ましくは、選択的に置換されたフェニルである。

【００３０】

Ａｒ^{1}の各置換基は、独立して、Ｏ、Ｓ、および、Ｎより選択される０～５個のヘテロ原子を含むヒドロカルビル残基（１～２０Ｃ）、もしくは、無機残基である。好ましい置換基としては、アルキル、アルケニル、アルキニル、アリール、アリールアルキル、アシル、アロイル、ヘテロアリール、ヘテロアルキル、ヘテロアルケニル、ヘテロアルキニル、ヘテロアルキルアリール、ＮＨ－アロイル、ハロ、ＯＲ、NR_2、ＳＲ、ＳＯＲ、SO_2R、ＯＣＯＲ、ＮＲＣＯＲ、$NRCONR_2$、ＮＲＣＯＯＲ、$OCONR_2$、ＲＣＯ、ＣＯＯＲ、アルキル－ＯＯＲ、SO_3R、$CONR_2$、SO_2NR_2、$NRSO_2NR_2$、ＣＮ、CF_3、R_3Si、及び、NO_2、からなる群より選択されるものが含まれ、ここで各Ｒは独立して、Ｈ、アルキル、アルケニルもしくはアリール、もしくは、そのヘテロ形態であり、ここで隣接した位置にある２つの選択的な置換基を連結することにより３～８員を含む縮合環、選択的に置換された芳香族もしくは非芳香族、飽和もしくは不飽和環を形成できる。更に好ましい置換基としては、ハロ、アルキル（１～４Ｃ）等であり、より好ましくはフルオロ、クロロ、および、メチルである。これらの置換基は、Ａｒ^{1}のアリール環の全ての可能な位置、好ましくは１つないし２つの位置、最も好ましくは１つの位置を占有し得る。これらの置換基は列挙したものと類似の置換基で選択的に置換し得る。当然いくつかの置換基、例えばハロ等は、当業者に知られているとおり、更に置換されない。

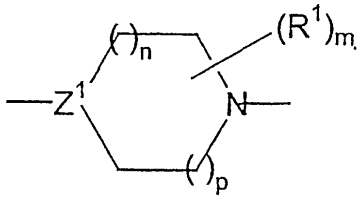
【００３１】

Ａｒ^{1}上の２つの置換基を連結することにより、縮合した、選択的に置換された３～８員を含む芳香族もしくは非芳香族環、飽和もしくは不飽和環を形成できる。

【００３２】

Ｌ^{1}およびＬ^{2}の間には下記の式で表されるピペリジン型部分が存在する。

【化１３７】



ここでＺ^{1}はＣＲ^{2}またはＮであり、Ｒ^{2}はＨまたは非妨害性置換基である。ｎおよびｐは各々、０～２の整数であり、ここでｎおよびｐの和は、０～３である。非妨害性置換基Ｒ^{2}としては、ハロ、アルキル、アルコキシ、アリール、アリールアルキル、アリールオキシ、ヘテロアリール、アシル、カルボキシ、または、ヒドロキシが含まれるが、これらに限定されない。Ｒ^{2}は、好ましくは、Ｈ、アルキル、ＯＲ、NR_2、ＳＲ、または、ハロであり、ここでＲは、Ｈまたはアルキルである。更に、Ｒ^{2}は、Ｒ^{1}置換基と結合して、Ｏ、Ｎおよび／またはＳ等の０～３個のヘテロ原子および３～８員を含む、選択的に置換された非芳香族飽和または不飽和ヒドロカルビル環を形成し得る。好ましい態様は、Ｚ^{1}がＣＨまたはＮであり、ｎおよびｐの両方が１である化合物を含む。

【００３３】

Ｒ^{1}は、Ｏ、ＳおよびＮより選択される０～５個のヘテロ原子を含むヒドロカルビル残基（１～２０Ｃ）等の非妨害性置換基を表す。Ｒ^{1}は、好ましくは、アルキル、アルコキシ、アリール、アリールアルキル、アリールオキシ、ヘテロアルキル、ヘテロアリール、ヘテロアリールアルキル、ＲＣＯ、＝Ｏ、アシル、ハロ、ＣＮ、ＯＲ、ＮＲＣＯＲ、ＮＲであり、ここでＲはＨ、アルキル（好ましくは１～４Ｃ）、アリール、もしくは、そのヘテロ形態である。適当な置換基の各々は、それ自身も１～３個の置換基で置換されていてもよい。置換基は、好ましくは独立して、アルキル、アルケニル、アルキニル、アリール、アリールアルキル、アシル、アロイル、ヘテロアリール、ヘテロアルキル、ヘテロアルケ

ニル、ヘテロアルキニル、ヘテロアルキルアリール、ＮＨ－アロイル、ハロ、ＯＲ、NR_2、ＳＲ、ＳＯＲ、SO_2R、ＯＣＯＲ、ＮＲＣＯＲ、$NRCONR_2$、ＮＲＣＯＯＲ、$OCONR_2$、ＲＣＯ、ＣＯＯＲ、アルキル－ＯＯＲ、SO_3R、$CONR_2$、SO_2NR_2、$NRSO_2NR_2$、ＣＮ、CF_3、R_3Si、及び、NO_2からなる群より選択され、ここで各Ｒは、独立して、Ｈ、アルキル、アルケニルもしくはアリール、もしくは、そのヘテロ形態であり、隣接した位置の２つのR^1を連結することにより縮合し、選択的に置換された３～８員を含む芳香族もしくは非芳香族環、飽和もしくは不飽和環を形成でき、または、R^1は＝Ｏ、もしくは、そのオキシム、オキシムエーテル、オキシムエステル、もしくは、ケタールである。R^1は環にｍ個存在してもよく、ｍは０～４の整数である。R^1の好ましい態様としては、アルキル（１～４Ｃ）特に２つのアルキル置換基およびカルボニルを含む。最も好ましくは、R^1は、ピペリジニルもしくはピペラジニル環の２位および５位、もしくは、３位および６位に２つのメチル基、もしくは、＝Ｏを好ましくは環の５位に含む。置換された形態は、キラルであってもよく、単離された鏡像異性体が好まれ得る。

【００３４】

Ｚは－W_i－ＣＯX_jＹであり、ここでＹはＣＯR^3またはその等配電子体であり、R^3は非妨害性置換基である。ＷおよびＸの各々は、スペーサーであり、例えば、選択的に置換されたアルキル、アルケニル、または、アルキニルであり、ｉおよびｊの各々は、０または１である。ＷおよびＸは、好ましくは、置換されていない。好ましくは、ｊは０であることにより２つのカルボニル基は互いに隣接する。更に、好ましくは、ｉは０であることにより、近傍のＣＯが環に隣接する。しかしながら、隣接するＣＯが環から距離をおいた位置にある化合物は、初めはグリオキサル置換されているAr^2を選択的に還元することにより容易に調製できる。

【００３５】

R^3がＨ以外である場合にR^3で表される非妨害性置換基は、Ｏ、Ｓ、及び／もしくは、Ｎより選択される０～５個のヘテロ原子を含むヒドロカルビル残基（１～２０Ｃ）であるか、もしくは無機残基である。好ましい態様においてR^3は、Ｈ、もしくは、直鎖もしくは分岐鎖のアルキル、アルケニル、アルキニル、アリール、アリールアルキル、ヘテロアルキル、ヘテロアリール、もしくは、ヘテロアリールアルキルであり、各々は、ハロ、アルキル、ヘテロアルキル、ＳＲ、ＯＲ、NR_2、ＯＣＯＲ、ＮＲＣＯＲ、$NRCONR_2$、$NRSO_2R$、$NRSO_2NR_2$、$OCONR_2$、ＣＮ、ＣＯＯＲ、$CONR_2$、ＣＯＲ、もしくはR_3Siで選択的に置換され、各Ｒは独立して、Ｈ、アルキル、アルケニルもしくはアリール、もしくは、そのヘテロ原子含有形態であり、ここでR^3はＯＲ、NR_2、ＳＲ、$NRCONR_2$、$OCONR_2$、もしくは、$NRSO_2NR_2$であり、ここで各Ｒは独立して、Ｈ、アルキル、アルケニルもしくはアリール、もしくは、そのヘテロ原子含有形態であり、同じ原子に結合した２つのＲが３～８員環を形成でき、ここで該環がアルキル、アルケニル、アルキニル、アリール、アリールアルキル、ヘテロアルキル、ヘテロアリール、ヘテロアリールアルキルで更に置換され、ハロ、ＳＲ、ＯＲ、NR_2、ＯＣＯＲ、ＮＲＣＯＲ、$NRCONR_2$、$NRSO_2R$、$NRSO_2NR_2$、$OCONR_2$、もしくは、R_3Siでそれぞれ選択的に置換され、各Ｒは独立して、Ｈ、アルキル、アルケニルもしくはアリール、もしくは、そのヘテロ原子含有形態であり、ここで同じ原子に結合した２つのＲは、前記定義と同様に選択的に置換された３～８員環を形成し得る。

【００３６】

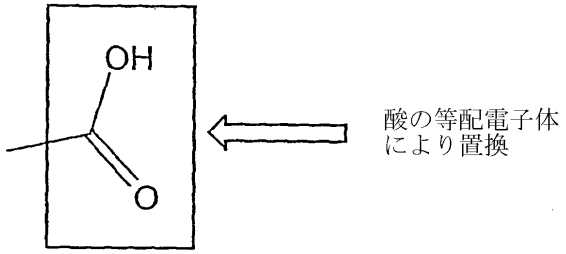
R^3のその他の好ましい形態は、Ｈ、ヘテロアリールアルキル、－NR_2、ヘテロアリール、－ＣＯＯＲ、－ＮＨＲNR_2、ヘテロアリール－ＣＯＯＲ、ヘテロアリールオキシ、－ＯＲ、ヘテロアリール－NR_2、－ＮＲＯＲおよびアルキルである。R^3は最も好ましくは、イソプロピル、ピペラジニル、メチルピペラジニル、ジメチルアミン、ピペラジニル、カルボン酸イソブチル、オキシカルボニルエチル、モルホリニル、アミノエチルジメチルアミン、カルボン酸イソブチルピペラジニル、オキシピペラジニル、カルボン酸エチルピペラジニル、メトキシ、エトキシ、ヒドロキシ、メチル、アミン、アミノエチル、ピ

ロリジニル、アミノプロパンジオール、ピペリジニル、ピロリジニル－ピペリジニル、もしくは、メチルピペリジニルである。

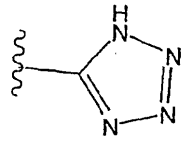
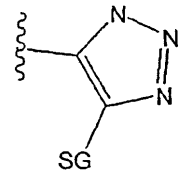
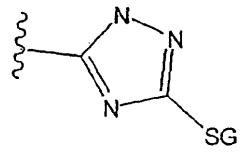
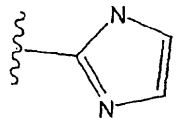
【００３７】

Ｙで表されるＣＯＲ^{3}の等配電子体は、下記のとおり定義される。等配電子体は多様な親油性を有し、代謝安定性の向上に寄与し得る。従って、下記のとおり、Ｙは表１に記載の等配電子体により置換してもよい。

【化１３８】



【表１】酸の等配電子体

基の名称	化学構造	置換基(SG)
テトラゾール		n/a
1,2,3-トリアゾール		H; SCH_3; $COCH_3$; Br; $SOCH_3$; SO_2CH_3; NO_2; CF_3; CN; COOMe
1,2,4-トリアゾール		H; SCH_3; $COCH_3$; Br; $SOCH_3$; SO_2CH_3; NO_2
イミダゾール		H; SCH_3; $COCH_3$; Br; $SOCH_3$; SO_2CH_3; NO_2

従って、等配電子体としては、テトラゾール、１，２，３－トリアゾール、１，２，４－トリアゾール、および、イミダゾールが含まれる。

【００３８】

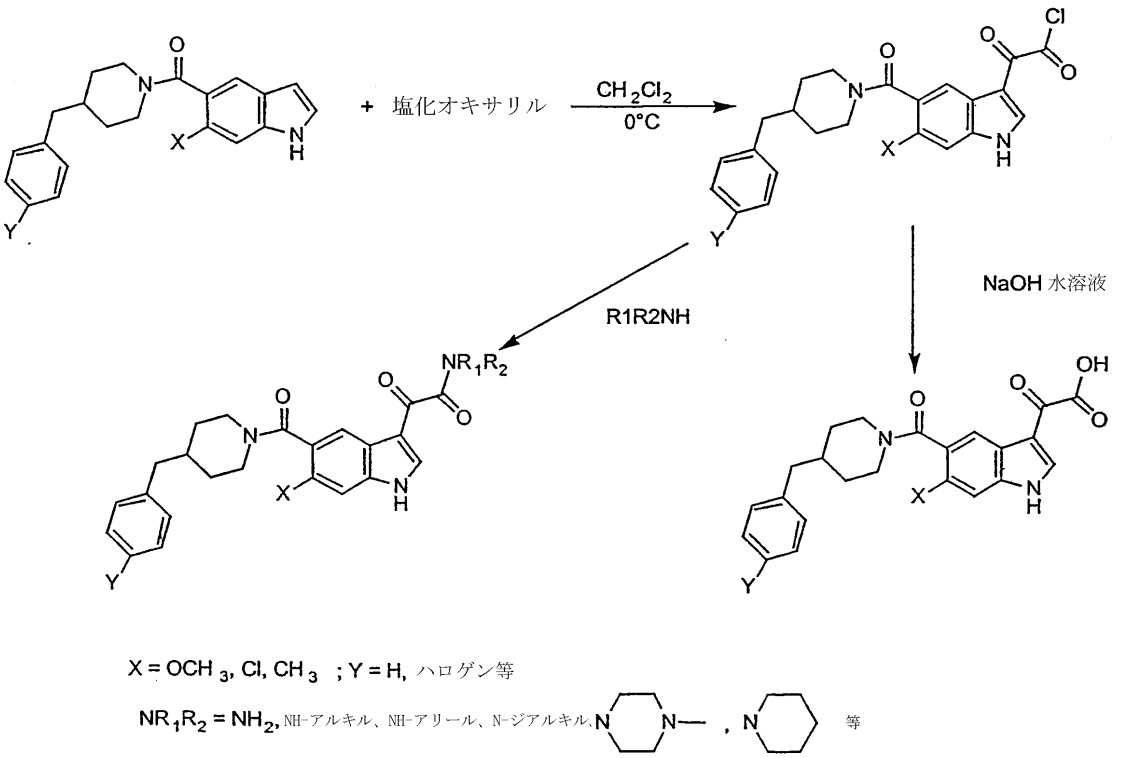
式（１）の化合物は、その薬学的に許容される酸付加塩、例えば、塩酸、硫酸、臭酸、もしくはリン酸等の無機酸の塩、もしくは、酢酸、酒石酸、コハク酸、安息香酸、サリチル酸等の有機酸の塩を含む形態で供給し得る。式（１）の化合物にカルボキシル部分が存在する場合、該化合物は薬学的に許容される陽イオンと共に塩として供給され得る。

【００３９】

本発明の化合物の合成

同時係属であり、共通に指定される米国特許出願第０９／５７５，０６０号は、その全体が参照として本明細書に組み入れられ、４－ベンジルピペリジニル－インドール－５－カルボキサミドの本発明のグリオキサル酸化合物およびその誘導体への変換を示す下記の反応スキームを説明する。

【化１３９】



【００４０】
本発明において、インドール部分は、式（１）においてＡｒ^{2}として一般化されており、Ａｒ^{2}は、１つまたはそれ以上の選択的な環構成ヘテロ原子を有する、実質的に平面、単環、または、多環式芳香族部分であって、該部分は、１つまたはそれ以上の非妨害性置換基で選択的に置換されていて、該部分２つまたはそれ以上で縮合環を形成し得る。Ａｒ^{2}部分は、好ましくは、選択的に置換された単環または多環式芳香核からなり、ここで該芳香核は、（ｉ）５員ヘテロ環または炭素環、（ｉｉ）６員炭素環またはヘテロ環、（ｉｉｉ）別の５員炭素環またはヘテロ環に縮合した５員炭素環またはヘテロ環、（ｉｖ）別の６員炭素環またはヘテロ環に縮合した６員炭素環またはヘテロ環、および（ｖ）６員炭素環またはヘテロ環に縮合した５員ヘテロ環または炭素環、から選択される炭素環またはヘテロ環からなる。前記の条件に従い、参照として本明細書に組み入れられる１９９９年５月２１日に出願された米国特許出願第０９／５７５，０６０号において開示され主張されているインドール型化合物は、式（１）から除外される。

【００４１】
共通に指定される米国特許出願第０９／５７５，０６０号において開示されているとおり、３位のグリオキサル型置換基は－Ｗ$_i$ＣＯＸ$_j$Ｙで総称できる。

【００４２】
Ａｒ^{2}部分は、

【化１４０】


【化１４１】


【化１４２】


【化１４３】


【化１４４】

【化１４５】

【化１４６】

【化１４７】

【化１４８】

【化１４９】

【化１５０】

【化１５１】

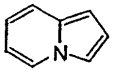
【化１５２】

【化１５３】

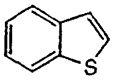
【化１５４】

【化１５５】

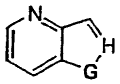
【化１５６】



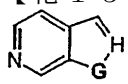
【化１５７】



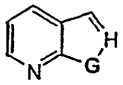
【化１５８】



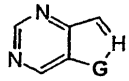
【化１５９】



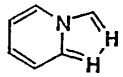
【化１６０】



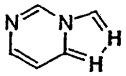
【化１６１】



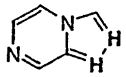
【化１６２】



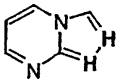
【化１６３】



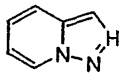
【化１６４】



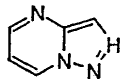
【化１６５】



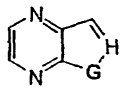
【化１６６】



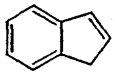
【化１６７】



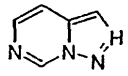
【化１６８】



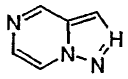
【化１６９】



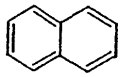
【化１７０】

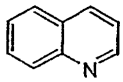


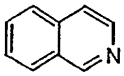
【化１７１】

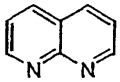


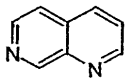
【化１７２】
G＝CR_2, NR, O または S
H＝N または CR

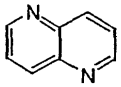
【化１７３】


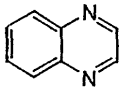
【化１７４】


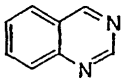
【化１７５】


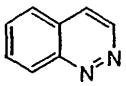
【化１７６】


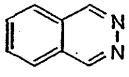
【化１７７】


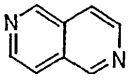
【化１７８】


【化１７９】


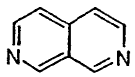
【化１８０】


【化１８１】


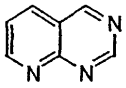
【化１８２】


【化１８３】


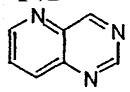
【化１８４】



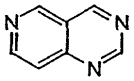
【化１８５】



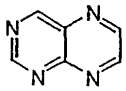
【化１８６】



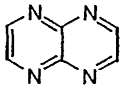
【化１８７】



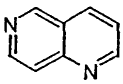
【化１８８】



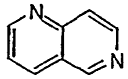
【化１８９】



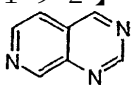
【化１９０】



【化１９１】

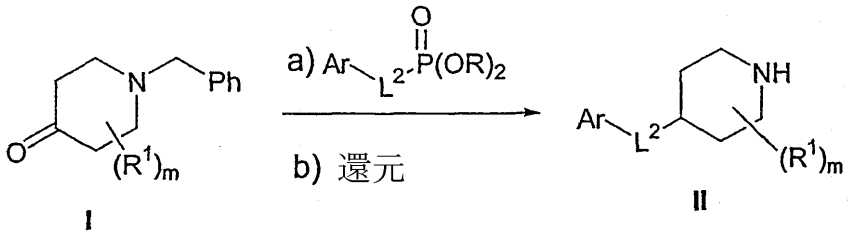


【化１９２】

および 

として総称し得る。本発明の化合物の合成方法は、一般的には、当技術分野において公知である。例えば、共通に指定され、その全体が参照として本明細書に組み入れられる米国特許出願第０９／５７５，０６０号は、下記の反応スキーム

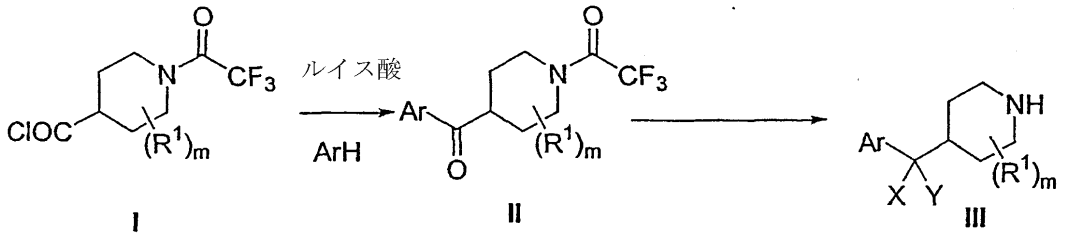
【化１９３】



I II

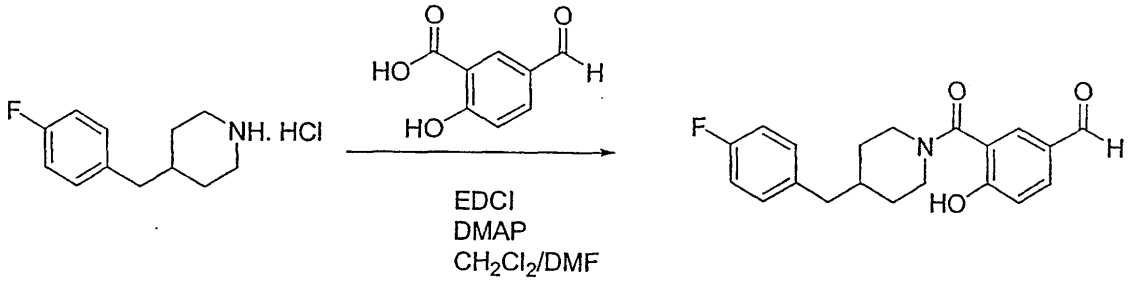
を使用することにより得られるピペリジン部分を開示し、Ｉ等の適当なピペリドンは、水素化ナトリウム等の塩基存在下、置換されたベンジルホスホン酸エステルで処理することにより、ＩＩ等の対応する置換された４－ベンジルピペリジンに還元できるアルケンを生成する。水素化は、典型的には、金属触媒存在下、メタノール、エタノール、および、酢酸エチル等の溶媒中で行われる。

【００４３】
米国特許出願第０９／５７５，０６０号に開示されている、上記のものの代わりのものとしては、下記の通りであり、
【化１９４】

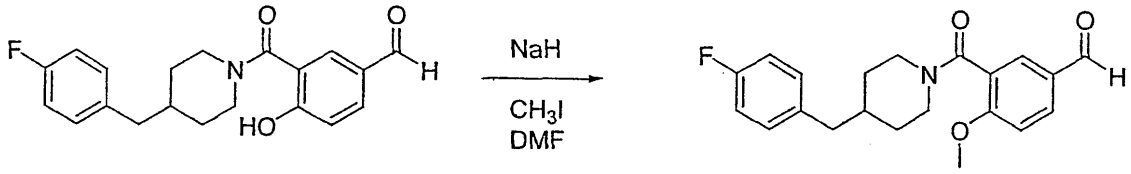


I II III

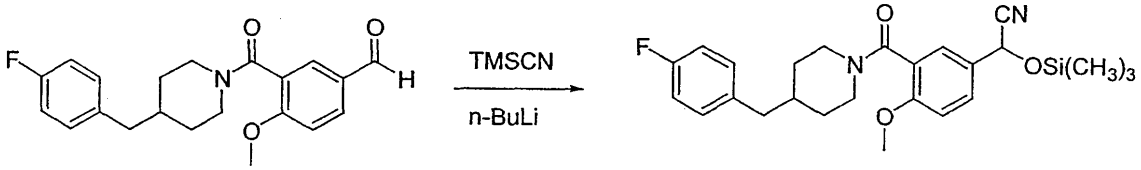
ここで、Ｉ等の塩化イソニペコトイルは、塩化アルミニウム等のルイス酸存在下、適当に置換されたベンゼン（ＡｒＨ）をアシル化し、ケトンＩＩを得るために使用できる。一般的に知られた方法および経路により、ＩＩのカルボニル部分を更に修飾し、目的化合物ＩＩへ導くことができる。
【００４４】
下記の反応スキームは、本発明の化合物の調製方法を説明するものである。
スキーム１
【化１９５】
工程 **A**



【化１９６】
工程 **B**

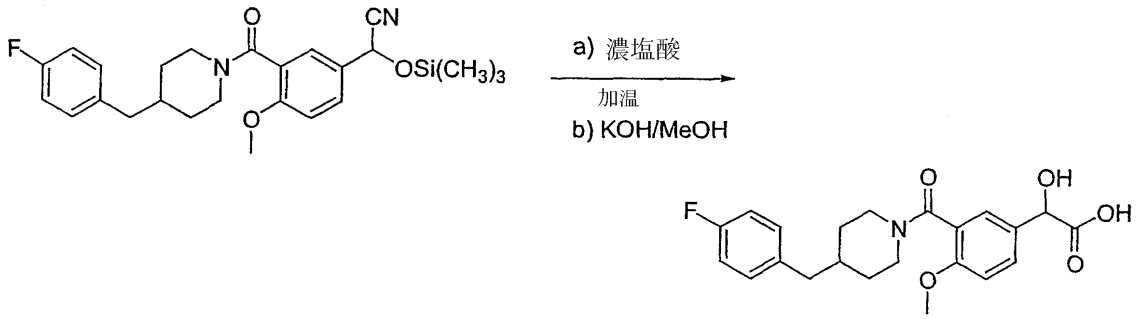


【化１９７】
工程 **C**



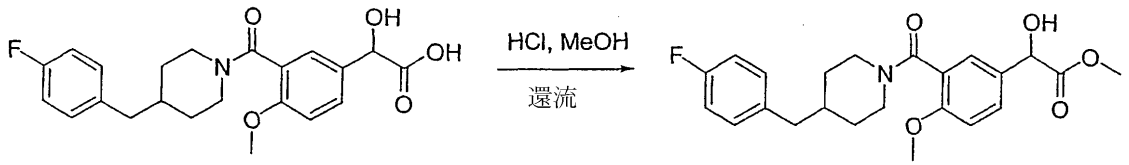
【化１９８】

工程 **D**



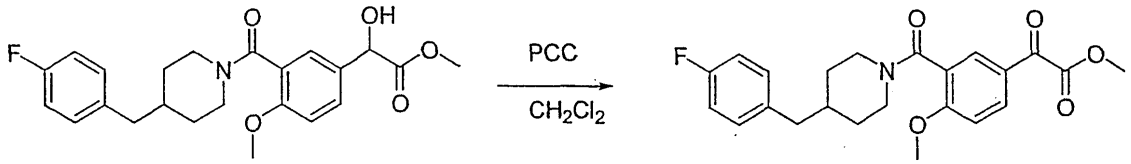
【化１９９】

工程 **E**



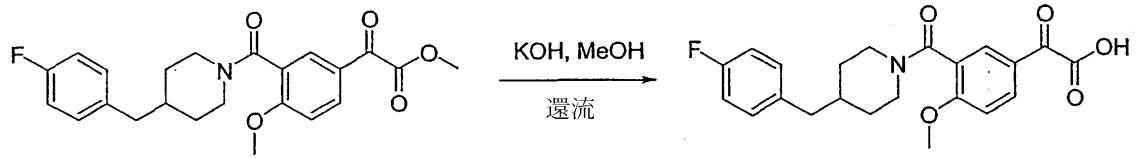
【化２００】

工程 **F**



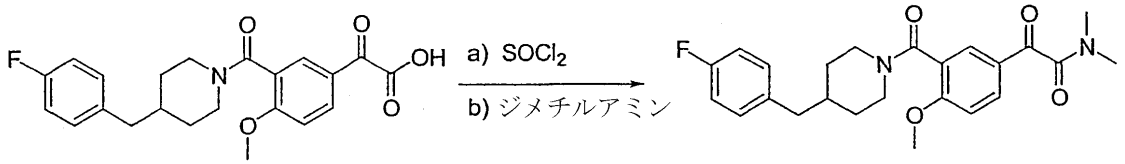
【化２０１】

工程 **G**



【化２０２】

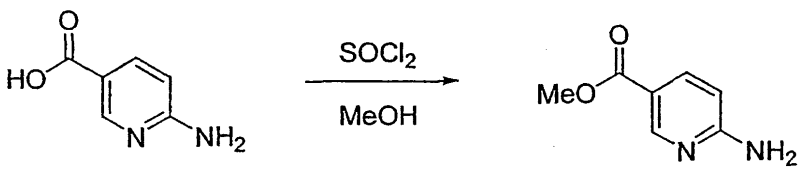
工程 **H**



スキームＩＩ

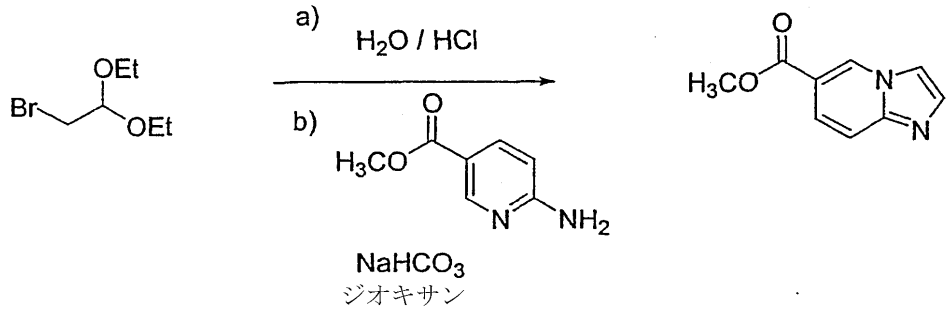
【化２０３】

工程 **A**



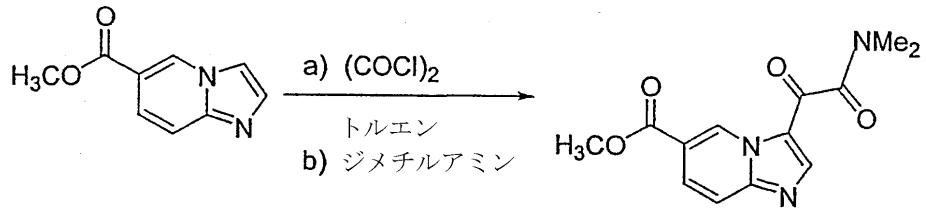
【化２０４】

工程 **B**



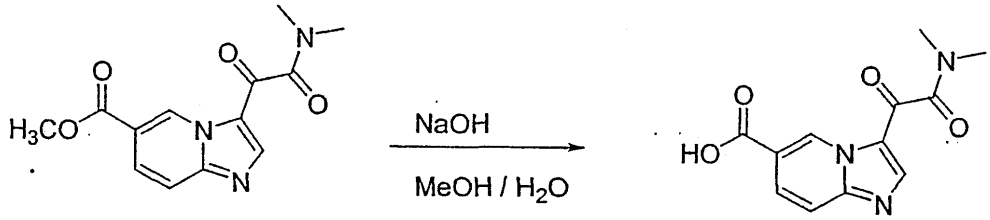
【化２０５】

工程 **C**



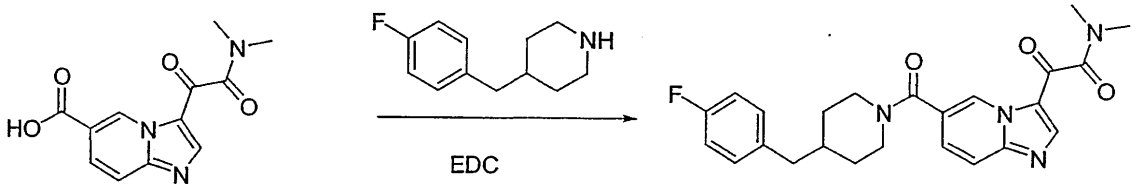
【化２０６】

工程 **D**



【化２０７】

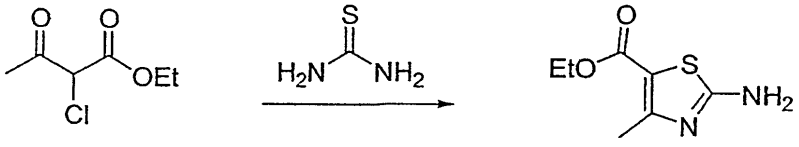
工程 **E**



スキームＩＩＩ

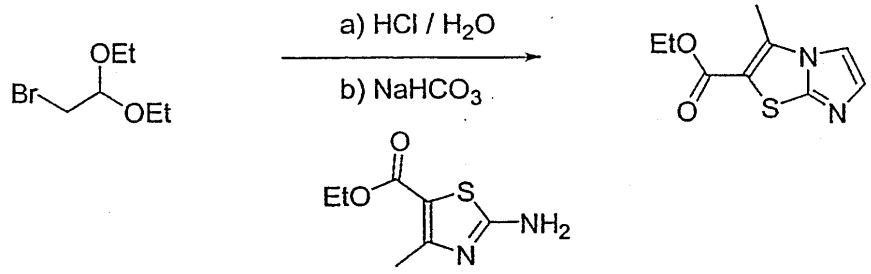
【化２０８】

工程 **A**



【化２０９】

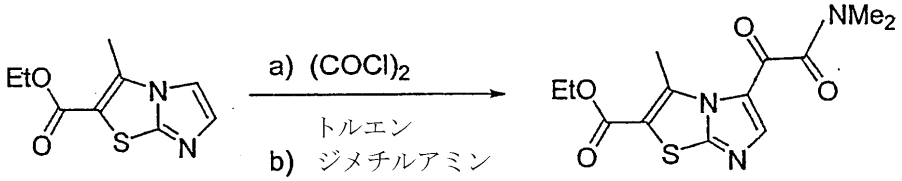
工程 **B**



H_2O / ジオキサン

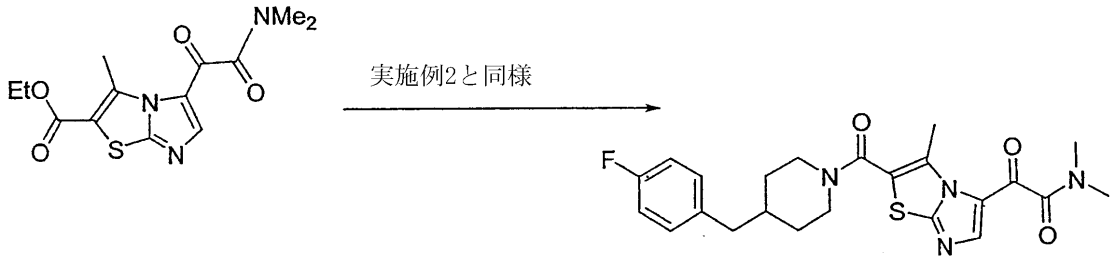
【化２１０】

工程 **C**



【化２１１】

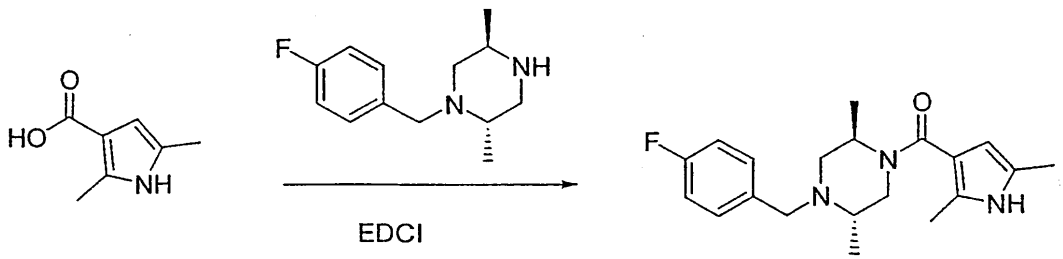
工程 **D**



スキーム ＩＶ

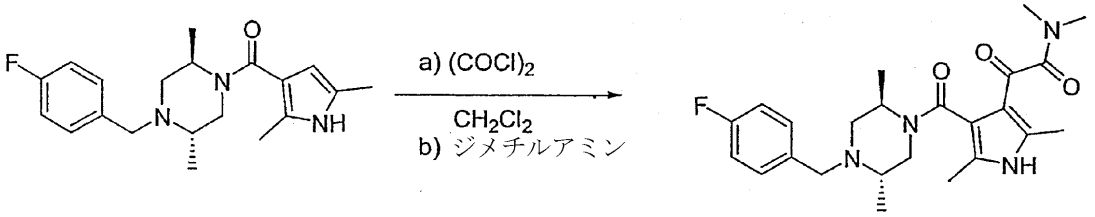
【化２１２】

工程 **A**



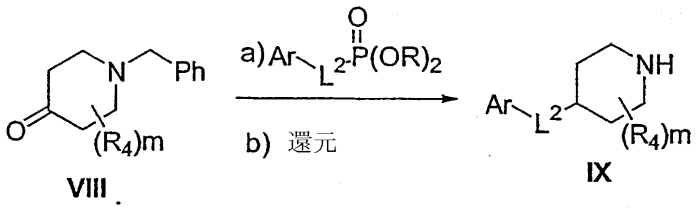
【化２１３】

工程 **B**



【化２１４】

スキーム４



【００４５】

ｐ３８αキナーゼ阻害のためのアッセイ法

以下に説明する各アッセイ手順において、ＴＮＦ－αの生産はｐ３８－αキナーゼの活性と関連する。

【００４６】

Ａ．　ｐ３８キナーゼ阻害のためのヒト全血アッセイ法

静脈血は、健康な男性ボランティアからヘパリン処理された注射器に採血され、採取から２時間以内に使用される。被験化合物を１００％ＤＭＳＯに溶解し、薬剤濃度を０から１ｍＭの範囲で１μＬずつ４重に、２４ウェルマイクロタイタープレート（Ｎｕｎｃｌｏｎ　Ｄｅｌｔａ　ＳＩ、Ａｐｐｌｉｅｄ　Ｓｃｉｅｎｔｉｆｉｃ，　Ｓｏ．　Ｓａｎ　Ｆｒａｎｃｉｓｃｏ、ＣＡ）に分配する。全血を１ｍｌ／ウェル加え、５％CO_2の加湿雰囲気下、３７で混合物を１５分間振盪培養する（Ｔｉｔｅｒ　Ｐｌａｔｅ　Ｓｈａｋｅｒ、Ｌａｂ－Ｌｉｎｅ　Ｉｎｓｔｒｕｍｅｎｔｓ，　Ｉｎｃ．、Ｍｅｌｒｏｓｅ　Ｐａｒｋ、ＩＬ）。全血は原液で、もしくは、ＲＰＭＩ　１６４０（Ｇｉｂｃｏ　３１８００　＋　$NaHCO_3$、Ｌｉｆｅ　Ｔｅｃｈｎｏｌｏｇｉｅｓ、Ｒｏｃｋｖｉｌｌｅ、ＭＤ　ａｎｄ　Ｓｃｉｏｓ，　Ｉｎｃ．、Ｓｕｎｎｙｖａｌｅ、ＣＡ）で１：１０まで希釈して培養する。培養終了時に、各ウェルに１０μＬのＬＰＳ（Ｅ．ｃｏｌｉ　０１１１：Ｂ４、Ｓｉｇｍａ　Ｃｈｅｍｉｃａｌ　Ｃｏ．、Ｓｔ．　Ｌｏｕｉｓ、ＭＯ）を加え、原液もしくは１：１０希釈の全血においてそれぞれ１μｇ／ｍｌもしくは０．１μｇ／ｍｌとなるように調製する。更に、培養を２時間継続する。マイクロタイタープレートを氷冷し、反応を終了させ、３０００ｒｐｍで１０分間４℃で遠心分離することにより血漿もしくは細胞を含まない上清を得る。血漿試料は、クオンティキンヒトＴＮＦ－α（Ｑｕａｎｔｉｋｉｎｅ　Ｈｕｍａｎ　ＴＮＦ－α）アッセイキット（Ｒ＆Ｄ　Ｓｙｓｔｅｍｓ、Ｍｉｎｎｅａｐｏｌｉｓ、ＭＮ）に添付の説明書に従ってＥＬＩＳＡによりＴＮＦ－αのレベルをアッセイするまで－８０℃で保存する。

【００４７】

IC_{50}値は、対照と比較して５０％の減少をもたらす阻害剤の濃度から計算される。

【００４８】

Ｂ．　ｐ３８キナーゼ阻害のための濃縮単核細胞アッセイ法

以下に手順を示す濃縮単核細胞アッセイ法は、凍結保存したヒト末梢血単核細胞（ＨＰＢＭＣ）（Ｃｌｏｎｅｔｉｃｓ　Ｃｏｒｐ．）をすすいで、温かい細胞増殖培地の混合物に再懸濁することから始まる。次に、再懸濁した細胞を数え、２４ウェルマイクロタイタープレートに細胞を$1x10^6$／ウェルで播く。プレートをインキュベーターで１時間放置し、各ウェルにおいて細胞を沈殿させる。細胞が沈殿した後、培地を吸引し、マイクロタイタープレートの各ウェルに１００ｎｇ／ｍｌのサイトカイン刺激因子リポ多糖（ＬＰＳ）および被験化合物を含む新しい培地を加える。従って、各ウェルは、ＨＰＢＭＣ、ＬＰＳ、および、被験化合物を含む。その後細胞を２時間培養し、酵素結合免疫測定法（ＥＬＩＳＡ）によりサイトカイン腫瘍壊死因子α（ＴＮＦ－α）の量を測定する。このようなＴＮＦ－αの生産量を検出するためのＥＬＩＳＡとしては、Ｒ＆Ｄシステムズ（Ｒ＆Ｄ　Ｓｙｓｔｅｍｓ）より市販のものがある。各ウェルにおけるＨＰＢＭＣによるＴＮＦ－αの生産量を対照ウェルのものと比較することにより、化合物がサイトカイン生産の阻害剤として作用するかを決定する。

【００４９】

ＨＰＢＭＣにおけるＬＰＳ誘導サイトカイン合成
凍結保存ＨＰＢＭＣ（カタログ番号ＣＣ－２７０２ Ｃｌｏｎｅｔｉｃｓ Ｃｏｒｐ）
ＬＧＭ－３倍地（カタログ番号ＣＣ－３２１２ Ｃｌｏｎｅｔｉｃｓ Ｃｏｒｐ）
ＬＰＳ原液１０μｇ／ｍｌ（カタログ番号Ｌ ２６３０血清型０１１１：Ｂ４ Ｓｉｇｍａ）
ヒトＴＮＦ－αＥＬＩＳＡ（Ｒ＆Ｄ Ｓｙｓｔｅｍｓ）
ＤＮａｓｅ Ｉ（１０ｍｇ／ｍｌ 原液）
【００５０】
細胞の調製
ＬＧＭ－３倍地を３７℃に昇温。
１０ｍｌの培地にＤＮａｓｅ Ｉ原液を５μＬ添加。
急激に細胞を解凍し、上記のものに懸濁。
室温で１０分間２００ｘｇで遠心分離。
滅菌ＰＢＳ１０ｍｌにペレットを回収。
室温で１０分間２００ｘｇで遠心分離。
１０ｍｌのＬＧＭ－３にペレットを再懸濁し、ＬＧＭ－３で５０ｍｌまで希釈。
細胞数の測定。
細胞数が１ｘＥ０６／ウェルとなるよう調整。
２４ウェルプレートに１ｍｌ／ウェル播く。
プレートをインキュベーターに入れ１時間沈降。
【００５１】
インキュベーション培地の調製
１００ｎｇ／ｍｌのＬＰＳを含むＬＧＭ－３（例えば、培地５０ｍｌとＬＰＳ原液０．５ｍｌ）
２ｍｌずつ分注し、１０００ｘ希釈の阻害剤を添加。
【００５２】
インキュベーション
細胞が沈降した後、培地を吸引し、１ｍＬの適切なインキュベーション培地を重層する。プレートを２時間もしくは２４時間インキュベーターに戻す。インキュベーション後、上清をラベルしたチューブへ移し、その直後にＴＮＦ（もしくはその外の）ＥＬＩＳＡを行うか、後のアッセイのために凍結する。IC_{50}値は、対照と比較して５０％の減少をもたらす阻害剤の濃度から計算される。
【００５３】
投与および使用
本発明の化合物は、兆候の中でも炎症に関連する状態の治療に有用である。従って、式（１）の化合物、もしくは、その薬学的に許容される塩は、サイトカインの過剰生産、及び／もしくは、心筋細胞、心線維芽細胞およびマクロファージ等の細胞に対する不適切もしくは無制御のサイトカイン活性を特徴とする状態におけるヒトを含む哺乳類に対する予防的もしくは治療的処置のための医薬品の製造に使用される。
【００５４】
本発明の化合物は、ＴＮＦ、ＩＬ－１、ＩＬ－６、および、ＩＬ－８等のサイトカイン、多くの異なる病態および症候群において重要な炎症誘発成分となるサイトカインの生産を阻害する。従って、これらのサイトカインの阻害は、多くの疾患を制御し、緩和する際に有利である。本発明の化合物は、ｐ３８ＭＡＰＫ（もしくはｐ３８）、ＣＳＢＰ、もしくは、ＳＡＰＫ－２等いろいろな名前で呼ばれるＭＡＰキナーゼファミリーの一員を阻害することが、本明細書に示されている。このタンパク質の活性化は、例えば、ＴＮＦおよびＩＬ－１等のサイトカインもしくはリポ多糖による処理により引き起されるストレスに応答して起こる疾患の悪化に伴っていることが示されている。従って、ｐ３８活性の抑制から、医薬品が、アルツハイマー病、冠動脈疾患、うっ血性心不全、心筋症、心筋炎、血管炎、冠動脈再建術等の後に起こる再狭窄、アテローム性動脈硬化症、ＩＢＤ、関節リウマ

チ、リウマチ様脊椎炎、変形性関節炎、通風性関節炎、および、その他の関節炎状態、多発性硬化症、急性呼吸窮迫症候群（ＡＲＤＳ）、喘息、慢性閉塞性肺疾患（ＣＯＰＤ）、珪肺症、肺サルコーシス、敗血症、敗血症性ショック、内毒素性ショック、グラム陰性敗血症、毒素ショック症候群、虚血および再灌流傷害により特徴づけられる心不全および脳不全（発作）、移植手順および移植片拒絶等の外科的手順、心肺バイパス、冠動脈バイパス移植、開放および非開放頭部損傷等のＣＮＳ傷害、結膜炎およびブドウ膜炎等の炎症性眼病、急性腎不全、糸球体腎炎、クローン病もしくは潰瘍性大腸炎等の炎症性腸疾患、移植片対宿主病、骨粗鬆症等の骨吸収病、２型糖尿病、発熱、乾癬、カヘキシー、ＨＩＶ、ＣＭＶおよびヘルペスによるウイルス性疾患、および脳性マラリア等の疾患の治療に有益な効果をもたらす能力を有するか予測できる。

【００５５】

過去数年間で、ｐ３８は、ｐ３８－α、ｐ３８－β、ｐ３８－γ、および、ｐ３８－δと呼ばれるＭＡＰキナーゼ群からなることが明らかとなった。ｐ３８－βが、ｐ３８－αに密接に関係した３７２アミノ酸からなるタンパク質であることを同定したことがジャング（Ｊｉａｎｇ，Ｙ．）ら、Ｊ Ｂｉｏｌ Ｃｈｅｍ（１９９６）２７１：１７９２０－１７９２６に報告されている。著者等によると、ｐ３８－αの活性をｐ３８－βのものと比較した場合、両者は炎症誘発性サイトカインおよび環境ストレスにより活性化される一方、ｐ３８－βは優先的にＭＡＰキナーゼキナーゼ－６（ＭＫＫ６）により活性化され優先的に転写因子２を活性化するため、これらの形態には別々の活性メカニズムが関連していると考えられる。

【００５６】

クメール（Ｋｕｍａｒ，Ｓ．）ら、Ｂｉｏｃｈｅｍ Ｂｉｏｐｈｙｓ Ｒｅｓ Ｃｏｍｍ（１９９７）２３５：５３３－５３８、および、ステイン（Ｓｔｅｉｎ，Ｂ．）ら、Ｊ Ｂｉｏｌ Ｃｈｅｍ（１９９７）２７２：１９５０９－１９５１７においてｐ３８－βの第２番目のイソ型であり、ｐ３８－αに対して７３％の同一性を示す３６４個のアミノ酸からなるｐ３８－β２が報告された。これら全ての報告は、ｐ３８－βが炎症誘発性サイトカインおよび環境ストレスにより活性化される証拠を示す一方、２番目に報告されたｐ３８－βイソ型であるｐ３８－β２は、ｐ３８－αのより遍在的な組織発現と比較すると、ＣＮＳ、心臓および骨格筋で優先的に発現していると見られる。更に、活性転写因子－２（ＡＴＦ－２）はｐ３８－αよりもｐ３８－β２に対してより良い基質であることが見出された為、これらの形態に別々の作用メカニズムが関与している可能性が示唆される。ｐ３８－β１は、ヒトの組織から発見されておらず、ｐ３８－αの基質に対して感知できる程度のキナーゼ活性を示さない為、その生体における役割が、後の２つの報告により疑問視されている。

【００５７】

ｐ３８－γの同定は、リー（Ｌｉ，Ｚ．）ら、Ｂｉｏｃｈｅｍ Ｂｉｏｐｈｙｓ Ｒｅｓ Ｃｏｍｍ（１９９６）２２８：３３４－３４０、ｐ３８－δの同定は、ワング（Ｗａｎｇ，Ｘ．）ら、Ｊ Ｂｉｏｌ Ｃｈｅｍ（１９９７）２７２：２３６６８－２３６７４およびクメール（Ｋｕｍａｒ，Ｓ．）ら、Ｂｉｏｃｈｅｍ Ｂｉｏｐｈｙｓ Ｒｅｓ Ｃｏｍｍ（１９９７）２３５：５３３－５３８により報告された。このデータから、これら２つのｐ３８イソ型（γおよびδ）は、その組織発現パターン、基質利用率、直接的および間接的刺激に対する応答、および、キナーゼ阻害剤に対する感受性から、ＭＡＰＫファミリーの特有のサブセットであることが示唆される。

【００５８】

ｐ３８－αと、ｐ３８－β１と見なされているものもしくはｐ３８－β２もしくはその両方の、ｐ３８ファミリーを標的とする薬剤に対する応答に関する様々な結果が、上記のジャング（Ｊｉａｎｇ）、クメール（Ｋｕｍａｒ）、および、ステイン（Ｓｔｅｉｎ）、並びに、アイヤーズ（Ｅｙｅｒｓ，Ｐ．Ａ．）ら、Ｃｈｅｍ ａｎｄ Ｂｉｏｌ（１９９５）５：３２１－３２８により報告されていた。ワング（Ｗａｎｇ，Ｙ．）ら、Ｊ Ｂｉｏｌ Ｃｈｅｍ（１９９８）２７３：２１６１－２１６８による更なる論文は、この

様な特異な効果の重要性を示唆するものである。ワング（Ｗａｎｇ）が指摘するように、多くの刺激、例えば、心筋梗塞、高血圧症、弁膜症、ウイルス性心筋炎、および、拡張型心筋症により心臓への荷重が増加し、心筋細胞に大きな機械的負担を与えることとなる。これらは、適応性肥大応答に至ると言われており、制御しない場合、明らかに負の結果をもたらす。ワング（Ｗａｎｇ）は、虚血再灌流治療を施した心臓において肥大症およびプログラム細胞死と共にｐ３８ＭＡＰＫ活性が向上していることを明らかにした先行の研究を引用している。ワング（Ｗａｎｇ） は、引用文献において、ｐ３８－βの活性化が肥大症をもたらす一方、ｐ３８－αの活性化が筋細胞の細胞死をもたらすことを示している。従って、ｐ３８－β活性と比べてｐ３８－α活性を選択的に阻害することは、心不全に関連する状態の治療に有益である。これらの状態としては、うっ血性心不全、心筋症、心筋炎、血管炎、血管再狭窄、弁膜症、心肺バイパスに関連する状態、冠動脈バイパス、移植片および血管移植等が挙げられる。更に、その他の種類の筋細胞においてα－イソ型が有毒である程度までに、α－選択的阻害剤は、ＴＮＦに基づくカヘキシーに関連する状態、もしくは、癌、感染症、もしくは、自己免疫疾患等のその他の状態に有用である。

【００５９】

従って、本発明は、ｐ３８－αの活性化に関連する状態、特に、心臓肥大、虚血もしくはその他の酸化傷害等の環境ストレス、高浸透圧もしくはｐ３８－αキナーゼを活性化するその他の薬剤もしくは要素、もしくは、うっ血性心不全、心筋症および心筋炎等の心不全に関連する状態を治療する為にｐ３８－αイソ型の作用を選択的に阻害する化合物の使用を含む。

【００６０】

本発明において有用な化合物およびそれに関連した化合物投与方法、並びに、製剤化方法は、状態の性質、状態の重篤さ、治療される特定の被験者、および医師の判断により決定され、製剤化は投与方法により決定される。本発明の化合物は低分子であるため、これらは、適切な製剤用賦形剤と調合することにより錠剤、カプセル、シロップ等として提供され、好都合に経口投与される。経口投与に適切な製剤は、緩衝剤、矯臭剤等の微量成分も含み得る。典型的には、製剤に含まれる有効成分の量は製剤全体の５％～９５％の範囲内であるが、担体によって大きく変化することが許容されている。適切な担体としては、ショ糖、ペクチン、ステアリン酸マグネシウム、乳糖、ラッカセイ油、オリーブ油、水等が挙げられる。

【００６１】

本発明において有用な化合物は坐薬もしくはその他の経粘膜媒体により投与してもよい。典型的に、このような製剤は、薬学的に許容される界面活性剤等の化合物による粘膜の通過を容易にする賦形剤を含む。

【００６２】

該化合物は、乾癬等の局所的状態の為に局所的に投与してもよく、もしくは、皮膚に浸透させるために製剤化されていてもよい。これらは、公知の方法により製剤化されてもよいローション、クリーム、および軟膏等を含む。また、該化合物は、静脈内、筋肉内、皮下もしくは腹腔内注射等の注射により投与し得る。このような用途における典型的な製剤は、ハンクス液もしくはリンゲル液等の等張性媒体中の液体製剤である。

【００６３】

その他の製剤としては、点鼻薬、リポゾーム製剤、および徐放製剤等が当技術分野において公知である。

【００６４】

如何なる適切な製剤も使用し得る。当技術分野において公知の製剤の概説は、最新版の「レミントンの製薬科学（Ｒｅｍｉｎｇｔｏｎ’ｓ Ｐｈａｒｍａｃｅｕｔｉｃａｌ Ｓｃｉｅｎｃｅｓ）」、Ｍａｃｋ Ｐｕｂｌｉｓｈｉｎｇ Ｃｏｍｐａｎｙ、Ｅａｓｔｏｎ、ＰＡ に記載されている。この手引書の参照は、当技術分野において日常的である。

【００６５】

本発明の化合物の投与量は、各患者において異なる多数の要因により決定される。しかし

ながら、一般的に用いられる一日あたりの経口投与量は、総体重１ｋｇあたり０．００１～１００ｍｇ、好ましくは０．０１～５０ｍｇ／ｋｇ、より好ましくは０．０１～１０ｍｇ／ｋｇと考えられている。しかしながら、処方量は、治療する状態および医師の判断に応じて変化する。

【００６６】

式（１）の化合物は、単独の有効成分として、もしくは、この式で表される多数の態様の混合物として投与できることを明記すべきである。更に、ｐ３８キナーゼの阻害剤は、単独の治療薬として、もしくは、その他の治療薬と一緒に使用できる。これらの化合物と有益に組合せることが可能な薬剤としては、天然もしくは合成副腎皮質ステロイド、特にプレドニゾンおよびその誘導体、免疫系の細胞を標的とするモノクローナル抗体、免疫もしくは非免疫サイトカインを標的とする抗体もしくは可溶性受容体もしくは受容体融合タンパク質、および、細胞分裂、蛋白質合成、もしくは、ｍＲＮＡの転写もしくは翻訳の低分子阻害剤、もしくは、免疫細胞分化もしくは活性化の阻害剤等が挙げられる。

【００６７】

上記に示唆されているとおり、本発明の化合物は、ヒトにおいて使用し得るが、これらは被験動物を治療するために獣医学的にも使用できる。

【００６８】

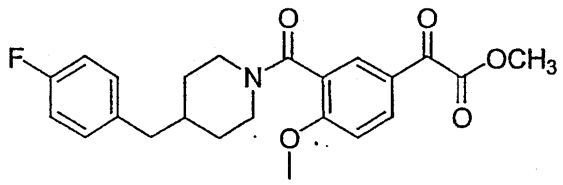
以下の実施例により本発明を説明するが、これらは本発明の範囲を限定するものではない。下記の実施例１～４において説明し、調製する化合物は、ｐ３８－αキナーゼの阻害剤である。

【００６９】

実施例１

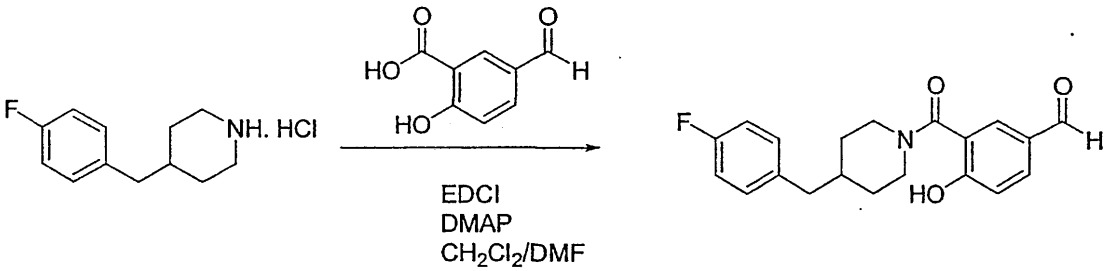
｛３－［４－（４－フルオロ－ベンジル）－ピペリジン－１－カルボニル］－４－メトキシ－フェニル｝－オキソ－酢酸メチルエステル

【化２１５】



【化２１６】

工程Ａ



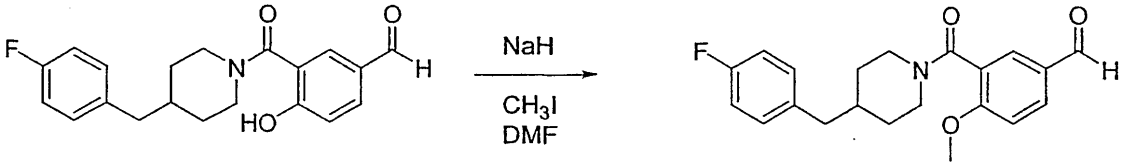
窒素雰囲気保護下で、乾燥させた２５０ｍｌ丸底フラスコ中の４－フルオロ－ベンジルピペリジン塩酸塩５．６ｇ（２４．４ミリモル）に無水塩化メチレン１００ｍｌを加え、続いてトリエチルアミン３．４８ｍｌ（２５ミリモル）を加えた。この懸濁液が透明な溶液になるまで、室温で数分間攪拌した。次に、この溶液に５－ホルミルサリチル酸４．３７ｇ（２５ミリモル）、１－エチル－３－（３－ジメチルアミノプロピル）－カルボジイミド４．８ｇ（２５ミリモル）、４－（ジメチルアミノ）－ピリジン０．１５３ｇ（１．２５ミリモル）を加えた。一晩攪拌後、反応混合物を、塩化メチレン１００ｍｌで希釈し、水と食塩水で洗浄した。有機層を、無水硫酸ナトリウムで乾燥後、濃縮し、塩化メチレンを溶出液として用いたカラムクロマトグラフィーで精製し、目的生成物３．６５ｇ（１０

．７ミリモル）を得た。（収率：４３．８％）

【００７０】

【化２１７】

工程Ｂ

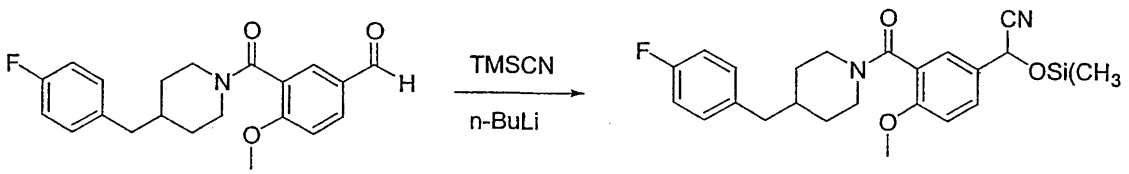


アルゴン雰囲気下、アルデヒド３．６２ｇ（１０．６ミリモル）を無水ジメチルホルムアミド１００ｍｌに溶解した。この溶液に、０℃で、水素化ナトリウム４．６６ｇ（６０％鉱油分散液、１１．７ミリモル）を加えた。反応液を０℃で０．５時間攪拌した後にこれを室温まで昇温させ、気泡が発生しなくなるまで攪拌した。フラスコを再度０℃に冷却後、ヨウ化メチル０．７３ｍｌ（１１．７ミリモル）を加えた。０℃で０．５時間攪拌後、反応液を室温まで昇温させ、更に４時間続けて攪拌した。ＤＭＦは減圧留去した。その結果得られた残渣を塩化メチレン１００ｍｌに再度溶解し、水と食塩水とで２回ずつ洗浄した。有機層を無水硫酸ナトリウムで乾燥後、濃縮し、１００％塩化メチレンから２％メタノール／塩化メチレンの濃度勾配におけるカラムクロマトグラフィーにより精製後、生成物２．６５ｇ（７．４６ミリモル）を７０．４％の収率で得た。

【００７１】

【化２１８】

工程Ｃ

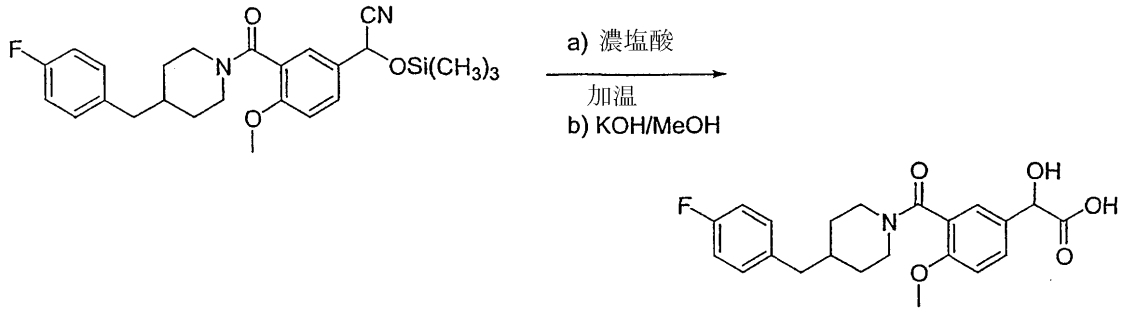


窒素雰囲気保護下で、アルデヒド２．６４ｇ（７．４３ミリモル）を無水テトラヒドロフラン７５ｍｌに溶解した。０℃下、この溶液にトリメチルシリルシアニド１．１ｍｌ（８．２ミリモル）を加え、次に２～３滴のｎ－ブチルリチウム（２．５Ｍヘキサン溶液）を加えた。０℃で２時間続けて攪拌後、室温まで昇温させ、一晩攪拌した。溶媒を回転式蒸発装置で留去後、生成物を白色粉末として、ほぼ定量的に得た。生成物は、精製することなく次の工程でそのまま用いた。

【００７２】

【化２１９】

工程Ｄ



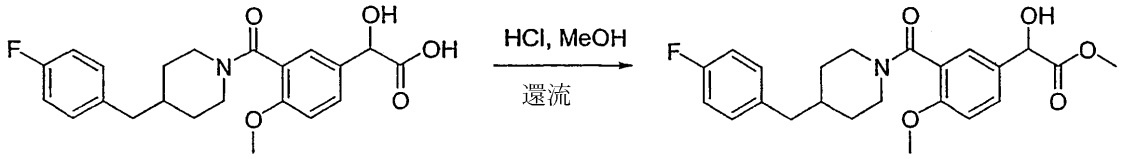
前工程より得られた生成物を濃塩酸６０ｍｌで希釈し、油浴で８０℃で一晩加温した。一晩加温後、この水溶液を水１００ｍｌで希釈し、水層を塩化メチレン（１００ｍｌｘ３）で抽出した。有機層を食塩水で洗浄し、硫酸ナトリウムで乾燥後、濃縮した。残渣をメタ

ノール約７０ｍｌに再度溶解後、水酸化カリウム１．７ｇ（３０．３ミリモル）を加え、その溶液を２時間加熱還流した。反応溶液を室温まで冷却し、濃縮後、真空下で乾燥させた。フラスコに数グラムの粉砕した氷を加え、１０％塩酸水溶液で酸性化した。水（６０ｍｌ）を添加し、溶液を希釈し、この水溶液を塩化メチレン（１００ｍｌｘ３）で抽出した。有機層を食塩水で洗浄し、硫酸ナトリウムで乾燥後、濃縮し、生成物２．５ｇ（６．２３ミリモル）を得た。

【００７３】

【化２２０】

工程Ｅ

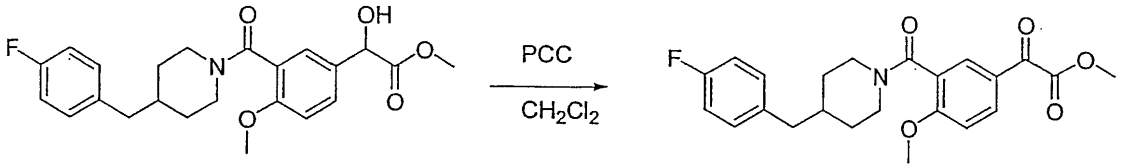


冷却器を備えた５０ｍｌ丸底フラスコ中でα－ヒドロキシ酸１３０ｍｇを濃塩酸：メタノール（１：９）４ｍｌに溶解し、これを加熱還流した。１時間後、反応液を室温まで冷却し、減圧下で濃縮した。得られた残渣を酢酸エチル２０ｍｌに再度溶解後、酢酸エチル層を水２０ｍｌ、飽和炭酸水素ナトリウム水溶液２０ｍｌで２回、および食塩水で洗浄した。有機層を無水硫酸ナトリウムで乾燥後、濃縮し、粗生成物１４１ｍｇを得た。

【００７４】

【化２２１】

工程Ｆ



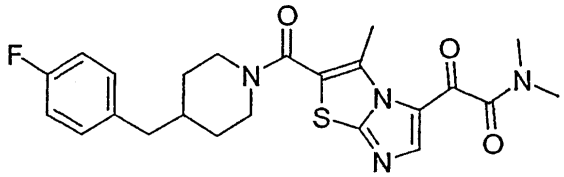
メチルエステル１２３ｍｇを塩化メチレン４ｍｌに溶解後、過剰のピリジニウムクロロメート（１ｇ、重量比２０％塩基性アルミナ担持）を加えた。得られた懸濁液を２４時間室温で攪拌した。固体を濾過し、塩化メチレンで洗浄した。混合した有機溶液を濃縮し、生成物を、１％メタノール／塩化メチレンを溶出液として用いた分取薄層クロマトグラフィーで精製し、目的生成物２６ｍｇを得た。

【００７５】

実施例２

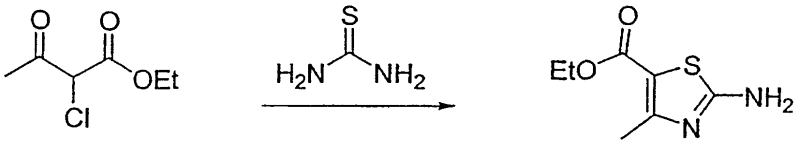
２－｛２－［４－（４－フルオロ－ベンジル）－ピペリジン－１－カルボニル］－３－メチル－イミダゾ［２，１－ｂ］チアゾル－５－イル｝－Ｎ，Ｎ－ジメチル－２－オキソ－アセトアミド

【化２２２】



【化２２３】

工程Ａ

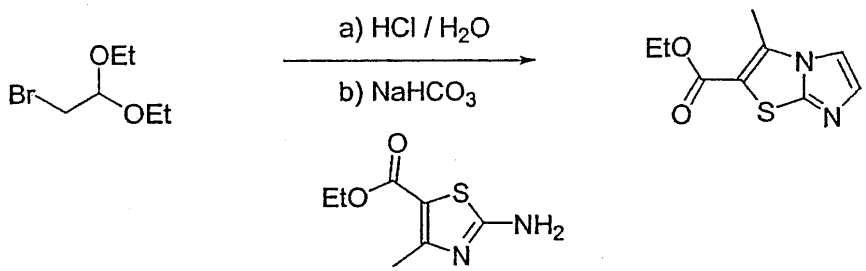


チオウレア（３．８１ｇ）と２－クロロアセト酢酸エチル（８．２３ｇ）をエタノール（１００ｍｌ）中で混合し、これを１４時間加熱還流した。室温まで冷却後、エタノールを減圧留去し、粗生成物を水に溶解後、炭酸水素ナトリウムで中和し、次に酢酸エチルで抽出した。混合した抽出液を乾燥後、濾過し、濃縮後、白色粉末（８．６９ｇ）を生成物として得た。

【００７６】

【化２２４】

工程Ｂ



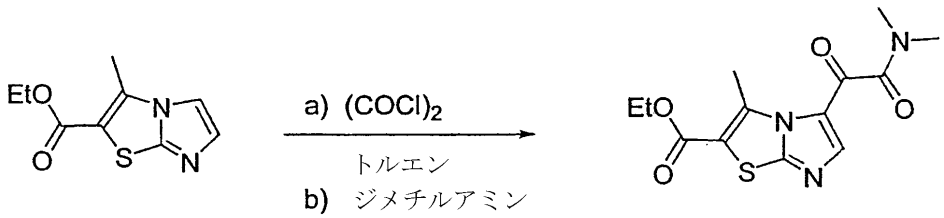
H_2O / ジオキサン

ブロモアセトアルデヒドジエチルアセタール（１１．２ミリモル、２．２０ｇ）の水（７５ｍｌ）溶液に濃塩酸（１．１５ｍｌ）を滴下した。室温で１４時間攪拌後、混合物を８０℃で３０分間加温した。室温まで冷却した後、炭酸水素ナトリウム（１４．５ミリモル、１．２２ｇ）を注意深く加え、続けて２時間攪拌した。次に、エステル（８．９ミリモル、１．６６ｇ）を加え、混合物を更に１時間攪拌し、その後ジオキサン（５０ｍｌ）を加えた。３０分後、混合物を１００℃で４８時間加温した。室温まで冷却後、ジオキサンを回転式蒸発装置で留去した。水層を塩化メチレンで抽出した。混合した有機層を乾燥後（無水硫酸ナトリウム）、濾過し、濃縮した。放射状クロマトグラフィー（１０％メタノールの塩化メチレン溶液）により、目的の生成物１２２ｍｇを得た。

【００７７】

【化２２５】

工程Ｃ



トルエン

ジメチルアミン

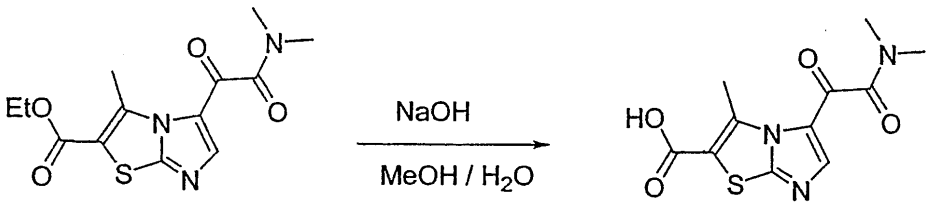
エステル（０．１９ミリモル、４０ｍｇ）のトルエン（０．７６ｍｌ）溶液に２．０Ｍ塩化オキサリルの塩化メチレン溶液（０．２８５ｍｌ）を室温で加えた。反応容器を窒素雰囲気下で置換後、密封し、１２５℃で１２時間加温した。室温まで冷却後、揮発性物質を減圧留去した。未精製の酸塩化物に塩化メチレン（０．７６ｍｌ）を加え、０℃に冷却後、２．０Ｍジメチルアミンのテトラヒドロフラン溶液（０．２８５ｍｌ）を滴下した。反応混合物を０℃で更に３０分間攪拌し、室温まで昇温させた。３０分後、水を加えて反応

を終了させ、これを塩化メチレンで抽出した。混合した抽出液を食塩水で洗浄後、乾燥し（無水硫酸ナトリウム）、濾過後、濃縮した。放射状クロマトグラフィー（１０％メタノールの塩化メチレン溶液）により生成物３８ｍｇを得た。

【００７８】

【化２２６】

工程Ｄ

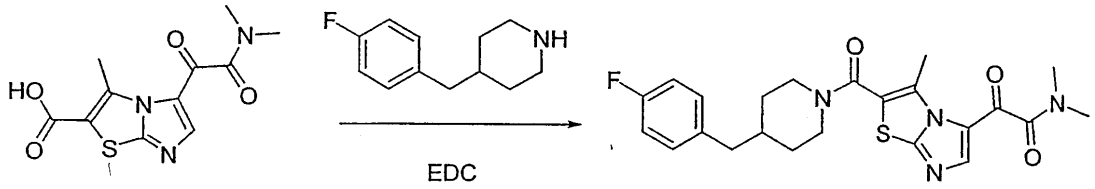


エステル（０．１２ミリモル、３８ｍｇ）とメタノール（０．２５ｍｌ）と水（０．２５ｍｌ）の混合溶液に水酸化ナトリウム（０．９８５規定水溶液、１２２μｌ）を加えた。混合物を室温で１４時間攪拌した時点で、塩酸水溶液を用いて酸性化し、酢酸エチルで抽出した。混合した抽出液を乾燥し（無水硫酸ナトリウム）、濾過後、濃縮し、生成物１９ｍｇを得、それを精製することなく次の工程で用いた。

【００７９】

【化２２７】

工程Ｅ



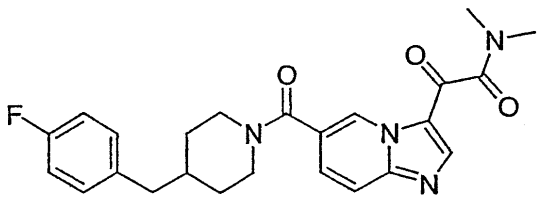
酸（０．１４ミリモル、１９ｍｇ）の塩化メチレン溶液（０．５６ｍｌ）に４－フルオロベンジルピペリジン（０．１７ミリモル、３９ｍｇ）を加え、その後、ＥＤＣ（０．１７ミリモル、３３ｍｇ）およびＤＭＡＰ（４ｍｇ）を加えた。混合物を室温で１４時間攪拌後、水を加えて反応を終了させ、塩化メチレンで抽出した。混合した抽出液を乾燥（無水硫酸ナトリウム）し、濾過後、濃縮した。放射状クロマトグラフィー後、目的化合物２０ｍｇを得た。

【００８０】

実施例３

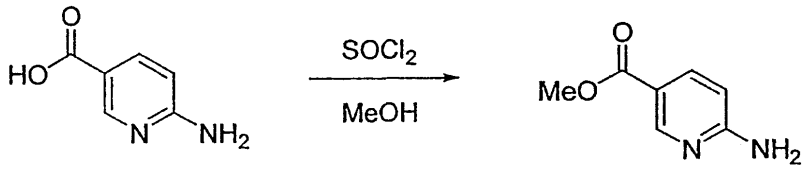
２－｛６－［４－（４－フルオロ－ベンジル）－ピペリジン－１－カルボニル］－イミダゾ［１，２－ａ］ピリジン－３－イル｝－Ｎ，Ｎ－ジメチル－２－オキソ－アトアタミド

【化２２８】



【化２２９】

工程Ａ

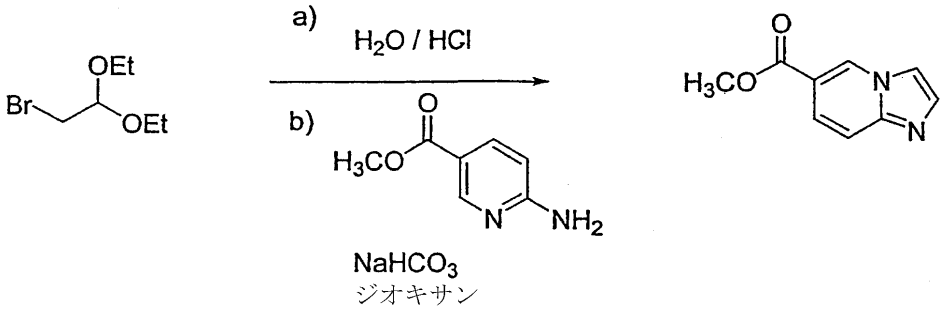


－７８℃に冷却した６－アミノニコチン酸（７５ミリモル、１０．３６ｇ）のメタノール（３００ｍｌ）溶液に塩化チオニル（１８７．５ミリモル、２２．３１ｇ、１３．７ｍｌ）を３０分間かけて滴下した。混合物を室温まで昇温させた。次に、混合物を１２時間加熱還流した時点で冷却し、揮発性物質を回転式蒸発装置を用いて留去した。得られた白色固体を水に溶解し、炭酸水素ナトリウムで中和後、酢酸エチルで抽出した。混合した有機層を乾燥し（無水硫酸ナトリウム）、濾過後、濃縮し、白色粉末１０．０６ｇを得た。

【００８１】

【化２３０】

工程Ｂ

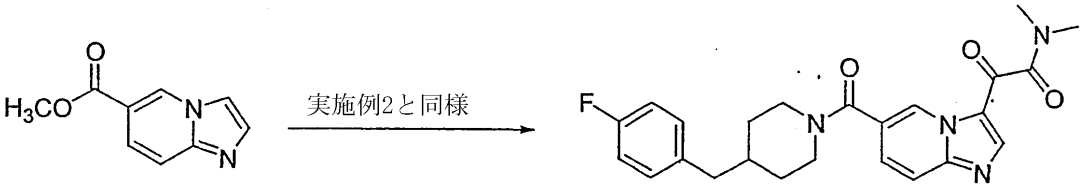


ブロモアセトアルデヒドジエチルアセタール（４４．６ミリモル、８．７９ｇ）の水（３００ｍｌ）溶液に濃塩酸（４．６ｍｌ）を滴下した。室温で１４時間攪拌後、混合物を８０℃で３０分間加温した。室温まで冷却し、注意しながら炭酸水素ナトリウム（５８．７ミリモル、４．８８ｇ）を加え、続けて２時間攪拌した。次にエステル（３５．６ミリモル、５．４１ｇ）を加え、混合物を更に１時間攪拌後、ジオキサン（２００ｍｌ）を加えた。３０分経過後、混合物を１００℃で４８時間加温した。室温まで冷却後、ジオキサンを回転式蒸発装置で留去した。水層を塩化メチレンで抽出した。混合した有機層を乾燥し（無水硫酸ナトリウム）、濾過後、濃縮し、黄色ペースト（２１７ｍｇ）を得、これは更に精製することなく次の工程で用いた。

【００８２】

【化２３１】

工程Ｃ



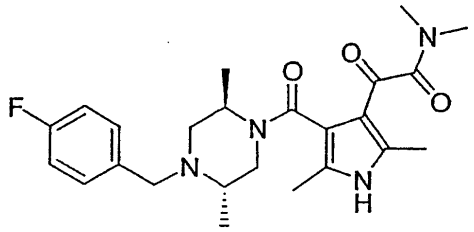
２－｛６－［４－（４－フルオロ－ベンジル）－ピペリジン－１－カルボニル］－イミダゾ［１，２－ａ］ピリジン－３－イル｝－Ｎ，Ｎ－ジメチル－２－オキソ－アセトアミドの合成は、２－｛２－［４－（４－フルオロ－ベンジル）－ピペリジン－１－カルボニル］－３－メチル－イミダゾ［２，１－ｂ］チアゾール－５－イル｝－Ｎ，Ｎ－ジメチル－２－オキソ－アセトアミドの場合と同様の一連の工程により行われた。

【００８３】

実施例４

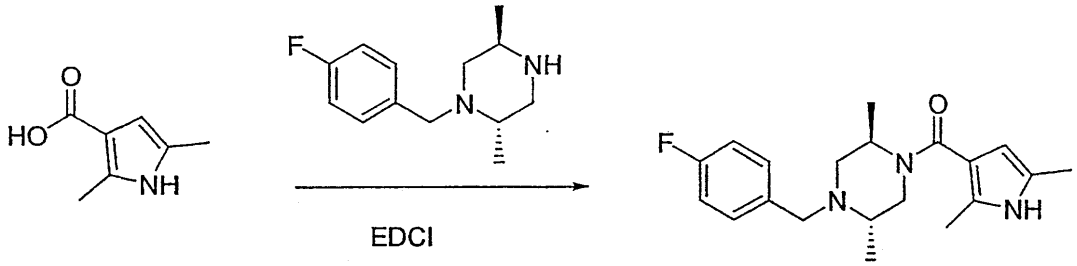
２－｛４－［４－（４－フルオロ－ベンジル）－２，５－トランス－ジメチル－ピペラジン－１－カルボニル］－２，５－ジメチル－１Ｈ－ピロール－３－イル｝－Ｎ，Ｎ－ジメチル－２－オキソ－アセトアミド

【化２３２】



【化２３３】

工程Ａ

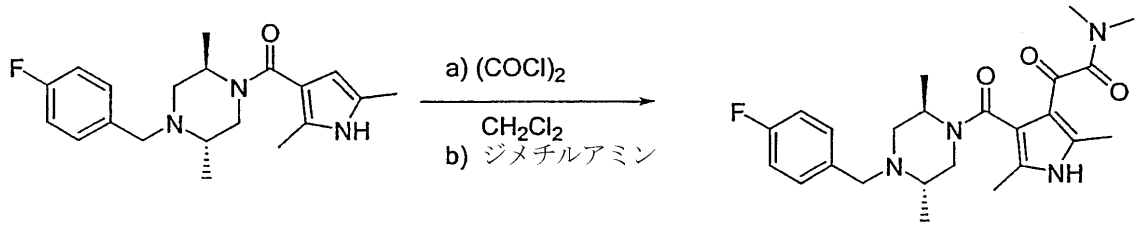


２，５－ジメチル－１Ｈ－ピロール－３－カルボン酸（１．０９ｇ）と１－（４－フルオロ－ベンジル）－トランス－２，５－ジメチル－ピペラジン（１．５９ｇ）の塩化メチレン混合溶液にＥＤＣＩ（１．５１ｇ）と触媒量のＤＭＡＰを加えた。反応混合液を室温で１２時間攪拌した時点で水を加えた。混合溶液を塩化メチレンで抽出した。混合した溶出液を乾燥し、濾過後、濃縮した。カラムクロマトグラフィー（シリカゲル、（１：２）酢酸エチル／ヘキサンから（７：３）酢酸エチル／ヘキサン）で精製することにより目的の生成物５４０ｍｇを得た。

【００８４】

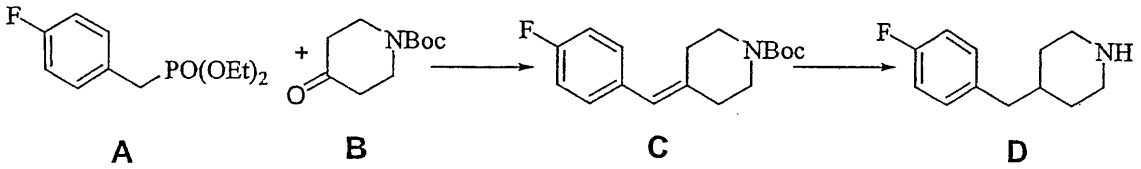
【化２３４】

工程Ｂ



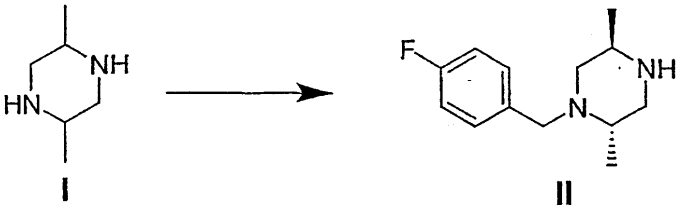
（２，５－ジメチル－１Ｈ－ピロール－３－イル）－［４－（４－フルオロ－ベンジル）－トランス－２，５－ジメチル－ピペラジン－１－イル］－メタノン（３４０ｍｇ）の塩化メチレン（２５ｍｌ）溶液を０℃に冷却し、塩化オキサリル（２．０Ｍの塩化メチレン溶液、２．０ｍｌ）を加えた。続けて０℃で１時間攪拌後、混合物を室温まで昇温させ、１時間攪拌した。溶媒を減圧留去し、塩化メチレン（２５ｍｌ）で置換した。０℃に冷却後、ジメチルアミン（２．０Ｍのテトラヒドロフラン溶液、４．０ｍｌ）を滴下した。３０分間攪拌した時点で室温に昇温させた。３０分後に水を加えて反応を終了させ、塩化メチレンで抽出した。混合した抽出液を乾燥し、濾過後、濃縮し、目的生成物を得、これをシリカゲルカラムクロマトグラフィー（（１：１）酢酸エチル／ヘキサンから酢酸エチル、次に（９５：５）酢酸エチル／メタノールから（９０：１０）酢酸エチル／メタノール）で精製し、生成物６０ｍｇを得た。

【００８５】
追加の実施例
【化２３５】



A　　B　　C　　D

Ｄの合成：
工程１：
ホスホン酸エステルＡ（３８．４ｇ）およびピペリドンＢ（３５．４ｇ）を無水ジメチルホルムアミド（４００ｍｌ）に溶解した。反応液を０℃に保ちながら、これに水素化ナトリウム（６０％の油性分散液）を数回に分けて加えた。水素化ナトリウム添加が終了した後、反応混合物を３０分間攪拌し、氷浴を外した後、反応液を６時間攪拌し、常温までゆっくりと昇温させた。反応液を再度氷冷し、メタノールを加えて反応を終了させた。反応混合物に水を加え、生成物を酢酸エチルで抽出した。酢酸エチル層を飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥させた。溶媒を留去し、未精製のアルケンを得、これを酢酸エチル／ヘキサン（１：９）で溶出することによりカラムクロマトグラフィーで精製し、目的生成物Ｃを２１．８ｇ得た。
【００８６】
工程２：
１０．１ｇのＣをメタノール５０ｍｌに溶解した。溶液を窒素置換した後、５％パラジウム－炭素（１ｇ）触媒を加え、次に酢酸１ｍｌを加えた。パール社製容器に入れた反応混合物を４０～５０ｐｓｉのもとで４時間水素付加した。反応混合物をセライトで濾過し、濃縮した。残渣を２Ｍ塩酸のエーテル溶液で処理し、塩酸塩に変換した。得られた白色固体を減圧下でしっかりと濃縮乾燥し、７．８ｇのＤを塩酸塩として得た。
【００８７】
【化２３６】



Ⅰ　　Ⅱ

ＩＩの合成：
工程１：
ジメチルピペラジンＩ（２５ｇ）の無水エタノール３００ｍｌ溶液に２規定塩酸のジエチルエーテル溶液を４００ｍｌ加えた。油浴で溶液を７０℃まで昇温し、２０分間加温した。溶液を室温まで冷まし、６℃下で一晩放置した。得られた固体を濾過し、回収した。一晩高真空条件下で乾燥し、３９．８ｇの生成物（トランス－２，５－ジメチルピペラジンのジヒドロクロライド塩）を得た。
【００８８】
工程２：
工程１より得られたジメチルピペラジンジヒドロクロライド４２．９ｇのエタノール溶液とトランス－２，５－ジメチルピペラジン２６．１ｇを、出発物質が完全に溶解するまで８０℃の油浴で激しく攪拌した。油浴の温度を６５℃に下げ、４－フルオロベンジルクロライド３３．１ｇを加えた。同温度で３０分間攪拌後、溶液を６℃の冷蔵庫で一晩放置した。濾過することにより溶液から固体を取り除き、過剰の２規定塩酸のジエチルエーテル溶液を濾液に加えた。濾液を６℃下で一晩放置した後、固体を回収した。固体を５％水酸

化ナトリウム水溶液に懸濁させ、酢酸エチルで３回抽出した。有機層を硫酸ナトリウムで乾燥後、濃縮し、黄色油状物を得た。

【００８９】

工程３：

（Ｌ）－酒石酸５０．７ｇの沸騰メタノール１３０ｍｌ溶液を、工程２の生成物３７．５ｇの温メタノール７０ｍｌ溶液に加えた。溶液を６℃で９６時間放置した後、白色の細かい結晶を濾過し、回収した。この物質を沸騰メタノールより再結晶した。６℃で一晩放置した後、濾過により生成物を回収し、二酒石酸塩３０．５ｇを得た（［α］＝＋４３．２°、Ｃ＝１）。

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(54) Title: PIPERIDINE/PIPERAZINE-TYPE INHIBITORS OF P38 KINASE

(57) Abstract: The invention is directed to inhibition of p38-α kinase using compounds of the formula (1) and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein: Ar^1 is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring; L^1 and L^2 are linkers; each R^1 is independently a noninterfering substitutent; Z^1 is CR^2 or N wherein R^2 is hydrogen or a noninterfering substituent; m is 0-4; each of n and p is an integer from 0-2 wherein the some of n and p is 0-3; Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring; Z is W_i-COX_jY wherein Y is COR^3 or an isotere thereof; R^3 is a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1; wherein the smallest number of covalent bonds is the compound separating the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of Ar^1 bonded to L^2 and the atom of Ar^2 bonded to L^1 is 4.5-24 angstroms; with the proviso that the protion of the compound represented by Ar^2-Z is not formula (2) wherein formula (3) represents a singel or double bond; n is 0-3; one Z^2 is CA or CRA and the other is CR, CR_2, NR or N; A is W_i-COX_jY wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 ot 1; Z^3 is NR or O; and each R independently hydrogen or a mominterfering substituent.

WO 02/46158 A2

PIPERIDINE/PIPERAZINE-TYPE INHIBITORS OF p38 KINASE

Field of the Invention

The invention relates to treating various disorders associated with enhanced activity of kinase p38-α. More specifically, it concerns piperadine and piperazine derivatives useful in these methods.

Background Art

A large number of chronic and acute conditions have been recognized to be associated with perturbation of the inflammatory response. A large number of cytokines participate in this response, including IL-1, IL-6, IL-8 and TNF. It appears that the activity of these cytokines in the regulation of inflammation rely at least in part on the activation of an enzyme on the cell signaling pathway, a member of the MAP kinase family generally known as p38 and alternatively known as CSBP and RK. This kinase is activated by dual phosphorylation after stimulation by physiochemical stress, treatment with lipopolysaccharides or with proinflammatory cytokines such as IL-1 and TNF. Therefore, inhibitors of the kinase activity of p38 are useful anti-inflammatory agents.

Eye diseases associated with a fibroproliferative condition include retinal reattachment surgery accompanying proliferative vitreoretinopathy, cataract extraction with intraocular lens implantation, and post glaucoma drainage surgery.

PCT applications WO98/06715, WO98/07425, and WO 96/40143, all of which are incorporated herein by reference, describe the relationship of p38 kinase inhibitors with various disease states. As mentioned in these applications, inhibitors of p38 kinase are useful in treating a variety of diseases associated with chronic inflammation. These applications list rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, CNS injuries such as neural trauma and ischemia, psoriasis, restenosis, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone

resorption diseases such as osteoporosis, graft-versus-host reaction, Crohn's Disease, ulcerative colitis including inflammatory bowel disease (IBD) and pyresis.

The above-referenced PCT applications disclose compounds which are p38 kinase inhibitors said to be useful in treating these disease states. These compounds are either imidazoles or are indoles substituted at the 3- or 4-position with a piperazine ring linked through a carboxamide linkage. Additional compounds which are conjugates of piperazines with indoles are described as insecticides in WO97/26252, also incorporated herein by reference.

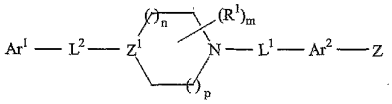
Certain aroyl/phenyl-substituted piperazines and piperidines which inhibit p38-α kinase are described in PCT publication WO00/12074 published 9 March 2000. In addition, indolyl substituted piperidines and piperazines which inhibit this enzyme are described in PCT publication No. WO99/61426 published 2 December 1999. Carbolene derivatives of piperidine and piperazine as p38-α inhibitors are described in PCT/US00/07934 filed 24 March 2000.

None of the foregoing patents describes the piperadine type derivatives described herein which specifically inhibit p38-α.

Summary of the Invention

The invention is directed to methods and compounds useful in treating conditions that are characterized by enhanced p38-α activity. These conditions include inflammation, proliferative diseases, and certain cardiovascular disorders as well as Alzheimer's disease as further described below.

Compounds of the invention inhibit p38 kinase, the α-isoform in particular, and are thus useful in treating diseases mediated by these activities. The compounds of the invention are of the formula (1):



(1)

and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein:

Ar^1 is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

L^1 and L^2 are linkers;

each R^1 is independently a noninterfering substituent;

Z^1 is CR^2 or N wherein R^2 is hydrogen or a noninterfering substituent;

m is 0-4;

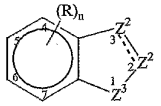
each of n and p is an integer from 0-2 wherein the sum of n and p is 0-3;

Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring;

Z is $-W_i-COX_jY$ wherein Y is COR^3 or an isostere thereof; R^3 is a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;

wherein the smallest number of covalent bonds in the compound separating the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of Ar^1 bonded to L^2 and the atom of Ar^2 bonded to L^1 is 4.5-24 angstroms;

with the proviso that the portion of the compound represented by Ar^2-Z is not



wherein ⫽ represents a single or double bond; n is 0-3; one Z^2 is CA or CRA and the other is CR, CR_2, NR or N; A is $-W_i-COX_jY$ wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1; Z^3 is NR or O; and each R is independently hydrogen or a noninterfering substituent.

The invention is further directed to methods of treating inflammation or proliferative conditions using these compounds. The invention is also directed to treating

conditions associated with cardiac failure and Alzheimer's disease using the invention compounds.

Detailed Description

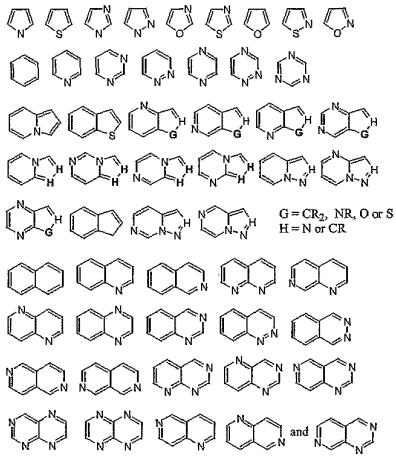
The compounds of formula (1) are useful in treating conditions which are characterized by overactivity of p38 kinase, in particular the α-isoform. Conditions "characterized by enhanced p38-α activity" include those where this enzyme is present in increased amount or wherein the enzyme has been modified to increase its inherent activity, or both. Thus, "enhanced activity" refers to any condition wherein the effectiveness of these proteins is undesirably high, regardless of the cause.

The compounds of the invention are useful in conditions where p38-α kinase shows enhanced activity. These conditions are those in which fibrosis and organ sclerosis are caused by, or accompanied by, inflammation, oxidation injury, hypoxia, altered temperature or extracellular osmolarity, conditions causing cellular stress, apoptosis or necrosis. These conditions include ischemia-reperfusion injury, congestive heart failure, progressive pulmonary and bronchial fibrosis, hepatitis, arthritis, inflammatory bowel disease, glomerular sclerosis, interstitial renal fibrosis, chronic scarring diseases of the eyes, bladder and reproductive tract, bone marrow dysplasia, chronic infectious or autoimmune states, spinal chord injury and traumatic or surgical wounds. These conditions, of course, would be benefited by compounds which inhibit p38-α. Methods of treatment with the compounds of the invention are further discussed below.

The compounds useful in the invention are derivatives of piperadine/piperazine-type compounds containing a mandatory substituent, Z attached to the aromatic moiety Ar^2 The aromatic moiety is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms. The aromatic moiety may be optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring.

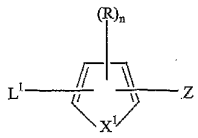
In somewhat greater detail the aromatic moiety Ar^2 comprises an optionally substituted monocyclic or polycyclic aromatic nucleus, wherein the aromatic nucleus consists of a carbocyclic or heterocyclic ring selected from (i) a five-membered heterocyclic or carbocyclic ring (ii) a six-membered carbocyclic or heterocyclic ring; (iii) a five-membered carbocyclic or heterocyclic ring fused to another five-membered carbocyclic or heterocyclic ring; (iv) a six-membered carbocyclic or heterocyclic ring fused to another six-

membered carbocyclic or heterocyclic ring; and (v) a five-membered heterocyclic or carbocyclic ring fused to a six-membered carbocyclic or heterocyclic ring. Examples of the foregoing include the following aromatic moieties:



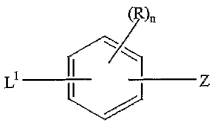
where R is a noninterfering substituent.

Particular examples of Ar^2 in formula (1) are such that the portion of compound (1) represented by L^1-Ar^2-Z is selected from the following:



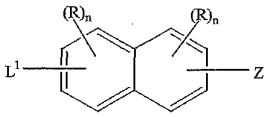
(I)

wherein n is 0, 1 or 2; X^1 is NR, CR_2, O or S; and each R is independently H or a noninterfering substituent; and two or more R groups may form a fused ring;



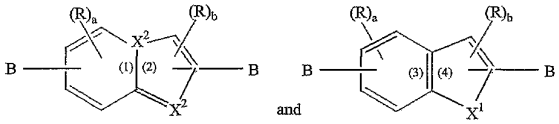
(II)

wherein n is 0-4; R is H or a noninterfering substituent where two or more R groups may form a fused ring; and one or more ring carbons may be optionally replaced with nitrogen;



(III)

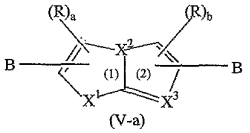
wherein each n is inpendently 0 to 3; R is H or a noninterfering substituent, where two or more R groups may form a fused ring; and one or more ring carbons may be optionally replaced with nitrogen;



(IV-a) and (IV-b)

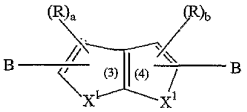
wherein, subject to the proviso set forth above with respect to formula (1), one B is L^1 and the other is Z; wherein a is 0 to 4 such that the positions on the six membered rings (1) and (3) to which $(R)_a$ is bonded can include X^2 when X^2 is C; b is 0 –3 such that the

positions on the five-membered rings (2) and (4) to which $(R)_b$ is bonded can include X^2 and X^1, when X^2 is C and X^1 is N or C; each X^2 is independently N or CR; $X^1$is NR, CR_2, O or S; each R is H or a noninterfering substituent where two or more R groups may form a fused ring; wherein one or more of the ring carbons that are at positions other than X^2 or X^1 and that are also not bound to B can be optionally replaced with N;



(V-a)

and



(V-b)

wherein one B is L^1 and the other is Z; a is 0-4 such that the positions on the rings (1) and (3) to which $(R)_a$ can be bonded include X^2 and X^1 where X^2 is C and X^1 is C or N; b is 0 or 3 such that the positions on the rings (2) and (4) to which $(R)_b$ can be bonded include X^1, X^2 and X^3 when X^1 is C or N and X^2 and/or X^3 are C; each X^1 is independently NR, $C(R)_2$, O or S; X^2 and X^3 are independently N or CR; each R is independently H or a noninterfering substituent where two or more R groups can optionally form a fused ring; wherein one or more of the ring carbons that are at positions other than X^1, X^2 or X^3, and that are also not bound to B, can be optionally replaced with N.

Certain positions of the molecule of formula I are described as permitting "noninterfering substituents." This terminology is used because the substituents in these positions generally speaking are not relevant to the essential activity of the molecule taken as a whole. A wide variety of substituents can be employed in these positions, and it is well within ordinary skill to determine whether any particular arbitrary substituent is or is not "noninterfering."

As used herein, a "noninterfering substituent" is a substituent which leaves the ability of the compound of formula (1) to inhibit p38-α activity qualitatively intact. Thus, the substituent may alter the degree of inhibition of p38-α. However, as long as the compound of formula (1) retains the ability to inhibit p38-α activity, the substituent will be classified as "noninterfering." A number of assays for determining the ability of any compound to inhibit p38- α activity are available in the art. A whole blood assay for this

evaluation is illustrated below. The gene for p38- α has been cloned and the protein can be prepared recombinantly and its activity assessed, including an assessment of the ability of an arbitrarily chosen compound to interfere with this activity. The essential features of the molecule are tightly defined. The positions which are occupied by "noninterfering substituents" can be substituted by conventional organic moieties as is understood in the art. It is irrelevant to the present invention to test the outer limits of such substitutions. The essential features of the compounds are those set forth with particularity herein.

In addition, L^1 and L^2 are described herein as linkers. The nature of such linkers is less important than the distance they impart between the portions of the molecule. Typical linkers include alkylene, *i.e.* $(CH_2)_n$-R; alkenylene - *i.e.*, an alkylene moiety which contains a double bond, including a double bond at one terminus. Other suitable linkers include, for example, substituted alkylenes or alkenylenes, carbonyl moieties, and the like.

As used herein, "hydrocarbyl residue" refers to a residue which contains only carbon and hydrogen. The residue may be aliphatic or aromatic, straight-chain, cyclic, branched, saturated or unsaturated. The hydrocarbyl residue, when so stated however, may contain heteroatoms over and above the carbon and hydrogen members of the substituent residue. Thus, when specifically noted as containing such heteroatoms, the hydrocarbyl residue may also contain carbonyl groups, amino groups, hydroxyl groups and the like, or contain heteroatoms within the "backbone" of the hydrocarbyl residue.

As used herein, "inorganic residue" refers to a residue that does not contain carbon. Examples include, but are not limited to, halo, hydroxy, NO_2, or NH_2.

As used herein, the term "alkyl," "alkenyl" and "alkynyl" include straight- and branched-chain and cyclic monovalent substituents. Examples include methyl, ethyl, isobutyl, cyclohexyl, cyclopentylethyl, 2-propenyl, 3-butynyl, and the like. Typically, the alkyl, alkenyl and alkynyl substituents contain 1-10C (alkyl) or 2-10C (alkenyl or alkynyl). Preferably they contain 1-6C (alkyl) or 2-6C (alkenyl or alkynyl). Heteroalkyl, heteroalkenyl and heteroalkynyl are similarly defined but may contain 1-2 O, S or N heteroatoms or combinations thereof within the backbone residue.

As used herein, "acyl" encompasses the definitions of alkyl, alkenyl, alkynyl and the related hetero-forms which are coupled to an additional residue through a carbonyl group.

The term "Aromatic" with respect to moiety Ar^1 refers to a monocyclic or fused bicyclic moiety such as phenyl or naphthyl; "heteroaromatic" also refers to monocyclic or fused bicyclic ring systems containing one or more heteroatoms selected from O, S and N. The inclusion of a heteroatom permits inclusion of 5-membered rings as well as 6-membered rings. Thus, typical aromatic systems include pyridyl, pyrimidyl, indolyl, benzimidazolyl, benzotriazolyl, isoquinolyl, quinolyl, benzothiazolyl, benzofuranyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl and the like. Any monocyclic or fused ring bicyclic system which has the characteristics of aromaticity in terms of electron distribution throughout the ring system is included in this definition. Typically, the ring systems contain 5-12 ring member atoms.

Similarly, "arylalkyl" and "heteroalkyl" refer to aromatic and heteroaromatic systems which are coupled to another residue through a carbon chain, including substituted or unsubstituted, saturated or unsaturated, carbon chains, typically of 1-6C. These carbon chains may also include a carbonyl group, thus making them able to provide substituents as an acyl moiety.

When the compounds of Formula (1) contain one or more chiral centers, the invention includes optically pure forms as well as mixtures of stereoisomers or enantiomers

With respect to the portion of the compound between the Ar^1 and Ar^2, linkers L^2 and L^1, in combination with the piperadine/piperazine ring, provide for separation of the atom of Ar^1 bonded to L^2 from the atom of Ar^2 bonded to L^1 by a defined minimum number of covalent bond lengths counted end-to-end through the compound, as opposed to a measurement of linear distance through space. More particularly, the smallest number of bonds counted end-to-end in the compound separating the atom of Ar^1 bonded to L^2 from the atom of Ar^2 bonded to L^1 is at least 5, and preferably from 6 to 12, wherein the length of each of such bonds is 1.2 to 2.0 angstroms. In terms of a linear distance through space, the linear distance measured through space from the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is a distance of 4.5-24Å, preferably 6-20Å, and more preferably 7.5-10Å.

Typical, but nonlimiting, embodiments of L^1 and L^2 are CO and isosteres thereof, or optionally substituted isosteres, or longer chain forms. L^2, in particular, may be alkylene or alkenylene optionally substituted with noninterfering substituents or L^1 or L^2 may be or may include a heteroatom such as N, S or O. Such substituents include, but are limited to, a

moiety selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two substituents on L^2 can be joined to form a non-aromatic saturated or unsaturated ring that includes 0-3 heteroatoms which are O, S and/or N and which contains 3 to 8 members or said two substituents can be joined to form a carbonyl moiety or an oxime, oximeether, oximeester or ketal of said carbonyl moiety.

Isosteres of CO and CH_2, include SO, SO_2, or CHOH. CO and CH_2 are preferred. Thus, L^2 is substituted with 0-2 substituents. Where appropriate, two optional substituents on L^2 can be joined to form a non-aromatic saturated or unsaturated hydrocarbyl ring that includes 0-3 heteroatoms such as O, S and/or N and which contains 3 to 8 members. Two optional substituents on L^2 can be joined to form a carbonyl moiety which can be subsequently converted to an oxime, an oximeether, an oximeester, or a ketal.

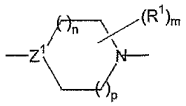
Ar^1 is aryl, heteroaryl, including 6-5 fused heteroaryl, cycloaliphatic or cycloheteroaliphatic that can be optionally substituted. Ar is preferably optionally substituted phenyl.

Each substituent on Ar^1 is independently a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and N, or is an inorganic residue. Preferred substituents include those selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said optional substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members. More preferred substituents include halo, alkyl (1-4C) and more preferably, fluoro, chloro and methyl. These substituents may occupy all available positions of the aryl ring of Ar^1, preferably 1-2 positions, most preferably one position. These substituents may be optionally substituted with substituents similar to those listed.

Of course some substituents, such as halo, are not further substituted, as known to one skilled in the art.

Two substituents on Ar^1 can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

Between L^1 and L^2 is a piperidine-type moiety of the following formula:



wherein Z^1 is CR^2 or N and R^2 is H or a noninterfering substituent. Each of n and p is an integer from 0-2 wherein the sum of n and p is 0-3. The noninterfering substituents R^2 include, without limitation, halo, alkyl, alkoxy, aryl, arylalkyl, aryloxy, heteroaryl, acyl, carboxy, or hydroxy. Preferably, R^2 is H, alkyl, OR, NR_2, SR or halo, where R is H or alkyl. Additionally, R^2 can be joined with an R^1 substituent to form an optionally substituted non-aromatic saturated or unsaturated hydrocarbyl ring which contains 3-8 members and 0-3 heteroatoms such as O, N and/or S. Preferred embodiments include compounds wherein Z^1 is CH or N, and those wherein both n and p are 1.

R^1 represents a noninterfering substituent such as a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and N. Preferably R^1 is alkyl, alkoxy, aryl, arylalkyl, aryloxy, heteroalkyl, heteroaryl, heteroarylalkyl, RCO, =O, acyl, halo, CN, OR, NRCOR, NR, wherein R is H, alkyl (preferably 1-4C), aryl, or hetero forms thereof. Each appropriate substituent is itself unsubstituted or substituted with 1-3 substituents. The substituents are preferably independently selected from a group that includes alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^1 on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, or R^1 is =O or an oxime, oximeether, oximeester or ketal thereof. R^1 may occur m times on the ring; m is an integer of 0-4. Preferred embodiments of R^1 comprise alkyl (1-4C) especially two alkyl substituents and carbonyl. Most preferably R^1

comprises two methyl groups at positions 2 and 5 or 3 and 6 of a piperidinyl or piperazinyl ring or =O preferably at the 5-position of the ring. The substituted forms may be chiral and an isolated enantiomer may be preferred.

Z is $-W_i-COX_jY$ wherein Y is COR^3 or an isostere thereof and R^3 is a noninterfering substituent. Each of W and X is a spacer and may be, for example, optionally substituted alkyl, alkenyl, or alkynyl, each of i and j is 0 or 1. Preferably, W and X are unsubstituted. Preferably, j is 0 so that the two carbonyl groups are adjacent to each other. Preferably, also, i is 0 so that the proximal CO is adjacent the ring. However, compounds wherein the proximal CO is spaced from the ring can readily be prepared by selective reduction of an initially glyoxal substituted Ar^2.

The noninterfering substituent represented by R^3, when R^3 is other than H, is a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and/or N or is an inorganic residue. Preferred are embodiments wherein R^3 is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted with halo, alkyl, heteroalkyl, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, CN, COOR, $CONR_2$, COR, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, or wherein R^3 is OR, NR_2, SR, $NRCONR_2$, $OCONR_2$, or $NRSO_2NR_2$, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, and wherein two R attached to the same atom may form a 3-8 member ring and wherein said ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined.

Other preferred embodiments of R^3 are H, heteroarylalkyl, $-NR_2$, heteroaryl, -COOR, $-NHRNR_2$, heteroaryl-COOR, heteroaryloxy, -OR, heteroaryl-NR_2, -NROR and alkyl. Most preferably R^3 is isopropyl piperazinyl, methyl piperazinyl, dimethylamine, piperazinyl, isobutyl carboxylate, oxycarbonylethyl, morpholinyl, aminoethyldimethylamine, isobutyl carboxylate piperazinyl, oxypiperazinyl,

ethylcarboxylate piperazinyl, methoxy, ethoxy, hydroxy, methyl, amine, aminoethyl pyrrolidinyl, aminopropanediol, piperidinyl, pyrrolidinyl-piperidinyl, or methyl piperidinyl.

Isosteres of COR^3 as represented by Y are defined as follows.

The isosteres have varying lipophilicity and may contribute to enhanced metabolic stability. Thus, Y, as shown, may be replaced by the isosteres in Table 1.

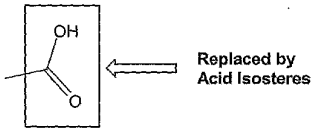
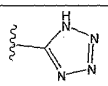
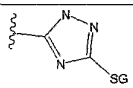


Table 1 - Acid Isosteres

Names of Groups	Chemical Structures	Substitution Groups (SG)
tetrazole		n/a
1,2,3-triazole		H; SCH_3; $COCH_3$; Br; $SOCH_3$; SO_2CH_3; NO_2; CF_3; CN; COOMe
1,2,4-triazole		H; SCH_3; $COCH_3$; Br; $SOCH_3$; SO_2CH_3; NO_2
imidazole		H; SCH_3; $COCH_3$; Br; $SOCH_3$; SO_2CH_3; NO_2

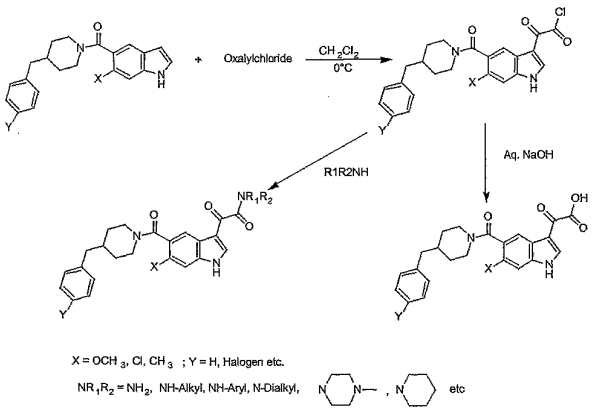
Thus, isosteres include tetrazole, 1,2,3-triazole, 1,2,4-triazole and imidazole.

The compounds of formula (1) may be supplied in the form of their pharmaceutically acceptable acid-addition salts including salts of inorganic acids such as hydrochloric, sulfuric, hydrobromic, or phosphoric acid or salts of organic acids such as

acetic, tartaric, succinic, benzoic, salicylic, and the like. If a carboxyl moiety is present on the compound of formula (1), the compound may also be supplied as a salt with a pharmaceutically acceptable cation.

Synthesis of the Invention Compounds

Copending, commonly-assigned U.S.S.N 09/575,060, incorporated herein by reference in its entirety, illustrated the following reaction scheme for conversion of a 4-benzyl piperidinyl-indole-5-carboxamide to the glyoxalic acid compounds of the invention and derivatives thereof:

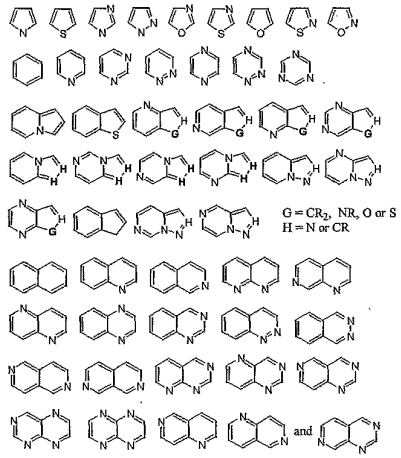


In the present invention, the indole moiety is generalized to Ar^2 in formula (1) above where Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring. Preferably the moiety Ar^2 comprises an optionally substituted monocyclic or polycyclic aromatic

nucleus, wherein said aromatic nucleus consists of carbocyclic or heterocyclic ring selected from (i) a five-membered heterocyclic or carbocyclic ring (ii) a six-membered carbocyclic or heterocyclic ring; (iii) a five-membered carbocyclic or heterocycloc ring fused to another five-membered carbocyclic or heterocyclic ring; (iv) a six-membered carbocyclic or heterocyclic ring fused to another six-membered carbocyclic or heterocyclic ring; and (v) a five-membered heterocyclic or carbocyclic ring fused to a six-membered carbocyclic or heterocyclic ring. Formula (1), as required by the proviso stated above, excludes the indole type compounds disclosed and claimed in U.S.S.N. 09/575,060 filed May 21, 1999 and incorporated herein by reference.

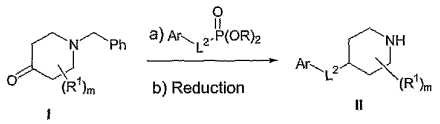
As disclosed commonly assigned in U.S.S.N 09/575,060, the glyoxal type substituent at position 3 can be generalized to -W_1COXjY.

The Ar^2 moiety may be generalized as:



Methods to synthesize the compounds of the invention are, in general, known in the art. For example, commonly assigned U.S.S.N 09/575,060, incorporated herein by reference in

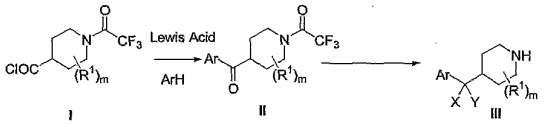
its entirety, disclosed that piperidine moieties can be obtained using the following reaction scheme



I II

where an appropriate piperidone such as **I**, is treated with substituted benzyl phosphonate esters in the presence of a base such as sodium hydride to give alkenes which can be reduced to the corresponding substituted 4-benzylpiperidine such as **II**. The hydrogenations are typically done in the presence of catalytic metals in solvents such as methanol, ethanol and ethyl acetate.

An alternative to the above disclosed in U.S.S.N 09/575,060 as follows:



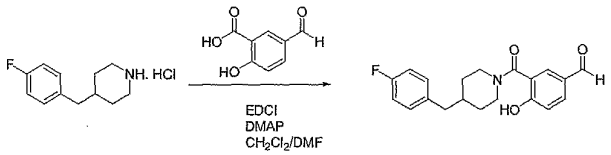
I II III

where isonipecotoyl chlorides such as **I** can be used to acylate appropriately substituted benzenes (ArH) in the presence of a Lewis acid such as aluminum chloride to give the ketones **II**. Further modifications of the carbonyl moiety of **II** using methods and routes generally known can then lead to the desired compounds **III**.

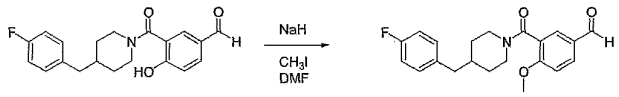
The following reaction schemes illustrate methods for preparing compounds of the present invention.

Scheme I

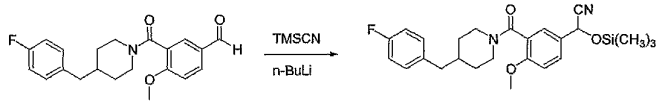
Step A



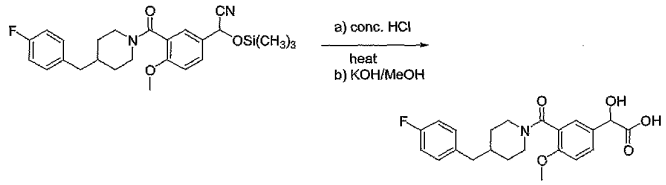
Step B



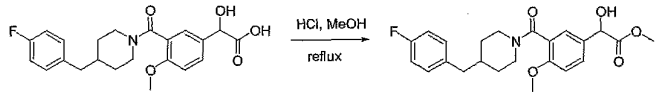
Step C



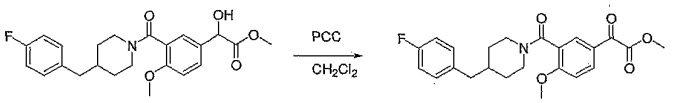
Step D



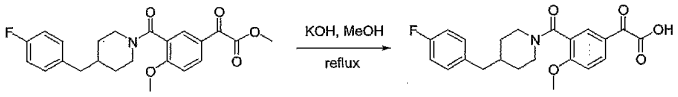
Step E



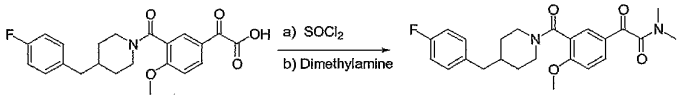
Step F



Step G

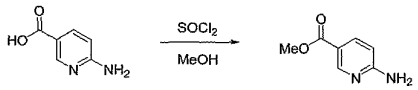


Step H

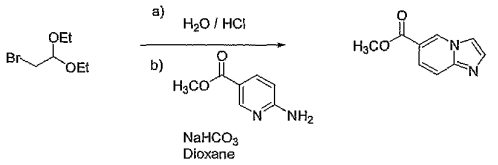


Scheme II

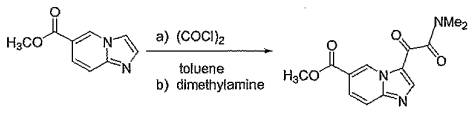
Step A



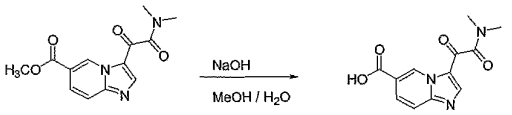
Step B



Step C



Step D



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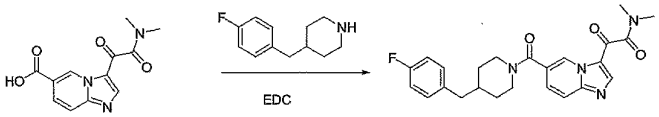
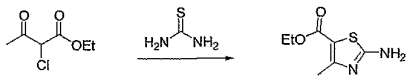
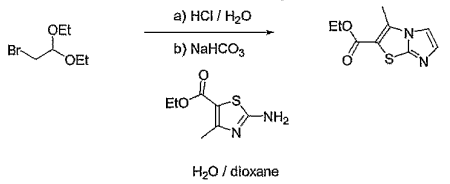


Scheme III

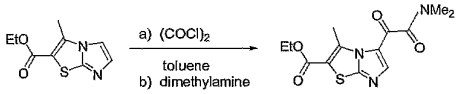
Step A



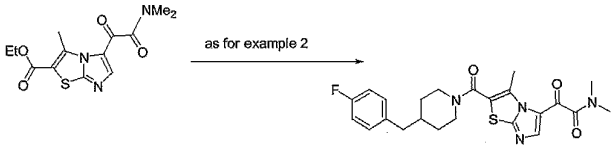
Step B



Step C

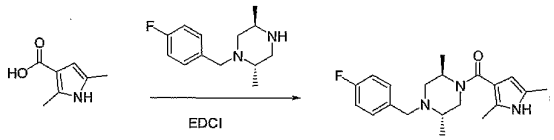


Step D

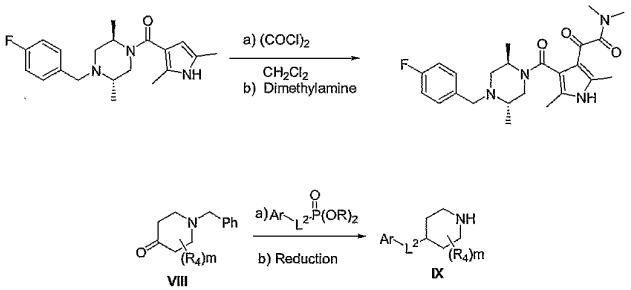


Scheme IV

Step A



Step B



Scheme 4

Assays for p38 α Kinase Inhibition

For each of the assay procedures described below, the TNF-α production correlates to the activity of p38-α kinase.

A. Human Whole Blood Assay for p38 Kinase Inhibition

Venous blood is collected from healthy male volunteers into a heparinized syringe and is used within 2 hours of collection. Test compounds are dissolved in 100% DMSO and 1 μl aliquots of drug concentrations ranging from 0 to 1 mM are dispensed into quadruplicate wells of a 24-well microtiter plate (Nunclon Delta SI, Applied Scientific, So. San Francisco, CA). Whole blood is added at a volume of 1 ml/well and the mixture is incubated for 15 minutes with constant shaking (Titer Plate Shaker, Lab-Line Instruments, Inc., Melrose Park, IL) at a humidified atmosphere of 5% CO_2 at 37 °C. Whole blood is cultured either undiluted or at a final dilution of 1:10 with RPMI 1640 (Gibco 31800 + $NaHCO_3$, Life Technologies, Rockville, MD and Scios, Inc., Sunnyvale, CA). At the end of the incubation period, 10 μl of LPS (*E. coli* 0111:B4, Sigma Chemical Co., St. Louis, MO) is added to each well to a final concentration of 1 or 0.1 μg/ml for undiluted or 1:10 diluted whole blood, respectively. The incubation is continued for an additional 2 hours.

The reaction is stopped by placing the microtiter plates in an ice bath and plasma or cell-free supernates are collected by centrifugation at 3000 rpm for 10 minutes at 4°C. The plasma samples are stored at -80°C until assayed for TNF-α levels by ELISA, following the directions supplied by Quantikine Human TNF-α assay kit (R&D Systems, Minneapolis, MN).

IC_{50} values are calculated using the concentration of inhibitor that causes a 50% decrease as compared to a control.

B. Enriched Mononuclear Cell Assay for p38 Kinase Inhibition

The enriched mononuclear cell assay, the protocol of which is set forth below, begins with cryopreserved Human Peripheral Blood Mononuclear Cells (HPBMCs) (Clonetics Corp.) that are rinsed and resuspended in a warm mixture of cell growth media. The resuspended cells are then counted and seeded at $1x10^6$ cells/well in a 24-well microtitre plate. The plates are then placed in an incubator for an hour to allow the cells to settle in each well. After the cells have settled, the media is aspirated and new media containing 100 ng/ml of the cytokine stimulatory factor Lipopolysaccharide (LPS) and a test chemical compound is added to each well of the microtiter plate. Thus, each well contains HPBMCs, LPS and a test chemical compound. The cells are then incubated for 2 hours, and the amount of the cytokine Tumor Necrosis Factor Alpha (TNF-α) is measured using an Enzyme Linked Immunoassay (ELISA). One such ELISA for detecting the levels of TNF-α is commercially available from R&D Systems. The amount of TNF-α production by the HPBMCs in each well is then compared to a control well to determine whether the chemical compound acts as an inhibitor of cytokine production.

LPS induced cytokine synthesis in HPBMCs

Cryopreserved HPBMC (cat#CC-2702 Clonetics Corp)

LGM-3 media (cat#CC-3212 Clonetics Corp)

LPS stock 10μg/ml (Cat. No. L 2630 serotype 0111:B4 Sigma)

Human TNF-α ELISA (R&D Systems)

DNase I (10mg/ml stock)

Preparation of cells.

LGM-3 media warmed to 37°C.

5μl of DNase I stock added to 10ml media.

Cells thawed rapidly and dispersed into above.

Centrifuge 200xg x10min @ RT.

Pellet up in 10ml sterile PBS.

Centrifuge 200xg x10min @ RT.

Pellet resuspended in 10ml LGM-3 then diluted to 50ml with LGM-3.

Perform cell count.

Adjust to 1xE06 cells/well.

Seed 1ml/well of a 24 well plate.

Place plate in incubator to plate down for 1 hour.

Preparation of incubation media.

LGM-3 containing 100ng/ml LPS (e.g. 50ml media plus 0.5ml LPS stock)

Aliquot into 2ml aliquots and add 1000X inhibitor dilutions.

Incubation

When cells have plated down aspirate media away and overlay with 1ml relevant incubation media. Return plate to incubator for 2 hours or 24 hours. Remove supernatants after incubation to a labeled tube and either perform TNF (or other) ELISA immediately or freeze for later assay.

IC_{50} values are calculated using the concentration of inhibitor that causes a 50% decrease as compared to a control.

Administration and Use

The compounds of the invention are useful among other indications in treating conditions associated with inflammation. Thus, the compounds of formula (1) or their pharmaceutically acceptable salts are used in the manufacture of a medicament for prophylactic or therapeutic treatment of mammals, including humans, in respect of conditions characterized by excessive production of cytokines and/or inappropriate or

unregulated cytokine activity on such cells as cardiomyocytes, cardiofibroblasts and macrophages.

The compounds of the invention inhibit the production of cytokines such as TNF, IL-1, IL-6 and IL-8, cytokines that are important proinflammatory constituents in many different disease states and syndromes. Thus, inhibition of these cytokines has benefit in controlling and mitigating many diseases. The compounds of the invention are shown herein to inhibit a member of the MAP kinase family variously called p38 MAPK (or p38), CSBP, or SAPK-2. The activation of this protein has been shown to accompany exacerbation of the diseases in response to stress caused, for example, by treatment with lipopolysaccharides or cytokines such as TNF and IL-1. Inhibition of p38 activity, therefore, is predictive of the ability of a medicament to provide a beneficial effect in treating diseases such as Alzheimer's, coronary artery disease, congestive heart failure, cardiomyopathy, myocarditis, vasculitis, restenosis, such as occurs following coronary angioplasty, atherosclerosis, IBD, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, multiple sclerosis, acute respiratory distress syndrome (ARDS), asthma, chronic obstructive pulmonary disease (COPD), silicosis, pulmonary sarcosis, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, heart and brain failure (stroke) that are characterized by ischemia and reperfusion injury, surgical procedures, such as transplantation procedures and graft rejections, cardiopulmonary bypass, coronary artery bypass graft, CNS injuries, including open and closed head trauma, inflammatory eye conditions such as conjunctivitis and uveitis, acute renal failure, glomerulonephritis, inflammatory bowel diseases, such as Crohn's disease or ulcerative colitis, graft vs. host disease, bone resorption diseases like osteoporosis, type II diabetes, pyresis, psoriasis, cachexia, viral diseases such as those caused by HIV, CMV, and Herpes, and cerebral malaria.

Within the last several years, p38 has been shown to comprise a group of MAP kinases designated p38-α, p38-β, p38-γ and p38-δ. Jiang, Y., *et al., J Biol Chem* (1996) 271:17920-17926 reported characterization of p38-β as a 372-amino acid protein closely related to p38-α. In comparing the activity of p38-α with that of p38-β, the authors state that while both are activated by proinflammatory cytokines and environmental stress, p38-β was preferentially activated by MAP kinase kinase-6 (MKK6) and preferentially activated

transcription factor 2, thus suggesting that separate mechanisms for action may be associated with these forms.

Kumar, S., *et al., Biochem Biophys Res Comm* (1997) 235:533-538 and Stein, B., *et al., J Biol Chem* (1997) 272:19509-19517 reported a second isoform of p38-β, p38-β2, containing 364 amino acids with 73% identity to p38-α. All of these reports show evidence that p38-β is activated by proinflammatory cytokines and environmental stress, although the second reported p38-β isoform, p38-β2, appears to be preferentially expressed in the CNS, heart and skeletal muscle compared to the more ubiquitous tissue expression of p38-α. Furthermore, activated transcription factor-2 (ATF-2) was observed to be a better substrate for p38-β2 than for p38-α, thus suggesting that separate mechanisms of action may be associated with these forms. The physiological role of p38-β1 has been called into question by the latter two reports since it cannot be found in human tissue and does not exhibit appreciable kinase activity with the substrates of p38-α.

The identification of p38-γ was reported by Li, Z., *et al., Biochem Biophys Res Comm* (1996) 228:334-340 and of p38-δ by Wang, X., *et al., J Biol Chem* (1997) 272:23668-23674 and by Kumar, S., *et al., Biochem Biophys Res Comm* (1997) 235:533-538. The data suggest that these two p38 isoforms (γ and δ) represent a unique subset of the MAPK family based on their tissue expression patterns, substrate utilization, response to direct and indirect stimuli, and susceptibility to kinase inhibitors.

Various results with regard to response to drugs targeting the p38 family as between p38-α and either the putative p38-β1 or p38-β2 or both were reported by Jiang, Kumar, and Stein cited above as well as by Eyers, P.A., *et al., Chem and Biol* (1995) 5:321-328. An additional paper by Wang, Y., *et al., J Biol Chem* (1998) 273:2161-2168 suggests the significance of such differential effects. As pointed out by Wang, a number of stimuli, such as myocardial infarction, hypertension, valvular diseases, viral myocarditis, and dilated cardiomyopathy lead to an increase in cardiac workload and elevated mechanical stress on cardiomyocytes. These are said to lead to an adaptive hypertrophic response which, if not controlled, has decidedly negative consequences. Wang cites previous studies which have shown that in ischemia reperfusion treated hearts, p38 MAPK activities are elevated in association with hypertrophy and programmed cell death. Wang shows in the cited paper that activation of p38-β activity results in hypertrophy, whereas activation of p38-α activity

leads to myocyte apoptosis. Thus, selective inhibition of p38-α activity as compared to p38-β activity will be of benefit in treating conditions associated with cardiac failure. These conditions include congestive heart failure, cardiomyopathy, myocarditis, vasculitis, vascular restenosis, valvular disease, conditions associated with cardiopulmonary bypass, coronary artery bypass, grafts and vascular grafts. Further, to the extent that the α-isoform is toxic in other muscle cell types, α-selective inhibitors would be useful for conditions associated with cachexia attributed to TNF or other conditions such as cancer, infection, or autoimmune disease.

Thus, the invention encompasses the use of compounds which selectively inhibit the activity of the p38-α isoform for treating conditions associated with activation of p38-α, in particular those associated with cardiac hypertrophy, ischemia or other environmental stress such as oxidation injury, hyperosmolarity or other agents or factors that activate p38-α kinase, or cardiac failure, for example, congestive heart failure, cardiomyopathy and myocarditis.

The manner of administration and formulation of the compounds useful in the invention and their related compounds will depend on the nature of the condition, the severity of the condition, the particular subject to be treated, and the judgement of the practitioner; formulation will depend on mode of administration. As the compounds of the invention are small molecules, they are conveniently administered by oral administration by compounding them with suitable pharmaceutical excipients so as to provide tablets, capsules, syrups, and the like. Suitable formulations for oral administration may also include minor components such as buffers, flavoring agents and the like. Typically, the amount of active ingredient in the formulations will be in the range of 5%-95% of the total formulation, but wide variation is permitted depending on the carrier. Suitable carriers include sucrose, pectin, magnesium stearate, lactose, peanut oil, olive oil, water, and the like.

The compounds useful in the invention may also be administered through suppositories or other transmucosal vehicles. Typically, such formulations will include excipients that facilitate the passage of the compound through the mucosa such as pharmaceutically acceptable detergents.

The compounds may also be administered topically, for topical conditions such as psoriasis, or in formulation intended to penetrate the skin. These include lotions, creams, ointments and the like which can be formulated by known methods.

The compounds may also be administered by injection, including intravenous, intramuscular, subcutaneous or intraperitoneal injection. Typical formulations for such use are liquid formulations in isotonic vehicles such as Hank's solution or Ringer's solution.

Alternative formulations include nasal sprays, liposomal formulations, slow-release formulations, and the like, as are known in the art.

Any suitable formulation may be used. A compendium of art-known formulations is found in Remington's Pharmaceutical Sciences, latest edition, Mack Publishing Company, Easton, PA. Reference to this manual is routine in the art.

The dosages of the compounds of the invention will depend on a number of factors which will vary from patient to patient. However, it is believed that generally, the daily oral dosage will utilize 0.001-100 mg/kg total body weight, preferably from 0.01-50 mg/kg and more preferably about 0.01 mg/kg-10 mg/kg. The dose regimen will vary, however, depending on the conditions being treated and the judgment of the practitioner.

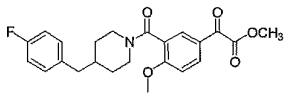
It should be noted that the compounds of formula (1) can be administered as individual active ingredients, or as mixtures of several embodiments of this formula. In addition, the inhibitors of p38 kinase can be used as single therapeutic agents or in combination with other therapeutic agents. Drugs that could be usefully combined with these compounds include natural or synthetic corticosteroids, particularly prednisone and its derivatives, monoclonal antibodies targeting cells of the immune system, antibodies or soluble receptors or receptor fusion proteins targeting immune or non-immune cytokines, and small molecule inhibitors of cell division, protein synthesis, or mRNA transcription or translation, or inhibitors of immune cell differentiation or activation.

As implied above, although the compounds of the invention may be used in humans, they are also available for veterinary use in treating animal subjects.

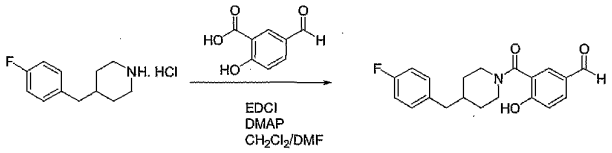
The following examples are intended to illustrate but not to limit the invention. The compounds described and prepared in examples 1-4 below are inhibitors of p38-α kinase.

Example 1

{3-[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-4-methoxy-phenyl}-oxo-acetic acid methyl ester

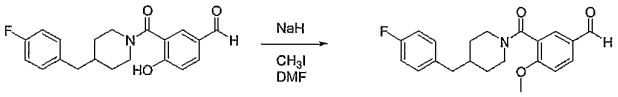


Step A



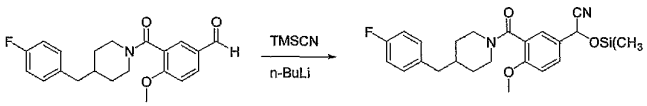
Under nitrogen protection, to a 250 mL R.B. dry flask containing 5.6 g (24.4 mMol) 4-fluoro-benzyl piperidine HCl salt was added 100 ml anhydrous CH_2Cl_2, followed by addition of 3.48 ml triethylamine (25 mMol). The suspension was allowed to stir at room temperature for a few minutes until it became a clear solution. To this solution was then added 4.37 g 5-formylsalicyclic acid (25 mMol), 4.8 g (25 mMol) of 1-ethyl-3-(3-dimethyl aminopropyl)-carbodiimide, 0.153 g (1.25 mMol) of 4-(dimethylamino)-pyridine. After overnight stirring, the reaction mixture was diluted with 100 mL of CH_2Cl_2, washed with H_2O, brine. The organic layers were then dried over anhydrous sodium sulfate, concentrated and purified by column chromatography eluting with CH_2Cl_2, giving 3.65 g (10.7 mMol) of desired product. (yield: 43.8%)

Step B



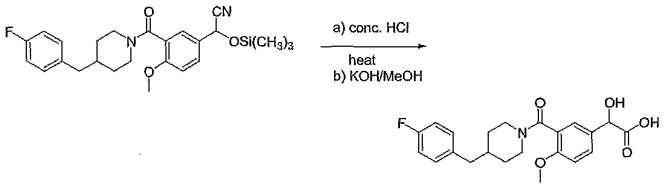
3.62 gram (10.6 mMol) aldehyde was dissolved in 100 mL anhydrous DMF under an argon atmosphere. To this solution, at 0 °C was added 4.66 g NaH (60 % dispersion in mineral oil, 11.7 mMol). The reaction was allowed to stir at 0 °C for 0.5 h before warming up to room temperature, stirring continued until there were no more bubbles produced. The flask was then cooled to 0 °C again, followed by addition of 0.73 mL of methyl iodide (11.7 mMol). After stirring at 0 °C for 0.5 h, the reaction was warmed up to room temperature, and continued stirring for another 4 h. DMF was evaporated off under reduced pressure. The resulting residue was re-dissolved in 100 mL of CH_2Cl_2, washed twice with H_2O, and brine. Organic layers were dried over anhydrous sodium sulfate, concentrated and purified by column chromatography in a gradient of 100% CH_2Cl_2 to 2% MeOH/CH_2Cl_2. 2.65 g (7.46 mMol) of product was obtained in a yield of 70.4%.

Step C



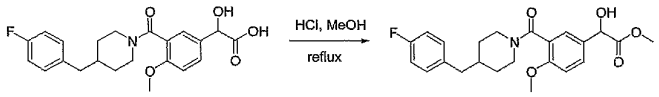
Under nitrogen protection, 2.64 g (7.43 mMol) of aldehyde was dissolved in 75 mL anhydrous THF. At 0 °C, to this solution was added 1.1 mL of trimethylsilyl cyanide (8.2 mMol), followed by addition of 2-3 drops of n-butyllithium (2.5 M solution in hexane). Stirring at 0 °C was continued for 2 h before warmed up to room temperature and stirred overnight. After removing solvents by rotary evaporation, product was obtained in almost quantitative yield as a white power. Without further purification, the material was used directly in next step.

Step D



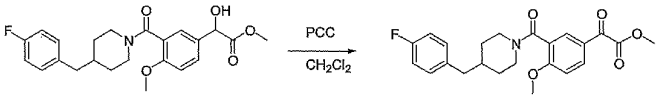
The material obtained from last step was diluted with 60 mL of concentrated HCl and heated to 80 °C with an oil bath overnight. After overnight heating, the aqueous solution was diluted with 100 mL H_2O and aqueous solution was extracted with CH_2Cl_2 (100 mL X 3). Organic layers were washed with brine, dried over sodium sulfate, and concentrated. The residue was then re-dissolved in about 70 mL MeOH, followed by addition of 1.7 g (30.3 mMol) of KOH and the solution was warmed to reflux for 2 h. Reaction was then cooled to room temperature, concentrated, and dried under vacuum. Several grams of crushed ice was added into the flask and acidified with 10 % aqueous HCl. Water (60 mL) was added to dilute the solution, and this aqueous solution was extracted with CH_2Cl_2 (100 mL X 3). Organic layers were washed with brine, dried over sodium sulfate, concentrated to give 2.5g (6.23 mMol) of product.

Step E



In a 50 mL R.B. flask containing a condenser, 130 mg of α-hydroxy acid was dissolved in 4 ml of concentrated HCl:MeOH (1:9) and warmed to reflux. After 1 h, the reaction was cooled to RT and concentrated under reduced pressure. Resulting residue was re-dissolved in 20 mL ethyl acetate and the ethyl acetate layer was washed with 20 mL H_2O, twice with 20 ml saturated $NaHCO_3$ solution, and brine. Organic layer was dried over anhydrous sodium sulfate and concentrated to give 141 mg of crude product.

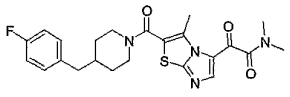
Step F



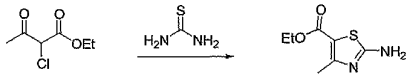
123 mg of methyl ester was dissolved in 4 ml CH_2Cl_2 followed by addition of excess of pyridinium chloromate (1 g, 20 wt. % on basic alumina). The resulting suspension was stirred at room temperature over 24 hours. Solid was filtered and washed with CH_2Cl_2. Combined organic solution was concentrated and product was purified by Preparative thin-layer chromatography with 1% MeOH/CH_2Cl_2 as eluting solution, to give 26 mg of desired product.

Example 2

2-{2-[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-3-methyl-imidazo[2,1-b]thiazol-5-yl}-N,N-dimethyl-2-oxo-acetamide

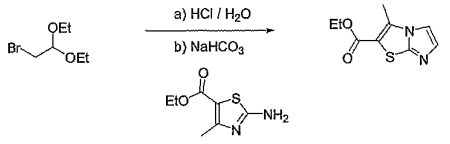


Step A



Thiourea (3.81 g) and ethyl 2-chloroacetoacetate (8.23g)were combined in EtOH (100 mL) and heated at reflux for 14 h. After cooling to RT the EtOH was removed in vacuo and the crude product dissolved in H_2O and neutralized with $NaHCO_3$ followed by extraction with ethyl acetate. The combined extracts were dried, filtered, and concentrated to yield the product as a white powder (8.69 g).

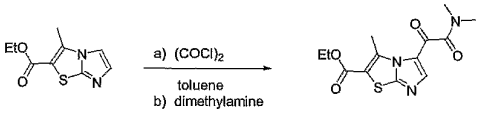
Step B



H_2O / dioxane

To bromoacetaldehyde diethylacetal (11.2 mMol, 2.20 g) in H_2O (75 mL) was added concentrated HCl (1.15 mL) dropwise. After stirring at RT for 14 h the mixture was heated at 80 °C for 30 min. After cooling to RT $NaHCO_3$ (14.5 mMol, 1.22 g) was cautiously added and stirring was continued for 2 h. The ester (8.9 mMol, 1.66 g) was then added and the mix was stirred an additional 1 h before adding dioxane (50 mL). After 30 min the mix was heated to 100 °C for 48 h. After cooling to RT the dioxane was removed by rotary evaporation. The aqueous layer was extracted with CH_2Cl_2. The combined organics were dried (Na_2SO_4), filtered and concentrated. Radial chromatography (10 % MeOH in CH_2Cl_2) yielded 122 mg of the desired product.

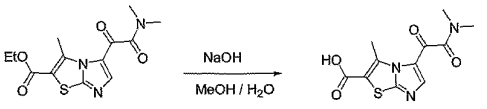
Step C



To the ester (0.19 mMol, 40 mg) in toluene (0.76 mL) at RT was added a 2.0 M solution of oxalyl chloride in CH_2Cl_2 (0.285 mL). The reaction vessel was placed under N_2, sealed, and placed at 125 °C for 12 h. After cooling to RT the volatiles were removed under vacuum. To the crude acid chloride was added CH_2Cl_2 (0.76 mL) and after cooling to 0 °C a 2.0 M solution of dimethylamine in THF (0.285 mL)was added dropwise. The reaction mixture was stirred an additional 30 min at 0 °C and then warmed to RT. After 30

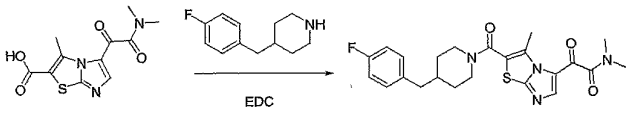
min the reaction was quenched with H_2O and extracted with CH_2Cl_2. The combined extracts were washed with brine and then dried (Na_2SO_4), filtered and concentrated. After radial chromatography (10 % MeOH in CH_2Cl_2) 38 mg of the product was obtained.

Step D



To the ester (0.12 mMol, 38 mg) in MeOH (0.25 mL) and H_2O (0.25 mL) was added NaOH (0.985 N in H_2O, 122 μL). The mixture was stirred at RT for14 h at which time it was acidified with aq. HCl and extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4), filtered, and concentrated to yield 19 mg of the product which carried on to the next step without purification.

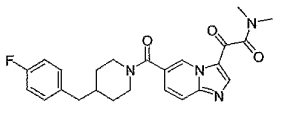
Step E



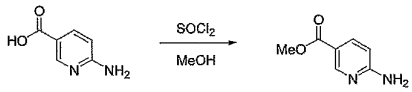
To the acid (0.14 mMol, 19 mg) in CH_2Cl_2 (0.56 mL) was added 4-fluorobenzylpiperidine (0.17 mMol, 39 mg) followed by EDC (0.17 mMol, 33 mg) and DMAP (4 mg). The mix was stirred at RT for 14 h before quenching with H_2O and extracting with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered, and concentrated. After radial chromatography 20 mg of the desired compound was obtained.

Example 3

2-{6-[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-imidazo[1,2-a]pyridin-3-yl}-N,N-dimethyl-2-oxo-acetamide

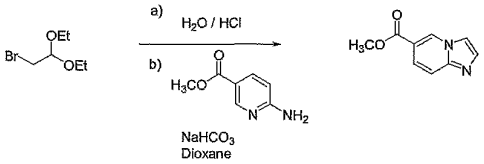


Step A



To 6-aminonicotinic acid (75 mMol, 10.36 g) in MeOH (300 mL) at –78 °C was added $SOCl_2$ (187.5 mMol, 22.31 g, 13.7 mL) dropwise over 30 min. The mixture was then allowed to RT. The mix was then refluxed for 12 h at which time it was cooled and the volatiles removed using rotary evaporation. The resulting white solid was dissolved in H_2O, neutralized with $NaHCO_3$, and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4), filtered, and concentrated to yield 10.06 g of a white powder.

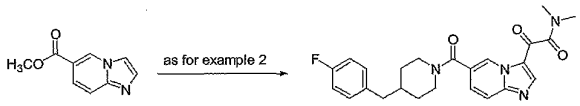
Step B



To bromoacetaldehyde diethylacetal (44.6 mMol, 8.79 g) in H_2O (300 mL) was added concentrated HCl (4.6 mL) dropwise. After stirring at RT for 14 h the mixture was heated at 80 °C for 30 min. After cooling to RT, $NaHCO_3$ (58.7 mMol, 4.88 g) was cautiously added and stirring was continued for 2 h. The ester (35.6 mMol, 5.41 g) was

then added and the mix was stirred an additional 1 h before adding dioxane (200 mL). After 30 min the mix was heated to 100 °C for 48 h. After cooling to RT the dioxane was removed by rotary evaporation. The aqueous layer was extracted with CH_2Cl_2. The combined organics were dried (Na_2SO_4), filtered and concentrated to yield a yellow paste (217 mg) which was carried on to the next step without further purification.

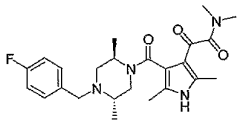
Step C



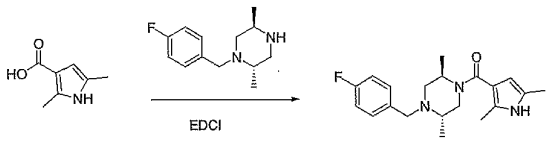
Synthesis of 2-{6-[4-(4-fluoro-benzyl)-piperidine-1-carbonyl]-imidazo[1,2-a]pyridin-3-yl}-N,N-dimethyl-2-oxo-acetamide was carried out through the same series of steps as for 2-{2-[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-3-methyl-imidazo[2,1-b]thiazol-5-yl}-N,N-dimethyl-2-oxo-acetamide.

Example 4

2-{4-[4-(4-Fluoro-benzyl)-2,5-trans-dimethyl-piperazine-1-carbonyl]-2,5-dimethyl-1H-pyrrol-3-yl}-N,N-dimethyl-2-oxo-acetamide

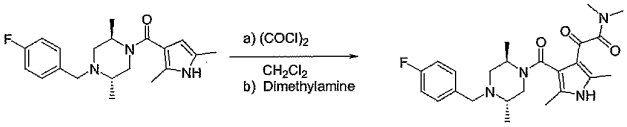


Step A



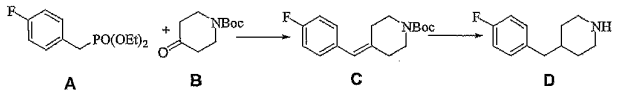
To 2,5-Dimethyl-1H-pyrrole-3-carboxylic acid (1.09 g) and 1-(4-Fluoro-benzyl)-trans-2,5-dimethyl-piperazine (1.59 g) in CH_2Cl_2 was added EDCI (1.51 g) and catalytic DMAP. The reaction mixture was stirred at RT for 12 h at which time it H_2O was added. The mix was extracted with CH_2Cl_2. The combined extracts were dried, filtered, and concentrated. After column chromatography (silica gel, (1:2) ethyl acetate / hexane to (7:3) ethyl acetate / hexane) 540 mg of the desired product was obtained.

Step B



A solution of (2,5-dimethyl-1H-pyrrol-3-yl)-[4-(4-fluoro-benzyl)-trans-2,5-dimethyl-piperazine-1-yl]-methanone (340 mg) in CH_2Cl_2 (25 mL)was cooled to 0 °C and a solution of oxalyl chloride (2.0 M in CH_2Cl_2, 2.0 mL) was added. Stirring was continued for 1 h at 0 °C and then the mix was allowed to warm to RT and stir for 1 h. The solvent was removed in vacuo and then replaced with CH_2Cl_2 (25 mL). After cooling to 0 °C dimethylamine (2.0 M solution in THF, 4.0 mL)was added dropwise. Stirring was continued for 30 min at which time it was warmed to RT. After 30 min the reaction was quenched with H_2O and extracted with CH_2Cl_2. The combined extracts were dried, filtered, and concentrated to yield the desired product which was purified by silica gel column chromatography ((1:1) ethyl acetate / hexane to ethyl acetate followed by (95:5) ethyl acetate / methanol to (90:10) ethyl acetate / methanol) to yield 60 mg of the product.

ADDITIONAL EXAMPLES

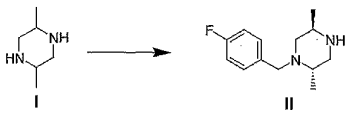


A B C D

Synthesis of D:

STEP 1: The phosphonate **A** (38.4 g) and the piperidone **B** (35.4) were dissolved in anhydrous dimethylformamide (400 mL). To this sodium hydride (60% suspension in oil) was added in portions while the reaction is maintained at 0°C. After the addition of sodium hyride was complete the reaction mixture was stirred for 30 min. and then the ice bath was removed, the reaction was allowed to stir for 6h as it slowly warmed to ambient temperature. The reaction was again cooled in an ice bath and quenched with methanol. Water was added to the reaction mixture, and the product extracted with ethyl acetate. The ethyl acetate layer was washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed to gives the crude alkene, which is purified by column chromatography eluting with ethyl acetate/hexane (1:9) to give 21.8 g of the desired product **C**.

STEP 2: 10 .1 g of **C** was dissolved in 50 mL methanol. After purging the solution with nitrogen, 5% Palladium on carbon (1g) catalyst was added followed by 1 mL acetic acid. The parr container containing the reaction mixture was hydrogenated for 4 h at 40-50 psi. The reaction mixture was filtered through celite and concentrated. The residue was treated with 2 M hydrochloric acid in ether to convert to the hydrochloric acid salt. The white solid that was obtained was dried under vacuum, extensively, to give 7.8 g of **D** as the hydrochloric acid salt.



I II

Synthesis of II:

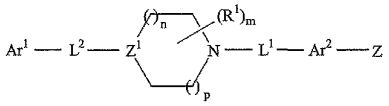
STEP 1: To a solution of dimethyl piperazine **I** (25g) in 300 ml of absolute ethanol was added 400 ml of 2N hydrogen chloride in diethyl ether. The solution was warmed to 70 °C in an oil bath for 20 minutes. The solution was then cooled to room temperature and set at 6 °C overnight. The solid obtained, was collected by filtration. Yield 39.8 g (dihydrochloride salt of trans-2,5 dimethylpiperazine) after drying overnight under high vacuum.

STEP 2: An ethanol solution of 42.9g of dimethyl piperazine dihydrochloride from STEP 1 and 26.1g *trans*-2,5 dimethylpiperazine was vigorously stirred in an oil bath at 80 °C until all starting materials were dissolved. The temperature of oil bath was reduced to 65 °C and 33.1g of 4-fluro benzylchloride was added. After stirring at this temperature for 30 min., the solution was placed in a 6 °C refrigerator overnight. The solid was removed from the solution by filtration and excess of 2N hydrogen chloride in diethyl ether was added to the filtrate. The filtrate was kept at 6 °C overnight and the solid collected. The solid was suspended in 5% sodium hydroxide aqueous solution and extracted three times with ethyl acetate. The organic layer was dried over sodium sulfate and dried down to give a yellow oil.

STEP 3: A solution of 50.7 g (L)-tartaric acid in 130 ml of boiling methanol was added to 70 ml of hot methanol solution of 37.5 g of the product from STEP 2. The solution was set at 6 °C for 96 hours before collection of white fine crystals by filtration. This material was recrystallized from boiling methanol. The product was collected by filtration after being kept at a 6 °C overnight. Yield 30.5 g of ditartaric acid salt ($[\alpha]$= + 43.2°, c=1).

Claims

1. A compound of the formula:



and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein:

Ar^1 is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

L^1 and L^2 are linkers;

each R^1 is independently a noninterfering substituent;

Z^1 is CR^2 or N wherein R^2 is hydrogen or a noninterfering substituent;

m is 0-4;

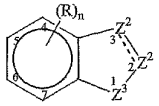
each of n and p is an integer from 0-2 wherein the sum of n and p is 0-3;

Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring;

Z is $-W_i-COX_jY$ wherein Y is COR^3 or an isostere thereof; R^3 is a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;

wherein the smallest number of covalent bonds in the compound separating the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of Ar^1 bonded to L^2 and the atom of Ar^2 bonded to L^1 is 4.5-24 angstroms;

with the proviso that the portion of the compound represented by Ar^2-Z is not



wherein ⋰ represents a single or double bond; n is 0-3; one Z^2 is CA or CRA and the other is CR, CR_2, NR or N; A is $-W_i-COX_jY$ wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1; Z^3 is NR or O; and each R is independently hydrogen or a noninterfering substituent.

2. The compound of claim 1 wherein said smallest number of bonds is 6-12.

3. The compound of claim 1 wherein Z is $COXjCOR^3$, and

wherein R^3 is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted with halo, alkyl, heteroalkyl, SR, SOR, SO_2R, SO_2NR_2, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, CN, COOR, $CONR_2$, COR, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, or

wherein R^3 is OR, NR_2, SR, $NRCONR_2$, $OCONR_2$, or $NRSO_2NR_2$, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, and wherein two R attached to the same atom may form a 3-8 member carbocyclic or heterocyclic ring and wherein said ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing

forms thereof wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined; and

X, if present, is CR_2 where R is as defined above.

4. The compound of claim 1 wherein Y is an isostere of COR^3.

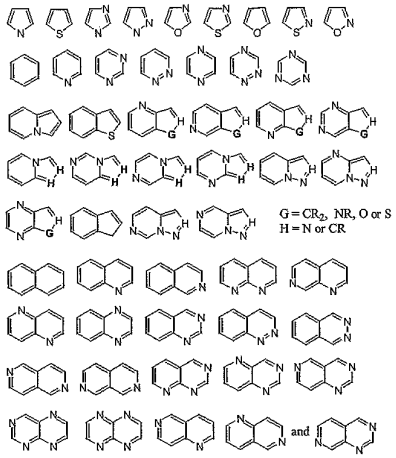
5. The compound of claim 4 wherein Y is tetrazole; 1,2,3-triazole; 1,2,4-triazole; or imidazole.

6. The compound of claim 1 wherein each of i and j is 0.

7. The compound of claim 3 wherein j is 0.

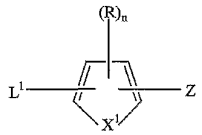
8. The compound of claim 1 wherein $-Ar^2-$ comprises an optionally substituted monocyclic or polycyclic aromatic nucleus, wherein said aromatic nucleus consists of carbocyclic or heterocyclic ring selected from (i) a five-membered heterocyclic or carbocyclic ring (ii) a six-membered carbocyclic or heterocyclic ring; (iii) a five-membered carbocyclic or heterocycloc ring fused to another five-membered carbocyclic or heterocyclic ring; (iv) a six-membered carbocyclic or heterocyclic ring fused to another six-membered carbocyclic or heterocyclic ring; and (v) a five-membered heterocyclic or carbocyclic ring fused to a six-membered carbocyclic or heterocyclic ring.

9. The compound of claim 8 wherein Ar^2 is selected from:



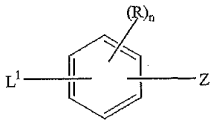
where R is a noninterfering substituent.

10. The compound of claim 8 wherein the portion of said compound represented by L^1-Ar^2-Z is selected from the following:



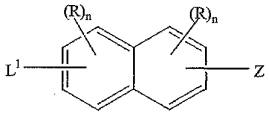
(I)

wherein n is 0, 1 or 2; X^1 is NR, CR_2, O or S; and each R is independently H or a noninterfering substituent; and two or more R groups may form a fused ring;



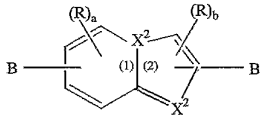
(II)

wherein n is 0-4; R is H or a noninterfering substituent where two or more R groups may form a fused ring; and one or more ring carbons may be optionally replaced with nitrogen;



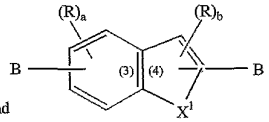
(III)

wherein each n is inpendently 0 to 3; R is H or a noninterfering substituent, where two or more R groups may form a fused ring; and one or more ring carbons may be optionally replaced with nitrogen;



(IV-a)

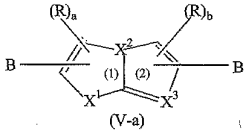
and



(IV-b)

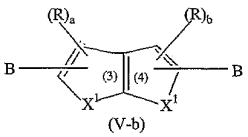
wherein, subject to the proviso of claim 1, one B is L^1 and the other is Z; wherein a is 0 to 4 such that the positions on the six membered rings (1) and (3) to which $(R)_a$ is bonded can include X^2 when X^2 is C; b is 0 –3 such that the positions on the five-membered rings (2) and (4) to which $(R)_b$ is bonded can include X^2 and X^1, when X^2 is C and X^1 is N or C; each X^2 is independently N or CR; $X^1$is NR, CR_2, O or S; each R is H or a noninterfering substituent where two or more R groups may form a fused ring; wherein

one or more of the ring carbons that are at positions other than X^2 or X^1 and that are also not bound to B can be optionally replaced with N;



(V-a)

and



(V-b)

wherein one B is L^1 and the other is Z; a is 0-4 such that the positions on the rings (1) and (3) to which $(R)_a$ can be bonded include X^2 and X^1 where X^2 is C and X^1 is C or N; b is 0 or 3 such that the positions on the rings (2) and (4) to which $(R)_b$ can be bonded include X^1, X^2 and X^3 when X^1 is C or N and X^2 and/or X^3 are C; each X^1 is independently NR, $C(R)_2$, O or S; X^2 and X^3 are independently N or CR; each R is independently H or a noninterfering substituent where two or more R groups can optionally form a fused ring; wherein one or more of the ring carbons that are at positions other than X^1, X^2 or X^3, and that are also not bound to B, can be optionally replaced with N.

11. The compound of claim 10 wherein L^1-Ar^2-Z is structure (I).

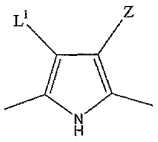
12. The compound of claim 11 wherein X^1 in structure (I) is NR.

13. The compound of claim 12 wherein X^1 in structure (I) is NH.

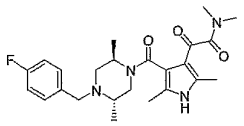
14. The compound of claim 13 wherein R is methyl.

15. The compound of claim 14 wherein n is 2.

16. The compound of claim 15 wherein structure (I) is:



17. The compound of claim 16 where the compound is:

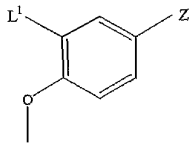


10. The compound of claim 10 wherein L^1-Ar^2-Z is structure (II).

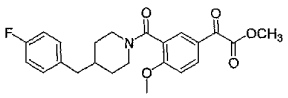
19. The compound of claim 18 wherein the R in structure (II) is methoxy.

20. The compound of claim 19 wherein n in structure (II) is 1.

21. The compound of claim 20 wherein structure (II) is



22. The compound of claim 21 wherein the compound is:

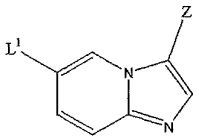


23. The compound of claim 10 wherein L^1-Ar^2-Z is structure (III).

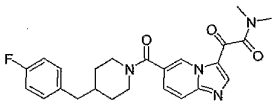
24. The compound of claim 10 wherein L^1-Ar^2-Z is structure (IV-a) or (IV-b).

25. The compound of claim 24 wherein L^1-Ar^2-Z is (IV-a) and both X^2 in structure (IV-a) are nitrogen.

26. The compound of claim 25 wherein structure (IV) is:



27. The compound of claim 26 wherein the compound is:



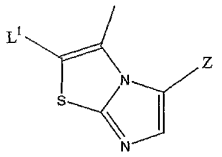
28. The compound of claim 8 wherein L^1-Ar^2-Z is structure (V-a) or (V-b).

29. The compound of claim 28 wherein L^1-Ar^2-Z is structure (V-a) and X^2 and X^3 in structure (V-a) are N.

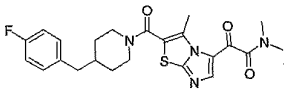
30. The compound of claim 29 wherein at least one R in structure (V) is methyl.

31. The compound of claim 29 wherein X^1 in structure (V) is S.

32. The compound of claim 31 wherein structure (V) is:



33. The compound of claim 32 wherein the compound is:



34. The compound of claim 1 wherein both n and p are 1.

35. The compound of claim 1 wherein L^1 is CO, CHOH or CH_2.

36. The compound of claim 35 wherein L^1 is CO.

37. The compound of claim 1 wherein Z^1 is N.

38. The compound of claim 1 wherein Z^1 is CR^2 wherein R^2 is H, OR, NR_2, SR or halo, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof.

39. The compound of claim 1 wherein L^2 is alkylene (1-4C) or alkenylene (1-4C) optionally substituted with a moiety selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR,

NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two substituents on L^2 can be joined to form a non-aromatic saturated or unsaturated ring that includes 0-3 heteroatoms which are O, S and/or N and which contains 3 to 8 members or said two substituents can be joined to form a carbonyl moiety or an oxime, oximeether, oximeester or ketal of said carbonyl moiety.

40. The compound of claim 39 wherein L^2 is unsubstituted alkylene.

41. The compound of claim 39 wherein L^2 is unsubstituted methylene, methylene substituted with alkyl, or -CH=.

42. The compound of claim 1 wherein Ar^1 is optionally substituted with 0-5 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said optional substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

43. The compound of claim 42 wherein Ar^1 is optionally substituted phenyl.

44. The compound of claim 43 wherein said optional substitution is by halo, OR, or alkyl.

45. The compound of claim 44 wherein said phenyl is unsubstituted or has a single substituent.

46. The compound of claim 1 wherein R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^4 on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, or R^4 is =O or an oxime, oximeether, oximeester or ketal thereof.

47. The compound of claim 46 wherein each R^1 is halo, OR, or alkyl.

48. The compound of claim 47 wherein m is 0, 1, or 2.

49. The compound of claim 48 wherein m is 2 and both R^1 are alkyl.

50. The compound of claim 10 wherein each of the non-interfering groups R, when bonded to a ring carbon atom, are selected from the group consisting of:

(a) hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl and halo; or

(b) or from OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R in the preceding (b) selections is independently H, alkyl, alkenyl or aryl or heteroforms thereof;

and wherein two of the non-interfering groups R can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

51. The compound of claim 50 wherein the non-interfering groups R are independently selected from the group consisting of H, alkyl, acyl, aryl, arylalkyl,

heteroalkyl, heteroaryl, halo, OR, NR_2, SR, NRCOR, alkyl-OOR, RCO, COOR, and CN, wherein each R is independently H, alkyl, or aryl or heteroforms thereof.

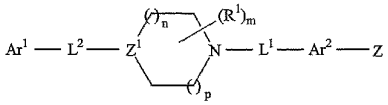
52. The compound of claim 10 wherein the noninterfering groups R, when bonded to a nitrogen ring atom, are selected from the group consisting of:

(a) H, or alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl; and

(b) SOR, SO_2R, RCO, COOR, alkyl-COR, SO_3R, $CONR_2$, SO_2NR_2, CN, CF_3, or R_3Si wherein each R in the preceding (b) selections is independently H, alkyl, alkenyl or aryl or heteroforms thereof.

53. A pharmaceutical composition for treating conditions characterized by enhanced p38-α activity which composition comprises

a therapeutically effective amount of a compound of the formula



and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein:

Ar^1 is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

L^1 and L^2 are linkers;

each R^1 is independently a noninterfering substituent;

Z^1 is CR^2 or N wherein R^2 is hydrogen or a noninterfering substituent;

m is 0-4;

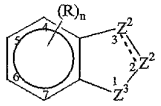
each of n and p is an integer from 0-2 wherein the sum of n and p is 0-3;

Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring;

Z is -W_i-COX_jY wherein Y is COR^3 or an isostere thereof; R^3 is a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;

wherein the smallest number of covalent bonds in the compound separating the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of Ar^1 bonded to L^2 and the atom of Ar^2 bonded to L^1 is 4.5-24 angstroms;

with the proviso that the portion of the compound represented by Ar^2-Z is not



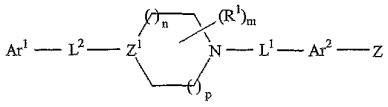
wherein ⩬ represents a single or double bond; n is 0-3; one Z^2 is CA or CRA and the other is CR, CR_2, NR or N; A is -W_i-COX_jY wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1; Z^3 is NR or O; and each R is independently hydrogen or a noninterfering substituent.

54. The pharmaceutical composition of claim 53 wherein said smallest number of bonds is 6-12.

55. The composition of claim 53 which further contains an additional therapeutic agent.

56. The composition of claim 55 wherein said additional therapeutic agent is a corticosteroid, a monoclonal antibody, or an inhibitor of cell division.

57. A method to treat a condition mediated by p38-α kinase comprising administering to a subject in need of such treatment a compound of the formula:



and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein

Ar^1 is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

L^1 and L^2 are linkers;

each R^1 is independently a noninterfering substituent;

Z^1 is CR^2 or N wherein R^2 is hydrogen or a noninterfering substituent;

m is 0-4;

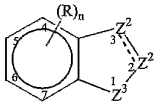
each of n and p is an integer from 0-2 wherein the sum of n and p is 0-3;

Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring;

Z is $-W_i-COX_jY$ wherein Y is COR^3 or an isostere thereof; R^3 is a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;

wherein the smallest number of covalent bonds in the compound separating the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of Ar^1 bonded to L^2 and the atom of Ar^2 bonded to L^1 is 4.5-24 angstroms;

with the proviso that the portion of the compound represented by Ar^2-Z is not



wherein ⚌ represents a single or double bond; n is 0-3; one Z^2 is CA or CRA and the other is CR, CR_2, NR or N; A is $-W_i-COX_jY$ wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1; Z^3 is NR or O; and each R is independently hydrogen or a noninterfering substituent.

58. The method of claim 57 wherein said smallest number of bonds is 6-12.

59. The method of claim 57 wherein said condition is a proinflammation response.

60. The method of claim 59 wherein said proinflammation response is multiple sclerosis, IBD, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, other arthritic conditions, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, CNS injury, psoriasis, restenosis, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, a bone resorption disease, graft-versus-host reaction, Crohn's Disease, ulcerative colitis, Alzheimer's, pyresis or heart disease.

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(54) Title: PIPERIDINE/PIPERAZINE-TYPE INHIBITORS OF P38 KINASE

(57) Abstract: The invention is directed to inhibition of p38-α kinase using compounds of the formula (1) and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein: Ar^1 is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring; L^1 and L^2 are linkers; each R^1 is independently a noninterfering substitutent; Z^1 is CR^2 or N wherein R^2 is hydrogen or a noninterfering substituent; m is 0-4; each of n and p is an integer from 0-2 wherein the some of n and p is 0-3; Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring; Z is W_i-COX_jY wherein Y is COR^3 or an isotere thereof; R^3 is a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1; wherein the smallest number of covalent bonds is the compound separating the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of Ar^1 bonded to L^2 and the atom of Ar^2 bonded to L^1 is 4.5-24 angstroms; with the proviso that the protion of the compound represented by Ar^2-Z is not formula (2) wherein formula (3) represents a singel or double bond; n is 0-3; one Z^2 is CA or CRA and the other is CR, CR_2, NR or N; A is W_i-COX_jY wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 ot 1; Z^3 is NR or O; and each R independently hydrogen or a morninterfering substituent.

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PIPERIDINE/PIPERAZINE-TYPE INHIBITORS OF p38 KINASE

Field of the Invention

The invention relates to treating various disorders associated with enhanced activity of kinase p38-α. More specifically, it concerns piperadine and piperazine derivatives useful in these methods.

Background Art

A large number of chronic and acute conditions have been recognized to be associated with perturbation of the inflammatory response. A large number of cytokines participate in this response, including IL-1, IL-6, IL-8 and TNF. It appears that the activity of these cytokines in the regulation of inflammation rely at least in part on the activation of an enzyme on the cell signaling pathway, a member of the MAP kinase family generally known as p38 and alternatively known as CSBP and RK. This kinase is activated by dual phosphorylation after stimulation by physiochemical stress, treatment with lipopolysaccharides or with proinflammatory cytokines such as IL-1 and TNF. Therefore, inhibitors of the kinase activity of p38 are useful anti-inflammatory agents.

Eye diseases associated with a fibroproliferative condition include retinal reattachment surgery accompanying proliferative vitreoretinopathy, cataract extraction with intraocular lens implantation, and post glaucoma drainage surgery.

PCT applications WO98/06715, WO98/07425, and WO 96/40143, all of which are incorporated herein by reference, describe the relationship of p38 kinase inhibitors with various disease states. As mentioned in these applications, inhibitors of p38 kinase are useful in treating a variety of diseases associated with chronic inflammation. These applications list rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, CNS injuries such as neural trauma and ischemia, psoriasis, restenosis, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone

resorption diseases such as osteoporosis, graft-versus-host reaction, Crohn's Disease, ulcerative colitis including inflammatory bowel disease (IBD) and pyresis.

The above-referenced PCT applications disclose compounds which are p38 kinase inhibitors said to be useful in treating these disease states. These compounds are either imidazoles or are indoles substituted at the 3- or 4-position with a piperazine ring linked through a carboxamide linkage. Additional compounds which are conjugates of piperazines with indoles are described as insecticides in WO97/26252, also incorporated herein by reference.

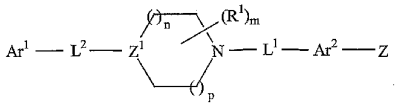
Certain aroyl/phenyl-substituted piperazines and piperidines which inhibit p38-α kinase are described in PCT publication WO00/12074 published 9 March 2000. In addition, indolyl substituted piperidines and piperazines which inhibit this enzyme are described in PCT publication No. WO99/61426 published 2 December 1999. Carbolene derivatives of piperidine and piperazine as p38-α inhibitors are described in PCT/US00/07934 filed 24 March 2000.

None of the foregoing patents describes the piperadine type derivatives described herein which specifically inhibit p38-α.

Summary of the Invention

The invention is directed to methods and compounds useful in treating conditions that are characterized by enhanced p38-α activity. These conditions include inflammation, proliferative diseases, and certain cardiovascular disorders as well as Alzheimer's disease as further described below.

Compounds of the invention inhibit p38 kinase, the α-isoform in particular, and are thus useful in treating diseases mediated by these activities. The compounds of the invention are of the formula (1):



(1)

and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein:

Ar^1 is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

L^1 and L^2 are linkers;

each R^1 is independently a noninterfering substituent;

Z^1 is CR^2 or N wherein R^2 is hydrogen or a noninterfering substituent;

m is 0-4;

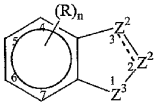
each of n and p is an integer from 0-2 wherein the sum of n and p is 0-3;

Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring;

Z is $-W_i-COX_jY$ wherein Y is COR^3 or an isostere thereof; R^3 is a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;

wherein the smallest number of covalent bonds in the compound separating the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of Ar^1 bonded to L^2 and the atom of Ar^2 bonded to L^1 is 4.5-24 angstroms;

with the proviso that the portion of the compound represented by Ar^2-Z is not



wherein ⋰ represents a single or double bond; n is 0-3; one Z^2 is CA or CRA and the other is CR, CR_2, NR or N; A is $-W_i-COX_jY$ wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1; Z^3 is NR or O; and each R is independently hydrogen or a noninterfering substituent.

The invention is further directed to methods of treating inflammation or proliferative conditions using these compounds. The invention is also directed to treating

conditions associated with cardiac failure and Alzheimer's disease using the invention compounds.

Detailed Description

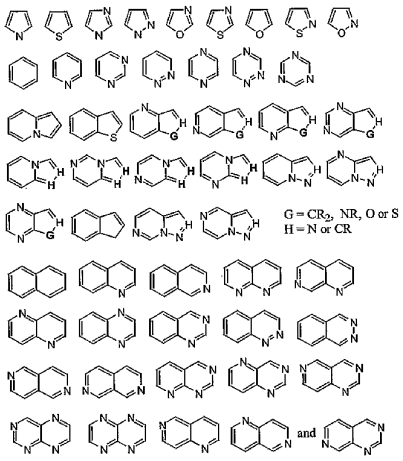
The compounds of formula (1) are useful in treating conditions which are characterized by overactivity of p38 kinase, in particular the α-isoform. Conditions "characterized by enhanced p38-α activity" include those where this enzyme is present in increased amount or wherein the enzyme has been modified to increase its inherent activity, or both. Thus, "enhanced activity" refers to any condition wherein the effectiveness of these proteins is undesirably high, regardless of the cause.

The compounds of the invention are useful in conditions where p38-α kinase shows enhanced activity. These conditions are those in which fibrosis and organ sclerosis are caused by, or accompanied by, inflammation, oxidation injury, hypoxia, altered temperature or extracellular osmolarity, conditions causing cellular stress, apoptosis or necrosis. These conditions include ischemia-reperfusion injury, congestive heart failure, progressive pulmonary and bronchial fibrosis, hepatitis, arthritis, inflammatory bowel disease, glomerular sclerosis, interstitial renal fibrosis, chronic scarring diseases of the eyes, bladder and reproductive tract, bone marrow dysplasia, chronic infectious or autoimmune states, spinal chord injury and traumatic or surgical wounds. These conditions, of course, would be benefited by compounds which inhibit p38-α. Methods of treatment with the compounds of the invention are further discussed below.

The compounds useful in the invention are derivatives of piperadine/piperazine-type compounds containing a mandatory substituent, Z attached to the aromatic moiety Ar^2 The aromatic moiety is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms. The aromatic moiety may be optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring.

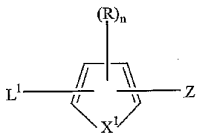
In somewhat greater detail the aromatic moiety Ar^2 comprises an optionally substituted monocyclic or polycyclic aromatic nucleus, wherein the aromatic nucleus consists of a carbocyclic or heterocyclic ring selected from (i) a five-membered heterocyclic or carbocyclic ring (ii) a six-membered carbocyclic or heterocyclic ring; (iii) a five-membered carbocyclic or heterocyclic ring fused to another five-membered carbocyclic or heterocyclic ring; (iv) a six-membered carbocyclic or heterocyclic ring fused to another six-

membered carbocyclic or heterocyclic ring; and (v) a five-membered heterocyclic or carbocyclic ring fused to a six-membered carbocyclic or heterocyclic ring. Examples of the foregoing include the following aromatic moieties:



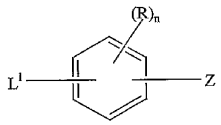
where R is a noninterfering substituent.

Particular examples of Ar^2 in formula (1) are such that the portion of compound (1) represented by L^1-Ar^2-Z is selected from the following:



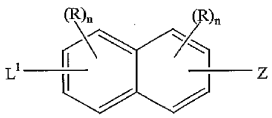
(I)

wherein n is 0, 1 or 2; X^1 is NR, CR_2, O or S; and each R is independently H or a noninterfering substituent; and two or more R groups may form a fused ring;



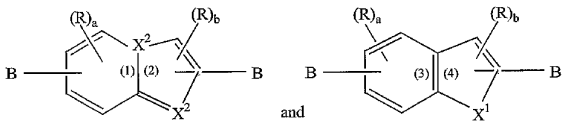
(II)

wherein n is 0-4; R is H or a noninterfering substituent where two or more R groups may form a fused ring; and one or more ring carbons may be optionally replaced with nitrogen;



(III)

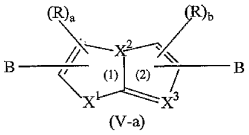
wherein each n is inpendently 0 to 3; R is H or a noninterfering substituent, where two or more R groups may form a fused ring; and one or more ring carbons may be optionally replaced with nitrogen;



(IV-a) and (IV-b)

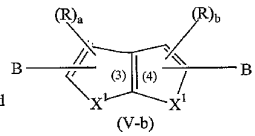
wherein, subject to the proviso set forth above with respect to formula (1), one B is L^1 and the other is Z; wherein a is 0 to 4 such that the positions on the six membered rings (1) and (3) to which $(R)_a$ is bonded can include X^2 when X^2 is C; b is 0 –3 such that the

positions on the five-membered rings (2) and (4) to which $(R)_b$ is bonded can include X^2 and X^1, when X^2 is C and X^1 is N or C; each X^2 is independently N or CR; $X^1$is NR, CR_2, O or S; each R is H or a noninterfering substituent where two or more R groups may form a fused ring; wherein one or more of the ring carbons that are at positions other than X^2 or X^1 and that are also not bound to B can be optionally replaced with N;



(V-a)

and



(V-b)

wherein one B is L^1 and the other is Z; a is 0-4 such that the positions on the rings (1) and (3) to which $(R)_a$ can be bonded include X^2 and X^1 where X^2 is C and X^1 is C or N; b is 0 or 3 such that the positions on the rings (2) and (4) to which $(R)_b$ can be bonded include X^1, X^2 and X^3 when X^1 is C or N and X^2 and/or X^3 are C; each X^1 is independently NR, $C(R)_2$, O or S; X^2 and X^3 are independently N or CR; each R is independently H or a noninterfering substituent where two or more R groups can optionally form a fused ring; wherein one or more of the ring carbons that are at positions other than X^1, X^2 or X^3, and that are also not bound to B, can be optionally replaced with N.

Certain positions of the molecule of formula I are described as permitting "noninterfering substituents." This terminology is used because the substituents in these positions generally speaking are not relevant to the essential activity of the molecule taken as a whole. A wide variety of substituents can be employed in these positions, and it is well within ordinary skill to determine whether any particular arbitrary substituent is or is not "noninterfering."

As used herein, a "noninterfering substituent" is a substituent which leaves the ability of the compound of formula (1) to inhibit p38-α activity qualitatively intact. Thus, the substituent may alter the degree of inhibition of p38-α. However, as long as the compound of formula (1) retains the ability to inhibit p38-α activity, the substituent will be classified as "noninterfering." A number of assays for determining the ability of any compound to inhibit p38- α activity are available in the art. A whole blood assay for this

evaluation is illustrated below. The gene for p38- α has been cloned and the protein can be prepared recombinantly and its activity assessed, including an assessment of the ability of an arbitrarily chosen compound to interfere with this activity. The essential features of the molecule are tightly defined. The positions which are occupied by "noninterfering substituents" can be substituted by conventional organic moieties as is understood in the art. It is irrelevant to the present invention to test the outer limits of such substitutions. The essential features of the compounds are those set forth with particularity herein.

In addition, L^1 and L^2 are described herein as linkers. The nature of such linkers is less important than the distance they impart between the portions of the molecule. Typical linkers include alkylene, *i.e.* $(CH_2)_n$-R; alkenylene - *i.e.*, an alkylene moiety which contains a double bond, including a double bond at one terminus. Other suitable linkers include, for example, substituted alkylenes or alkenylenes, carbonyl moieties, and the like.

As used herein, "hydrocarbyl residue" refers to a residue which contains only carbon and hydrogen. The residue may be aliphatic or aromatic, straight-chain, cyclic, branched, saturated or unsaturated. The hydrocarbyl residue, when so stated however, may contain heteroatoms over and above the carbon and hydrogen members of the substituent residue. Thus, when specifically noted as containing such heteroatoms, the hydrocarbyl residue may also contain carbonyl groups, amino groups, hydroxyl groups and the like, or contain heteroatoms within the "backbone" of the hydrocarbyl residue.

As used herein, "inorganic residue" refers to a residue that does not contain carbon. Examples include, but are not limited to, halo, hydroxy, NO_2, or NH_2.

As used herein, the term "alkyl," "alkenyl" and "alkynyl" include straight- and branched-chain and cyclic monovalent substituents. Examples include methyl, ethyl, isobutyl, cyclohexyl, cyclopentylethyl, 2-propenyl, 3-butynyl, and the like. Typically, the alkyl, alkenyl and alkynyl substituents contain 1-10C (alkyl) or 2-10C (alkenyl or alkynyl). Preferably they contain 1-6C (alkyl) or 2-6C (alkenyl or alkynyl). Heteroalkyl, heteroalkenyl and heteroalkynyl are similarly defined but may contain 1-2 O, S or N heteroatoms or combinations thereof within the backbone residue.

As used herein, "acyl" encompasses the definitions of alkyl, alkenyl, alkynyl and the related hetero-forms which are coupled to an additional residue through a carbonyl group.

The term "Aromatic" with respect to moiety Ar^1 refers to a monocyclic or fused bicyclic moiety such as phenyl or naphthyl; "heteroaromatic" also refers to monocyclic or fused bicyclic ring systems containing one or more heteroatoms selected from O, S and N. The inclusion of a heteroatom permits inclusion of 5-membered rings as well as 6-membered rings. Thus, typical aromatic systems include pyridyl, pyrimidyl, indolyl, benzimidazolyl, benzotriazolyl, isoquinolyl, quinolyl, benzothiazolyl, benzofuranyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl and the like. Any monocyclic or fused ring bicyclic system which has the characteristics of aromaticity in terms of electron distribution throughout the ring system is included in this definition. Typically, the ring systems contain 5-12 ring member atoms.

Similarly, "arylalkyl" and "heteroalkyl" refer to aromatic and heteroaromatic systems which are coupled to another residue through a carbon chain, including substituted or unsubstituted, saturated or unsaturated, carbon chains, typically of 1-6C. These carbon chains may also include a carbonyl group, thus making them able to provide substituents as an acyl moiety.

When the compounds of Formula (1) contain one or more chiral centers, the invention includes optically pure forms as well as mixtures of stereoisomers or enantiomers

With respect to the portion of the compound between the Ar^1 and Ar^2, linkers L^2 and L^1, in combination with the piperadine/piperazine ring, provide for separation of the atom of Ar^1 bonded to L^2 from the atom of Ar^2 bonded to L^1 by a defined minimum number of covalent bond lengths counted end-to-end through the compound, as opposed to a measurement of linear distance through space. More particularly, the smallest number of bonds counted end-to-end in the compound separating the atom of Ar^1 bonded to L^2 from the atom of Ar^2 bonded to L^1 is at least 5, and preferably from 6 to 12, wherein the length of each of such bonds is 1.2 to 2.0 angstroms. In terms of a linear distance through space, the linear distance measured through space from the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is a distance of 4.5-24Å, preferably 6-20Å, and more preferably 7.5-10Å.

Typical, but nonlimiting, embodiments of L^1 and L^2 are CO and isosteres thereof, or optionally substituted isosteres, or longer chain forms. L^2, in particular, may be alkylene or alkenylene optionally substituted with noninterfering substituents or L^1 or L^2 may be or may include a heteroatom such as N, S or O. Such substituents include, but are limited to, a

moiety selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two substituents on L^2 can be joined to form a non-aromatic saturated or unsaturated ring that includes 0-3 heteroatoms which are O, S and/or N and which contains 3 to 8 members or said two substituents can be joined to form a carbonyl moiety or an oxime, oximeether, oximeester or ketal of said carbonyl moiety.

Isosteres of CO and CH_2, include SO, SO_2, or CHOH. CO and CH_2 are preferred. Thus, L^2 is substituted with 0-2 substituents. Where appropriate, two optional substituents on L^2 can be joined to form a non-aromatic saturated or unsaturated hydrocarbyl ring that includes 0-3 heteroatoms such as O, S and/or N and which contains 3 to 8 members. Two optional substituents on L^2 can be joined to form a carbonyl moiety which can be subsequently converted to an oxime, an oximeether, an oximeester, or a ketal.

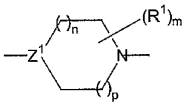
Ar^1 is aryl, heteroaryl, including 6-5 fused heteroaryl, cycloaliphatic or cycloheteroaliphatic that can be optionally substituted. Ar is preferably optionally substituted phenyl.

Each substituent on Ar^1 is independently a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and N, or is an inorganic residue. Preferred substituents include those selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said optional substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members. More preferred substituents include halo, alkyl (1-4C) and more preferably, fluoro, chloro and methyl. These substituents may occupy all available positions of the aryl ring of Ar^1, preferably 1-2 positions, most preferably one position. These substituents may be optionally substituted with substituents similar to those listed.

Of course some substituents, such as halo, are not further substituted, as known to one skilled in the art.

Two substituents on Ar^1 can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

Between L^1 and L^2 is a piperidine-type moiety of the following formula:



wherein Z^1 is CR^2 or N and R^2 is H or a noninterfering substituent. Each of n and p is an integer from 0-2 wherein the sum of n and p is 0-3. The noninterfering substituents R^2 include, without limitation, halo, alkyl, alkoxy, aryl, arylalkyl, aryloxy, heteroaryl, acyl, carboxy, or hydroxy. Preferably, R^2 is H, alkyl, OR, NR_2, SR or halo, where R is H or alkyl. Additionally, R^2 can be joined with an R^1 substituent to form an optionally substituted non-aromatic saturated or unsaturated hydrocarbyl ring which contains 3-8 members and 0-3 heteroatoms such as O, N and/or S. Preferred embodiments include compounds wherein Z^1 is CH or N, and those wherein both n and p are 1.

R^1 represents a noninterfering substituent such as a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and N. Preferably R^1 is alkyl, alkoxy, aryl, arylalkyl, aryloxy, heteroalkyl, heteroaryl, heteroarylalkyl, RCO, =O, acyl, halo, CN, OR, NRCOR, NR, wherein R is H, alkyl (preferably 1-4C), aryl, or hetero forms thereof. Each appropriate substituent is itself unsubstituted or substituted with 1-3 substituents. The substituents are preferably independently selected from a group that includes alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^1 on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, or R^1 is =O or an oxime, oximeether, oximeester or ketal thereof. R^1 may occur m times on the ring; m is an integer of 0-4. Preferred embodiments of R^1 comprise alkyl (1-4C) especially two alkyl substituents and carbonyl. Most preferably R^1

comprises two methyl groups at positions 2 and 5 or 3 and 6 of a piperidinyl or piperazinyl ring or =O preferably at the 5-position of the ring. The substituted forms may be chiral and an isolated enantiomer may be preferred.

Z is $-W_i-COX_jY$ wherein Y is COR^3 or an isostere thereof and R^3 is a noninterfering substituent. Each of W and X is a spacer and may be, for example, optionally substituted alkyl, alkenyl, or alkynyl, each of i and j is 0 or 1. Preferably, W and X are unsubstituted. Preferably, j is 0 so that the two carbonyl groups are adjacent to each other. Preferably, also, i is 0 so that the proximal CO is adjacent the ring. However, compounds wherein the proximal CO is spaced from the ring can readily be prepared by selective reduction of an initially glyoxal substituted Ar^2.

The noninterfering substituent represented by R^3, when R^3 is other than H, is a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and/or N or is an inorganic residue. Preferred are embodiments wherein R^3 is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted with halo, alkyl, heteroalkyl, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, CN, COOR, $CONR_2$, COR, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, or wherein R^3 is OR, NR_2, SR, $NRCONR_2$, $OCONR_2$, or $NRSO_2NR_2$, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, and wherein two R attached to the same atom may form a 3-8 member ring and wherein said ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined.

Other preferred embodiments of R^3 are H, heteroarylalkyl, $-NR_2$, heteroaryl, -COOR, -NHRNR$_2$, heteroaryl-COOR, heteroaryloxy, -OR, heteroaryl-NR_2, -NROR and alkyl. Most preferably R^3 is isopropyl piperazinyl, methyl piperazinyl, dimethylamine, piperazinyl, isobutyl carboxylate, oxycarbonylethyl, morpholinyl, aminoethyldimethylamine, isobutyl carboxylate piperazinyl, oxypiperazinyl,

ethylcarboxylate piperazinyl, methoxy, ethoxy, hydroxy, methyl, amine, aminoethyl pyrrolidinyl, aminopropanediol, piperidinyl, pyrrolidinyl-piperidinyl, or methyl piperidinyl.

Isosteres of COR^3 as represented by Y are defined as follows.

The isosteres have varying lipophilicity and may contribute to enhanced metabolic stability. Thus, Y, as shown, may be replaced by the isosteres in Table 1.

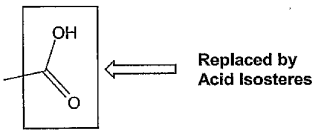
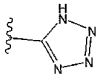
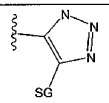
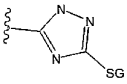
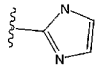


Table 1 - Acid Isosteres

Names of Groups	Chemical Structures	Substitution Groups (SG)
tetrazole		n/a
1,2,3-triazole		H; SCH_3; $COCH_3$; Br; $SOCH_3$; SO_2CH_3; NO_2; CF_3; CN; COOMe
1,2,4-triazole		H; SCH_3; $COCH_3$; Br; $SOCH_3$; SO_2CH_3; NO_2
imidazole		H; SCH_3; $COCH_3$; Br; $SOCH_3$; SO_2CH_3; NO_2

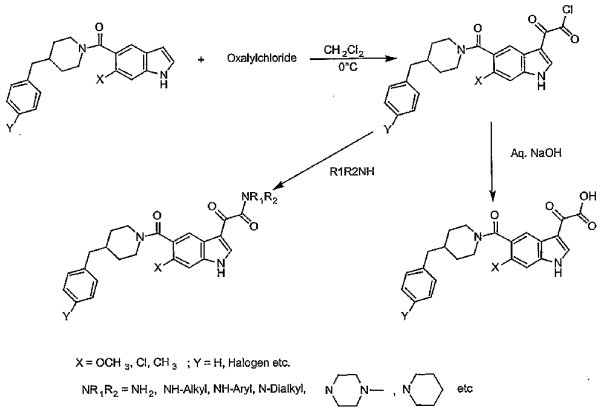
Thus, isosteres include tetrazole, 1,2,3-triazole, 1,2,4-triazole and imidazole.

The compounds of formula (1) may be supplied in the form of their pharmaceutically acceptable acid-addition salts including salts of inorganic acids such as hydrochloric, sulfuric, hydrobromic, or phosphoric acid or salts of organic acids such as

acetic, tartaric, succinic, benzoic, salicylic, and the like. If a carboxyl moiety is present on the compound of formula (1), the compound may also be supplied as a salt with a pharmaceutically acceptable cation.

Synthesis of the Invention Compounds

Copending, commonly-assigned U.S.S.N 09/575,060, incorporated herein by reference in its entirety, illustrated the following reaction scheme for conversion of a 4-benzyl piperidinyl-indole-5-carboxamide to the glyoxalic acid compounds of the invention and derivatives thereof:

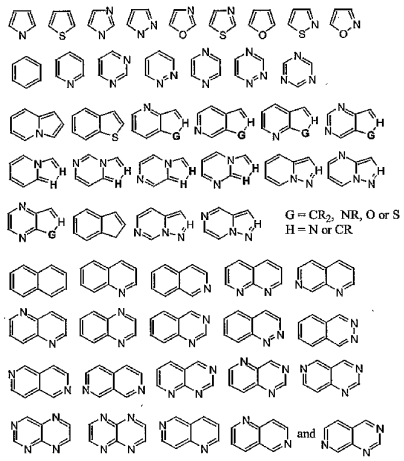


In the present invention, the indole moiety is generalized to Ar^2 in formula (1) above where Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring. Preferably the moiety Ar^2 comprises an optionally substituted monocyclic or polycyclic aromatic

nucleus, wherein said aromatic nucleus consists of carbocyclic or heterocyclic ring selected from (i) a five-membered heterocyclic or carbocyclic ring (ii) a six-membered carbocyclic or heterocyclic ring; (iii) a five-membered carbocyclic or heterocycloc ring fused to another five-membered carbocyclic or heterocyclic ring; (iv) a six-membered carbocyclic or heterocyclic ring fused to another six-membered carbocyclic or heterocyclic ring; and (v) a five-membered heterocyclic or carbocyclic ring fused to a six-membered carbocyclic or heterocyclic ring. Formula (1), as required by the proviso stated above, excludes the indole type compounds disclosed and claimed in U.S.S.N. 09/575,060 filed May 21, 1999 and incorporated herein by reference.

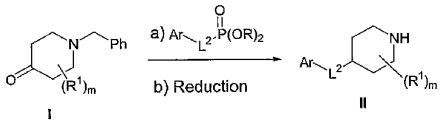
As disclosed commonly assigned in U.S.S.N 09/575,060, the glyoxal type substituent at position 3 can be generalized to $-W_iCOXjY$.

The Ar^2 moiety may be generalized as:



Methods to synthesize the compounds of the invention are, in general, known in the art. For example, commonly assigned U.S.S.N 09/575,060, incorporated herein by reference in

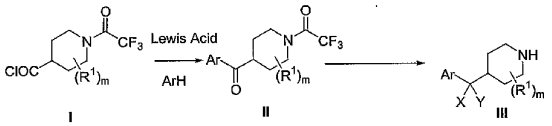
its entirety, disclosed that piperidine moieties can be obtained using the following reaction scheme



I II

where an appropriate piperidone such as **I**, is treated with substituted benzyl phosphonate esters in the presence of a base such as sodium hydride to give alkenes which can be reduced to the corresponding substituted 4-benzylpiperidine such as **II**. The hydrogenations are typically done in the presence of catalytic metals in solvents such as methanol, ethanol and ethyl acetate.

An alternative to the above disclosed in U.S.S.N 09/575,060 as follows:



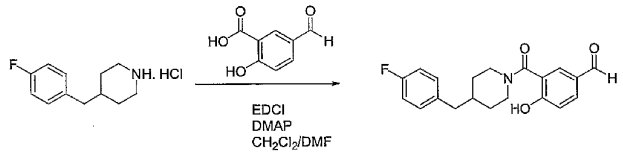
I II III

where isonipecotoyl chlorides such as **I** can be used to acylate appropriately substituted benzenes (ArH) in the presence of a Lewis acid such as aluminum chloride to give the ketones **II**. Further modifications of the carbonyl moiety of **II** using methods and routes generally known can then lead to the desired compounds **III**.

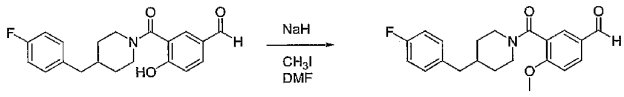
The following reaction schemes illustrate methods for preparing compounds of the present invention.

Scheme I

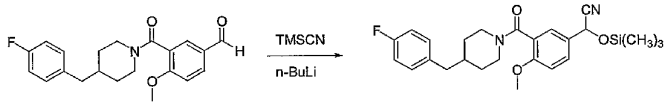
Step A



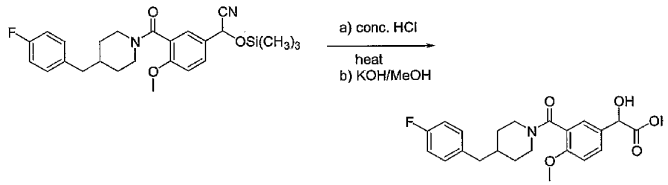
Step B



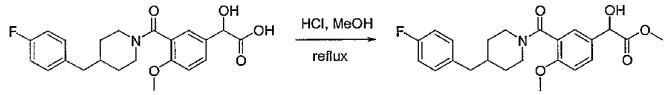
Step C



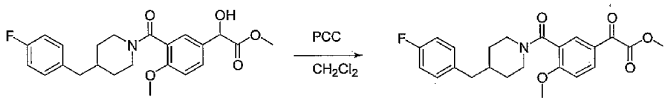
Step D



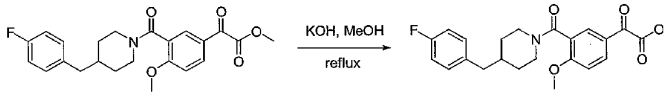
Step E



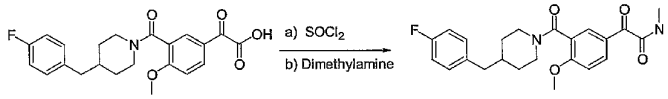
Step F



Step G

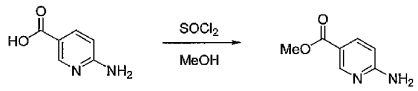


Step H

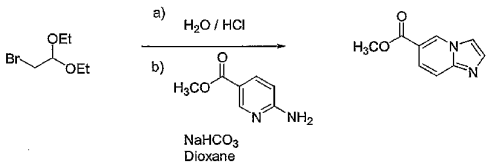


Scheme II

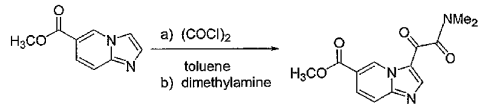
Step A



Step B



Step C



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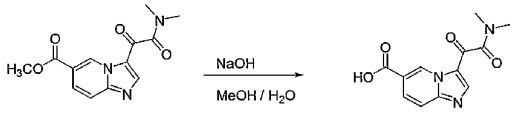

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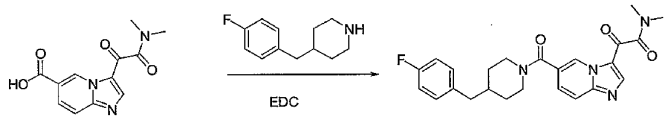
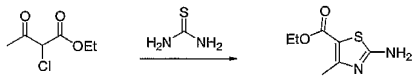


Scheme III

Step A



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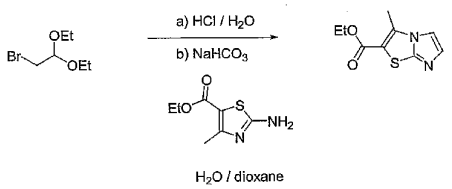

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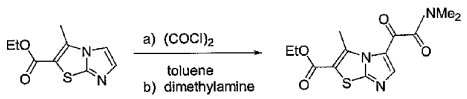
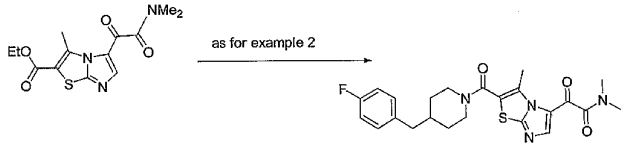
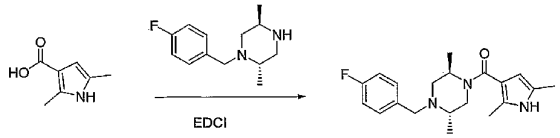


Step D

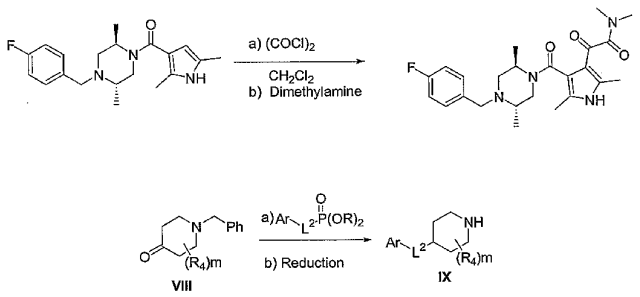


Scheme IV

Step A



Step B



Scheme 4

Assays for p38 α Kinase Inhibition

For each of the assay procedures described below, the TNF-α production correlates to the activity of p38-α kinase.

A. Human Whole Blood Assay for p38 Kinase Inhibition

Venous blood is collected from healthy male volunteers into a heparinized syringe and is used within 2 hours of collection. Test compounds are dissolved in 100% DMSO and 1 μl aliquots of drug concentrations ranging from 0 to 1 mM are dispensed into quadruplicate wells of a 24-well microtiter plate (Nunclon Delta SI, Applied Scientific, So. San Francisco, CA). Whole blood is added at a volume of 1 ml/well and the mixture is incubated for 15 minutes with constant shaking (Titer Plate Shaker, Lab-Line Instruments, Inc., Melrose Park, IL) at a humidified atmosphere of 5% CO_2 at 37 °C. Whole blood is cultured either undiluted or at a final dilution of 1:10 with RPMI 1640 (Gibco 31800 + $NaHCO_3$, Life Technologies, Rockville, MD and Scios, Inc., Sunnyvale, CA). At the end of the incubation period, 10 μl of LPS (*E. coli* 0111:B4, Sigma Chemical Co., St. Louis, MO) is added to each well to a final concentration of 1 or 0.1 μg/ml for undiluted or 1:10 diluted whole blood, respectively. The incubation is continued for an additional 2 hours.

The reaction is stopped by placing the microtiter plates in an ice bath and plasma or cell-free supernates are collected by centrifugation at 3000 rpm for 10 minutes at 4°C. The plasma samples are stored at -80°C until assayed for TNF-α levels by ELISA, following the directions supplied by Quantikine Human TNF-α assay kit (R&D Systems, Minneapolis, MN).

IC_{50} values are calculated using the concentration of inhibitor that causes a 50% decrease as compared to a control.

B. Enriched Mononuclear Cell Assay for p38 Kinase Inhibition

The enriched mononuclear cell assay, the protocol of which is set forth below, begins with cryopreserved Human Peripheral Blood Mononuclear Cells (HPBMCs) (Clonetics Corp.) that are rinsed and resuspended in a warm mixture of cell growth media. The resuspended cells are then counted and seeded at $1x10^6$ cells/well in a 24-well microtitre plate. The plates are then placed in an incubator for an hour to allow the cells to settle in each well. After the cells have settled, the media is aspirated and new media containing 100 ng/ml of the cytokine stimulatory factor Lipopolysaccharide (LPS) and a test chemical compound is added to each well of the microtiter plate. Thus, each well contains HPBMCs, LPS and a test chemical compound. The cells are then incubated for 2 hours, and the amount of the cytokine Tumor Necrosis Factor Alpha (TNF-α) is measured using an Enzyme Linked Immunoassay (ELISA). One such ELISA for detecting the levels of TNF-α is commercially available from R&D Systems. The amount of TNF-α production by the HPBMCs in each well is then compared to a control well to determine whether the chemical compound acts as an inhibitor of cytokine production.

LPS induced cytokine synthesis in HPBMCs

Cryopreserved HPBMC (cat#CC-2702 Clonetics Corp)

LGM-3 media (cat#CC-3212 Clonetics Corp)

LPS stock 10μg/ml (Cat. No. L 2630 serotype 0111:B4 Sigma)

Human TNF-α ELISA (R&D Systems)

DNase I (10mg/ml stock)

Preparation of cells.

LGM-3 media warmed to 37°C.

5μl of DNase I stock added to 10ml media.

Cells thawed rapidly and dispersed into above.

Centrifuge 200xg x10min @ RT.

Pellet up in 10ml sterile PBS.

Centrifuge 200xg x10min @ RT.

Pellet resuspended in 10ml LGM-3 then diluted to 50ml with LGM-3.

Perform cell count.

Adjust to 1xE06 cells/well.

Seed 1ml/well of a 24 well plate.

Place plate in incubator to plate down for 1 hour.

Preparation of incubation media.

LGM-3 containing 100ng/ml LPS (e.g. 50ml media plus 0.5ml LPS stock)

Aliquot into 2ml aliquots and add 1000X inhibitor dilutions.

Incubation

When cells have plated down aspirate media away and overlay with 1ml relevant incubation media. Return plate to incubator for 2 hours or 24 hours. Remove supernatants after incubation to a labeled tube and either perform TNF (or other) ELISA immediately or freeze for later assay.

IC_{50} values are calculated using the concentration of inhibitor that causes a 50% decrease as compared to a control.

Administration and Use

The compounds of the invention are useful among other indications in treating conditions associated with inflammation. Thus, the compounds of formula (1) or their pharmaceutically acceptable salts are used in the manufacture of a medicament for prophylactic or therapeutic treatment of mammals, including humans, in respect of conditions characterized by excessive production of cytokines and/or inappropriate or

unregulated cytokine activity on such cells as cardiomyocytes, cardiofibroblasts and macrophages.

The compounds of the invention inhibit the production of cytokines such as TNF, IL-1, IL-6 and IL-8, cytokines that are important proinflammatory constituents in many different disease states and syndromes. Thus, inhibition of these cytokines has benefit in controlling and mitigating many diseases. The compounds of the invention are shown herein to inhibit a member of the MAP kinase family variously called p38 MAPK (or p38), CSBP, or SAPK-2. The activation of this protein has been shown to accompany exacerbation of the diseases in response to stress caused, for example, by treatment with lipopolysaccharides or cytokines such as TNF and IL-1. Inhibition of p38 activity, therefore, is predictive of the ability of a medicament to provide a beneficial effect in treating diseases such as Alzheimer's, coronary artery disease, congestive heart failure, cardiomyopathy, myocarditis, vasculitis, restenosis, such as occurs following coronary angioplasty, atherosclerosis, IBD, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, multiple sclerosis, acute respiratory distress syndrome (ARDS), asthma, chronic obstructive pulmonary disease (COPD), silicosis, pulmonary sarcosis, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, heart and brain failure (stroke) that are characterized by ischemia and reperfusion injury, surgical procedures, such as transplantation procedures and graft rejections, cardiopulmonary bypass, coronary artery bypass graft, CNS injuries, including open and closed head trauma, inflammatory eye conditions such as conjunctivitis and uveitis, acute renal failure, glomerulonephritis, inflammatory bowel diseases, such as Crohn's disease or ulcerative colitis, graft vs. host disease, bone resorption diseases like osteoporosis, type II diabetes, pyresis, psoriasis, cachexia, viral diseases such as those caused by HIV, CMV, and Herpes, and cerebral malaria.

Within the last several years, p38 has been shown to comprise a group of MAP kinases designated p38-α, p38-β, p38-γ and p38-δ. Jiang, Y., *et al., J Biol Chem* (1996) 271:17920-17926 reported characterization of p38-β as a 372-amino acid protein closely related to p38-α. In comparing the activity of p38-α with that of p38-β, the authors state that while both are activated by proinflammatory cytokines and environmental stress, p38-β was preferentially activated by MAP kinase kinase-6 (MKK6) and preferentially activated

transcription factor 2, thus suggesting that separate mechanisms for action may be associated with these forms.

Kumar, S., *et al., Biochem Biophys Res Comm* (1997) 235:533-538 and Stein, B., *et al., J Biol Chem* (1997) 272:19509-19517 reported a second isoform of p38-β, p38-β2, containing 364 amino acids with 73% identity to p38-α. All of these reports show evidence that p38-β is activated by proinflammatory cytokines and environmental stress, although the second reported p38-β isoform, p38-β2, appears to be preferentially expressed in the CNS, heart and skeletal muscle compared to the more ubiquitous tissue expression of p38-α. Furthermore, activated transcription factor-2 (ATF-2) was observed to be a better substrate for p38-β2 than for p38-α, thus suggesting that separate mechanisms of action may be associated with these forms. The physiological role of p38-β1 has been called into question by the latter two reports since it cannot be found in human tissue and does not exhibit appreciable kinase activity with the substrates of p38-α.

The identification of p38-γ was reported by Li, Z., *et al., Biochem Biophys Res Comm* (1996) 228:334-340 and of p38-δ by Wang, X., *et al., J Biol Chem* (1997) 272:23668-23674 and by Kumar, S., *et al., Biochem Biophys Res Comm* (1997) 235:533-538. The data suggest that these two p38 isoforms (γ and δ) represent a unique subset of the MAPK family based on their tissue expression patterns, substrate utilization, response to direct and indirect stimuli, and susceptibility to kinase inhibitors.

Various results with regard to response to drugs targeting the p38 family as between p38-α and either the putative p38-β1 or p38-β2 or both were reported by Jiang, Kumar, and Stein cited above as well as by Eyers, P.A., *et al., Chem and Biol* (1995) 5:321-328. An additional paper by Wang, Y., *et al., J Biol Chem* (1998) 273:2161-2168 suggests the significance of such differential effects. As pointed out by Wang, a number of stimuli, such as myocardial infarction, hypertension, valvular diseases, viral myocarditis, and dilated cardiomyopathy lead to an increase in cardiac workload and elevated mechanical stress on cardiomyocytes. These are said to lead to an adaptive hypertrophic response which, if not controlled, has decidedly negative consequences. Wang cites previous studies which have shown that in ischemia reperfusion treated hearts, p38 MAPK activities are elevated in association with hypertrophy and programmed cell death. Wang shows in the cited paper that activation of p38-β activity results in hypertrophy, whereas activation of p38-α activity

leads to myocyte apoptosis. Thus, selective inhibition of p38-α activity as compared to p38-β activity will be of benefit in treating conditions associated with cardiac failure. These conditions include congestive heart failure, cardiomyopathy, myocarditis, vasculitis, vascular restenosis, valvular disease, conditions associated with cardiopulmonary bypass, coronary artery bypass, grafts and vascular grafts. Further, to the extent that the α-isoform is toxic in other muscle cell types, α-selective inhibitors would be useful for conditions associated with cachexia attributed to TNF or other conditions such as cancer, infection, or autoimmune disease.

Thus, the invention encompasses the use of compounds which selectively inhibit the activity of the p38-α isoform for treating conditions associated with activation of p38-α, in particular those associated with cardiac hypertrophy, ischemia or other environmental stress such as oxidation injury, hyperosmolarity or other agents or factors that activate p38-α kinase, or cardiac failure, for example, congestive heart failure, cardiomyopathy and myocarditis.

The manner of administration and formulation of the compounds useful in the invention and their related compounds will depend on the nature of the condition, the severity of the condition, the particular subject to be treated, and the judgement of the practitioner; formulation will depend on mode of administration. As the compounds of the invention are small molecules, they are conveniently administered by oral administration by compounding them with suitable pharmaceutical excipients so as to provide tablets, capsules, syrups, and the like. Suitable formulations for oral administration may also include minor components such as buffers, flavoring agents and the like. Typically, the amount of active ingredient in the formulations will be in the range of 5%-95% of the total formulation, but wide variation is permitted depending on the carrier. Suitable carriers include sucrose, pectin, magnesium stearate, lactose, peanut oil, olive oil, water, and the like.

The compounds useful in the invention may also be administered through suppositories or other transmucosal vehicles. Typically, such formulations will include excipients that facilitate the passage of the compound through the mucosa such as pharmaceutically acceptable detergents.

The compounds may also be administered topically, for topical conditions such as psoriasis, or in formulation intended to penetrate the skin. These include lotions, creams, ointments and the like which can be formulated by known methods.

The compounds may also be administered by injection, including intravenous, intramuscular, subcutaneous or intraperitoneal injection. Typical formulations for such use are liquid formulations in isotonic vehicles such as Hank's solution or Ringer's solution.

Alternative formulations include nasal sprays, liposomal formulations, slow-release formulations, and the like, as are known in the art.

Any suitable formulation may be used. A compendium of art-known formulations is found in Remington's Pharmaceutical Sciences, latest edition, Mack Publishing Company, Easton, PA. Reference to this manual is routine in the art.

The dosages of the compounds of the invention will depend on a number of factors which will vary from patient to patient. However, it is believed that generally, the daily oral dosage will utilize 0.001-100 mg/kg total body weight, preferably from 0.01-50 mg/kg and more preferably about 0.01 mg/kg-10 mg/kg. The dose regimen will vary, however, depending on the conditions being treated and the judgment of the practitioner.

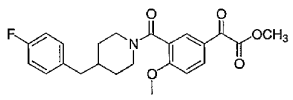
It should be noted that the compounds of formula (1) can be administered as individual active ingredients, or as mixtures of several embodiments of this formula. In addition, the inhibitors of p38 kinase can be used as single therapeutic agents or in combination with other therapeutic agents. Drugs that could be usefully combined with these compounds include natural or synthetic corticosteroids, particularly prednisone and its derivatives, monoclonal antibodies targeting cells of the immune system, antibodies or soluble receptors or receptor fusion proteins targeting immune or non-immune cytokines, and small molecule inhibitors of cell division, protein synthesis, or mRNA transcription or translation, or inhibitors of immune cell differentiation or activation.

As implied above, although the compounds of the invention may be used in humans, they are also available for veterinary use in treating animal subjects.

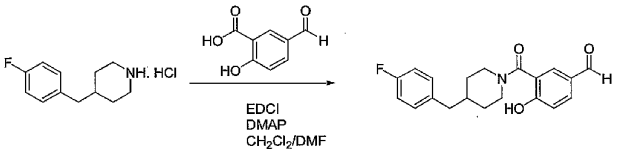
The following examples are intended to illustrate but not to limit the invention. The compounds described and prepared in examples 1-4 below are inhibitors of p38-α kinase.

Example 1

{3-[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-4-methoxy-phenyl}-oxo-acetic acid methyl ester

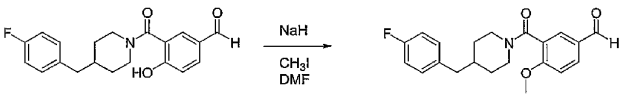


Step A



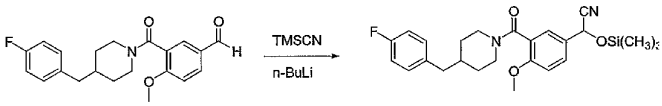
Under nitrogen protection, to a 250 mL R.B. dry flask containing 5.6 g (24.4 mMol) 4-fluoro-benzyl piperidine HCl salt was added 100 ml anhydrous CH_2Cl_2, followed by addition of 3.48 ml triethylamine (25 mMol). The suspension was allowed to stir at room temperature for a few minutes until it became a clear solution. To this solution was then added 4.37 g 5-formylsalicyclic acid (25 mMol), 4.8 g (25 mMol) of 1-ethyl-3-(3-dimethyl aminopropyl)-carbodiimide, 0.153 g (1.25 mMol) of 4-(dimethylamino)-pyridine. After overnight stirring, the reaction mixture was diluted with 100 mL of CH_2Cl_2, washed with H_2O, brine. The organic layers were then dried over anhydrous sodium sulfate, concentrated and purified by column chromatography eluting with CH_2Cl_2, giving 3.65 g (10.7 mMol) of desired product. (yield: 43.8%)

Step B



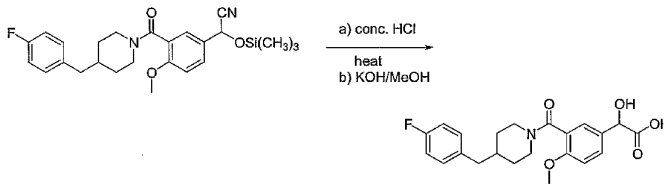
3.62 gram (10.6 mMol) aldehyde was dissolved in 100 mL anhydrous DMF under an argon atmosphere. To this solution, at 0 °C was added 4.66 g NaH (60 % dispersion in mineral oil, 11.7 mMol). The reaction was allowed to stir at 0 °C for 0.5 h before warming up to room temperature, stirring continued until there were no more bubbles produced. The flask was then cooled to 0 °C again, followed by addition of 0.73 mL of methyl iodide (11.7 mMol). After stirring at 0 °C for 0.5 h, the reaction was warmed up to room temperature, and continued stirring for another 4 h. DMF was evaporated off under reduced pressure. The resulting residue was re-dissolved in 100 mL of CH_2Cl_2, washed twice with H_2O, and brine. Organic layers were dried over anhydrous sodium sulfate, concentrated and purified by column chromatography in a gradient of 100% CH_2Cl_2 to 2% MeOH/CH_2Cl_2. 2.65 g (7.46 mMol) of product was obtained in a yield of 70.4%.

Step C



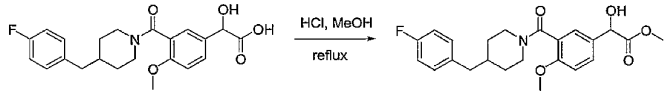
Under nitrogen protection, 2.64 g (7.43 mMol) of aldehyde was dissolved in 75 mL anhydrous THF. At 0 °C, to this solution was added 1.1 mL of trimethylsilyl cyanide (8.2 mMol), followed by addition of 2-3 drops of n-butyllithium (2.5 M solution in hexane). Stirring at 0 °C was continued for 2 h before warmed up to room temperature and stirred overnight. After removing solvents by rotary evaporation, product was obtained in almost quantitative yield as a white power. Without further purification, the material was used directly in next step.

Step D



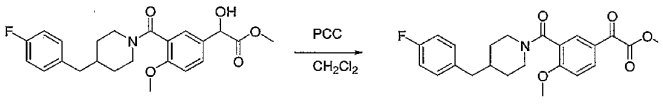
The material obtained from last step was diluted with 60 mL of concentrated HCl and heated to 80 °C with an oil bath overnight. After overnight heating, the aqueous solution was diluted with 100 mL H_2O and aqueous solution was extracted with CH_2Cl_2 (100 mL X 3). Organic layers were washed with brine, dried over sodium sulfate, and concentrated. The residue was then re-dissolved in about 70 mL MeOH, followed by addition of 1.7 g (30.3 mMol) of KOH and the solution was warmed to reflux for 2 h. Reaction was then cooled to room temperature, concentrated, and dried under vacuum. Several grams of crushed ice was added into the flask and acidified with 10 % aqueous HCl. Water (60 mL) was added to dilute the solution, and this aqueous solution was extracted with CH_2Cl_2 (100 mL X 3). Organic layers were washed with brine, dried over sodium sulfate, concentrated to give 2.5g (6.23 mMol) of product.

Step E



In a 50 mL R.B. flask containing a condenser, 130 mg of α-hydroxy acid was dissolved in 4 ml of concentrated HCl:MeOH (1:9) and warmed to reflux. After 1 h, the reaction was cooled to RT and concentrated under reduced pressure. Resulting residue was re-dissolved in 20 mL ethyl acetate and the ethyl acetate layer was washed with 20 mL H_2O, twice with 20 ml saturated $NaHCO_3$ solution, and brine. Organic layer was dried over anhydrous sodium sulfate and concentrated to give 141 mg of crude product.

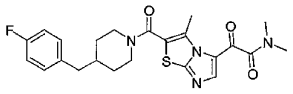
Step F



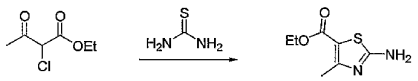
123 mg of methyl ester was dissolved in 4 ml CH_2Cl_2 followed by addition of excess of pyridinium chloromate (1 g, 20 wt. % on basic alumina). The resulting suspension was stirred at room temperature over 24 hours. Solid was filtered and washed with CH_2Cl_2. Combined organic solution was concentrated and product was purified by Preparative thin-layer chromatography with 1% MeOH/CH_2Cl_2 as eluting solution, to give 26 mg of desired product.

Example 2

2-{2-[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-3-methyl-imidazo[2,1-b]thiazol-5-yl}-N,N-dimethyl-2-oxo-acetamide

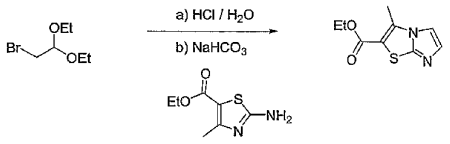


Step A



Thiourea (3.81 g) and ethyl 2-chloroacetoacetate (8.23g)were combined in EtOH (100 mL) and heated at reflux for 14 h. After cooling to RT the EtOH was removed in vacuo and the crude product dissolved in H_2O and neutralized with $NaHCO_3$ followed by extraction with ethyl acetate. The combined extracts were dried, filtered, and concentrated to yield the product as a white powder (8.69 g).

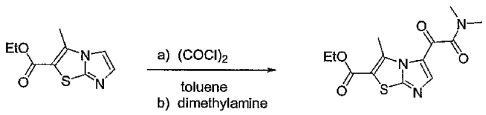
Step B



H_2O / dioxane

To bromoacetaldehyde diethylacetal (11.2 mMol, 2.20 g) in H_2O (75 mL) was added concentrated HCl (1.15 mL) dropwise. After stirring at RT for 14 h the mixture was heated at 80 °C for 30 min. After cooling to RT $NaHCO_3$ (14.5 mMol, 1.22 g) was cautiously added and stirring was continued for 2 h. The ester (8.9 mMol, 1.66 g) was then added and the mix was stirred an additional 1 h before adding dioxane (50 mL). After 30 min the mix was heated to 100 °C for 48 h. After cooling to RT the dioxane was removed by rotary evaporation. The aqueous layer was extracted with CH_2Cl_2. The combined organics were dried (Na_2SO_4), filtered and concentrated. Radial chromatography (10 % MeOH in CH_2Cl_2) yielded 122 mg of the desired product.

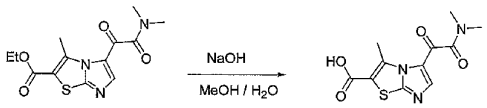
Step C



To the ester (0.19 mMol, 40 mg) in toluene (0.76 mL) at RT was added a 2.0 M solution of oxalyl chloride in CH_2Cl_2 (0.285 mL). The reaction vessel was placed under N_2, sealed, and placed at 125 °C for 12 h. After cooling to RT the volatiles were removed under vacuum. To the crude acid chloride was added CH_2Cl_2 (0.76 mL) and after cooling to 0 °C a 2.0 M solution of dimethylamine in THF (0.285 mL)was added dropwise. The reaction mixture was stirred an additional 30 min at 0 °C and then warmed to RT. After 30

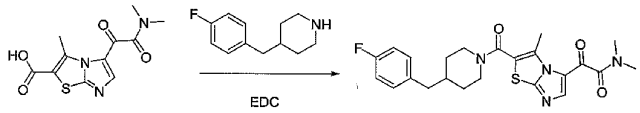
min the reaction was quenched with H_2O and extracted with CH_2Cl_2. The combined extracts were washed with brine and then dried (Na_2SO_4), filtered and concentrated. After radial chromatography (10 % MeOH in CH_2Cl_2) 38 mg of the product was obtained.

Step D



To the ester (0.12 mMol, 38 mg) in MeOH (0.25 mL) and H_2O (0.25 mL) was added NaOH (0.985 N in H_2O, 122 μL). The mixture was stirred at RT for14 h at which time it was acidified with aq. HCl and extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4), filtered, and concentrated to yield 19 mg of the product which carried on to the next step without purification.

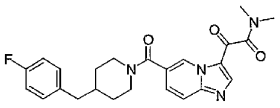
Step E



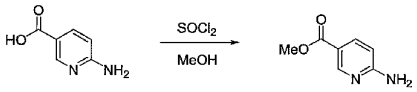
To the acid (0.14 mMol, 19 mg) in CH_2Cl_2 (0.56 mL) was added 4-fluorobenzylpiperidine (0.17 mMol, 39 mg) followed by EDC (0.17 mMol, 33 mg) and DMAP (4 mg). The mix was stirred at RT for 14 h before quenching with H_2O and extracting with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered, and concentrated. After radial chromatography 20 mg of the desired compound was obtained.

Example 3

2-{6-[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-imidazo[1,2-a]pyridin-3-yl}-N,N-dimethyl-2-oxo-acetamide

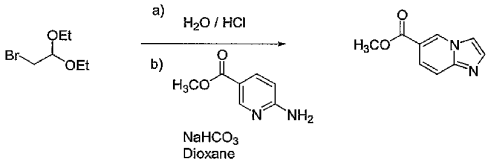


Step A



To 6-aminonicotinic acid (75 mMol, 10.36 g) in MeOH (300 mL) at –78 °C was added $SOCl_2$ (187.5 mMol, 22.31 g, 13.7 mL) dropwise over 30 min. The mixture was then allowed to RT. The mix was then refluxed for 12 h at which time it was cooled and the volatiles removed using rotary evaporation. The resulting white solid was dissolved in H_2O, neutralized with $NaHCO_3$, and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4), filtered, and concentrated to yield 10.06 g of a white powder.

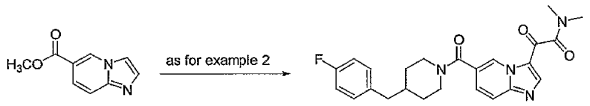
Step B



To bromoacetaldehyde diethylacetal (44.6 mMol, 8.79 g) in H_2O (300 mL) was added concentrated HCl (4.6 mL) dropwise. After stirring at RT for 14 h the mixture was heated at 80 °C for 30 min. After cooling to RT, $NaHCO_3$ (58.7 mMol, 4.88 g) was cautiously added and stirring was continued for 2 h. The ester (35.6 mMol, 5.41 g) was

then added and the mix was stirred an additional 1 h before adding dioxane (200 mL). After 30 min the mix was heated to 100 °C for 48 h. After cooling to RT the dioxane was removed by rotary evaporation. The aqueous layer was extracted with CH_2Cl_2. The combined organics were dried (Na_2SO_4), filtered and concentrated to yield a yellow paste (217 mg) which was carried on to the next step without further purification.

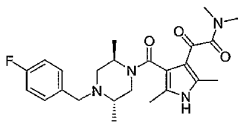
Step C



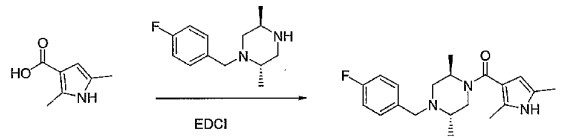
Synthesis of 2-{6-[4-(4-fluoro-benzyl)-piperidine-1-carbonyl]-imidazo[1,2-a]pyridin-3-yl}-N,N-dimethyl-2-oxo-acetamide was carried out through the same series of steps as for 2-{2-[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-3-methyl-imidazo[2,1-b]thiazol-5-yl}-N,N-dimethyl-2-oxo-acetamide.

Example 4

2-{4-[4-(4-Fluoro-benzyl)-2,5-trans-dimethyl-piperazine-1-carbonyl]-2,5-dimethyl-1H-pyrrol-3-yl}-N,N-dimethyl-2-oxo-acetamide

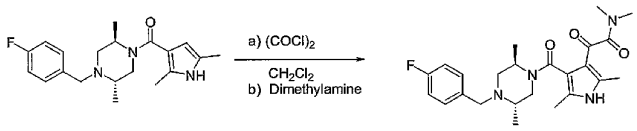


Step A



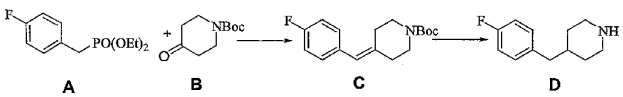
To 2,5-Dimethyl-1H-pyrrole-3-carboxylic acid (1.09 g) and 1-(4-Fluoro-benzyl)-trans-2,5-dimethyl-piperazine (1.59 g) in CH_2Cl_2 was added EDCI (1.51 g) and catalytic DMAP. The reaction mixture was stirred at RT for 12 h at which time it H_2O was added. The mix was extracted with CH_2Cl_2. The combined extracts were dried, filtered, and concentrated. After column chromatography (silica gel, (1:2) ethyl acetate / hexane to (7:3) ethyl acetate / hexane) 540 mg of the desired product was obtained.

Step B



A solution of (2,5-dimethyl-1H-pyrrol-3-yl)-[4-(4-fluoro-benzyl)-trans-2,5-dimethyl-piperazine-1-yl]-methanone (340 mg) in CH_2Cl_2 (25 mL)was cooled to 0 °C and a solution of oxalyl chloride (2.0 M in CH_2Cl_2, 2.0 mL) was added. Stirring was continued for 1 h at 0 °C and then the mix was allowed to warm to RT and stir for 1 h. The solvent was removed in vacuo and then replaced with CH_2Cl_2 (25 mL). After cooling to 0 °C dimethylamine (2.0 M solution in THF, 4.0 mL)was added dropwise. Stirring was continued for 30 min at which time it was warmed to RT. After 30 min the reaction was quenched with H_2O and extracted with CH_2Cl_2. The combined extracts were dried, filtered, and concentrated to yield the desired product which was purified by silica gel column chromatography ((1:1) ethyl acetate / hexane to ethyl acetate followed by (95:5) ethyl acetate / methanol to (90:10) ethyl acetate / methanol) to yield 60 mg of the product.

ADDITIONAL EXAMPLES

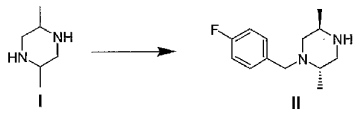


A B C D

Synthesis of D:

STEP 1: The phosphonate **A** (38.4 g) and the piperidone **B** (35.4) were dissolved in anhydrous dimethylformamide (400 mL). To this sodium hydride (60% suspension in oil) was added in portions while the reaction is maintained at 0°C. After the addition of sodium hyride was complete the reaction mixture was stirred for 30 min. and then the ice bath was removed, the reaction was allowed to stir for 6h as it slowly warmed to ambient temperature. The reaction was again cooled in an ice bath and quenched with methanol. Water was added to the reaction mixture, and the product extracted with ethyl acetate. The ethyl acetate layer was washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed to gives the crude alkene, which is purified by column chromatography eluting with ethyl acetate/hexane (1:9) to give 21.8 g of the desired product **C**.

STEP 2: 10 .1 g of **C** was dissolved in 50 mL methanol. After purging the solution with nitrogen, 5% Palladium on carbon (1g) catalyst was added followed by 1 mL acetic acid. The parr container containing the reaction mixture was hydrogenated for 4 h at 40-50 psi. The reaction mixture was filtered through celite and concentrated. The residue was treated with 2 M hydrochloric acid in ether to convert to the hydrochloric acid salt. The white solid that was obtained was dried under vacuum, extensively, to give 7.8 g of **D** as the hydrochloric acid salt.



I II

Synthesis of II:

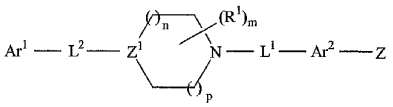
STEP 1: To a solution of dimethyl piperazine **I** (25g) in 300 ml of absolute ethanol was added 400 ml of 2N hydrogen chloride in diethyl ether. The solution was warmed to 70 °C in an oil bath for 20 minutes. The solution was then cooled to room temperature and set at 6 °C overnight. The solid obtained, was collected by filtration. Yield 39.8 g (dihydrochloride salt of trans-2,5 dimethylpiperazine) after drying overnight under high vacuum.

STEP 2: An ethanol solution of 42.9g of dimethyl piperazine dihydrochloride from STEP 1 and 26.1g *trans*-2,5 dimethylpiperazine was vigorously stirred in an oil bath at 80 °C until all starting materials were dissolved. The temperature of oil bath was reduced to 65 °C and 33.1g of 4-fluro benzylchloride was added. After stirring at this temperature for 30 min., the solution was placed in a 6 °C refrigerator overnight. The solid was removed from the solution by filtration and excess of 2N hydrogen chloride in diethyl ether was added to the filtrate. The filtrate was kept at 6 °C overnight and the solid collected. The solid was suspended in 5% sodium hydroxide aqueous solution and extracted three times with ethyl acetate. The organic layer was dried over sodium sulfate and dried down to give a yellow oil.

STEP 3: A solution of 50.7 g (L)-tartaric acid in 130 ml of boiling methanol was added to 70 ml of hot methanol solution of 37.5 g of the product from STEP 2. The solution was set at 6 °C for 96 hours before collection of white fine crystals by filtration. This material was recrystallized from boiling methanol. The product was collected by filtration after being kept at a 6 °C overnight. Yield 30.5 g of ditartaric acid salt ($[\alpha]= +$ 43.2°, c=1).

Claims

1. A compound of the formula:



and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein:

Ar^1 is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

L^1 and L^2 are linkers;

each R^1 is independently a noninterfering substituent;

Z^1 is CR^2 or N wherein R^2 is hydrogen or a noninterfering substituent;

m is 0-4;

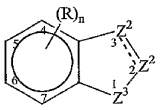
each of n and p is an integer from 0-2 wherein the sum of n and p is 0-3;

Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring;

Z is $-W_i-COX_jY$ wherein Y is COR^3 or an isostere thereof; R^3 is a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;

wherein the smallest number of covalent bonds in the compound separating the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of Ar^1 bonded to L^2 and the atom of Ar^2 bonded to L^1 is 4.5-24 angstroms;

with the proviso that the portion of the compound represented by Ar^2-Z is not



wherein ⋰ represents a single or double bond; n is 0-3; one Z^2 is CA or CRA and the other is CR, CR_2, NR or N; A is $-W_i-COX_jY$ wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1; Z^3 is NR or O; and each R is independently hydrogen or a noninterfering substituent.

2. The compound of claim 1 wherein said smallest number of bonds is 6-12.

3. The compound of claim 1 wherein Z is $COXjCOR^3$, and

wherein R^3 is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted with halo, alkyl, heteroalkyl, SR, SOR, SO_2R, SO_2NR_2, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, CN, COOR, $CONR_2$, COR, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, or

wherein R^3 is OR, NR_2, SR, $NRCONR_2$, $OCONR_2$, or $NRSO_2NR_2$, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, and wherein two R attached to the same atom may form a 3-8 member carbocyclic or heterocyclic ring and wherein said ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing

forms thereof wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined; and

X, if present, is CR_2 where R is as defined above.

4. The compound of claim 1 wherein Y is an isostere of COR^3.

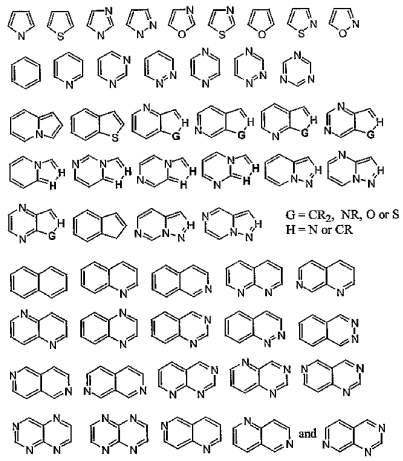
5. The compound of claim 4 wherein Y is tetrazole; 1,2,3-triazole; 1,2,4-triazole; or imidazole.

6. The compound of claim 1 wherein each of i and j is 0.

7. The compound of claim 3 wherein j is 0.

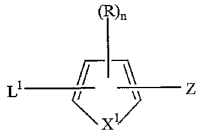
8. The compound of claim 1 wherein $-Ar^2-$ comprises an optionally substituted monocyclic or polycyclic aromatic nucleus, wherein said aromatic nucleus consists of carbocyclic or heterocyclic ring selected from (i) a five-membered heterocyclic or carbocyclic ring (ii) a six-membered carbocyclic or heterocyclic ring; (iii) a five-membered carbocyclic or heterocycloc ring fused to another five-membered carbocyclic or heterocyclic ring; (iv) a six-membered carbocyclic or heterocyclic ring fused to another six-membered carbocyclic or heterocyclic ring; and (v) a five-membered heterocyclic or carbocyclic ring fused to a six-membered carbocyclic or heterocyclic ring.

9. The compound of claim 8 wherein Ar^2 is selected from:



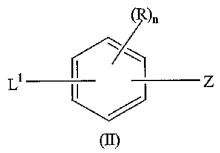
where R is a noninterfering substituent.

10. The compound of claim 8 wherein the portion of said compound represented by L^1-Ar^2-Z is selected from the following:



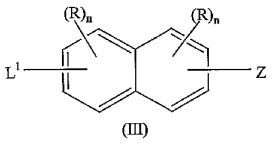
(I)

wherein n is 0, 1 or 2; X^1 is NR, CR_2, O or S; and each R is independently H or a noninterfering substituent; and two or more R groups may form a fused ring;



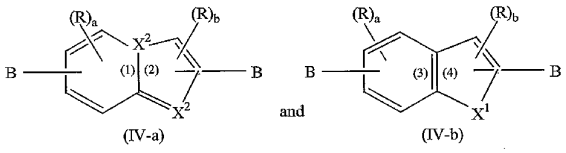
(II)

wherein n is 0-4; R is H or a noninterfering substituent where two or more R groups may form a fused ring; and one or more ring carbons may be optionally replaced with nitrogen;



(III)

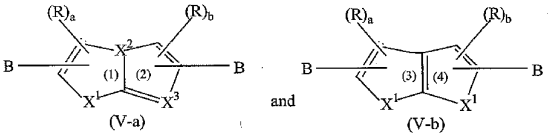
wherein each n is inpendently 0 to 3; R is H or a noninterfering substituent, where two or more R groups may form a fused ring; and one or more ring carbons may be optionally replaced with nitrogen;



(IV-a) and (IV-b)

wherein, subject to the proviso of claim 1, one B is L^1 and the other is Z; wherein a is 0 to 4 such that the positions on the six membered rings (1) and (3) to which $(R)_a$ is bonded can include X^2 when X^2 is C; b is 0 –3 such that the positions on the five-membered rings (2) and (4) to which $(R)_b$ is bonded can include X^2 and X^1, when X^2 is C and X^1 is N or C; each X^2 is independently N or CR; $X^1$is NR, CR_2, O or S; each R is H or a noninterfering substituent where two or more R groups may form a fused ring; wherein

one or more of the ring carbons that are at positions other than X^2 or X^1 and that are also not bound to B can be optionally replaced with N;



(V-a)

and

(V-b)

wherein one B is L^1 and the other is Z; a is 0-4 such that the positions on the rings (1) and (3) to which $(R)_a$ can be bonded include X^2 and X^1 where X^2 is C and X^1 is C or N; b is 0 or 3 such that the positions on the rings (2) and (4) to which $(R)_b$ can be bonded include X^1, X^2 and X^3 when X^1 is C or N and X^2 and/or X^3 are C; each X^1 is independently NR, $C(R)_2$, O or S; X^2 and X^3 are independently N or CR; each R is independently H or a noninterfering substituent where two or more R groups can optionally form a fused ring; wherein one or more of the ring carbons that are at positions other than X^1, X^2 or X^3, and that are also not bound to B, can be optionally replaced with N.

11. The compound of claim 10 wherein L^1-Ar^2-Z is structure (I).

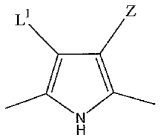
12. The compound of claim 11 wherein X^1 in structure (I) is NR.

13. The compound of claim 12 wherein X^1 in structure (I) is NH.

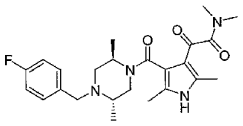
14. The compound of claim 13 wherein R is methyl.

15. The compound of claim 14 wherein n is 2.

16. The compound of claim 15 wherein structure (I) is:



17. The compound of claim 16 where the compound is:

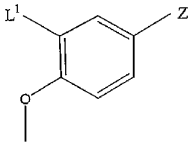


18. The compound of claim 10 wherein L^1-Ar^2-Z is structure (II).

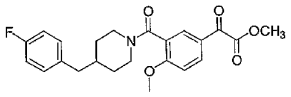
19. The compound of claim 18 wherein the R in structure (II) is methoxy.

20. The compound of claim 19 wherein n in structure (II) is 1.

21. The compound of claim 20 wherein structure (II) is



22. The compound of claim 21 wherein the compound is:

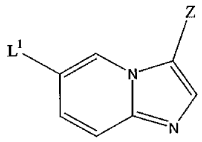


23. The compound of claim 10 wherein L^1-Ar^2-Z is structure (III).

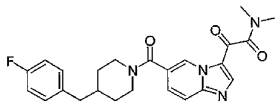
24. The compound of claim 10 wherein L^1-Ar^2-Z is structure (IV-a) or (IV-b).

25. The compound of claim 24 wherein L^1-Ar^2-Z is (IV-a) and both X^2 in structure (IV-a) are nitrogen.

26. The compound of claim 25 wherein structure (IV) is:



27. The compound of claim 26 wherein the compound is:



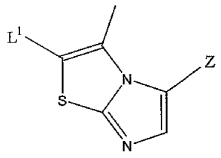
28. The compound of claim 8 wherein L^1-Ar^2-Z is structure (V-a) or (V-b).

29. The compound of claim 28 wherein L^1-Ar^2-Z is structure (V-a) and X^2 and X^3in structure (V-a) are N.

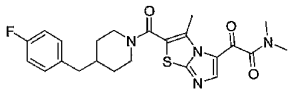
30. The compound of claim 29 wherein at least one R in structure (V) is methyl.

31. The compound of claim 29 wherein X^1 in structure (V) is S.

32. The compound of claim 31 wherein structure (V) is:



33. The compound of claim 32 wherein the compound is:



34. The compound of claim 1 wherein both n and p are 1.

35. The compound of claim 1 wherein L^1 is CO, CHOH or CH_2.

36. The compound of claim 35 wherein L^1 is CO.

37. The compound of claim 1 wherein Z^1 is N.

38. The compound of claim 1 wherein Z^1 is CR^2 wherein R^2 is H, OR, NR_2, SR or halo, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof.

39. The compound of claim 1 wherein L^2 is alkylene (1-4C) or alkenylene (1-4C) optionally substituted with a moiety selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR,

NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two substituents on L^2 can be joined to form a non-aromatic saturated or unsaturated ring that includes 0-3 heteroatoms which are O, S and/or N and which contains 3 to 8 members or said two substituents can be joined to form a carbonyl moiety or an oxime, oximeether, oximeester or ketal of said carbonyl moiety.

40. The compound of claim 39 wherein L^2 is unsubstituted alkylene.

41. The compound of claim 39 wherein L^2 is unsubstituted methylene, methylene substituted with alkyl, or -CH=.

42. The compound of claim 1 wherein Ar^1 is optionally substituted with 0-5 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said optional substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

43. The compound of claim 42 wherein Ar^1 is optionally substituted phenyl.

44. The compound of claim 43 wherein said optional substitution is by halo, OR, or alkyl.

45. The compound of claim 44 wherein said phenyl is unsubstituted or has a single substituent.

46. The compound of claim 1 wherein R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^4 on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, or R^4 is =O or an oxime, oximeether, oximeester or ketal thereof.

47. The compound of claim 46 wherein each R^1 is halo, OR, or alkyl.

48. The compound of claim 47 wherein m is 0, 1, or 2.

49. The compound of claim 48 wherein m is 2 and both R^1 are alkyl.

50. The compound of claim 10 wherein each of the non-interfering groups R, when bonded to a ring carbon atom, are selected from the group consisting of:

(a) hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl and halo; or

(b) or from OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R in the preceding (b) selections is independently H, alkyl, alkenyl or aryl or heteroforms thereof;

and wherein two of the non-interfering groups R can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

51. The compound of claim 50 wherein the non-interfering groups R are independently selected from the group consisting of H, alkyl, acyl, aryl, arylalkyl,

heteroalkyl, heteroaryl, halo, OR, NR_2, SR, NRCOR, alkyl-OOR, RCO, COOR, and CN, wherein each R is independently H, alkyl, or aryl or heteroforms thereof.

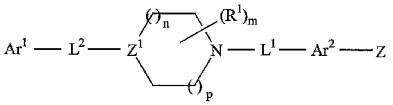
52. The compound of claim 10 wherein the noninterfering groups R, when bonded to a nitrogen ring atom, are selected from the group consisting of:

(a) H, or alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl; and

(b) SOR, SO_2R, RCO, COOR, alkyl-COR, SO_3R, $CONR_2$, SO_2NR_2, CN, CF_3, or R_3Si wherein each R in the preceding (b) selections is independently H, alkyl, alkenyl or aryl or heteroforms thereof.

53. A pharmaceutical composition for treating conditions characterized by enhanced p38-α activity which composition comprises

a therapeutically effective amount of a compound of the formula



and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein:

Ar^1 is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

L^1 and L^2 are linkers;

each R^1 is independently a noninterfering substituent;

Z^1 is CR^2 or N wherein R^2 is hydrogen or a noninterfering substituent;

m is 0-4;

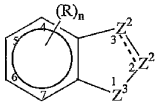
each of n and p is an integer from 0-2 wherein the sum of n and p is 0-3;

Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring;

Z is -W_i-COX_jY wherein Y is COR^3 or an isostere thereof; R^3 is a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;

wherein the smallest number of covalent bonds in the compound separating the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of Ar^1 bonded to L^2 and the atom of Ar^2 bonded to L^1 is 4.5-24 angstroms;

with the proviso that the portion of the compound represented by Ar^2-Z is not



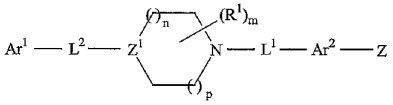
wherein ⫻ represents a single or double bond; n is 0-3; one Z^2 is CA or CRA and the other is CR, CR_2, NR or N; A is -W_i-COX_jY wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1; Z^3 is NR or O; and each R is independently hydrogen or a noninterfering substituent.

54. The pharmaceutical composition of claim 53 wherein said smallest number of bonds is 6-12.

55. The composition of claim 53 which further contains an additional therapeutic agent.

56. The composition of claim 55 wherein said additional therapeutic agent is a corticosteroid, a monoclonal antibody, or an inhibitor of cell division.

57. A method to treat a condition mediated by p38-α kinase comprising administering to a subject in need of such treatment a compound of the formula:



and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein

Ar^1 is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

L^1 and L^2 are linkers;

each R^1 is independently a noninterfering substituent;

Z^1 is CR^2 or N wherein R^2 is hydrogen or a noninterfering substituent;

m is 0-4;

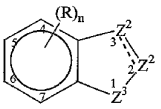
each of n and p is an integer from 0-2 wherein the sum of n and p is 0-3;

Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring;

Z is $-W_i-COX_jY$ wherein Y is COR^3 or an isostere thereof; R^3 is a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;

wherein the smallest number of covalent bonds in the compound separating the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of Ar^1 bonded to L^2 and the atom of Ar^2 bonded to L^1 is 4.5-24 angstroms;

with the proviso that the portion of the compound represented by Ar^2-Z is not



wherein ⚌ represents a single or double bond; n is 0-3; one Z^2 is CA or CRA and the other is CR, CR_2, NR or N; A is $-W_i-COX_jY$ wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1; Z^3 is NR or O; and each R is independently hydrogen or a noninterfering substituent.

58. The method of claim 57 wherein said smallest number of bonds is 6-12.

59. The method of claim 57 wherein said condition is a proinflammation response.

60. The method of claim 59 wherein said proinflammation response is multiple sclerosis, IBD, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, other arthritic conditions, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, CNS injury, psoriasis, restenosis, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, a bone resorption disease, graft-versus-host reaction, Crohn's Disease, ulcerative colitis, Alzheimer's, pyresis or heart disease.

【国際公開パンフレット（コレクトバージョン）】

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(71) Applicant: SCIOS INC. [US/US]; 749 North Mary Avenue, Sunnyvale, CA 94086 (US).

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(81) Designated States (national): 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, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

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Previous Correction:
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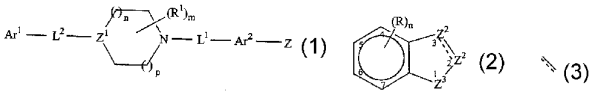
[Continued on next page]

(54) Title: PIPERIDINE/PIPERAZINE-TYPE INHIBITORS OF P38 KINASE



(57) Abstract: The invention is directed to inhibition of p38-α kinase using compounds of the formula (1) and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein: Ar^1 is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring; L^1 and L^2 are linkers; each R^1 is independently a noninterfering substitutent; Z^1 is CR^2 or N wherein R^2 is hydrogen or a noninterfering substituent; m is 0-4; each of n and p is an integer from 0-2 wherein the some of n and p is 0-3; Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring; Z is W_i-COX_jY wherein Y is COR^3 or an isotere thereof; R^3 is a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1; wherein the smallest number of covalent bonds is the compound separating the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of Ar^1 bonded to L^2 and the atom of Ar^2 bonded to L^1 is 4.5-24 angstroms; with the proviso that the protion of the compound represented by Ar^2-Z is not formula (2) wherein formula (3) represents a singel or double bond; n is 0-3; one Z^2 is CA or CRA and the other is CR, CR_2, NR or N; A is W_i-COX_jY wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 ot 1; Z^3 is NR or O; and each R independently hydrogen or a mominterfering substituent.

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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.

【国際調査報告】

INTERNATIONAL SEARCH REPORT

Internat pplication No
PCT/US 01/43824

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/18 C07D513/04 C07D471/04 C07D207/40 A61K31/445 A61P29/00

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 C07D A61K 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, 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	WO 99 61426 A (SCIOS INC) 2 December 1999 (1999-12-02) cited in the application table 5	1-60
X	WO 99 31096 A (LIPHA ;SHAMAN PHARMACEUTICALS INC (US)) 24 June 1999 (1999-06-24) example 96	1,53
X	EP 0 512 352 A (HOFFMANN LA ROCHE) 11 November 1992 (1992-11-11) examples 244,245,248,249	1,53

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[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
10 February 2003	26/02/2003

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	Diederen, J

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INTERNATIONAL SEARCH REPORT

Interna Application No
PCT/US 01/43824

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	SCOTT M K ET AL: "PIPERAZINYLALKYL HETEROCYCLES AS POTENTIAL ANTIPSYCHOTIC AGENTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 38, no. 21, 1995, pages 4198-4210, XP002092071 ISSN: 0022-2623 compounds 2-5 ---	1,53
A	US 6 130 235 A (LIU DAVID Y ET AL) 10 October 2000 (2000-10-10) the whole document ---	1,53,57
A	WO 98 06715 A (RAHMAN SHIRLEY K ;SMITHKLINE BEECHAM PLC (GB); ADAMS JERRY LEROY () 19 February 1998 (1998-02-19) examples ---	1,53,57
P,A	WO 00 71535 A (SCIOS INC) 30 November 2000 (2000-11-30) proviso of the present application compound 55 ------	1,53,57

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

INTERNATIONAL SEARCH REPORT

Inte al application No.
PCT/US 01/43824

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 57-60 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-16 (in part) 18-21 (in part) 23-26 (in part) 28-32 (in part) 34-60 (in part)

Present claims 1-16, 18-21, 23-26, 28-32, 34-60 relate to an extremely large number of possible compounds, compositions and methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds, compositions and methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of the formula as disclosed on page 2 of the description in which:

* n=1, p=1 (piperidine and piperazine compounds, see page 12, line 1; page 9, line 19)
* Z = C(O)Y (j=0 and i=o : see page 12, lines 4-10)
* Y = C(O) or an isostere as described on page 13

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Application No
PCT/US 01/43824

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9961426	A	02-12-1999	US	6130235 A	10-10-2000
			US	6340685 B1	22-01-2002
			AU	4092099 A	13-12-1999
			BR	9911069 A	06-02-2001
			CN	1305464 T	25-07-2001
			EP	1080078 A1	07-03-2001
			JP	2002516314 T	04-06-2002
			NO	20005881 A	09-01-2001
			PL	346345 A1	11-02-2002
			WO	9961426 A1	02-12-1999
			US	6448257 B1	10-09-2002
			AU	3920900 A	23-10-2000
			WO	0059904 A2	12-10-2000
WO 9931096	A	24-06-1999	AU	1924099 A	05-07-1999
			WO	9931096 A1	24-06-1999
EP 0512352	A	11-11-1992	US	5344843 A	06-09-1994
			AT	136018 T	15-04-1996
			AU	653398 B2	29-09-1994
			AU	1600392 A	12-11-1992
			BR	9201769 A	29-12-1992
			CA	2068076 A1	10-11-1992
			CZ	9201385 A3	17-02-1993
			DE	69209357 D1	02-05-1996
			EP	0512352 A2	11-11-1992
			FI	922095 A	10-11-1992
			HU	63602 A2	28-09-1993
			IE	921489 A1	18-11-1992
			JP	5279353 A	26-10-1993
			JP	7107060 B	15-11-1995
			MX	9202153 A1	01-11-1992
			NO	921840 A	10-11-1992
			NZ	242626 A	27-01-1995
			RO	109938 B1	28-07-1995
			RU	2059603 C1	10-05-1996
			ZA	9203279 A	27-01-1993
US 6130235	A	10-10-2000	AU	4092099 A	13-12-1999
			BR	9911069 A	06-02-2001
			CN	1305464 T	25-07-2001
			EP	1080078 A1	07-03-2001
			JP	2002516314 T	04-06-2002
			NO	20005881 A	09-01-2001
			PL	346345 A1	11-02-2002
			WO	9961426 A1	02-12-1999
			US	6340685 B1	22-01-2002
			US	6448257 B1	10-09-2002
WO 9806715	A	19-02-1998	EP	0922042 A1	16-06-1999
			JP	2001506230 T	15-05-2001
			WO	9806715 A1	19-02-1998
WO 0071535	A	30-11-2000	AU	3920900 A	23-10-2000
			AU	5442400 A	12-12-2000
			BG	106091 A	28-06-2002
			BR	0011274 A	26-02-2002
			CN	1351599 T	29-05-2002

Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/US 01/43824

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0071535 A		CZ 20014126 A3	13-03-2002
		EP 1178983 A1	13-02-2002
		HU 0201261 A2	28-08-2002
		NO 20015655 A	18-01-2002
		SK 16482001 A3	04-04-2002
		WO 0059904 A2	12-10-2000
		WO 0071535 A1	30-11-2000
		US 6448257 B1	10-09-2002

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【要約の続き】
サーであり、かつ、ｉおよびｊの各々が独立して０または１であり、ここで、L^2に結合したAr^1の原子とL^1に結合したAr^2の原子を隔てている化合物内の共有結合の数の最小値が少なくとも６であり、該結合の各々の結合距離が１．２Åないし２．０Åであり、および／または、ここでL^2に結合したAr^1の原子とL^1に結合したAr^2の原子の間の空間の距離が４．５～２４Åであり、Ar^2－Ｚで示される化合物の部分が式（２）ではないという条件であって、ここで式（３）が単結合または二重結合を示し、ｎが０～３であり、１つのZ^2がＣＡまたはＣＲＡであり、かつその他のZ^2がＣＲ、CR_2、ＮＲまたはＮであり、ＡがW_i－COX_j Ｙであり、ここでＹがＣＯＲまたはその等配電子体であり、ＷおよびＸの各々が２～６Åのスペーサーであり、かつ、ｉおよびｊの各々が独立して０または１であり、Z^3がＮＲまたはＯであり、各Ｒが独立して、水素または非妨害性置換基である。