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(54) Epígrafe: **INIBIDORES DE PROTEASE DE HCV**

(57) Resumo:

ESTA INVENÇÃO REFERE-SE A COMPOSTOS MACROCÍCLICOS APRESENTADOS NA ESPECIFICAÇÃO. ESTES COMPOSTOS PODEM SER USADOS PARA TRATAR A INFEÇÃO POR VÍRUS DA HEPATITE C

RESUMO

"INIBIDORES DE PROTEASE DE HCV"

Esta invenção refere-se a compostos macrocíclicos apresentados na especificação. Estes compostos podem ser usados para tratar a infecção por vírus da hepatite C.

DESCRIÇÃO**"INIBIDORES DE PROTEASE DE HCV"****BASES DA INVENÇÃO**

O vírus da hepatite C (HCV), um vírus de RNA monocatenário de sentido (+), é o principal agente causador da maioria dos casos de hepatite não-A, não-B. A infecção por HCV é um problema de saúde humana constrangedor. Ver, por exemplo, WO 05/007681; WO 89/04669; EP 381216; Alberti et al., *J. Hepatology*, 31 (Supl. 1), 17-24 (1999); Alter, *J. Hepatology*, 31 (Supl. 1), 88-91 (1999); e Lavanchy, *J. Viral Hepatitis*, 6, 35-47 (1999).

A hepatite provocada por infecção por HCV é difícil de tratar uma vez que o vírus pode mutar rapidamente e escapar à resposta imune natural. As únicas terapias anti-HCV atualmente disponíveis são interferão- α , interferão- α /combinação de ribavirina e interferão- α peguilado. No entanto, observou-se que as taxas de resposta contínuas para o interferão- α ou interferão- α /combinação de ribavirina são <50% e os pacientes sofrem consideravelmente de efeitos secundários destes agentes terapêuticos. Ver, por exemplo, Walker, *DDT*, 4, 518-529 (1999); Weiland, *FEMS Microbial. Rev.*, 14.279-288 (1994); e WO 02/18369. Assim,

continua a haver necessidade de desenvolvimento de drogas terapêuticas mais eficazes e que sejam mais bem toleradas.

Uma protease de HCV necessária para a replicação viral contém cerca de 3000 aminoácidos. Inclui uma proteína de nucleocapsídeo (C), proteínas envelope (E1 e E2), e várias proteínas não estruturais (NS2, NS3, NS4a, NS5a e NS5b).

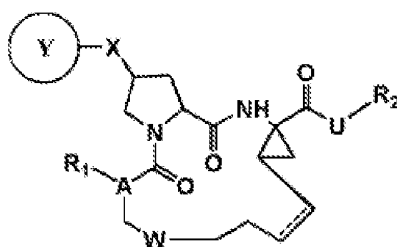
A proteína NS3 possui atividade de serino protease e é considerada essencial para a replicação e infecciosidade viral. A essencialidade da protease NS3 foi inferida a partir do facto de que as mutações na protease NS3 no vírus da febre-amarela diminuíram a infecciosidade viral. Ver, por exemplo, Chamber et al., *Proc. Natl. Acad. Sci. EUA* 87, 8898-8902 (1990). Foi também demonstrado que as mutações no centro activo da protease NS3 de HCV inibiram completamente a infeção por HCV no modelo de chimpanzé. Ver, por exemplo, Rice et al., *J. Virol.* 74 (4) 2046-51 (2000). Além disso, verificou-se que a protease NS3 de HCV facilita a proteólise nas junções NS3/NS4a, NS4a/NS4b, NS4b/NS5a, NS5a/NS5b e foi portanto responsável por gerar quatro proteínas virais durante a replicação viral. Ver, por exemplo, US 2003/0207861. Consequentemente, a enzima da protease NS3 de HCV é um alvo atrativo no tratamento da infeção por HCV. Potenciais inibidores da protease NS3 de HCV podem ser encontrados em WO2008/02006, WO2009/055335, WO 02/18369, WO 00/09558, WO 00/09543, WO 99/64442, WO 99/07733, WO 99/07734, WO 99/50230, WO

98/46630, WO 98/17679, WO 97/43310, US 5.990.276, Dunsdon et al., *Biorg. Med. Chem. Lett.* 10, 1571-1579 (2000); Llinas-Brunet et al., *Biorg. Med. Chem. Lett.* 10, 2267-2270 (2000); e S. LaPlante et al., *Biorg. Med. Chem. Lett.* 10, 2271-2274 (2000).

SUMÁRIO

Esta invenção é baseada em descobertas inesperadas de que certos compostos macrocíclicos bloqueiam a atividade de proteases NS3-4A, diminuem os níveis RNA de HCV, inibem mutantes de protease de HCV resistentes a outros inibidores, e apresentam uma meia-vida prolongada no sistema sanguíneo.

Num aspeto, este pedido de patente refere-se a compostos de fórmula (I):

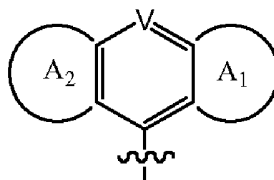


Fórmula (I)

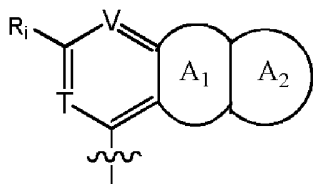
em que R₁ é -H, -OH, alquilo C₁₋₆, alcoxilo C₁₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo, heteroarilo, -Z-R, ou -NH-Z-R; em que R é H, ou é uma metade seleccionada de alquilo C₁₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀,

arilo e heteroarilo, cada uma das quais é opcionalmente mono-, di- ou tri-substituída com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, arilo ou heteroarilo; e Z é -C(O)-, -C(O)O-, -C(O)C(O)O-, -C(O)C(O)NH-, -C(O)NR'-, -OC(S)-, -C(S)NR'- ou -C(NH)O-, sendo R' H, alquilo C₁₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo; R₂ é H, ou é uma metade selecionada de alquilo C₁₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo e heteroarilo, sendo cada uma das quais opcionalmente mono-, di-, ou tri-substituída com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, arilo ou heteroarilo; A é N ou CH; U é -O-, -NH-, -NH(CO)-, -NHSO- ou -NH₂SO₂-; W é -(CH₂)_m-, -NH(CH₂)_n-, -(CH₂)_nNH-, -O(CH₂)_n-, -(CH₂)_nO-, -S(CH₂)_n-, -(CH₂)_nS-, -S(O)-, -SO(CH₂)_n-, -(CH₂)_nS(O)-, -SO₂(CH₂)_n ou -(CH₂)_nSO₂-, sendo m 1, 2, ou 3 e sendo n 0, 1 ou 2; X é -O-,

-S-, -NH-, ou -OCH₂-; Y é



ou



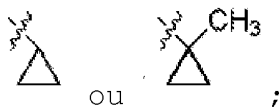
, em que cada um de V e T é, independentemente, -CH- ou -N-; cada um de A₁ e A₂ é, independentemente, uma metade selecionada de cicloalquilo C₄₋₁₀, heterocicloalquilo C₁₋₁₀, arilo e heteroarilo, sendo cada uma das quais opcionalmente mono-, di-, ou tri-substituída com halo, nitro, ciano, amino, alquilo C₁₋₆,

alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, arilo ou heteroarilo, ou opcionalmente fundida com cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo; e R é H, halo, nitro, ciano ou amino, ou é uma metade selecionada de alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo e heteroarilo, sendo cada um de alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆ e alquinilo C₂₋₆ opcionalmente mono-, di- ou tri-substituído com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀ arilo ou heteroarilo, e sendo cada um de cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo e heteroarilo opcionalmente mono-, di- ou tri-substituído com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, arilo ou heteroarilo, opcionalmente fundida com cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo; e R_i é H, halo, nitro, ciano ou amino, ou é uma metade selecionada de alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo e heteroarilo, sendo cada um de alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆ e alquinilo C₂₋₆ opcionalmente mono-, di- ou tri-substituído com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo, e sendo cada um de cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo e heteroarilo opcionalmente mono-, di- ou tri-substituído com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, cicloalquilo

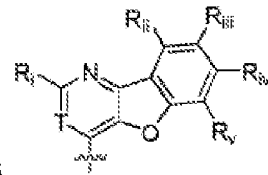
C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo, opcionalmente fundida com cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo; e --- é uma ligação simples ou uma ligação dupla.

Os grupos atribuídos às variáveis U, W, X e Z são bivalentes. Cada um dos grupos é apresentado acima na mesma orientação como aquela em que a variável é apresentada na fórmula. Tomando, por exemplo, o grupo -NHSO- atribuído à variável U, a qual, conforme apresentado na fórmula, é interposta entre C=O e R₂. O átomo de N neste grupo -NHSO- encontra-se ligado a C=O e o átomo de S ligado a R₂. Como outro exemplo, o grupo -C(O)O- atribuído à variável Z é interposto entre NH e R (ou seja, -NH-Z-R). O átomo de C em -C(O)O- está ligado a NH e o átomo de O ligado a R.

Relativamente à Fórmula (I), um subconjunto das características dos compostos é aquele em que R₁ é -NH-Z-R, onde Z é -C(O)-, -C(O)O-, -C(O)C(O)O- ou -C(O)C(O)NH-; R₂ é



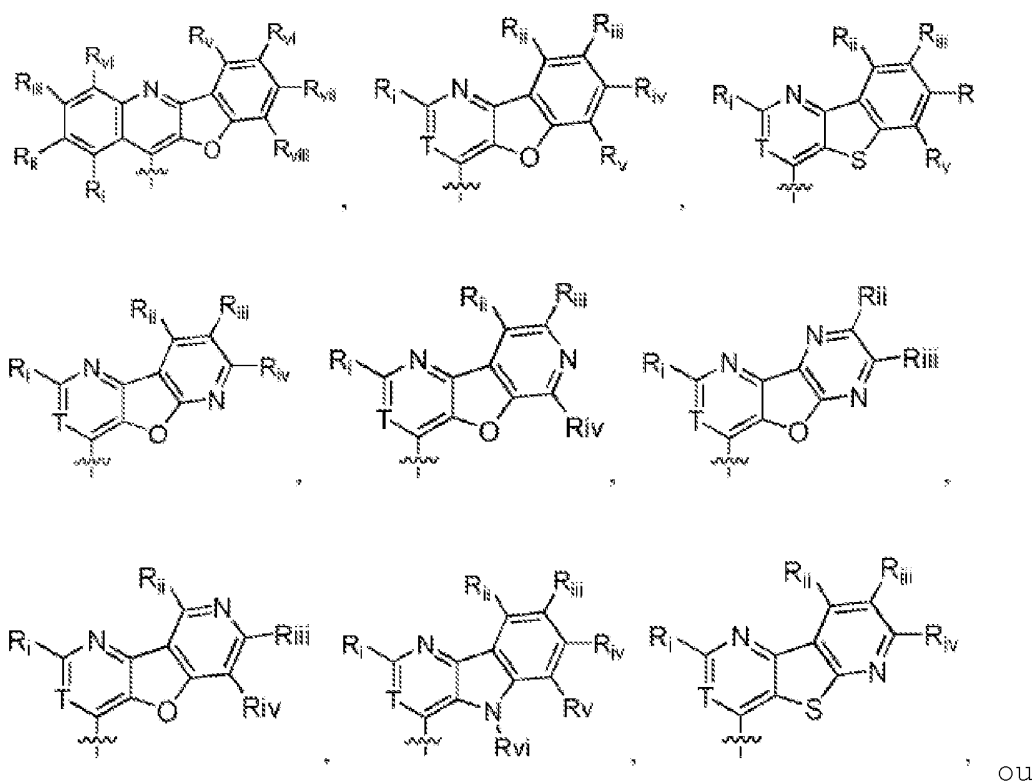
X é O; A é CH; W é -CH₂CH₂-, -OCH₂-, -SCH₂- ou -SOCH₂-; U é

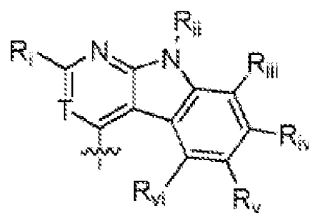


-NHSO₂-; --- é uma ligação dupla; ou Y é : , onde T é CH ou N; R_i é fenilo ou tiazolilo opcionalmente substituído com halo, amino, alquilo C₁₋₆ ou alcoxilo C₁₋₆; e cada um de R_{ii}, R_{iii}, R_{iv} e R_v é, independentemente, H, halo,

nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆ ou alquinilo C₂₋₆, ou é uma metade selecionada de cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo e heteroarilo, sendo cada um das quais opcionalmente mono-, di- ou tri-substituída com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo, C₂₋₆, alquinilo C₂₋₆, arilo ou heteroarilo, ou opcionalmente fundida com cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo. Exemplos de R₁ são -NH-C(O)O-t-Bu, -NH-C(O)O-ciclopentilo e -NH-C(O)-furilo.

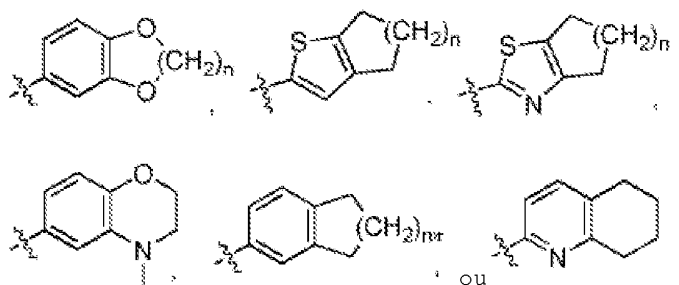
Outro subconjunto das características dos compostos é tal que Y é





em que cada um de R_i , R_{ii} , R_{iii} , R_{iv} , R_v e R_{vi} é, independentemente, H, halo, nitro, ciano, amino, alquilo C_{1-6} , alcoxilo C_{1-6} , alcenilo C_{2-6} , alquinilo C_{2-6} , cicloalquilo C_{3-10} , heterocicloalquilo C_{1-10} , arilo ou heteroarilo, sendo cada um de cicloalquilo, heterocicloalquilo, arilo e heteroarilo opcionalmente mono-, di- ou tri-substituídos com halo, nitro, ciano, amino, alquilo C_{1-6} , alcoxilo C_{1-6} , alcenilo C_{2-6} , alquinilo C_{2-6} , arilo ou heteroarilo; e opcionalmente fundido com cicloalquilo C_{3-10} , heterocicloalquilo C_{1-10} , arilo ou heteroarilo.

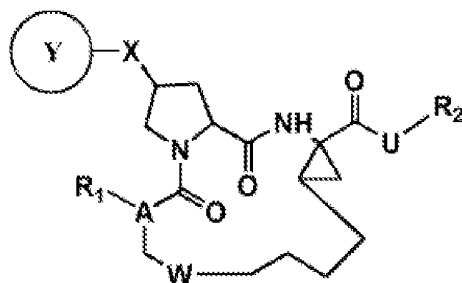
Nos compostos acima, R_i pode ser, por exemplo,



em que o n é 1 ou 2.

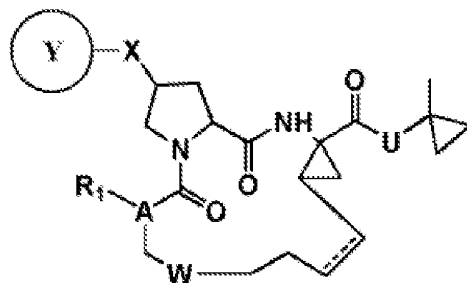
Numa concretização, os compostos desta invenção

têm a seguinte fórmula:



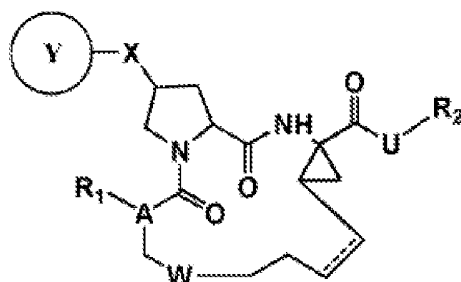
onde R₁, R₂, A, U, W, X e Y são conforme acima definido.

Numa outra concretização, os compostos desta invenção têm a seguinte fórmula:



onde R₁, A, U, W, X e Y são conforme acima definido.

Ainda numa outra concretização, os compostos desta invenção têm a seguinte fórmula:



em que R_1 é -H, -OH, alquilo C_{1-6} , alcoxilo C_{1-6} , cicloalquilo C_{3-10} , heterocicloalquilo C_{1-10} , arilo, heteroarilo ou -Z-R; em que R é H, ou é uma metade selecionada de alquilo C_{1-6} , cicloalquilo C_{3-10} , heterocicloalquilo C_{1-10} , arilo e heteroarilo, sendo cada uma das quais opcionalmente mono-, di- ou tri-substituída com halo, nitro, ciano, amino, alquilo C_{1-6} , alcoxilo C_{1-6} , alcenilo C_{2-6} , alquinilo C_{2-6} , arilo ou heteroarilo; e Z é -C(O)-, -C(O)O-, -C(O)C(O)O-, -C(O)C(O)NH-, -C(O)NR'-, -OC(S)-, -C(S)NR'- ou -C(NH)O-, sendo R' H, alquilo C_{1-6} , cicloalquilo C_{3-10} , heterocicloalquilo C_{1-10} , arilo ou heteroarilo; e R_2 , A, U, W, X e Y são conforme acima definido.

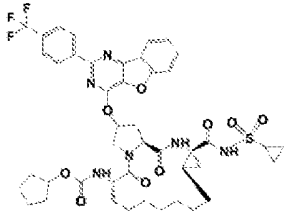
O termo "alquilo" refere-se a uma metade de hidrocarboneto saturado, linear ou ramificado, tal como -CH₃ ou -CH(CH₃)₂. O termo "alcoxi" refere-se a um radical -O-(alquilo C_{1-6}). O termo "alcenilo" refere-se a uma metade de hidrocarboneto linear ou ramificado que contém pelo menos uma ligação dupla, tal como -CH=CH-CH₃. O termo "alquinilo" refere-se a uma metade de hidrocarboneto linear ou ramificado que contém pelo menos uma ligação tripla, tal

como $-C\equiv C-CH_3$. O termo "cicloalquilo" refere-se a uma metade de hidrocarboneto saturado, cíclico, tal como ciclo-hexilo. O termo "cicloalcenilo" refere-se a uma metade de hidrocarboneto não aromático, cíclico, que contém pelo menos uma ligação dupla, tal como ciclo-hexenilo. O termo "heterocicloalquilo" refere-se a uma metade saturada, cíclica, tendo pelo menos um heteroátomo no anel (por exemplo, N, O ou S), tal como 4-tetra-hidropiraniolo. O termo "heterocicloalcenilo" refere-se a uma metade não aromática, cíclica, tendo pelo menos um heteroátomo no anel (por exemplo, N, O ou S) e pelo menos uma ligação dupla no anel, tal como piraniolo. O termo "arilo" refere-se a uma metade de hidrocarboneto possuindo um ou mais anéis aromáticos. Exemplos de metades arilo incluem fenilo (Ph), fenileno, naftilo, naftileno, pirenilo, antrilo e fenantrilo. O termo "heteroarilo" refere-se a uma metade com um ou mais anéis aromáticos que contém pelo menos um heteroátomo (por exemplo, N, O ou S). Exemplos de metades heteroarilo incluem furilo, furileno, fluorenilo, pirro-lilo, tienilo, oxazolilo, imidazolilo, tiazolilo, piridilo, pirimidinilo, quinazolinilo, quinolilo, isoquinolilo e indolilo. O termo "amino" refere-se a um radical de $-NH_2$, $-NH-(\text{alquilo } C_{1-6})$ ou $-N(\text{alquilo } C_{1-6})_2$.

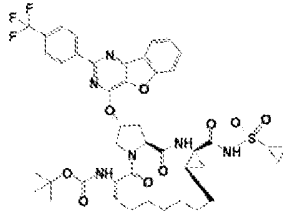
O alquilo, alcenilo, alquinilo, cicloalquilo, cicloalcenilo, heterocicloalquilo, heterocicloalcenilo, arilo e heteroarilo aqui mencionados incluem ambas as metades, substituídas e não substituídas, a menos que seja

especificado de outra forma. Substituintes possíveis em cicloalquilo, cicloalcenilo, heterocicloalquilo, heterocicloalcenilo, arilo e heteroarilo incluem, mas não estão limitados a, alquilo C₁-C₁₀, alcenilo C₂-C₁₀, alquinilo C₂-C₁₀, cicloalquilo C₃-C₂₀, cicloalcenilo C₃-C₂₀, heterocicloalquilo C₁-C₂₀, heterocicloalcenilo C₁-C₂₀, alcoxi C₁-C₁₀, arilo, ariloxi, heteroarilo, heteroariloxi, amino, alquilamino C₁-C₁₀, dialquilamino C₁-C₂₀, arilamino, diarilamino, alquilsulfonamino C₁-C₁₀, arilsulfonamino, alquilimino C₁-C₁₀, arilimino, alquilsulfonimino C₁-C₁₀, arilsulfonimino, hidroilo, halo, tio, alquiltio C₁-C₁₀, ariltio, alquilsulfonilo C₁-C₁₀, arilsulfonilo, acilamino, aminoacilo, aminotioacilo, amidino, guanidina, ureído, ciano, nitro, nitroso, azido, acilo, tioacilo, aciloxi, carboxilo e éster carboxílico. Por outro lado, substituintes possíveis em alquilo, alcenilo ou alquinilo incluem todos os substituintes acima citados exceto alquilo C₁-C₁₀. Cicloalquilo, cicloalcenilo, heterocicloalquilo, heterocicloalcenilo, arilo e heteroarilo podem também ser fundidos uns com os outros.

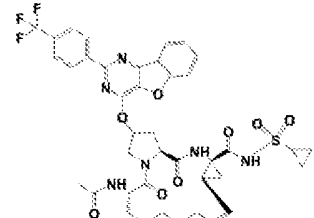
Abaixo são apresentados 281 compostos exemplificativos desta invenção.



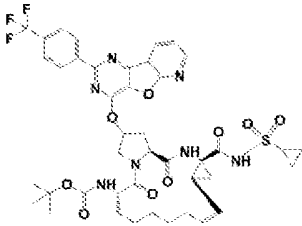
Composto 1



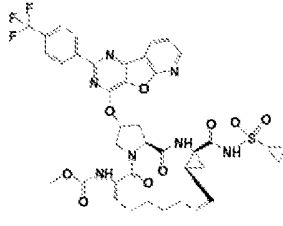
Composto 2



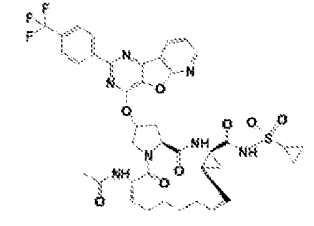
Composto 3



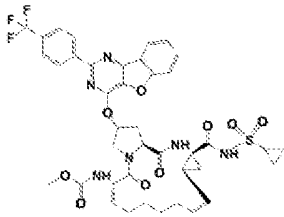
Composto 4



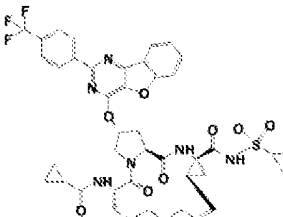
Composto 5



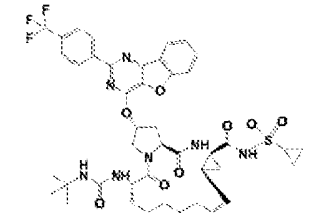
Composto 6



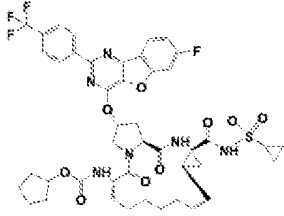
Composto 7



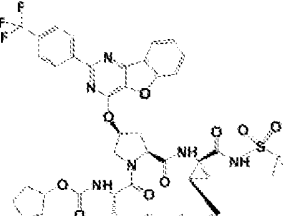
Composto 8



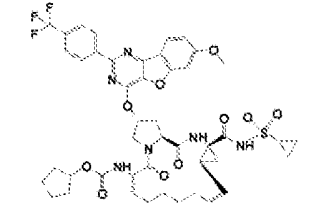
Composto 9



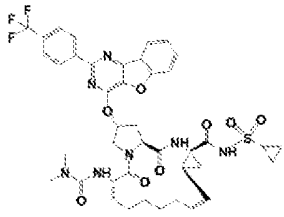
Composto 10



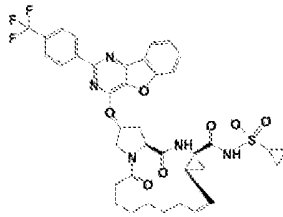
Composto 11



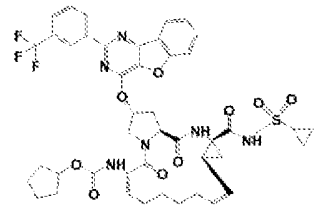
Composto 12



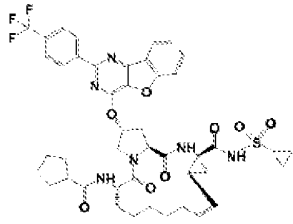
Composto 13



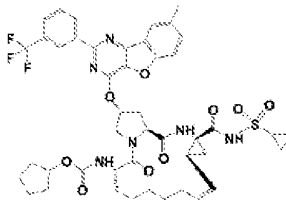
Composto 14



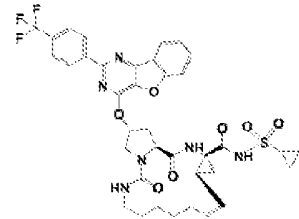
Composto 15



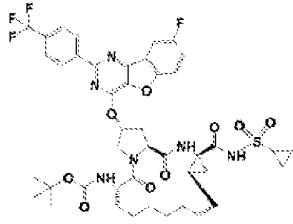
Composto 16



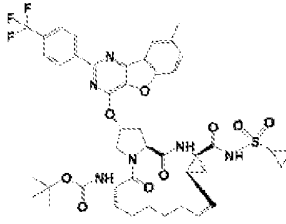
Composto 17



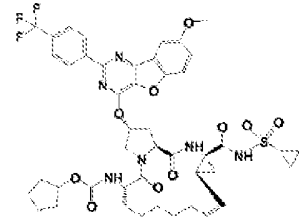
Composto 18



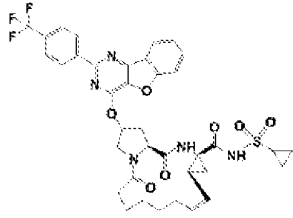
Composto 19



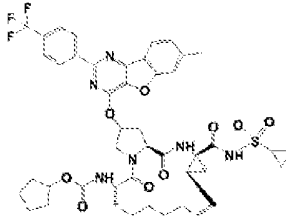
Composto 20



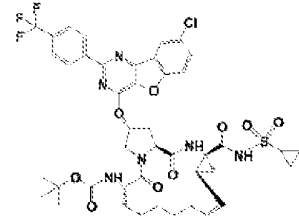
Composto 21



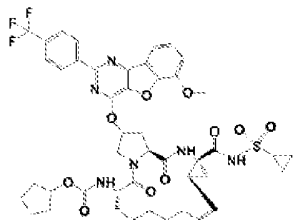
Composto 22



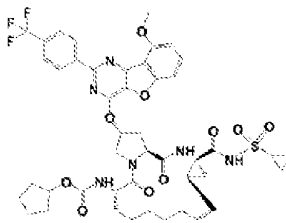
Composto 23



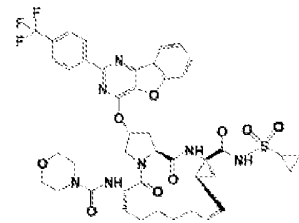
Composto 24



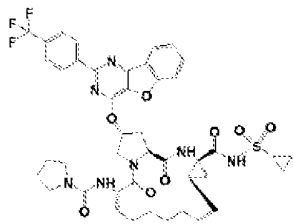
Composto 25



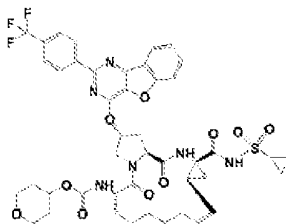
Composto 26



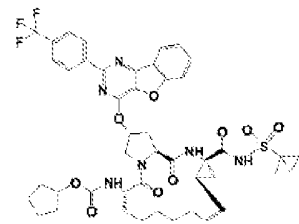
Composto 27



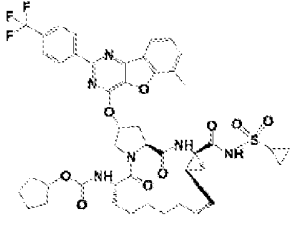
Composto 28



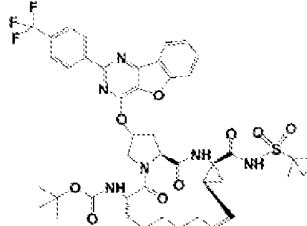
Composto 29



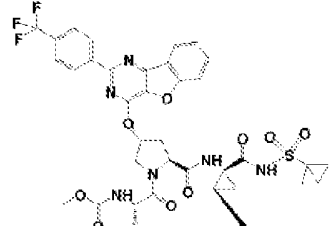
Composto 30



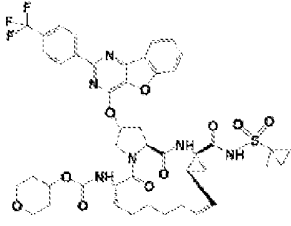
Composto 31



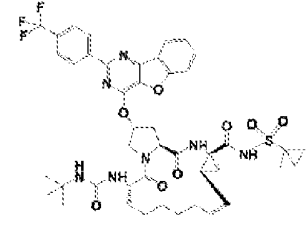
Composto 32



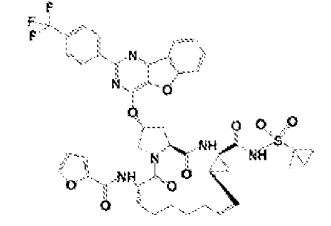
Composto 33



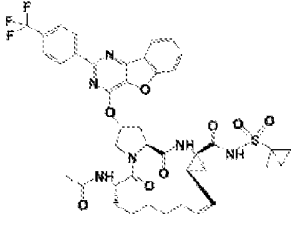
Composto 34



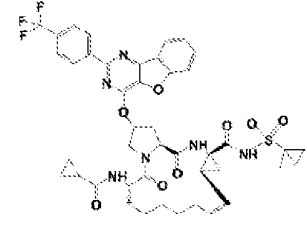
Composto 35



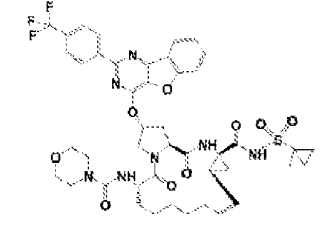
Composto 36



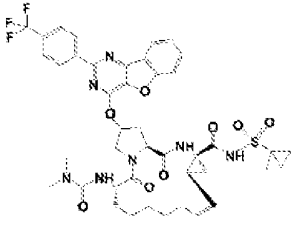
Composto 37



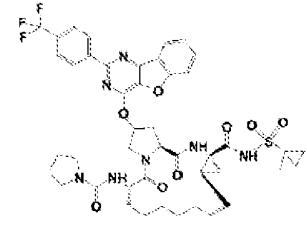
Composto 38



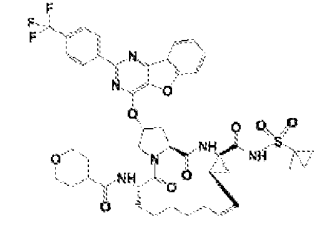
Composto 39



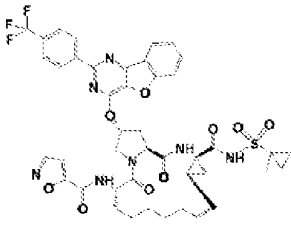
Composto 40



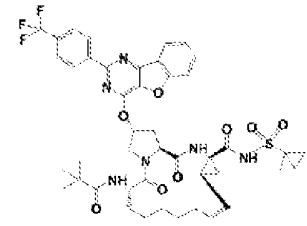
Composto 41



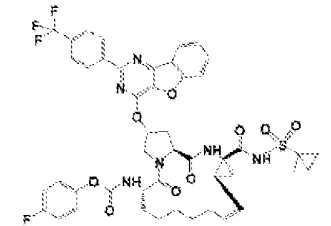
Composto 42



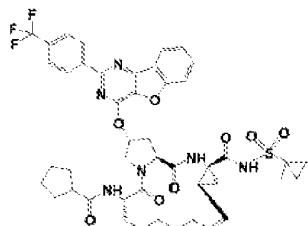
Composto 43



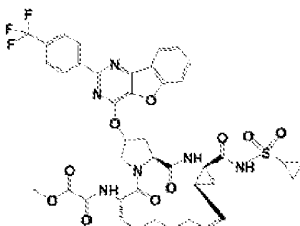
Composto 44



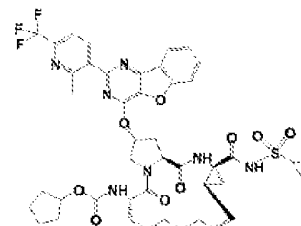
Composto 45



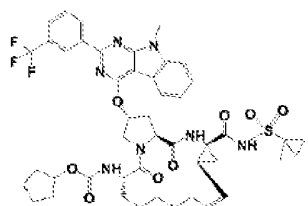
Composto 46



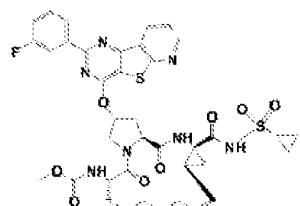
Composto 47



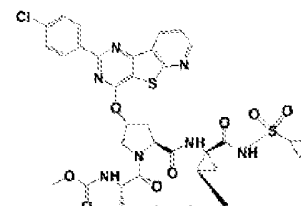
Composto 48



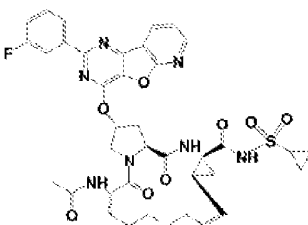
Composto 49



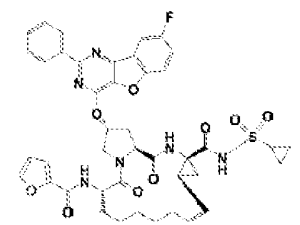
Composto 50



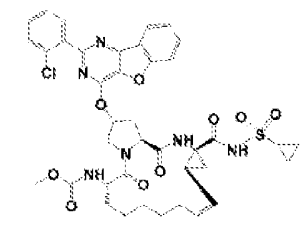
Composto 51



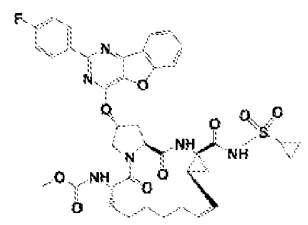
Composto 52



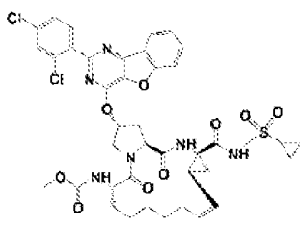
Composto 53



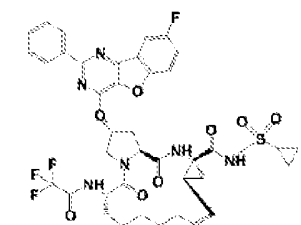
Composto 54



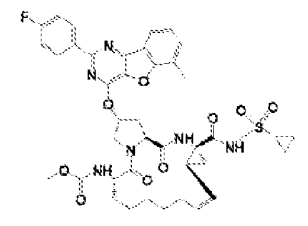
Composto 55



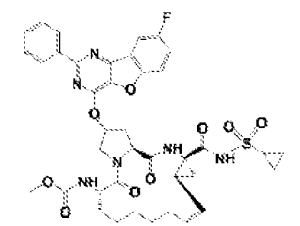
Composto 56



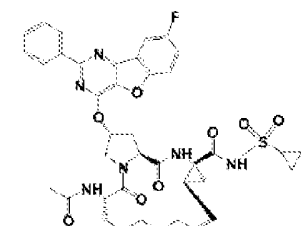
Composto 57



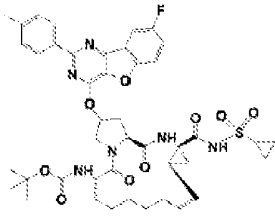
Composto 58



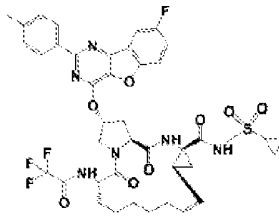
Composto 59



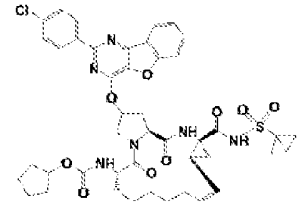
Composto 60



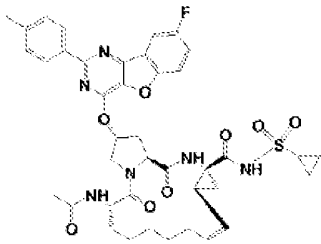
Composto 61



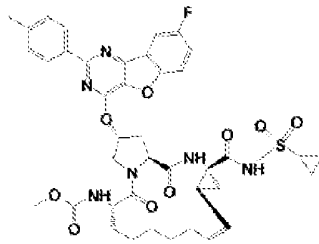
Composto 62



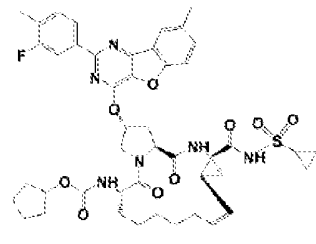
Composto 63



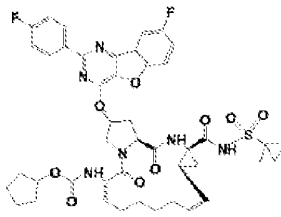
Composto 64



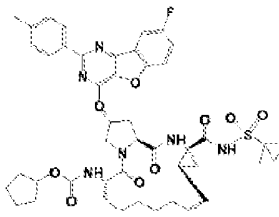
Composto 65



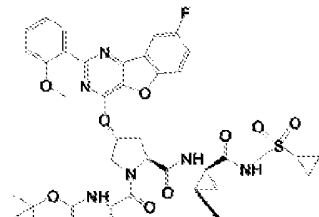
Composto 66



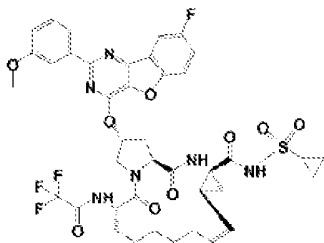
Composto 67



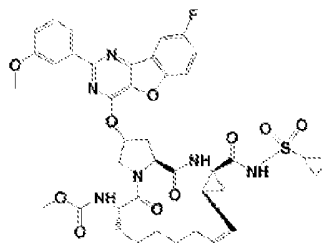
Composto 68



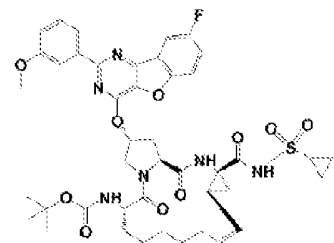
Composto 69



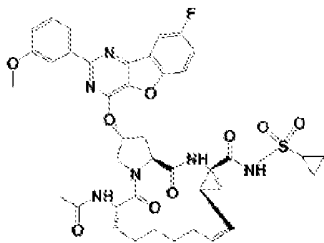
Composto 70



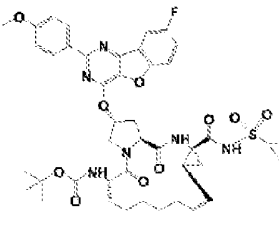
Composto 71



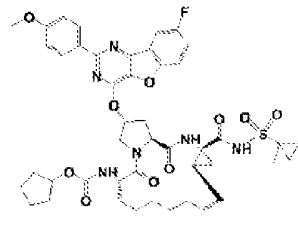
Composto 72



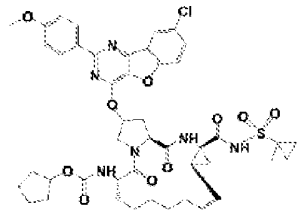
Composto 73



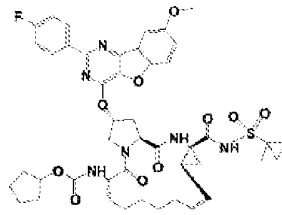
Composto 74



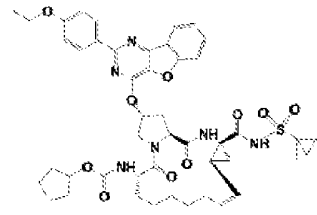
Composto 75



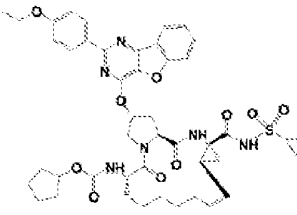
Composto 76



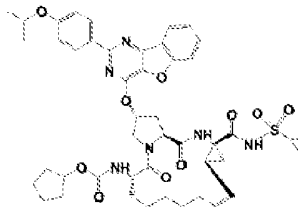
Composto 77



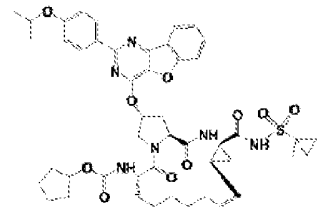
Composto 78



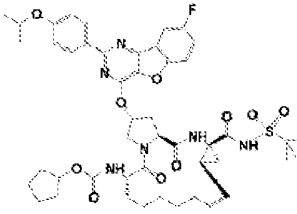
Composto 79



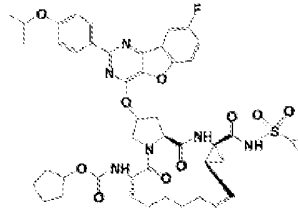
Composto 80



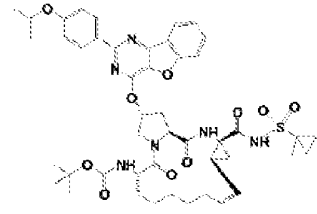
Composto 81



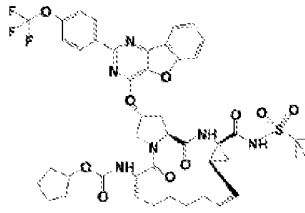
Composto 82



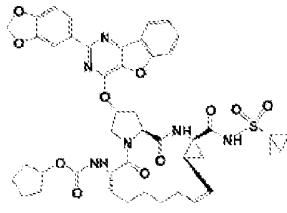
Composto 83



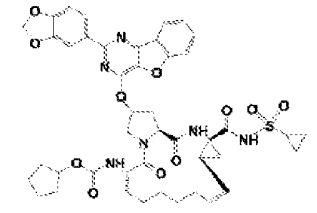
Composto 84



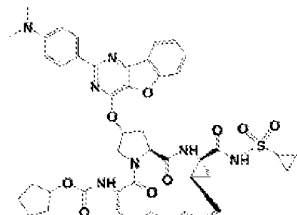
Composto 85



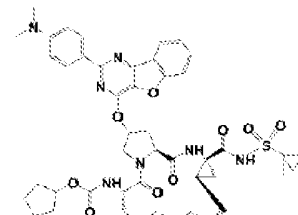
Composto 86



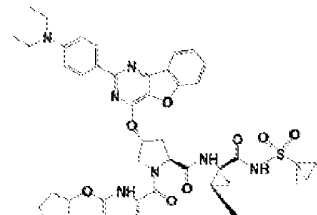
Composto 87



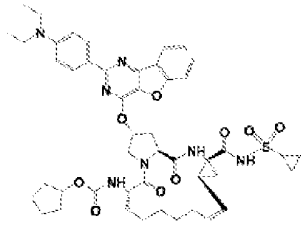
Composto 88



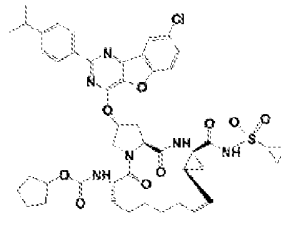
Composto 89



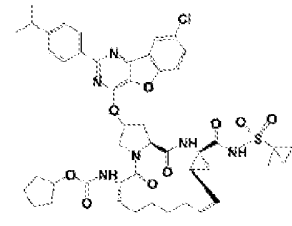
Composto 90



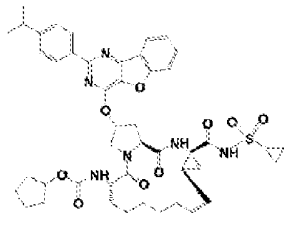
Composto 91



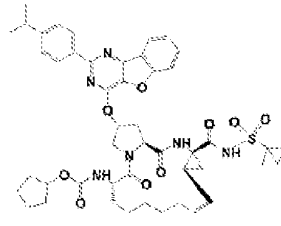
Composto 92



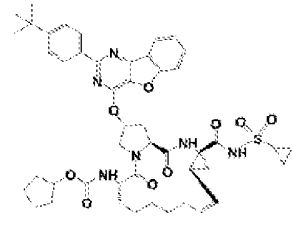
Composto 93



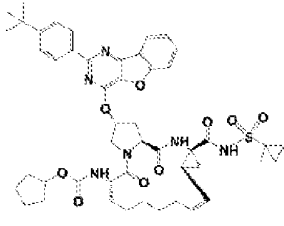
Composto 94



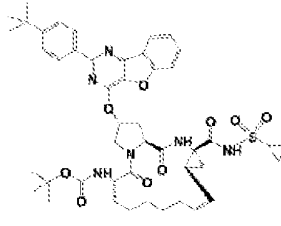
Composto 95



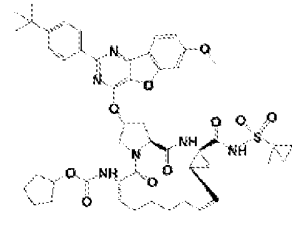
Composto 96



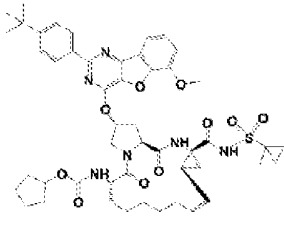
Composto 97



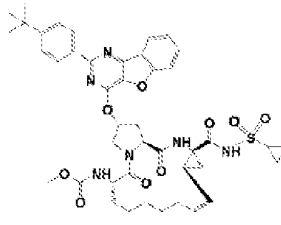
Composto 98



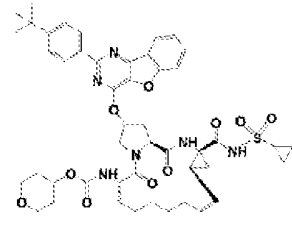
Composto 99



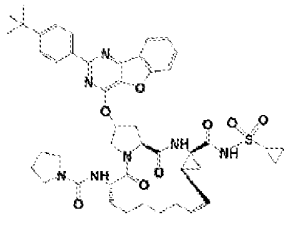
Composto 100



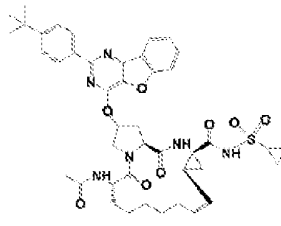
Composto 101



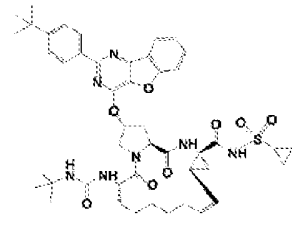
Composto 102



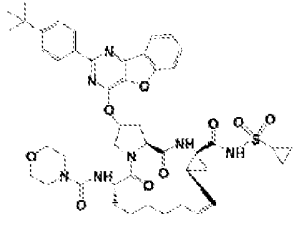
Composto 103



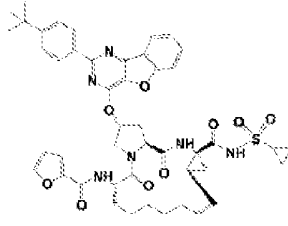
Composto 104



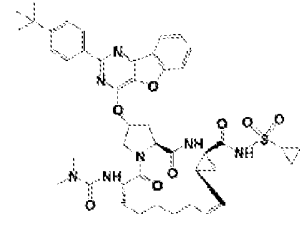
Composto 105



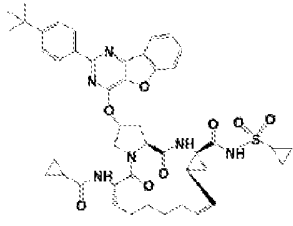
Composto 106



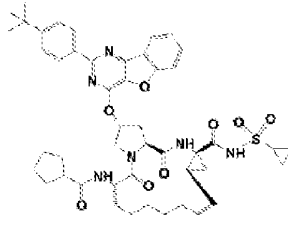
Composto 107



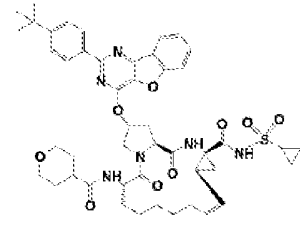
Composto 108



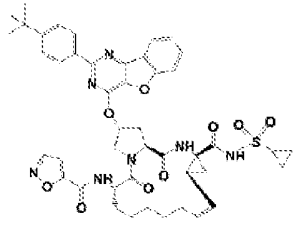
Composto 109



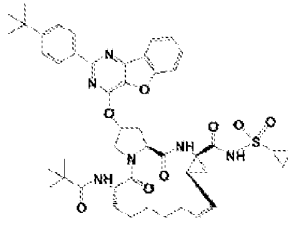
Composto 110



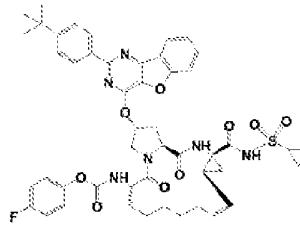
Composto 111



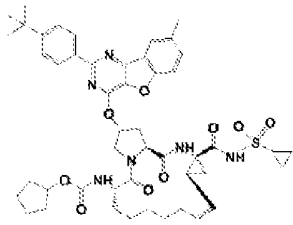
Composto 112



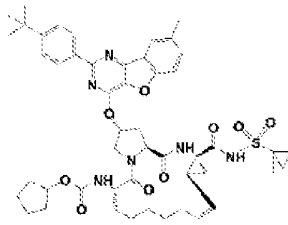
Composto 113



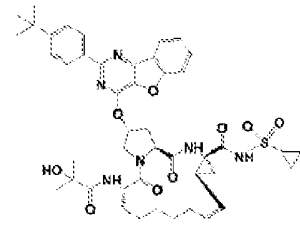
Composto 114



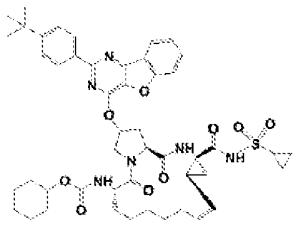
Composto 115



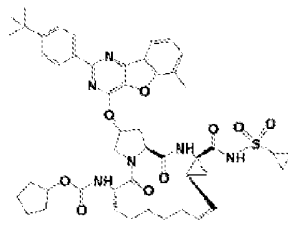
Composto 116



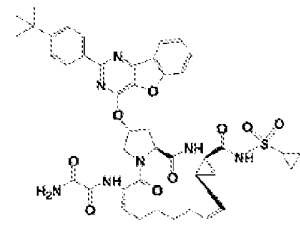
Composto 117



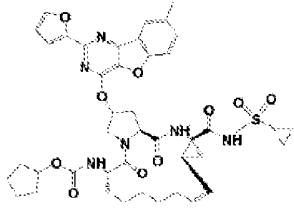
Composto 118



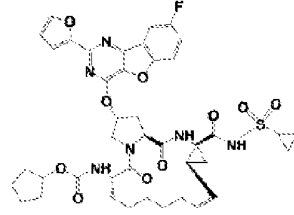
Composto 119



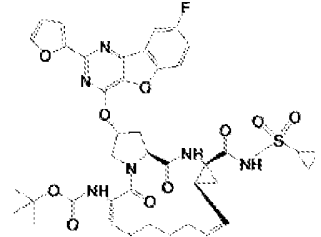
Composto 120



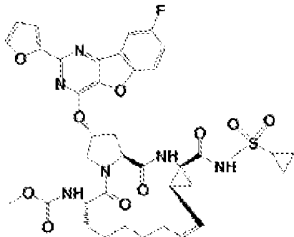
Composto 121



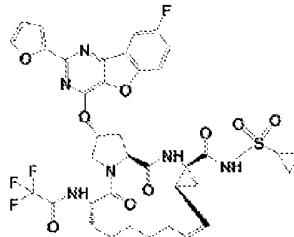
Composto 122



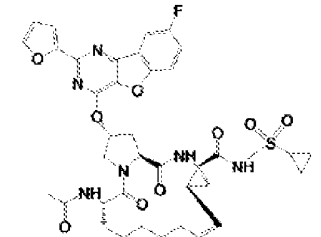
Composto 123



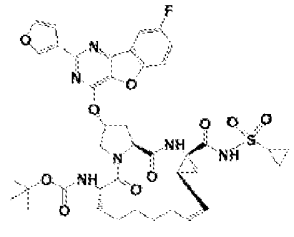
Composto 124



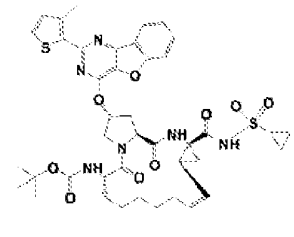
Composto 125



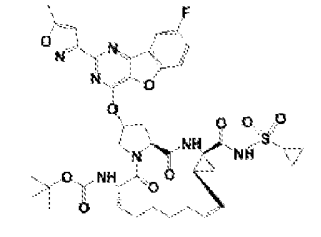
Composto 126



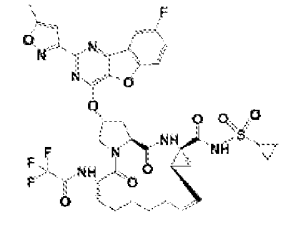
Composto 127



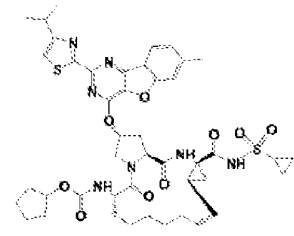
Composto 128



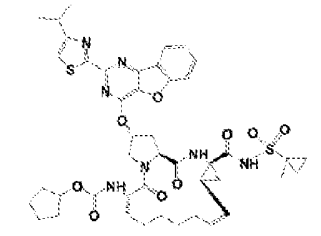
Composto 129



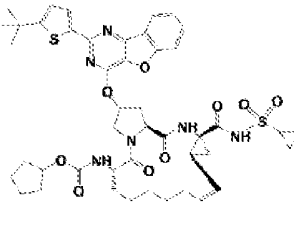
Composto 130



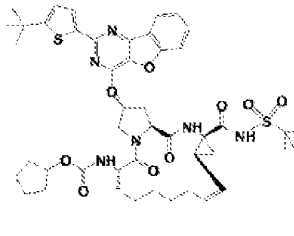
Composto 131



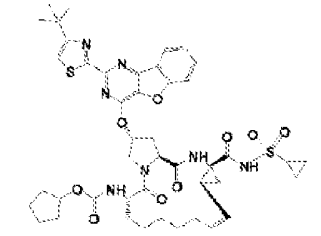
Composto 132



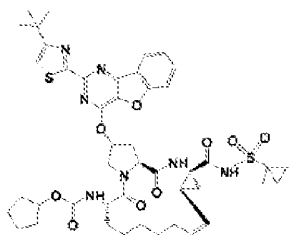
Composto 133



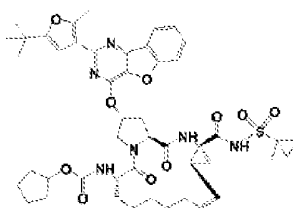
Composto 134



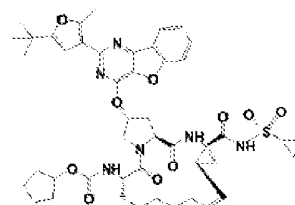
Composto 135



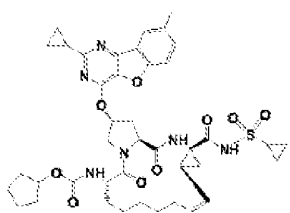
Composto 136



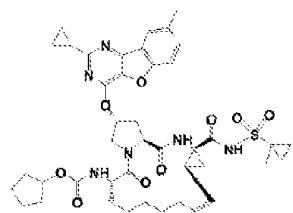
Composto 137



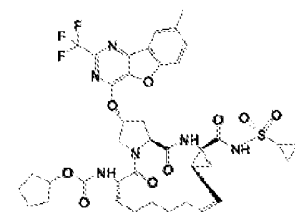
Composto 138



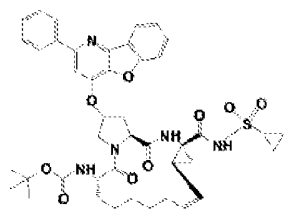
Composto 139



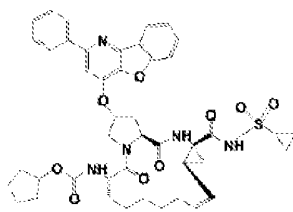
Composto 140



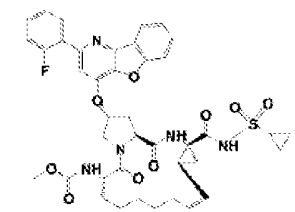
Composto 141



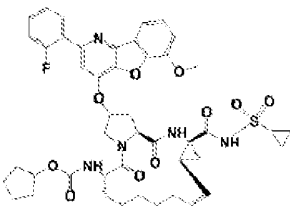
Composto 142



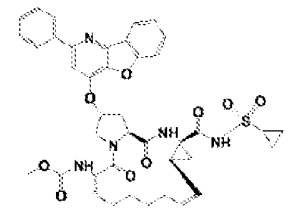
Composto 143



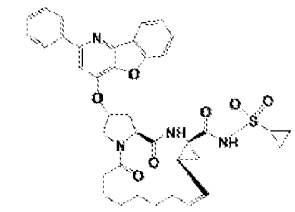
Composto 144



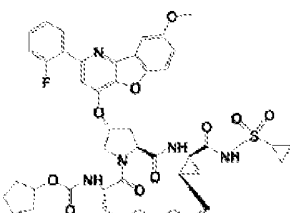
Composto 145



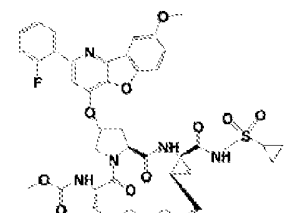
Composto 146



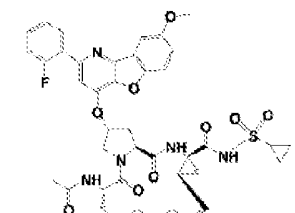
Composto 147



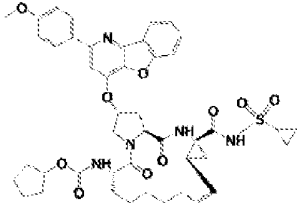
Composto 148



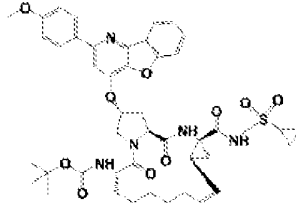
Composto 149



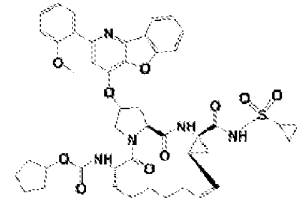
Composto 150



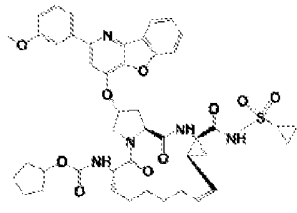
Composto 151



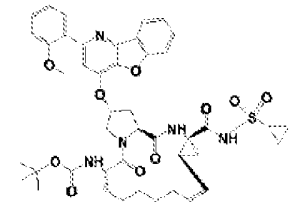
Composto 152



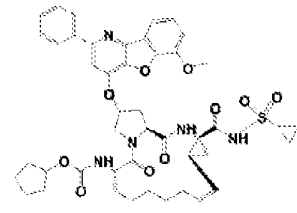
Composto 153



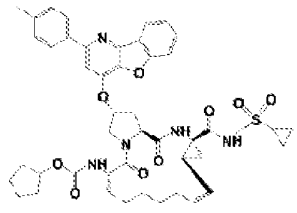
Composto 154



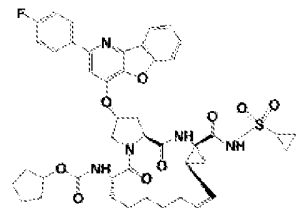
Composto 155



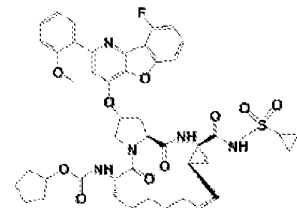
Composto 156



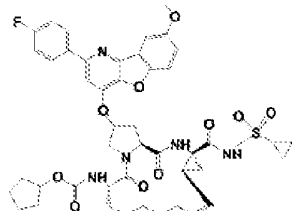
Composto 157



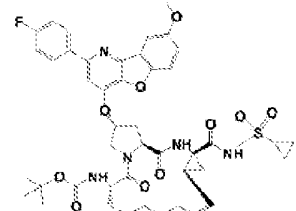
Composto 158



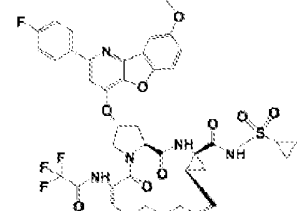
Composto 159



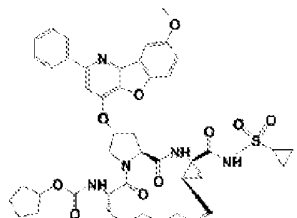
Composto 160



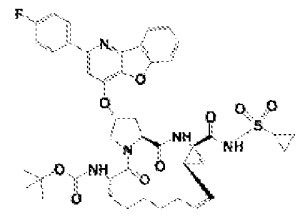
Composto 161



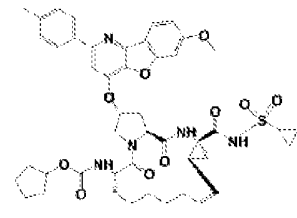
Composto 162



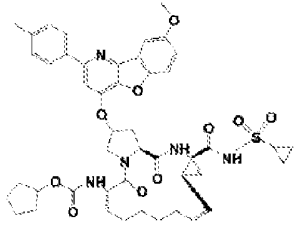
Composto 163



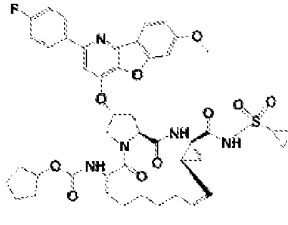
Composto 164



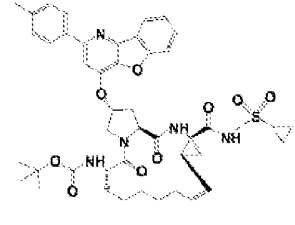
Composto 165



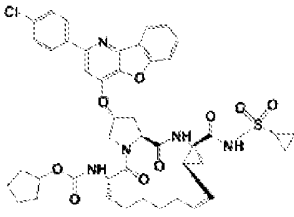
Composto 166



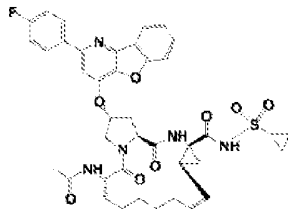
Composto 167



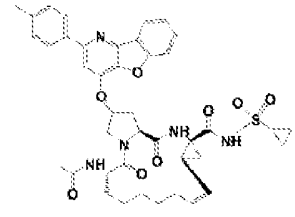
Composto 168



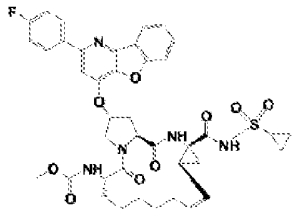
Composto 169



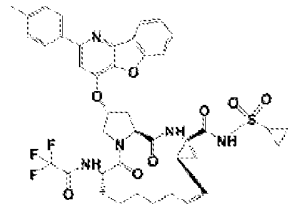
Composto 170



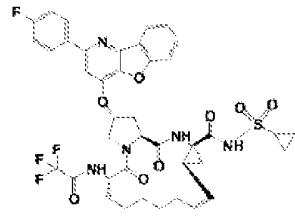
Composto 171



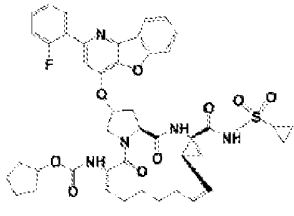
Composto 172



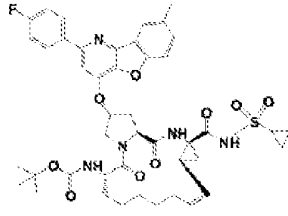
Composto 173



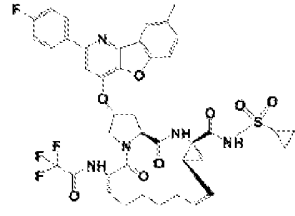
Composto 174



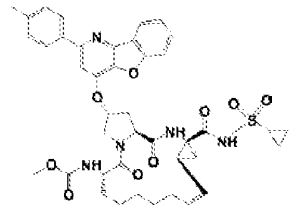
Composto 175



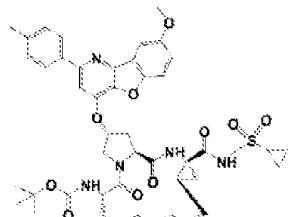
Composto 176



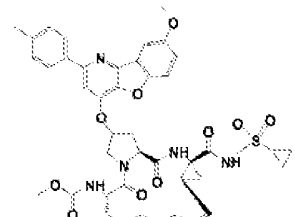
Composto 177



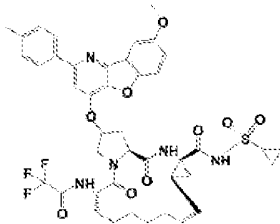
Composto 178



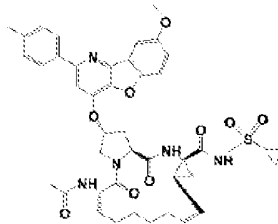
Composto 179



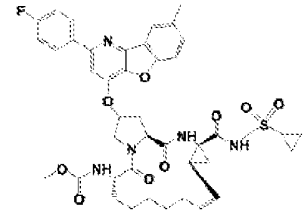
Composto 180



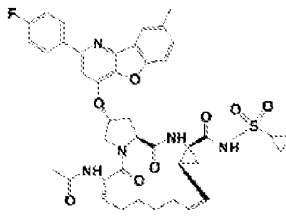
Composto 181



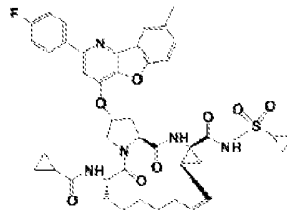
Composto 182



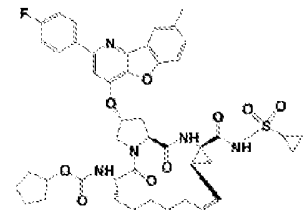
Composto 183



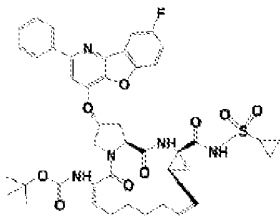
Composto 184



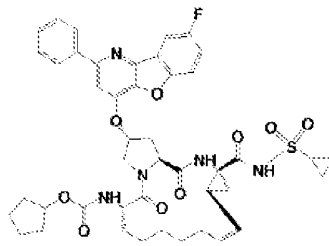
Composto 185



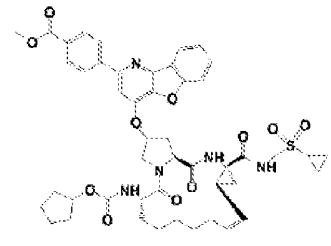
Composto 186



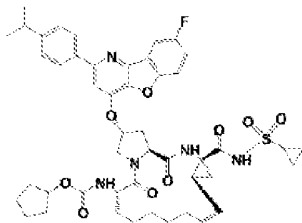
Composto 187



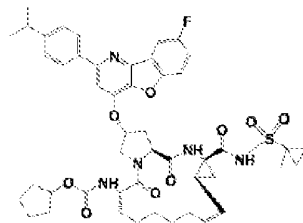
Composto 188



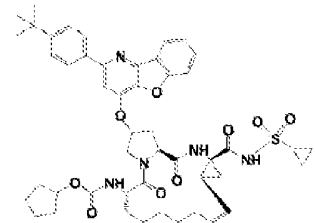
Composto 189



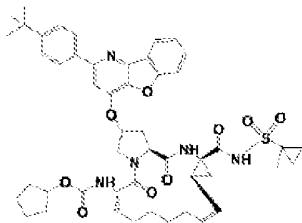
Composto 190



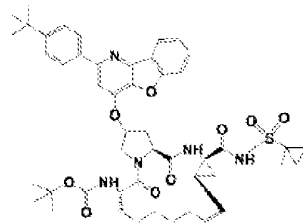
Composto 191



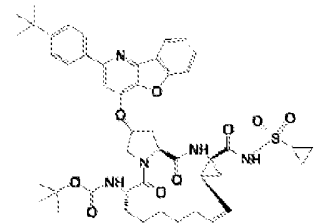
Composto 192



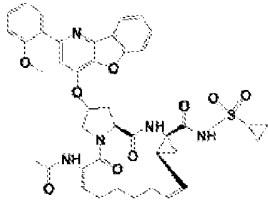
Composto 193



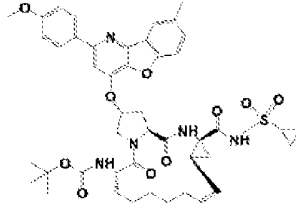
Composto 194



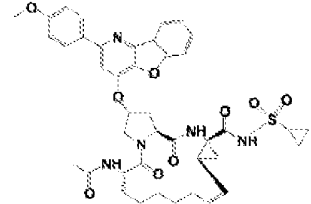
Composto 195



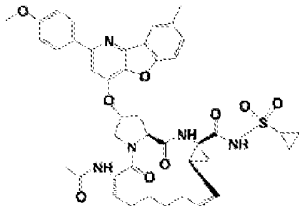
Composto 196



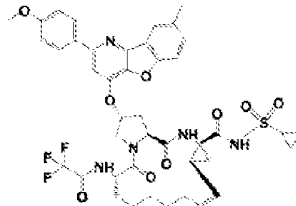
Composto 197



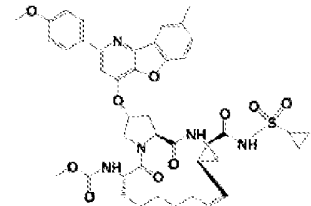
Composto 198



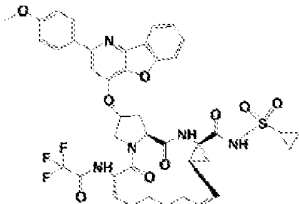
Composto 199



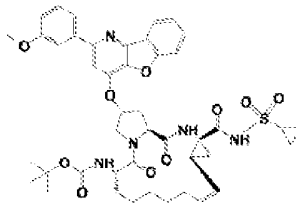
Composto 200



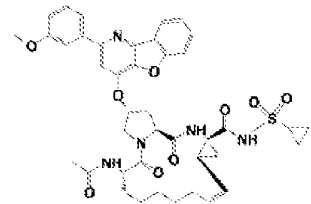
Composto 201



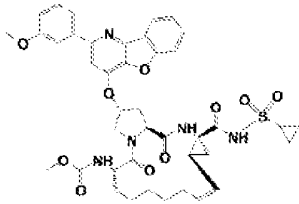
Composto 202



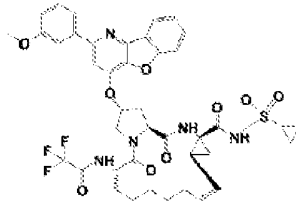
Composto 203



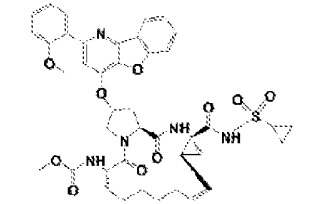
Composto 204



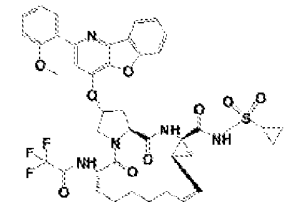
Composto 205



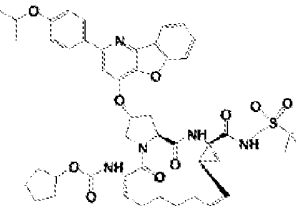
Composto 206



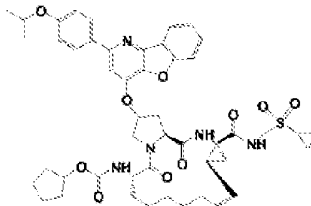
Composto 207



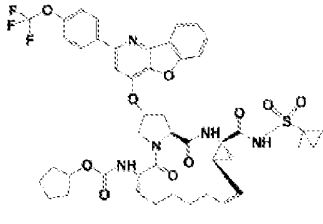
Composto 208



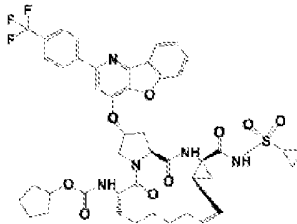
Composto 209



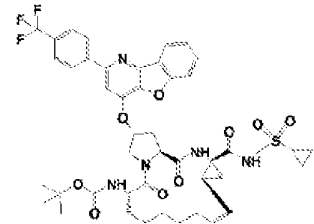
Composto 210



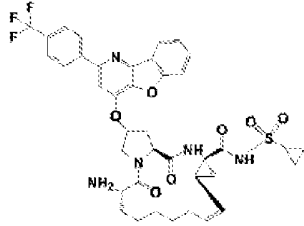
Composto 211



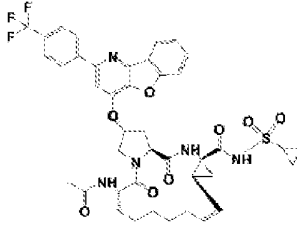
Composto 212



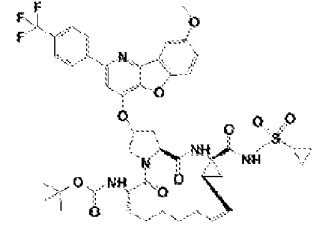
Composto 213



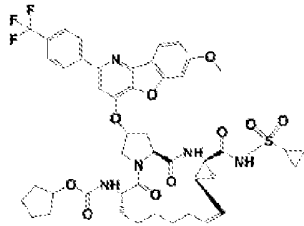
Composto 214



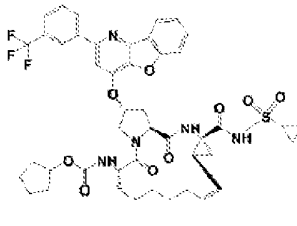
Composto 215



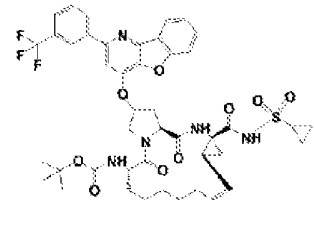
Composto 216



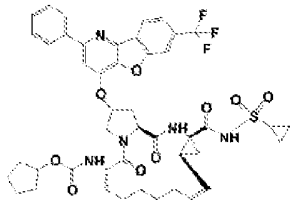
Composto 217



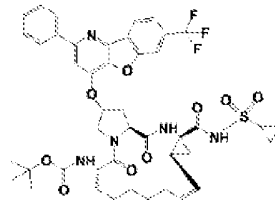
Composto 218



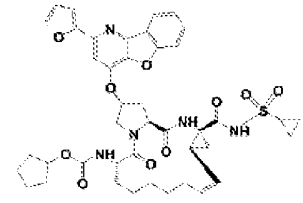
Composto 219



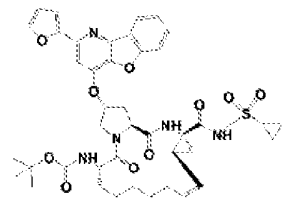
Composto 220



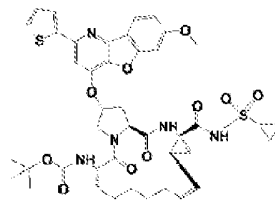
Composto 221



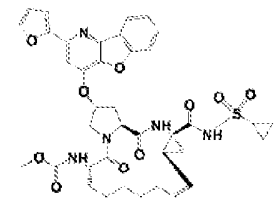
Composto 222



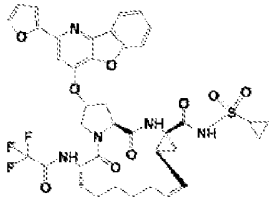
Composto 223



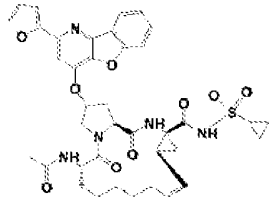
Composto 224



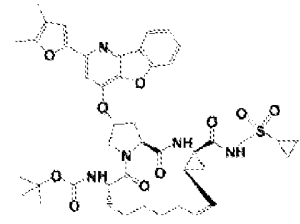
Composto 225



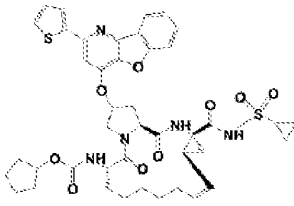
Composto 226



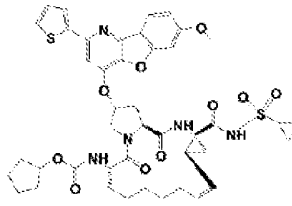
Composto 227



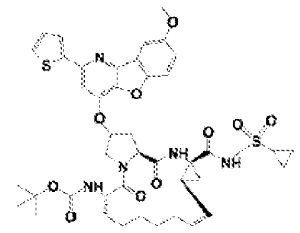
Composto 228



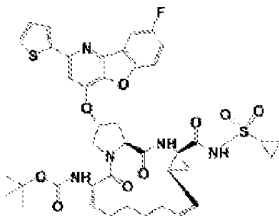
Composto 229



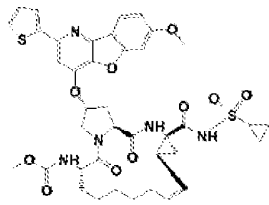
Composto 230



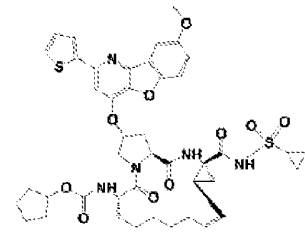
Composto 231



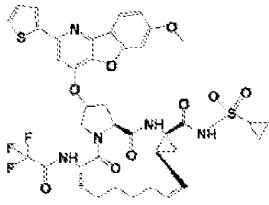
Composto 232



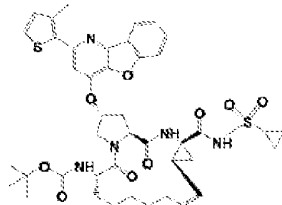
Composto 233



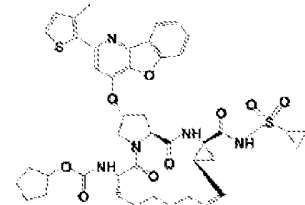
Composto 234



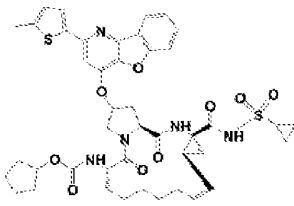
Composto 235



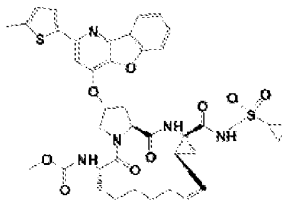
Composto 236



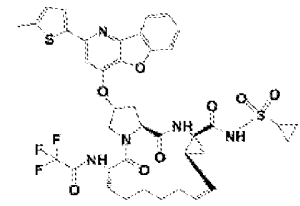
Composto 237



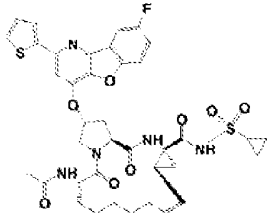
Composto 238



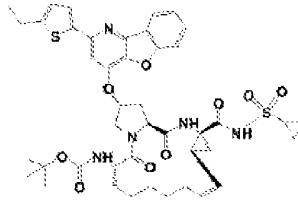
Composto 239



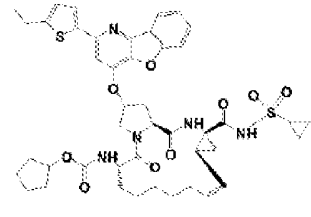
Composto 240



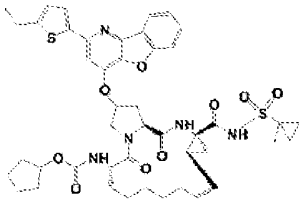
Composto 241



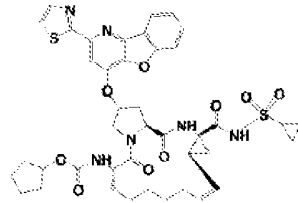
Composto 242



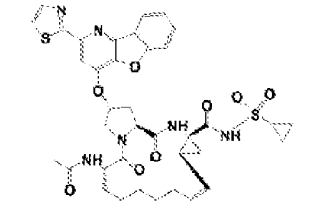
Composto 243



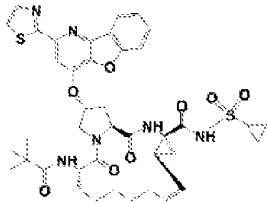
Composto 244



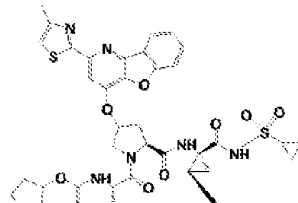
Composto 245



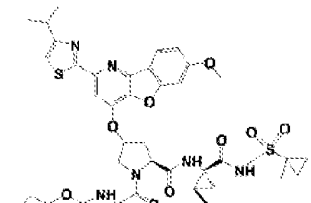
Composto 246



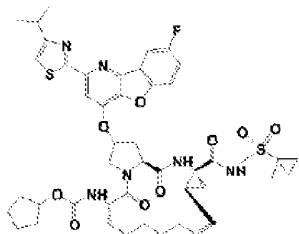
Composto 247



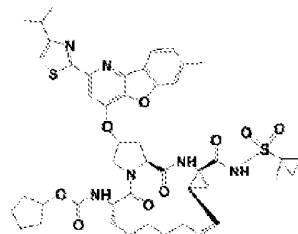
Composto 248



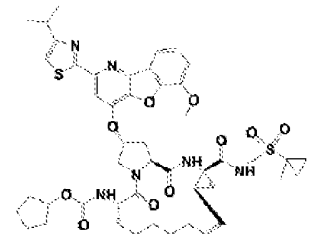
Composto 249



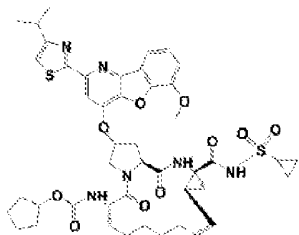
Composto 250



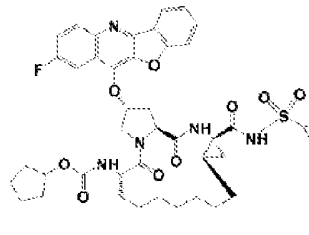
Composto 251



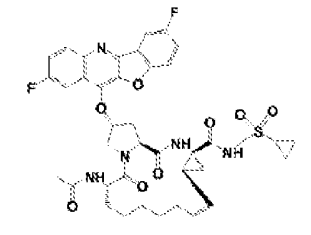
Composto 252



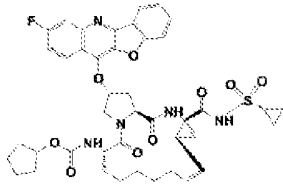
Composto 253



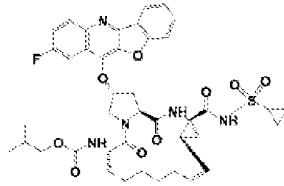
Composto 254



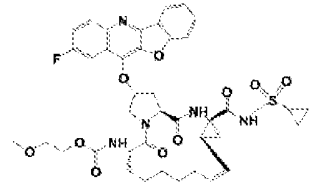
Composto 255



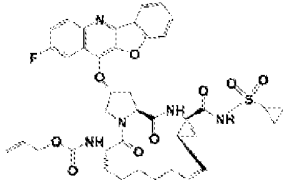
Composto 256



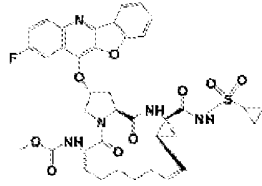
Composto 257



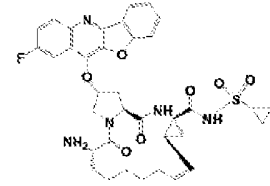
Composto 258



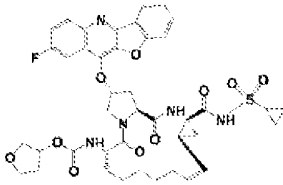
Composto 259



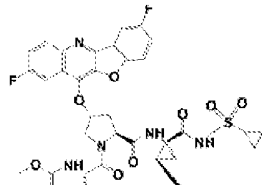
Composto 260



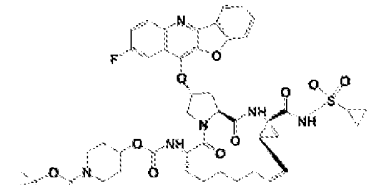
Composto 261



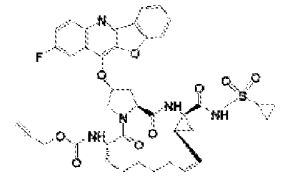
Composto 262



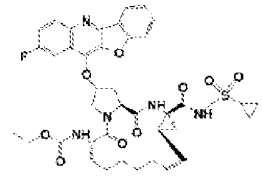
Composto 263



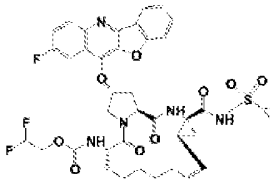
Composto 264



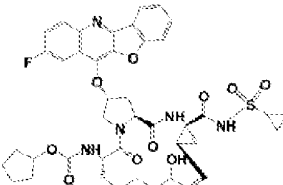
Composto 265



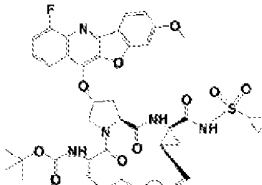
Composto 266



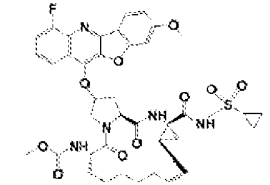
Composto 267



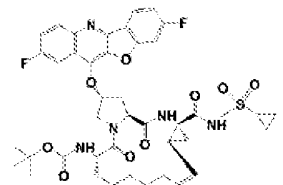
Composto 268



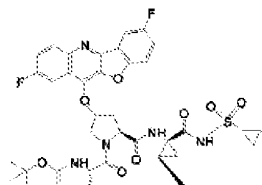
Composto 269



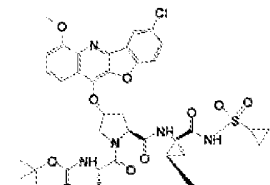
Composto 270



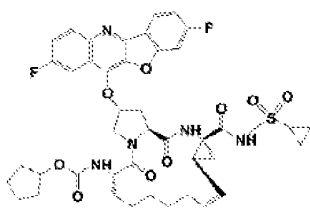
Composto 271



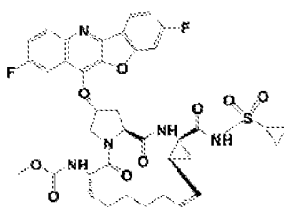
Composto 272



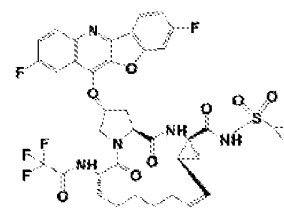
Composto 273



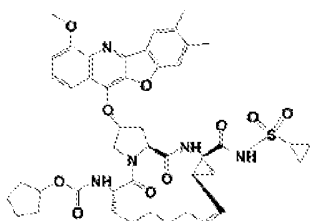
Composto 274



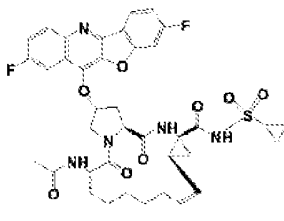
Composto 275



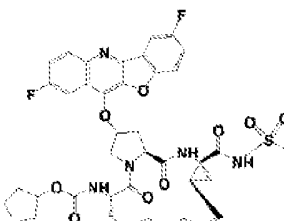
Composto 276



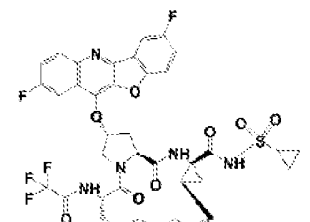
Composto 277



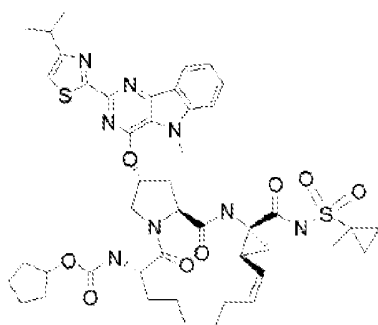
Composto 278



Composto 279



Composto 280



Composto 281

Noutro aspeto, esta invenção refere-se a compostos para uso num método para o tratamento de infeção por vírus da hepatite C. O método inclui a administração a um indivíduo necessitado do mesmo de uma quantidade eficaz de composto de fórmula (I) apresentado anteriormente.

Ainda noutro aspeto, esta invenção refere-se a uma composição farmacêutica para uso no tratamento de infeção por HCV. A composição contém uma quantidade eficaz de pelo menos um dos compostos de fórmula (I) e de um

portador farmacologicamente aceitável. Pode incluir um inibidor de um alvo que não protease NS3 de HCV no ciclo de vida de HCV, por exemplo, polimerase NS5B, NS5A, NS4B ou p7.

Exemplos de tais agentes incluem, mas não estão limitados a, N-[3-(1-ciclobutilmetil-4-hidroxi-2-oxo-1,2-di-hidro-quinolin-3-il)-1,1-dioxo-1,4-di-hidro-116-benzo-[1,2,4]tiadiazin-7-il]-metanossulfonamida (WO0441818), trans-1,2-di-4-[(fenilacetil-pirrolidina-2-(S)-carbonil)-amino]-feniletileno (WO0401413) e 1-aminoadamantano (Amen-tadine, Griffin, 2004, J. Gen. Virol. 85: p 451). A composição farmacêutica pode também conter um agente imunomodulador ou um segundo agente antiviral. Um agente imunomodulador refere-se a um agente ativo que medeia a resposta imune. Exemplos de agentes imunomoduladores incluem, mas não estão limitados a, Nov-205 (Novelos Therapeutics Inc., WO02076490) e IMO-2125 (Idera Pharmaceuticals Inc., WO05001055). Um agente antiviral refere-se a um agente ativo que mata um vírus ou suprime a sua replicação. Exemplos de agentes antivirais incluem, mas não estão limitados a, ribavirina, ribamidina, interferão- α , interferão peguillado e inibidores de protease de HCV, tais como (1-ciclopropilaminoxalil-butil)-amida do ácido 2-(2-{2-ciclo-hexil-2-[(pirazina-2-carbonil)-amino]-acetilamino}-3,3-dimetil-butiril)-octa-hidro-ciclopenta[c]pirrolo-1-carboxílico (Telaprevir, Vertex Pharmaceuticals Inc.,

WO02018369), (2-carbamoil-1-ciclobutilmetil-2-oxo-etil)-amida do ácido 3-[2-(3-terc-butyl-ureído)-3,3-dimetil-butiril]-6,6-dimetil-3-aza-biciclo[3.1.0]hexano-2-carboxílico (Boceprevir, Schering-Plough Research Institute, WO03062265), e éster 14-terc-butoxicarbonilamino-4-ciclopropanossulfonilaminocarbonil-2,15-dioxo-3,16-diaza-triciclo[14.3.0.04,6]nonadec-7-en-18-ílico do ácido 4-fluoro-1,3-di-hidro-isoindol-2-carboxílico (ITMN-191, InterMune Inc., US2005/0267018).

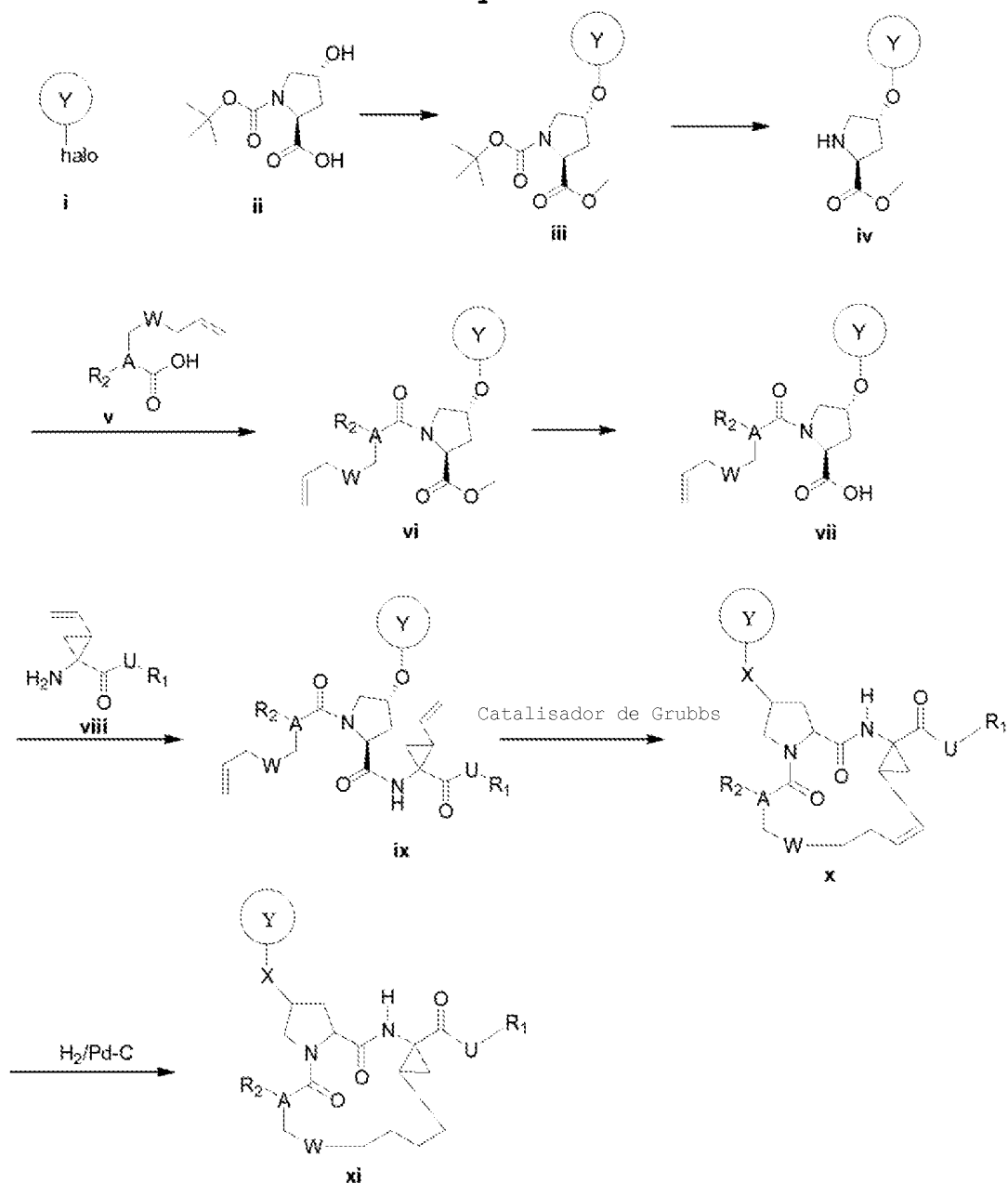
Está também dentro do âmbito desta invenção uma tal composição para uso no tratamento de infecção por HCV ou para o fabrico de um medicamento para o tratamento.

Os detalhes de uma ou mais concretizações da invenção são apresentados na descrição abaixo. Outras características, objetos e vantagens da invenção serão evidentes a partir da descrição e das reivindicações.

DESCRIÇÃO DETALHADA

Os compostos desta invenção podem ser sintetizados a partir de materiais de partida comercialmente disponíveis através de métodos bem conhecidos na técnica. Por exemplo, podem-se preparar os compostos desta invenção através da via mostrada no Esquema 1 abaixo:

Esquema 1

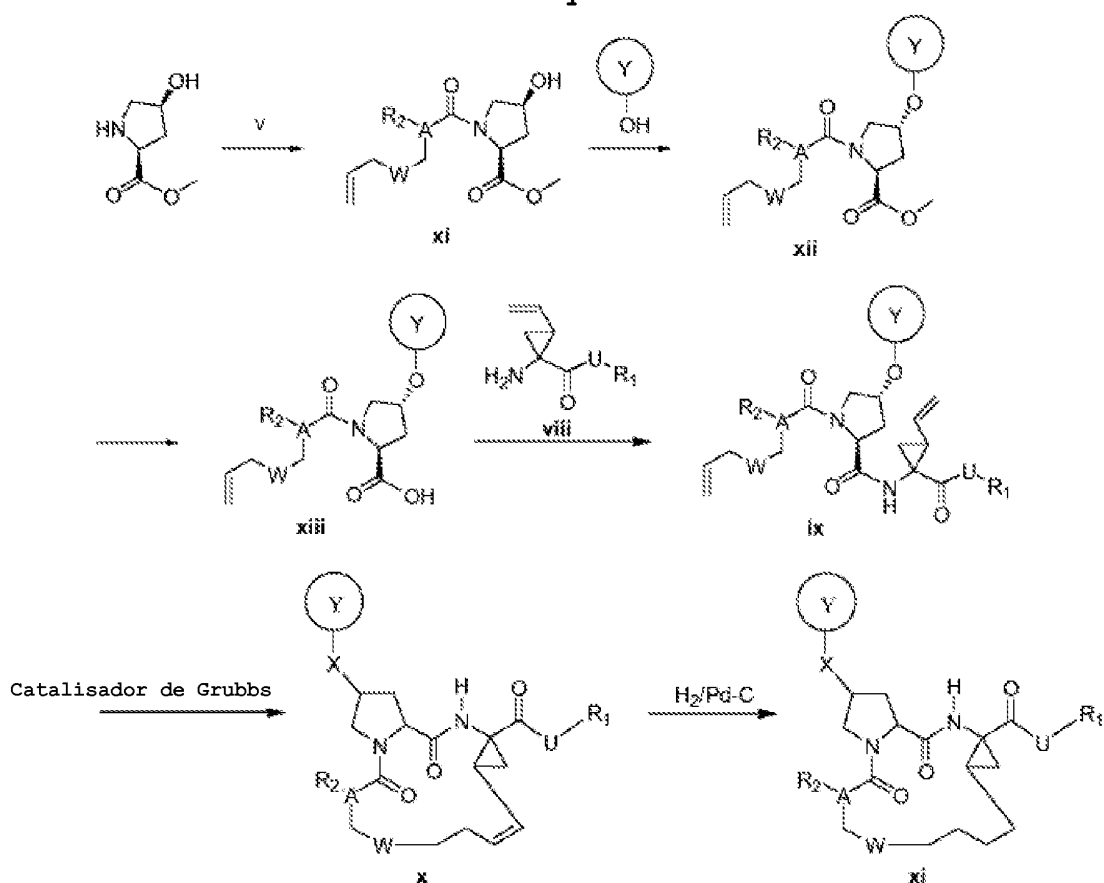


Conforme ilustrado no Esquema 1, o composto multicíclico (**i**) é primeiramente acoplado com N-(t-butoxicarbonil)-L-prolina (**ii**), seguindo-se metilação, para formar-se o intermediário (**iii**). O intermediário (**iii**) é desprotegido para se remover o grupo N-butoxicarbonilo para se produzir o composto (**iv**) isento de N, o qual é acoplado com o ácido carboxílico (**v**) para proporcionar o

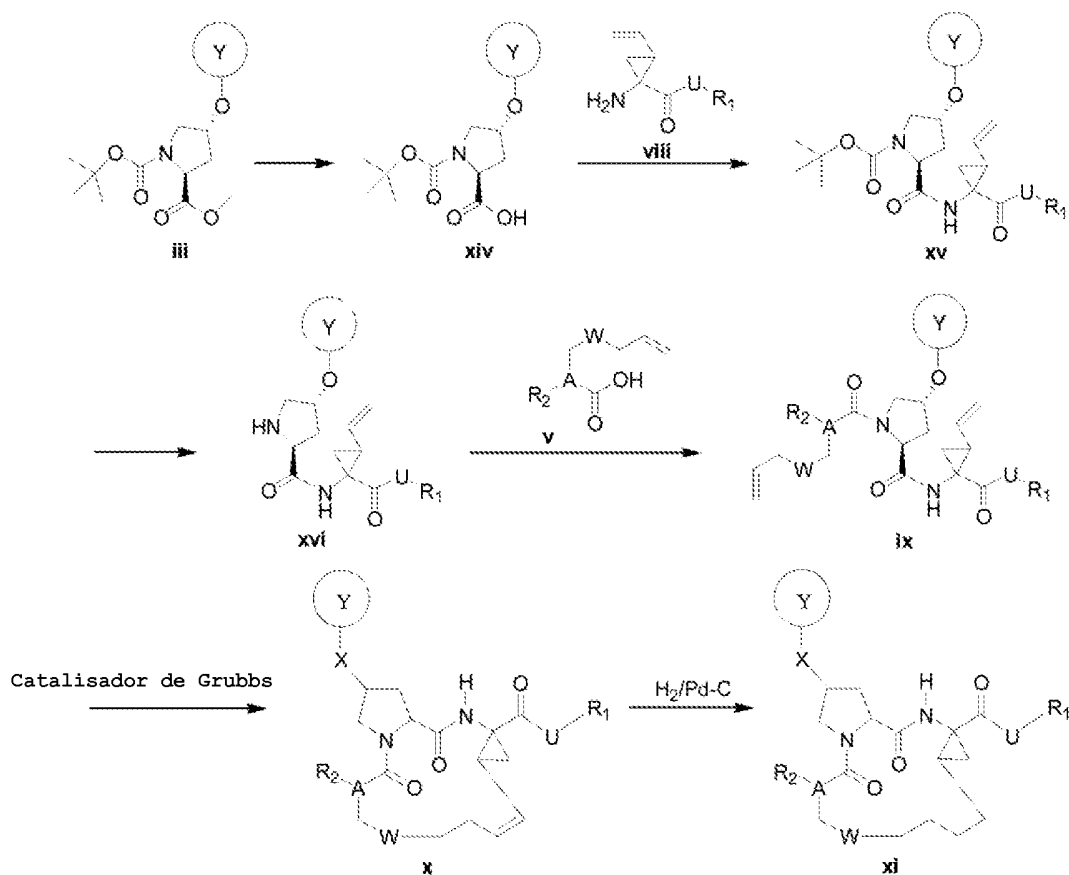
intermediário (**vi**). O intermediário (**vi**) é hidrolisado para dar o ácido (**vii**), o qual é acoplado com o composto de amina (**viii**) para proporcionar o composto de pirrolidina (**ix**) com dois grupos alcenilo terminais. O intermediário (**ix**) é submetido a metátese de olefina na presença de catalisador de Grubbs para proporcionar o composto macrocíclico desejado (**x**). A ligação dupla do análogo macrocíclico (**xi**) pode ainda ser submetida a hidrogenação na presença de Pd-C para se obter o composto macrocíclico saturado (**xi**).

Os Esquemas 2 e 3 abaixo ilustram duas vias alternativas de síntese para os compostos desta invenção.

Esquema 2



Esquema 3

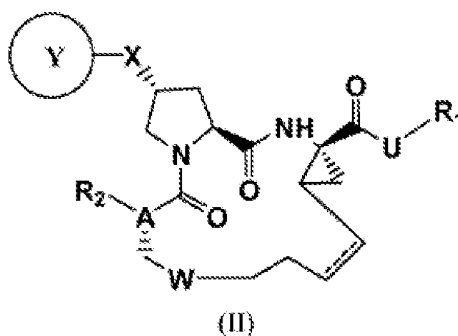


Os métodos descritos anteriormente podem também adicionalmente incluir etapas, antes ou após as etapas descritas especificamente nos Esquemas 1-3, para se adicionarem ou removerem grupos protetores adequados com o objetivo último de se permitir a síntese dos compostos desejados. Além disso, podem ser realizadas várias etapas de síntese numa sequência ou ordem alternada para darem os compostos desejados. As transformações de síntese química e as metodologias de proteção de grupos (proteção e desproteção) úteis na síntese de compostos aplicáveis de fórmula (I) são conhecidas na técnica e incluem, por

exemplo, as descritas em R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene e P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2^a Ed., John Wiley and Sons (1991); L. Fieser e M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); e L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) e edições posteriores das mesmas.

Os exemplos 1-281 abaixo proporcionam descrições detalhadas de como os compostos exemplares 1-281 foram realmente preparados.

Os compostos aqui mencionados contêm uma ligação dupla não aromática e centros assimétricos. Assim, podem ocorrer como racematos e misturas racêmicas, enantiômeros individuais, diastereómeros individuais, misturas diastereoméricas, tautômeros e formas isoméricas cis ou trans. Estão contempladas todas estas formas isoméricas. Por exemplo, os compostos de fórmulas (I) apresentados anteriormente podem possuir as seguintes configurações estereoquímicas (II):



Os compostos descritos acima incluem os próprios compostos, bem como os seus sais, pró-drogas e solvatos, se aplicável. Um sal, por exemplo, pode ser formado entre um anião e um grupo carregado positivamente (por exemplo, amino) num composto de fórmula (I). Aniões adequados incluem cloreto, brometo, iodeto, sulfato, nitrato, fosfato, citrato, metanossulfonato, trifluoroacetato, acetato, malato, tosilato, tartarato, fumarato, glutamato, glucuronato, lactato, glutarato e maleato. Da mesma forma, um sal pode também ser formado entre um catião e um grupo carregado negativamente (por exemplo, carboxilato) num composto de fórmula (I). Catiões adequados incluem ião sódio, ião potássio, ião magnésio, ião cálcio e um catião de amónio tal como o ião tetrametilamónio. Os compostos de fórmula (I) também incluem aqueles sais que contêm átomos de azoto quaternário. Exemplos de pró-drogas incluem ésteres e outros derivados farmacologicamente aceitáveis, os quais, após administração a um indivíduo, são capazes de proporcionarem compostos ativos de fórmula (I). Um solvato refere-se a um complexo formado entre um composto ativo de fórmula (I) e um solvente farmacologicamente aceitável. Exemplos de solventes farmacologicamente aceitáveis incluem água, etanol, isopropanol, acetato de etilo, ácido acético e etanolamina.

Também dentro do âmbito desta invenção estão compostos para uso num método de tratamento de infeção por HCV através da administração de uma quantidade eficaz de um

ou mais dos compostos de fórmula (I) a um paciente. O termo "tratar" ou "tratamento" refere-se à administração dos compostos a um indivíduo, o qual tem infecção por HCV, um sintoma da mesma ou uma predisposição para a mesma, com o propósito de conferir um efeito terapêutico, por exemplo, curar, aliviar, alterar, afetar, melhorar ou prevenir a infecção por HCV, o sintoma da mesma ou a predisposição para a mesma. O termo "uma quantidade eficaz" refere-se à quantidade de um composto ativo desta invenção que é requerida para conferir um efeito terapêutico no indivíduo tratado. As doses eficazes irão variar, como é reconhecido pelos peritos na técnica, dependendo dos tipos de doenças tratadas, da via de administração, da utilização de excipiente e da possibilidade de co-utilização com outro tratamento terapêutico.

Os compostos desta invenção podem permanecer no sistema sanguíneo a um nível eficaz durante um período prolongado. Assim, estes compostos podem ser administrados numa quantidade eficaz uma vez por dia para conferirem o efeito terapêutico.

Para praticar o dito método, pode ser administrada uma composição contendo um ou mais compostos desta invenção por via parentérica, oral, nasal, retal, tópica ou bucal. O termo "parentérico", da forma como é aqui utilizado, refere-se a injeção subcutânea, intracutânea, intravenosa, intramuscular, intra-articular, intra-arterial, intra-sinovial, intra-esternal, intratecal, intra-

lesional ou intracraniana, bem como a qualquer técnica de infusão adequada.

Uma composição injetável estéril pode ser uma solução ou suspensão num diluente ou solvente não tóxico parentericamente aceitável, tal como uma solução em 1,3-butanodiol. Entre os veículos e solventes aceitáveis que podem ser empregues estão manitol, água, solução de Ringer e solução isotónica de cloreto de sódio. Além disso, são convencionalmente empregues óleos fixos como um solvente ou meio de suspensão (por exemplo, mono- ou diglicéridos sintéticos). Ácidos gordos, tais como ácido oleico e seus derivados de glicérido, são úteis na preparação de injetáveis, tal como são óleos naturais farmacologicamente aceitáveis, tais como azeite ou óleo de rícino, especialmente nas suas versões polioxietiladas. Estas soluções ou suspensões oleosas podem também conter um diluente ou dispersante alcoólico de cadeia longa, carboximetilcelulose, ou agentes de dispersão semelhantes. Outros tensioativos vulgarmente utilizados, tais como Tweens ou Spans, ou outros agentes emulsionantes ou intensificadores de biodisponibilidade semelhantes que são vulgarmente utilizados no fabrico de sólidos, líquidos ou outras formas de dosagem farmacologicamente aceitáveis podem também ser utilizados com o propósito de formulação.

Uma composição para administração oral pode ser qualquer forma de dosagem oralmente aceitável incluindo cápsulas, comprimidos, emulsões e suspensões, dispersões e

soluções aquosas. No caso de comprimidos, portadores vulgarmente utilizados incluem lactose e amido de milho. Agentes lubrificantes, tais como estearato de magnésio, são também tipicamente adicionados. Para administração oral numa forma de cápsula, diluentes úteis incluem lactose e amido de milho seco. Quando são administradas oralmente suspensões ou emulsões aquosas, o ingrediente ativo pode ser suspenso ou dissolvido numa fase oleosa combinada com agentes emulsionantes ou de suspensão. Se desejado, podem ser adicionados certos agentes edulcorantes, aromatizantes ou corantes.

Um aerossol nasal ou uma composição de inalação podem ser preparados de acordo com técnicas bem conhecidas na técnica da formulação farmacêutica. Por exemplo, uma tal composição pode ser preparada como uma solução em solução salina, utilizando-se álcool benzílico ou outros conservantes adequados, promotores de absorção para melhorarem a biodisponibilidade, fluorocarbonetos e/ou outros agentes solubilizantes ou dispersantes conhecidos na técnica.

Uma composição com um ou mais compostos ativos desta invenção pode também ser administrada na forma de supositórios para administração retal.

O portador na composição farmacêutica deve ser "aceitável" no sentido de que deve ser compatível com o ingrediente ativo da composição (e, de preferência, capaz

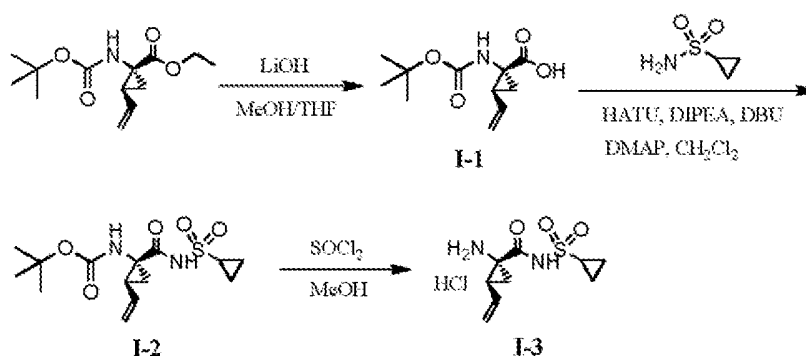
de estabilizar o ingrediente ativo) e não ser prejudicial ao indivíduo a ser tratado. Pode ser utilizado um ou mais agentes solubilizantes como excipientes farmacêuticos para a libertação de um composto ativo desta invenção. Exemplos de outros portadores incluem óxido de silício coloidal, estearato de magnésio, celulose, lauril sulfato de sódio, e D&C Yellow # 10.

O composto desta invenção pode ser utilizado para tratar HCV juntamente com um segundo agente anti-HCV, tal como um inibidor de um alvo diferente de protease NS3 de HCV no ciclo de vida de HCV, um agente imunomodulador e um outro agente antiviral. O composto desta invenção e o segundo agente anti-HCV podem ser administrados simultaneamente ou em alturas diferentes. Para administração simultânea, podem ser misturados para formarem um único comprimido, ou preparados como comprimidos separados. Estes dois agentes podem ser utilizados numa quantidade tal que o total de ambos seja reconhecido por um perito na técnica como eficaz para o tratamento de HCV.

Os compostos desta invenção descritos anteriormente podem ser preliminarmente avaliados quanto à sua eficácia no tratamento de infeção por HCV através de um ensaio *in vitro* (ver Exemplos 282 e 283) e posteriormente confirmados por experiências com animais e ensaios clínicos. Outros métodos serão também evidentes para os indivíduos de perícia vulgar na técnica.

Exemplo 1: Síntese de Éster ciclopentílico do ácido {4-ciclopropano-sulfonilaminocarbonil-2,15-dioxo-18-[2-(4-trifluorometil-fenil)-benzo[4,5]furo[3,2-d]pirimidin-4-iloxi]-3,16-diaza-triciclo[14.3.0.04,6]nonadec-14-il}-carbâmico (Composto 1)

O composto I-3 foi primeiramente preparado a partir de éster etílico do ácido 1-*t*-butoxicarbonilamino-2-vinil-ciclopropanocarboxílico disponível comercialmente através da via ilustrada abaixo:

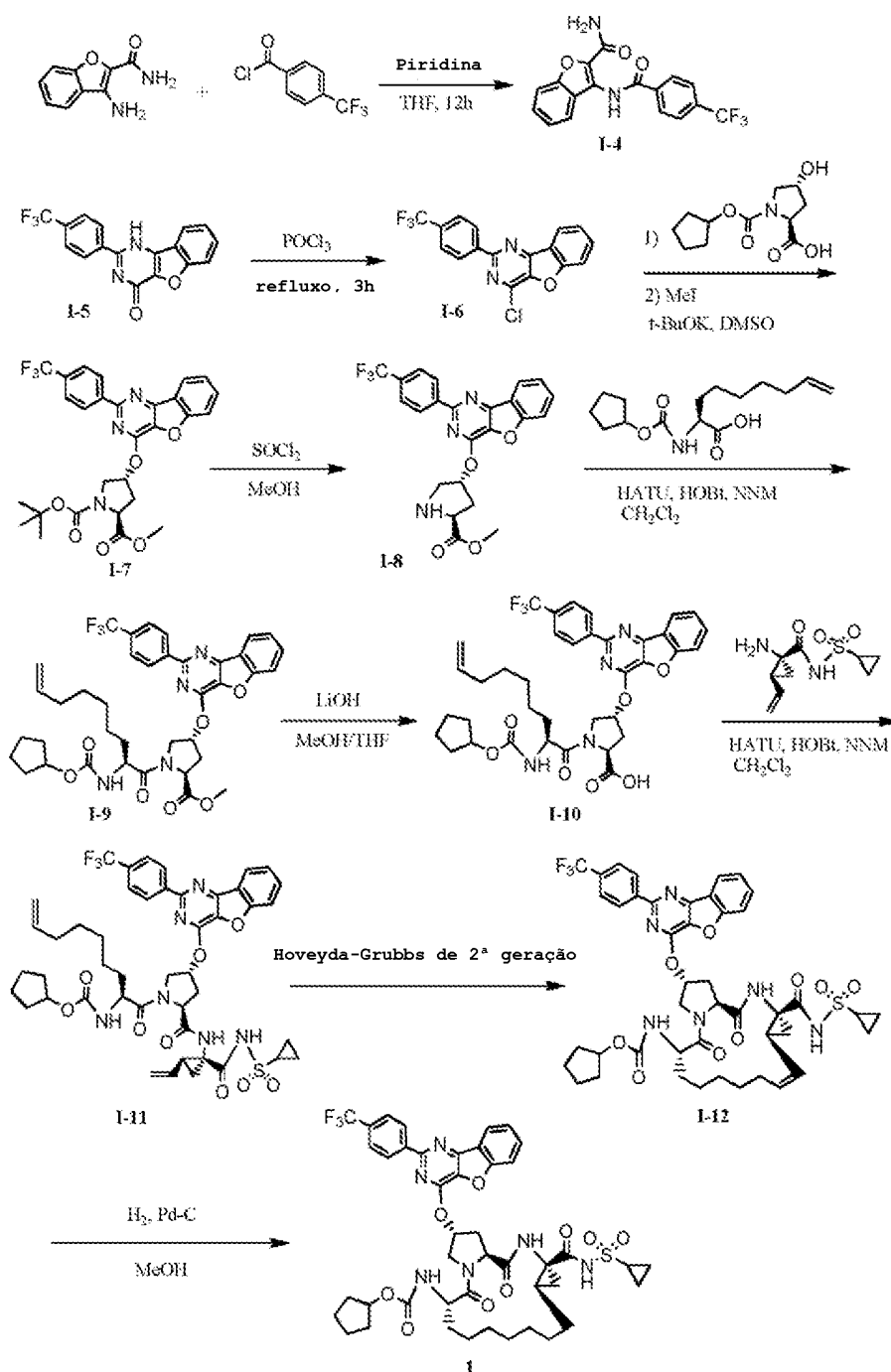


A uma solução de éster etílico do ácido 1-*t*-butoxicarbonilamino-2-vinil-ciclopropanocarboxílico (0,34 g, 1,3 mmol) em THF (5 mL) e metanol (5 mL) adicionou-se uma suspensão de LiOH (0,13 g, 5,3 mmol) em água (1,4 mL). Após ter sido agitada durante a noite à temperatura ambiente, a reação foi extinta com HCl a 10% (2 mL) e o solvente foi removido sob vácuo. O pó sólido resultante foi lavado com água (10 mL) para dar o composto I-1 (0,27 g, 90%). MS m/z 249,9 (M^++23); ^1H NMR (CDCl_3) δ 10,35 (brs, 1H), 5,84-5,71 (m, 1H), 5,29 (d, $J = 17,4$ Hz, 1H), 5,12 (d, $J = 10,2$ Hz, 1H), 2,23-2,14 (m, 1H), 1,87-1,65 (m, 1H), 1,58-1,41 (m, 1H), 1,43 (s, 9H).

Agitou-se uma solução do composto I-1 (0,52 g, 2,3 mmol), hexafluoro-fosfato de 2-(1H-7-azabenzotriazol-1-il)-1,1,3,3-tetrametilurônio metanamínio (HATU, 1,74 g, 4,6 mmol), e 4-dimetilaminopiridina (1,39 g, 11,6 mmol) em CH₂Cl₂ (40 mL) à temperatura ambiente durante 1 hora, seguindo-se a adição lenta de ciclopropanosulfonamida (0,57 g, 4,7 mmol), diisopropiletilamina (1,81 mL, 14,0 mmol), e 1,8-diazabicyclo[5,4,0]undec-7-eno (1,80 g, 11,7 mmol) durante 15 minutos. Após a mistura reacional ter sido agitada à temperatura ambiente durante a noite, o solvente foi removido sob vácuo. O resíduo foi purificado por cromatografia em coluna de sílica gel para dar o composto I-2 (0,51 g, 66%). MS m/z 353,1 (M⁺+23); ¹H NMR (CDCl₃) δ 9,75 (brs, 1H), 5,64-5,51 (m, 1H), 5,30 (d, J = 17,4 Hz), 5,16 (d, J = 10,2 Hz, 1H), 2,95-2,89 (m, 1H), 2,19-2,10 (m, 1H), 1,93-1,88 (m, 1H), 1,47 (s, 9H), 1,46-1,38 (m, 1H), 1,32-1,23 (m, 2H), 1,15-1,00 (m, 2H).

A uma solução do composto I-2 (0,50 g, 1,5 mmol) em MeOH (8 mL) adicionou-se SOCl₂ (0,26 g, 2,2 mmol) à temperatura ambiente. Depois da mistura reacional ter sido submetida a refluxo durante 1 hora, removeu-se MeOH e SOCl₂ sob vácuo. O resíduo foi triturado a partir de pentano e filtrado para dar o intermediário I-3 como um sólido esbranquiçado (0,32 g, 91%). MS m/z (M⁺+1); ¹H NMR (CD₃CO₂D) δ 5,77-5,65 (m, 1H), 5,43 (d, J = 17,4 Hz, 1H), 5,32 (d, J = 10,2 Hz, 1H), 3,06-2,97 (m, 1H), 2,45 (dd, J = 17,4 Hz, J = 7,8 Hz, 1H), 2,16 (dd, J = 8,0 Hz, J = 7,8 Hz, 1H), 1,75 (dd, J = 10,1 Hz, J = 7,8 Hz, 1H), 1,32-0,86 (m, 4H).

O Composto 1 foi preparado através da via ilustrada abaixo:



Agitou-se uma solução de amida do ácido 3-amino-

benzofuran-2-carboxílico (1,00 g, 5,7 mmol) e piridina (1 mL, 12,26 mmol) em THF (25 mL) a 0 °C durante 10 min. À solução resultante adicionou-se lentamente cloreto de 4-trifluorometil-benzoílo (1,48 g, 7,1 mmol). Em seguida elevou-se a temperatura até à temperatura ambiente e agitou-se a mistura durante 12 h. Após o solvente ter sido removido sob pressão reduzida, o sólido resultante foi recolhido, lavado com água e seco ao ar para originar I-4 (1,92 g, 96,0%). MS: m/z 349,0 ($M^+ + 1$).

Aqueceu-se uma suspensão de I-4 (1,92 g, 5,5 mmol) e NaOH 2 N (13 ml) em EtOH (25 mL) a 85 °C durante 12 h. Depois de arrefecida, a mistura foi acidificada e em seguida removeu-se o EtOH. O sólido resultante foi recolhido, filtrado, lavado com água e seco para proporcionar I-5 (1,71 g, 95,0%). MS m/z 331 ($M^+ + 1$).

Submeteu-se a refluxo durante 2 horas uma solução de I-5 (1,71 g, 5,2 mmol) e excesso de oxicloreto de fósforo (POCl_3). Depois de arrefecida e cuidadosamente concentrada, a mistura foi submetida a extração com cloreto de metileno e hidróxido de sódio a 10%. A camada orgânica foi seca sobre MgSO_4 , concentrada e cristalizada a partir de CH_2Cl_2 e *n*-hexano para dar o composto I-6 (1,49 g, 82%). MS m/z 348,8, 350,9 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 8,70 (d, 2H), 8,34 (d, 1H), 7,82-7,75 (m, 4H), 7,57 (ddd, 1H).

A uma suspensão de boc-trans-4-hidroxi-L-prolina (0,53 g, 2,3 mmol) em DMSO (25 mL) adicionou-se *t*-BuOK

(0,82 g, 5,1 mmol) a 0 °C. Após a mistura ter sido deixada aquecer até à temperatura ambiente e agitada durante 1 hora, adicionou-se lentamente o composto I-6 (0,81 g, 2,3 mmol) a 10 °C. A agitação foi continuada durante a noite. Adicionou-se iodometano (1,02 g, 6,9 mmol) e agitou-se a mistura reacional à temperatura ambiente durante mais 30 minutos. A mistura reacional foi neutralizada para pH 6~7 por solução aquosa de HCl a 10% e sujeita a extração com cloreto de metileno. A camada orgânica foi seca sobre MgSO₄, evaporada sob vácuo, e purificado por cromatografia em coluna de sílica gel para dar o composto I-7 (1,12 g, 86%). MS m/z 557,8 (M⁺+1); ¹H NMR (CDCl₃) δ 8,63 (d, 2H), 8,28 (d, 1H), 7,80-7,74 (m, 2H), 7,70 (d, 2H), 7,51 (ddd, 1H).

A uma solução do composto I-7 (1,13 g, 2,0 mmol) em MeOH (20 mL) foi adicionado SOCl₂ (1,21 g, 9,8 mmol) à temperatura ambiente. A mistura reacional foi submetida a refluxo durante 1 hora, e removeu-se o MeOH e o SOCl₂. O resíduo foi triturado em pentano. A suspensão foi filtrada para dar o composto I-8 como um sólido esbranquiçado (0,87 g, 95%). MS m/z 458,1 (M⁺+1).

A uma solução de HATU (1,12 g, 3,0 mmol), 1-hidroxibenzotriazol (HOBT, 0,41 g, 3,0 mmol), I-8 (0,86 g, 1,9 mmol), e ácido 2-*t*-butoxicarbonilamino-non-8-enóico (1,21 g, 1,9 mmol) em CH₂Cl₂ (40 mL) à temperatura ambiente foi adicionada N-metilmorfolina (NMM, 1,02 g, 9,9 mmol). Depois de agitada durante a noite, a mistura foi

concentrada sob vácuo. O resíduo foi purificado por cromatografia em coluna de sílica gel para dar o composto I-9 (1,03 g, 73%). MS m/z 711,3 ($M^+ + 1$).

A uma solução do composto I-9 (1,01 g, 1,4 mmol) em THF (20 mL) adicionou-se LiOH 0,5 M (5,7 mL, 2,9 mmol) à temperatura ambiente. Depois de agitada durante a noite, a mistura reaccional foi neutralizada por HCl a 10% até pH <7 e concentrada sob vácuo. O resíduo resultante foi filtrado e lavado com água para dar o composto I-10 (0,91 g, 2%). MS: m/z 697,3 ($M^+ + 1$).

Adicionou-se NMM (0,12 g, 1,2 mmol) a uma solução do composto I-3 (0,28 g, 0,4 mmol), HATU (0,31 g, 0,8 mmol), HOBT (0,08 g, 0,6 mmol) e composto I-10 (0,09 g, 0,4 mmol) em CH_2Cl_2 (10 mL) à temperatura ambiente. Depois de agitada durante a noite, a mistura reaccional foi concentrada sob vácuo. O resíduo foi purificado por cromatografia em coluna de sílica gel para dar o composto I-11 (0,10 g, 85%). MS m/z 921,3 ($M^+ + 1$); 1H NMR ($CDCl_3$) δ 10,24 (s, 1H), 8,61 (d, 2H), 8,26 (d, 1H), 7,77 (d, 2H), 7,73-7,64 (m, 2H), 7,54-7,47 (m, 1H), 7,11 (s, 1H), 6,19 (d, 1H), 5,88-5,70 (m, 2H), 5,38-5,25 (m, 2H), 5,16 (d, 1H), 5,00-4,90 (m, 2H), 4,60 (dd, 1H), 4,88-4,34 (m, 2H), 4,18-4,10 (m, 1H), 2,98-2,89 (m, 1H), 2,68 (dd, 2H), 2,18-1,96 (m, 6H), 1,50-1,32 (m, 7H), 1,28 (s, 9H), 1,09-1,25 (m, 2H).

A uma solução do composto I-11 (0,10 g, 0,11

mmol) em CH_2Cl_2 (10 mL) adicionou-se Hoveyda-Grubbs de 2^a geração (35 mg, 0,056 mmol) à temperatura ambiente sob N_2 . Em seguida, agitou-se a mistura reaccional a 40 °C durante 24 h para se levar a cabo a metátese de ciclização. A reação foi parada e a mistura reaccional foi purificada por cromatografia em coluna para dar o composto I-12 (30 mg, 31%). MS: m/z 893,3 ($\text{M}^+ + 1$); ^1H NMR (CDCl_3) δ 10,39 (s, 1H), 8,59 (d, 2H), 8,21 (d, 1H), 7,77 (d, 2H), 7,69-7,57 (m, 2H), 7,46 (dd, 1H), 7,20 (s, 1H), 6,12 (s, 1H), 5,69 (q, 1H), 5,12 (d, 1H), 4,97 (dd, 1H), 4,81-4,68 (m, 2H), 4,28-4,07 (m, 2H), 2,96-2,49 (m, 3H), 2,30 (q, 1H), 1,96-1,12 (m, 14H), 1,08 (s, 9H), 0,96-0,82 (m, 2H).

A uma solução do composto I-12 (30 mg, 0,034 mmol) em MeOH (10 mL) adicionou-se 5% Pd-C (5 mg) à temperatura ambiente sob N_2 . Em seguida, agitou-se a mistura reaccional sob hidrogénio à temperatura ambiente e a uma pressão de 60 psi durante 4 h. A mistura reaccional foi filtrada e purificada por cromatografia em coluna para dar o composto 1 (16,5 mg, 55%). MS: m/z 895,3 ($\text{M}^+ + 1$); ^1H NMR (CDCl_3) δ 10,79 (s, 1H), 8,57 (d, 2H), 8,21 (d, 1H), 7,75 (d, 2H), 7,64 (m, 2H), 7,46 (d, 1H), 7,11 (s, 1H), 6,11 (s, 1H), 5,29 (d, 1H), 4,72 (m, 2H), 4,38 (m, 2H), 4,12 (m, 1H), 3,02-2,58 (m, 3H), 1,98-0,86 (m, 29H).

Exemplos 2-141: Sínteses dos Compostos 2-141

Cada um dos Compostos 2-141 foi preparado de um modo semelhante ao descrito no Exemplo 1.

Composto 2: MS: m/z 883,3 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,51 (s, 1H), 8,53 (d, 2H), 8,16 (d, 1H), 7,73 (d, 2H), 7,62 (m, 2H), 7,22 (m, 2H), 6,07 (s, 1H), 5,23 (d, 1H), 4,77 (dd, 1H), 4,49 (d, 1H), 4,35 (m, 1H), 4,13 (m, 1H), 3,02-2,57 (m, 3H), 1,99-0,91 (m, 30H).

Composto 3: MS: m/z 823,2 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,38 (s, 1H), 8,53 (d, 2H), 8,16 (d, 1H), 7,73 (d, 2H), 7,61 (m, 2H), 7,41 (m, 2H), 6,13 (m, 2H), 5,69 (q, 1H), 4,98 (dd, 1H), 4,78 (m, 1H), 4,55 (m, 1H), 4,42 (m, 1H), 4,19 (m, 1H), 2,89 (m, 1H), 2,78 (m, 2H), 2,52 (m, 1H), 2,23 (q, 1H), 1,96-0,84 (m, 15H), 1,90 (s, 3H).

Composto 4: MS: m/z 882,3 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,47 (s, 1H), 8,64 (d, 1H), 8,52 (m, 3H), 7,70 (d, 2H), 7,44 (dd, 1H), 6,07 (s, 1H), 5,63 (q, 1H), 5,01-4,73 (m, 3H), 4,07-4,01 (m, 2H), 2,90-2,22 (m, 4H), 1,97-1,09 (m, 17H), 0,94 (s, 9H), 0,90-0,88 (m, 1H).

Composto 5: MS: m/z 840,2 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,42 (s, 1H), 8,64-8,47 (m, 4H), 7,80 (d, 2H), 7,50-7,27 (m, 2H), 6,15 (s, 1H), 5,69 (q, 1H), 5,23 (d, 1H), 5,02 (dd, 1H), 4,84 (dd, 1H), 4,53 (d, 1H), 4,25-4,11 (m, 2H), 3,32 (s, 3H), 2,93-2,15 (m, 4H), 1,92-0,83 (m, 16H).

Composto 6: MS: m/z 824,2 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,48 (s, 1H), 8,63 (d, 1H), 8,62-8,48 (m, 3H), 7,78 (d, 2H), 7,44-7,40 (m, 1H), 6,16-6,14 (m, 2H), 5,73 (q, 1H),

5,04 (dd, 1H), 4,85 (dd, 1H), 4,55 (s, 1H), 4,51 (s, 1H), 4,15 (d, 1H), 2,93-2,89 (m, 2H), 2,77-2,22 (m, 3H), 1,95-1,85 (m, 1H), 1,79 (s, 3H), 1,76-0,83 (m, 15H).

Composto 7: MS: m/z 839,2 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,39 (s, 1H), 8,46 (d, 2H), 8,15 (d, 1H), 7,71 (d, 2H), 7,62-7,37 (m, 3H), 7,16 (s, 1H), 6,08 (s, 1H), 5,71 (q, 1H), 5,25 (d, 1H), 4,96 (dd, 1H), 4,75 (dd, 1H), 4,44 (d, 1H), 4,35-4,09 (m, 2H), 3,34 (s, 3H), 2,96-2,71 (m, 2H), 2,57 (brs, 1H), 2,28 (q, 1H), 2,08-0,87 (m, 16H).

Composto 8: MS: m/z 849,3 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,54 (s, 1H), 8,45 (d, 2H), 8,06 (d, 1H), 7,71 (d, 2H), 7,57 (m, 3H), 7,35 (s, 1H), 6,28 (d, 1H), 6,04 (s, 1H), 5,71 (q, 1H), 4,96 (dd, 1H), 4,67 (dd, 1H), 4,47 (d, 1H), 4,45 (brs, 1H), 4,11 (m, 1H), 2,92-2,45 (m, 4H), 2,32 (q, 1H), 1,96-0,84 (m, 20H).

Composto 9: MS: m/z 880,3 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,45 (s, 1H), 8,40 (d, 2H), 8,14 (s, 1H), 7,97 (d, 1H), 7,64 (d, 2H), 7,48-7,41 (m, 2H), 7,25-7,20 (m, 1H), 5,96 (s, 1H), 5,63 (q, 1H), 4,92-4,86 (m, 2H), 4,77 (d, 1H), 4,44 (s, 1H), 4,20 (dd, 1H), 4,03 (dd, 1H), 2,90-2,84 (m, 2H), 2,80-2,63 (m, 1H), 2,38-2,32 (m, 1H), 1,98-1,02 (m, 15H), 0,91 (s, 9H), 0,90-0,086 (m, 1H).

Composto 10: MS: m/z 911,2 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,23 (s, 1H), 8,54 (d, 2H), 7,87-7,80 (m, 1H), 7,71 (d, 2H), 7,56 (dd, 1H), 7,33-7,20 (m, 1H), 6,88 (s, 1H), 6,13

(s, 1H), 5,65 (q, 1H), 5,07-4,94 (m, 2H), 4,69 (dd, 1H), 4,57 (d, 1H), 4,43-4,38 (m, 1H), 4,24-4,01 (m, 2H), 2,91-2,80 (m, 2H), 2,74 (s, 3H), 2,65-2,63 (m, 1H), 2,60-2,41 (m, 1H), 2,22 (q, 1H), 1,98-0,86 (m, 20H).

Composto 11: MS: m/z 907,3 (M^+1).

Composto 12: MS: m/z 923,3 (M^+1); ^1H NMR (CDCl_3) δ 10,42 (s, 1H), 8,57 (d, 2H), 8,06 (d, 1H), 7,76 (d, 2H), 7,51 (s, 1H), 7,14-6,93 (m, 2H), 6,13 (s, 1H), 5,80-5,60 (m, 1H), 5,31 (d, 1H), 4,97-4,83 (m, 2H), 4,79 (dd, 1H), 4,64-4,04 (m, 3H), 3,88 (s, 3H), 2,94-2,43 (m, 3H), 2,36-0,86 (m, 25H).

Composto 13: MS: m/z 852,3 (M^+1); ^1H NMR (CDCl_3) δ 10,68 (s, 1H), 8,38 (d, 2H), 7,95 (d, 1H), 7,72-7,58 (m, 3H), 7,47 (d, 2H), 7,24-7,19 (m, 1H), 6,01 (s, 1H), 5,69 (q, 1H), 4,94 (dd, 1H), 4,78 (dd, 1H), 4,70 (d, 1H), 4,46 (d, 1H), 4,22-3,98 (m, 2H), 2,97-2,80 (m, 2H), 2,57 (s, 6H), 2,67-2,41 (m, 1H), 2,23 (q, 1H), 1,85-0,84 (m, 16H).

Composto 14: MS: m/z 766,2 (M^+1); ^1H NMR (CDCl_3) δ 10,30 (s, 1H), 8,62 (m, 2H), 8,24 (m, 1H), 7,77 (d, 2H), 7,67 (m, 2H), 7,48 (m, 1H), 6,90 (s, 1H), 6,18 (s, 1H), 5,72 (q, 1H), 4,98 (dd, 1H), 4,65 (dd, 1H), 4,24 (m, 1H), 4,05 (m, 1H), 2,92 (m, 1H), 2,76 (m, 2H), 2,58-2,28 (m, 4H), 1,94-1,05 (m, 13H), 0,97-0,86 (m, 2H).

Composto 15: MS: m/z 893,3 (M^+1); ^1H NMR (CDCl_3)

δ 10,33 (s, 1H), 8,88 (s, 1H), 8,68 (d, 1H), 8,26 (d, 1H), 7,80-7,65 (m, 4H), 7,35-7,26 (m, 1H), 6,98 (d, 1H), 6,20 (d, 1H), 5,71 (q, 1H), 5,18 (d, 1H), 5,00 (dd, 1H), 4,77 (dd, 1H), 4,64 (d, 1H), 4,46 (s, 1H), 4,25 (dd, 1H), 4,15 (dd, 1H), 2,92-2,28 (m, 4H), 2,17-0,82 (m, 24H).

Composto 16: MS: m/z 877,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,40 (s, 1H), 8,45 (d, 2H), 8,04 (d, 1H), 7,62 (d, 2H), 7,58-7,50 (m, 2H), 7,44 (s, 1H), 7,35 (dd, 1H), 6,02 (s, 1H), 5,95 (d, 1H), 5,63 (q, 1H), 4,81 (dd, 1H), 4,70 (dd, 1H), 4,49 (d, 1H), 4,42-4,38 (m, 1H), 4,04 (dd, 1H), 2,90-2,20 (m, 6H), 1,96-0,83 (m, 23H).

Composto 17: MS: m/z 907,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,42 (s, 1H), 8,73 (s, 1H), 8,62 (d, 1H), 7,96 (s, 1H), 7,71 (d, 1H), 7,64 (dd, 1H), 7,59-7,25 (m, 3H), 6,11 (s, 1H), 5,62 (q, 1H), 5,21 (d, 1H), 4,99 (dd, 1H), 4,79 (dd, 1H), 4,61 (d, 1H), 4,52 (s, 1H), 4,25-4,10 (m, 2H), 2,95-2,51 (m, 3H), 2,47 (s, 3H), 2,31 (q, 1H), 2,03-0,91 (m, 24H).

Composto 18: MS: m/z 767,2 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,38 (s, 1H), 8,49 (d, 2H), 8,15 (d, 1H), 7,77 (d, 2H), 7,64-7,58 (m, 2H), 7,41-7,32 (m, 1H), 7,29 (s, 1H), 6,08 (s, 1H), 5,78 (q, 1H), 5,08 (dd, 1H), 4,66 (dd, 1H), 4,42 (d, 1H), 4,09-4,06 (m, 1H), 3,85-3,62 (m, 4H), 2,93-2,45 (m, 4H), 2,04-0,87 (m, 13H).

Composto 19: MS: m/z 899,3 (M^{+1}); ^1H NMR (CDCl_3)

δ 10,28 (s, 1H), 8,51 (d, 2H), 7,80 (dd, 1H), 7,70 (d, 2H), 7,51-7,42 (m, 1H), 7,37-7,23 (m, 1H), 6,97 (s, 1H), 6,06 (s, 1H), 5,63 (q, 1H), 4,96-4,85 (m, 2H), 4,75-4,63 (m, 2H), 4,09-4,02 (m, 2H), 2,93-2,43 (m, 4H), 2,21 (q, 1H), 1,96-0,76 (m, 24H).

Composto 20: MS: m/z 895,3 (M^+1); ^1H NMR (CDCl_3)
 δ 10,42 (s, 1H), 8,43 (d, 2H), 7,81 (s, 1H), 7,67 (d, 2H), 7,51 (s, 1H), 7,35-7,28 (m, 2H), 5,92 (s, 1H), 5,57 (q, 1H), 5,19 (d, 1H), 4,88-4,61 (m, 3H), 4,14-4,00 (m, 2H), 2,83-2,41 (m, 4H), 2,38 (s, 3H), 2,24 (q, 1H), 1,96-1,16 (m, 15H), 1,05 (s, 9H), 0,97-0,78 (m, 1H).

Composto 21: MS: m/z 923,3 (M^+1); ^1H NMR (CDCl_3)
 δ 10,33 (s, 1H), 8,50 (d, 2H), 7,67 (d, 2H), 7,59 (s, 1H), 7,41 (d, 1H), 7,34 (s, 1H), 7,16 (d, 1H), 6,06 (s, 1H), 5,64 (q, 1H), 5,23 (d, 1H), 4,94 (dd, 1H), 4,87 (dd, 1H), 4,58-4,42 (m, 2H), 4,30-4,02 (m, 2H), 3,84 (s, 3H), 2,88-2,44 (m, 4H), 2,21 (q, 1H), 1,84-0,78 (m, 23H).

Composto 22: MS: m/z 752,2 (M^+1); ^1H NMR (CDCl_3)
 δ 10,76 (s, 1H), 8,61 (d, 2H), 8,25 (m, 1H), 7,79 (d, 2H), 7,67 (d, 2H), 7,52 (m, 1H), 6,70 (s, 1H), 6,19 (s, 1H), 5,69 (q, 1H), 5,08 (m, 1H), 4,65 (dd, 1H), 4,23 (dd, 1H), 4,02 (m, 1H), 3,05-1,98 (m, 7H), 1,96-0,82 (m, 13H).

Composto 23: MS: m/z 907,3 (M^+1); ^1H NMR (CDCl_3)
 δ 10,40 (s, 1H), 8,56 (d, 2H), 8,08 (d, 1H), 7,73 (d, 2H), 7,29 (s, 1H), 7,26-7,20 (m, 2H), 6,13 (s, 1H), 5,71 (q,

1H), 5,22 (d, 1H), 4,95 (dd, 1H), 4,82-4,73 (m, 1H), 4,63-4,51 (m, 1H), 4,33-4,06 (m, 2H), 2,96-2,51 (m, 4H), 2,53 (s, 3H), 2,24 (q, 1H), 1,96-0,94 (m, 24H).

Composto 24: MS: m/z 916,3 (M^+1); ^1H NMR (CDCl_3) δ 10,37 (s, 1H), 8,48 (d, 2H), 8,08 (s, 1H), 7,68 (d, 2H), 7,50-7,37 (m, 3H), 6,01 (s, 1H), 5,59 (q, 1H), 5,13 (d, 1H), 4,83 (dd, 1H), 4,74-4,63 (m, 2H), 4,15 (dd, 1H), 4,05 (d, 1H), 2,94-2,41 (m, 4H), 2,21 (q, 1H), 1,89-1,14 (m, 14H), 1,03 (s, 9H), 0,96-0,85 (m, 1H).

Composto 25: MS: m/z 923,3 (M^+1).

Composto 26: MS: m/z 923,3 (M^+1); ^1H NMR (CDCl_3) δ 10,35 (s, 1H), 8,50 (d, 2H), 7,69 (d, 2H), 7,52 (dd, 1H), 7,40 (s, 1H), 7,12 (d, 1H), 6,75 (d, 1H), 6,05 (s, 1H), 5,63 (q, 1H), 5,27 (d, 1H), 4,97-4,83 (m, 1H), 4,75 (dd, 1H), 4,42 (brs, 1H), 4,28-4,08 (m, 2H), 4,08 (s, 3H), 2,91-2,38 (m, 4H), 2,23 (q, 1H), 1,96-0,82 (m, 24H).

Composto 27: MS: m/z 894,3 (M^+1); ^1H NMR (CDCl_3) δ 10,38 (s, 1H), 8,47 (d, 2H), 8,08 (d, 1H), 7,62 (d, 2H), 7,58-7,54 (m, 2H), 7,40-7,33 (m, 1H), 7,31 (s, 1H), 6,07 (s, 1H), 5,63 (q, 1H), 4,95 (dd, 1H), 4,83 (d, 1H), 4,87 (dd, 1H), 4,58 (d, 1H), 4,31-4,19 (m, 1H), 4,09 (dd, 1H), 3,40-3,32 (m, 4H), 3,01-2,41 (m, 8H), 2,19 (q, 1H), 1,92-0,83 (m, 15H).

Composto 28: MS: m/z 878,3 (M^+1); ^1H NMR (CDCl_3)

δ 10,56 (s, 1H), 8,41 (d, 2H), 8,02 (d, 1H), 7,74 (s, 1H), 7,68 (d, 2H), 7,53-7,47 (m, 2H), 7,35-7,32 (m, 1H), 6,01 (s, 1H), 5,62 (q, 1H), 4,90 (dd, 1H), 4,78 (dd, 1H), 4,59-4,43 (m, 2H), 4,35-4,25 (m, 1H), 4,05 (dd, 1H), 3,61-3,49 (m, 1H), 3,01-2,45 (m, 8H), 2,21 (q, 1H), 1,85-0,83 (m, 18H).

Composto 29: MS: m/z 909,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,27 (s, 1H), 8,53 (d, 2H), 8,16 (d, 1H), 7,67 (d, 2H), 7,64-7,43 (m, 4H), 6,03 (s, 1H), 5,61 (q, 1H), 5,22-5,19 (m, 1H), 4,87 (dd, 1H), 4,66 (dd, 1H), 4,57 (d, 1H), 4,19-4,01 (m, 3H), 3,71-3,42 (m, 4H), 3,19-2,97 (m, 2H), 2,91-2,43 (m, 4H), 2,20 (q, 1H), 1,95-0,81 (m, 17H).

Composto 30: MS: m/z 906,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,18 (s, 1H), 8,62 (d, 2H), 8,25 (d, 1H), 7,78 (d, 2H), 7,70-7,61 (m, 2H), 7,55-7,46 (m, 1H), 7,01 (1H), 6,18 (1H), 5,71 (q, 1H), 5,12 (d, 1H), 5,02 (dd, 1H), 4,77 (dd, 1H), 4,64 (d, 1H), 4,53-4,43 (1H), 4,31-4,18 (m, 2H), 2,83-2,44 (m, 3H), 2,28 (q, 1H), 1,95-1,22 (m, 23H), 0,83 (s, 3H).

Composto 31: MS: m/z 907,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,39 (s, 1H), 8,57 (d, 2H), 8,05 (d, 1H), 7,77 (d, 2H), 7,42-7,26 (m, 3H), 6,15 (s, 1H), 5,69 (q, 1H), 5,29 (d, 1H), 4,96 (dd, 1H), 4,78 (dd, 1H), 4,63-4,56 (m, 1H), 4,40-4,13 (m, 3H), 2,91-2,64 (m, 3H), 2,62 (s, 3H), 2,56-2,22 (m, 2H), 1,89-0,96 (m, 23H).

Composto 32: MS: m/z 895,2 ($M^+ + 1$); ^1H NMR (CDCl_3)

δ 10,45 (s, 1H), 8,60 (d, 2H), 8,22 (d, 1H), 7,55 (d, 2H), 7,67-7,60 (m, 2H), 7,45 (dd, 1H), 7,20 (s, 1H), 6,12 (s, 1H), 5,65 (q, 1H), 5,13 (d, 1H), 4,97 (dd, 1H), 4,81-4,71 (m, 2H), 4,14-4,10 (m, 2H), 2,82-2,45 (m, 3H), 2,27 (q, 1H), 1,97-1,21 (m, 14H), 1,08 (s, 9H), 0,89-0,80 (m, 4H).

Composto 33: MS: m/z 853,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,22 (s, 1H), 8,58 (s, 1H), 8,48 (d, 2H), 8,08 (d, 1H), 7,57 (d, 2H), 7,53-7,44 (m, 2H), 7,39-7,26 (m, 1H), 6,05 (s, 1H), 5,65 (q, 1H), 5,21 (d, 1H), 4,95 (dd, 1H), 4,82 (dd, 1H), 4,40 (d, 1H), 4,21-4,03 (m, 2H), 3,27 (s, 3H), 2,81-2,40 (m, 3H), 2,22 (q, 1H), 1,95-1,20 (m, 15H), 0,81 (s, 3H).

Composto 34: MS: m/z 923,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,17 (s, 1H), 8,61 (d, 2H), 8,25 (d, 1H), 7,80 (d, 2H), 7,65-7,50 (m, 2H), 7,41 (dd, 1H), 6,97 (s, 1H), 6,18 (s, 1H), 5,72 (q, 1H), 5,15 (d, 1H), 5,05 (dd, 1H), 4,77 (dd, 1H), 4,65 (d, 1H), 4,29-4,10 (m, 2H), 3,78-3,52 (m, 2H), 3,23-3,03 (m, 2H), 2,79-2,85 (m, 2H), 2,56 (brs, 1H), 2,27 (q, 1H), 1,98-1,19 (m, 20H), 0,88 (s, 3H).

Composto 35: MS: m/z 894,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,45 (s, 1H), 8,47 (d, 2H), 8,12 (s, 1H), 8,05 (d, 1H), 7,70 (d, 2H), 7,53-7,46 (m, 2H), 7,31-7,22 (m, 1H), 6,03 (s, 1H), 5,70 (q, 1H), 5,03-4,84 (m, 4H), 4,24 (d, 1H), 2,95-2,47 (m, 3H), 2,38 (q, 1H), 1,94-1,11 (m, 25H), 0,85 (s, 3H).

Composto 36: MS: m/z 889,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,26 (s, 1H), 8,47 (d, 2H), 8,07 (d, 1H), 7,65 (d, 2H),
7,57 (s, 1H), 7,55-7,42 (m, 2H), 7,38-7,27 (m, 2H), 6,82
(d, 1H), 6,62 (d, 1H), 5,63 (dd, 1H), 6,15 (s, 1H), 5,63
(q, 1H), 4,92 (dd, 1H), 4,74-4,59 (m, 2H), 4,42 (d, 1H),
4,17 (dd, 1H), 2,79-2,42 (m, 3H), 2,23 (q, 1H), 1,95-1,05
(m, 5H), 0,76 (s, 3H).

Composto 37: MS: m/z 837,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,16 (s, 1H), 8,48 (d, 2H), 8,11 (d, 1H), 7,69 (d, 2H),
7,58 (d, 2H), 7,36 (dd, 1H), 7,17 (s, 1H), 6,15 (s, 1H),
6,04 (d, 1H), 5,64 (q, 1H), 4,94 (dd, 1H), 4,67 (dd, 1H),
4,47 (dd, 1H), 4,41 (d, 1H), 4,12 (dd, 1H), 2,78-2,68 (m,
1H), 2,43 (brs, 1H), 2,22 (q, 1H), 1,98-1,64 (m, 7H), 1,53-
1,11 (m, 12H), 0,78 (s, 3H).

Composto 38: MS: m/z 863,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,52 (s, 1H), 8,38 (d, 2H), 7,92 (d, 1H), 7,88 (s, 1H),
7,65 (d, 2H), 7,58-7,52 (m, 2H), 7,35-7,21 (m, 1H), 6,19
(d, 1H), 5,92 (s, 1H), 5,71 (q, 1H), 5,01 (dd, 1H), 4,81
(dd, 1H), 4,62 (d, 1H), 4,37 (brs, 1H), 4,11-4,01 (m, 1H),
2,98-2,87 (m, 1H), 2,74-2,52 (m, 2H), 2,33 (q, 1H), 1,98-
1,19 (m, 16H), 0,88 (s, 3H), 0,68-0,41 (m, 4H).

Composto 39: MS: m/z 908,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,26 (s, 1H), 8,48 (d, 2H), 8,15 (d, 1H), 7,67 (d, 2H),
7,57-7,46 (m, 2H), 7,39-7,35 (m, 2H), 6,07 (s, 1H), 5,62
(q, 1H), 4,98-4,86 (m, 2H), 4,77 (dd, 1H), 4,58 (d, 1H),
4,02 (dd, 1H), 3,38-3,24 (m, 4H), 2,99-2,81 (m, 4H), 2,82-

2,42 (m, 3H), 2,19 (q, 1H), 1,88-1,04 (m, 15H), 0,92-0,72 (m, 4H).

Composto 40: MS: m/z 866,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,51 (s, 1H), 8,37 (d, 2H), 7,91 (d, 1H), 7,69 (s, 1H),
7,61 (d, 2H), 7,53-7,42 (m, 2H), 7,23-7,14 (m, 1H), 6,01
(s, 1H), 5,67 (q, 1H), 4,94 (dd, 1H), 4,72 (dd, 1H), 4,61
(d, 1H), 4,43 (d, 1H), 4,30-4,02 (m, 2H), 2,94-2,60 (m,
3H), 2,57 (s, 6H), 2,20 (q, 1H), 1,80-1,15 (m, 15H), 0,77
(s, 3H).

Composto 41: MS: m/z 892,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,40 (s, 1H), 8,51 (d, 2H), 8,16 (d, 1H), 7,85 (d, 2H),
7,65 (s, 1H), 7,58 (d, 1H), 7,41-7,37 (m, 1H), 6,14 (s,
1H), 5,59 (q, 1H), 4,99 (dd, 1H), 4,80 (dd, 1H), 4,62 (d,
1H), 4,57 (d, 1H), 4,45-4,37 (m, 1H), 4,17 (dd, 1H), 3,75-
3,65 (m, 2H), 3,60-3,48 (m, 2H), 2,80-2,45 (m, 3H), 2,24
(q, 1H), 1,89-1,41 (m, 20H), 0,8 (s, 3H).

Composto 42: MS: m/z 907,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,20 (s, 1H), 8,43 (d, 2H), 8,10 (d, 1H), 7,65 (d, 2H),
7,60-7,55 (m, 2H), 7,39-7,35 (m, 1H), 7,25 (s, 1H), 6,05
(s, 1H), 5,98 (d, 1H), 5,66 (q, 1H), 4,93 (dd, 1H), 4,72
(dd, 1H), 4,52-4,42 (m, 2H), 4,08 (dd, 1H), 3,78-3,60 (m,
2H), 3,21-3,11 (m, 2H), 3,81-2,43 (br, 3H), 2,19-2,05 (m,
2H), 1,85-1,09 (m, 19H), 0,77 (s, 3H).

Composto 43: MS: m/z 890,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,16 (s, 1H), 8,55 (d, 2H), 8,21 (d, 1H), 8,14 (s, 1H),

7,68 (d, 2H), 7,58-7,41 (m, 4H), 7,21 (s, 1H), 6,40 (s, 1H), 6,18 (s, 1H), 5,63 (q, 1H), 4,95 (dd, 1H), 4,78-4,62 (m, 2H), 4,44 (d, 1H), 4,16 (dd, 1H), 2,69-2,44 (m, 3H), 2,24 (q, 1H), 1,98-1,15 (m, 15H), 0,79 (s, 3H).

Composto 44: MS: m/z 879,3 (M^+1); ^1H NMR (CDCl_3)
 δ 10,22 (s, 1H), 8,59 (d, 2H), 8,22 (d, 1H), 7,76 (d, 2H), 7,75-7,60 (m, 2H), 7,48-7,42 (m, 1H), 7,17 (s, 1H), 6,20 (s, 1H), 6,16 (d, 1H), 5,71 (q, 1H), 5,02 (dd, 1H), 4,77 (dd, 1H), 4,60-4,52 (m, 2H), 4,20 (dd, 1H), 2,79-2,45 (m, 3H), 2,21 (q, 1H), 1,96-1,07 (m, 15H), 1,03 (s, 9H), 0,82 (s, 3H).

Composto 45: MS: m/z 933,3 (M^+1); ^1H NMR (CDCl_3)
 δ 10,22 (s, 1H), 8,56 (d, 2H), 8,19 (d, 1H), 7,88 (d, 2H), 7,69-7,42 (m, 3H), 7,19 (s, 1H), 6,81-6,62 (m, 4H), 6,11 (s, 1H), 5,68 (q, 1H), 5,00 (dd, 1H), 4,77 (dd, 1H), 4,55 (d, 2H), 4,41-4,12 (m, 2H), 2,82-2,42 (m, 3H), 2,28 (q, 1H), 2,01-1,11 (m, 15H), 0,83 (s, 1H).

Composto 46: MS: m/z 891,3 (M^+1); ^1H NMR (CDCl_3)
 δ 10,34 (s, 1H), 8,35 (d, 2H), 7,94 (d, 1H), 7,66 (s, 1H), 7,62 (d, 2H), 7,54-7,46 (m, 2H), 7,22 (dd, 1H), 5,93-5,84 (m, 2H), 5,61 (q, 1H), 4,92 (dd, 1H), 4,87 (dd, 1H), 4,58 (d, 1H), 4,41-4,36 (m, 1H), 4,04 (dd, 1H), 2,82-2,75 (m, 1H), 2,65-2,50 (m, 2H), 2,24 (q, 1H), 1,80-1,00 (m, 24H), 0,81 (s, 3H).

Composto 47: MS: m/z 867,3 (M^+1); ^1H NMR (CDCl_3)

δ 10,35 (s, 1H), 8,54 (d, 2H), 8,18 (d, 1H), 7,86 (d, 1H), 7,66 (d, 2H), 7,61 (m, 2H), 7,46 (m, 2H), 6,13 (s, 1H), 5,67 (q, 1H), 4,94 (dd, 1H), 4,77 (m, 1H), 4,61 (m, 1H), 4,40 (d, 1H), 4,20 (m, 1H), 3,72 (s, 3H), 2,91 (m, 1H), 2,72-2,39 (m, 3H), 2,25 (q, 1H), 1,96-0,82 (m, 15H).

Composto 48: MS: m/z 908,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,28 (s, 1H), 8,44 (d, 1H), 8,23 (d, 1H), 7,67 (m, 3H), 7,52 (m, 1H), 7,07 (s, 1H), 6,04 (s, 1H), 5,68 (q, 1H), 5,12 (d, 1H), 4,98 (dd, 1H), 4,79-4,68 (m, 2H), 4,34 (s, 1H), 4,20 (dd, 1H), 4,00 (m, 1H), 2,95 (s, 3H), 2,93 (m, 1H), 2,72 (m, 2H), 2,52 (m, 1H), 2,26 (q, 1H), 1,94-0,82 (23H).

Composto 49: MS: m/z 920,2 ($M^+ + 1$).

Composto 50: MS: m/z 806,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,47 (s, 1H), 8,77-8,53 (m, 2H), 8,19 (d, 1H), 8,13 (d, 1H), 7,73 (s, 1H), 7,53-7,30 (m, 2H), 7,26-7,18 (m, 1H), 6,07 (s, 1H), 5,70-5,40 (m, 2H), 4,98-4,61 (m, 2H), 4,40-4,03 (m, 3H), 3,47 (s, 3H), 2,95-2,90 (m, 1H), 2,87-2,50 (m, 3H), 2,20 (dd, 1H), 2,10-1,86 (m, 3H), 1,61-1,08 (m, 11H), 0,96 (m, 1H).

Composto 51: MS: m/z 822,3, 824,3 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,42 (s, 1H), 8,69-8,44 (m, 3H), 8,34 (d, 2H), 7,65 (s, 1H), 7,42-7,30 (m, 3H), 6,04 (s, 1H), 5,70-5,45 (m, 2H), 4,91-4,63 (m, 2H), 4,35-4,03 (m, 3H), 3,42 (s, 3H), 2,84 (s, 1H), 2,72-2,50 (m, 3H), 2,22 (dd, 1H), 2,19 (m, 3H), 1,54-0,78 (m, 11H).

Composto 52: MS: m/z 774,2 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,33 (s, 1H), 8,65-8,58 (m, 1H), 8,46 (d, 1H), 8,18 (d, 1H), 8,06 (d, 1H), 7,46-7,38 (m, 3H), 7,19-7,11 (m, 1H), 6,13 (s, 1H), 6,04 (d, 1H), 5,66 (dd, 1H), 5,27-5,08 (m, 1H), 5,07-4,67 (m, 2H), 4,52-4,39 (m, 2H), 4,13-4,09 (m, 1H), 3,62-3,60 (m, 1H), 2,95-2,10 (m, 4H), 1,98 (s, 3H), 1,90-0,81 (m, 14H).

Composto 53: MS: m/z 825,3 ($M^+ + 1$).

Composto 54: MS: m/z 805,3, 807,3 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,46 (s, 1H), 8,28-8,19 (m, 1H), 7,98 (s, 1H), 7,88-7,85 (m, 1H), 7,63-7,39 (m, 6H), 6,07 (s, 1H), 5,67-5,46 (m, 2H), 4,96-4,79 (m, 2H), 4,41-4,09 (m, 3H), 3,37 (s, 3H), 2,97-0,88 (m, 20H).

Composto 55: MS: m/z 789,2 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,61 (s, 1H), 8,49 (s, 1H), 8,39-8,24 (m, 2H), 8,05-7,94 (m, 2H), 7,56-7,04 (m, 5H), 5,90 (s, 1H), 5,47 (br, 1H), 4,93-4,69 (br, 2H), 4,40-4,07 (m, 3H), 3,46 (s, 1H), 3,23 (s, 3H), 2,91-2,07 (m, 11H), 1,99-1,54 (m, 4H), 1,32-0,81 (m, 5H).

Composto 56: MS: m/z 839,3, 843,3 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,27 (s, 1H), 8,24 (d, 1H), 7,89 (d, 1H), 7,63 (d, 1H), 7,56 (s, 1H), 7,52-7,40 (m, 2H), 7,14 (brs, 1H), 6,08 (s, 1H), 5,69 (q, 1H), 5,30 (brs, 1H), 4,97 (dd, 1H), 4,74 (dd, 1H), 4,46 (d, 1H), 4,40-4,22 (m, 1H), 4,13-4,08

(m, 1H), 3,36 (s, 3H), 2,99-2,05 (m, 5H), 1,90-1,10 (m, 15H), 0,99-0,88 (m, 1H).

Composto 57: MS: m/z 827,2 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,17 (s, 1H), 8,42 (d, 2H), 7,84 (d, 1H), 7,49-7,41 (m, 4H), 7,28 (m, 1H), 7,13 (brs, 1H), 6,16 (s, 1H), 5,63 (q, 1H), 4,95 (m, 1H), 4,70 (dd, 1H), 4,63 (m, 1H), 4,31-4,11 (m, 2H), 2,97-2,70 (m, 3H), 2,50-1,06 (m, 17H), 0,91 (m, 1H).

Composto 58: MS: m/z 803,3 (M^{+1}).

Composto 59: MS: m/z 789,2 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,39 (s, 1H), 8,53-8,41 (m, 3H), 7,81 (d, 1H), 7,59-7,42 (m, 4H), 7,26 (m, 1H), 7,18 (s, 1H), 6,17 (s, 1H), 5,17 (q, 1H), 5,28 (dd, 1H), 4,95 (dd, 1H), 4,75 (m, 1H), 4,43 (d, 1H), 4,38-4,04 (m, 2H), 3,40 (s, 3H), 2,96-2,67 (m, 3H), 2,60-2,41 (m, 1H), 2,37-2,22 (m, 1H), 1,99-0,85 (m, 14H).

Composto 60: MS: m/z 773,2 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,33 (s, 1H), 8,46 (d, 2H), 7,88-7,84 (m, 1H), 7,60-7,50 (m, 4H), 7,35-7,17 (m, 1H), 6,20 (s, 1H), 6,08 (d, 1H), 5,72 (q, 1H), 4,98 (dd, 1H), 4,72 (dd, 1H), 4,56 (m, 1H), 4,41 (d, 1H), 4,21 (m, 1H), 2,94-2,90 (m, 1H), 2,80-2,77 (m, 1H), 2,55-2,52 (m, 1H), 2,23 (q, 1H), 1,98-1,90 (m, 1H), 1,84 (s, 3H), 1,80-0,80 (m, 16H).

Composto 61: MS: m/z 845,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,41 (s, 1H), 8,34 (d, 2H), 7,84 (d, 1H), 7,53-7,44 (m,

1H), 7,40-7,33 (m, 3H), 7,19 (s, 1H), 6,14 (s, 1H), 5,71 (q, 1H), 5,15 (d, 1H), 4,98 (dd, 1H), 4,89-4,80 (m, 2H), 4,25-4,19 (m, 2H), 2,95-2,90 (m, 1H), 2,88-2,42 (m, 3H), 2,44 (s, 3H), 2,29 (m, 1H), 1,98-1,20 (m, 14H), 1,11 (s, 9H), 1,00-0,87 (1H).

Composto 62: MS: m/z 841,2 (M^+1); ^1H NMR (CDCl_3) δ 10,21 (s, 1H), 8,35 (d, 2H), 7,89 (d, 1H), 7,60-7,57 (m, 1H), 7,33 (d, 2H), 7,17 (d, 1H), 7,05 (s, 1H), 6,22 (s, 1H), 5,68 (q, 1H), 4,97 (dd, 1H), 4,77-4,64 (m, 2H), 4,33-4,17 (m, 2H), 2,93-2,74 (m, 3H), 2,44 (s, 3H), 2,21 (m, 1H), 1,95-0,91 (m, 17H).

Composto 63: MS: m/z 903,3; 905,3 (M^+1); ^1H NMR (CDCl_3) δ 10,18 (s, 1H), 8,45 (d, 2H), 8,23 (d, 1H), 7,64 (m, 2H), 7,49 (d, 3H), 7,01 (s, 1H), 6,17 (s, 1H), 5,72 (q, 1H), 5,13 (d, 1H), 4,99 (dd, 1H), 4,77 (dd, 1H), 4,58 (d, 1H), 4,53 (brs, 1H), 4,27 (m, 1H), 4,14 (m, 1H), 2,83-2,44 (m, 3H), 2,27 (q, 1H), 1,95-1,22 (m, 23H), 0,83 (s, 3H).

Composto 64: MS: m/z 787,3 (M^+1); ^1H NMR (CDCl_3) δ 10,45 (s, 1H), 8,25 (d, 2H), 7,75 (d, 1H), 7,67 (s, 1H), 7,53-7,52 (m, 1H), 7,26 (d, 2H), 6,29 (d, 1H), 6,19 (s, 1H), 5,67 (q, 1H), 4,94 (dd, 1H), 4,75 (dd, 1H), 4,52 (brs, 1H), 4,42 (d, 1H), 4,10-4,18 (m, 1H), 2,89-2,50 (m, 3H), 2,43 (s, 3H), 2,35-2,20 (m, 1H), 1,98-1,85 (m, 1H), 1,82 (s, 3H), 1,62-0,81 (m, 16H).

Composto 65: MS: m/z 803,2 (M^+1); ^1H NMR (CDCl_3)

δ 10,46 (s, 1H), 8,30 (d, 1H), 8,17 (d, 2H), 7,63 (d, 1H), 7,55 (s, 1H), 7,45-7,41 (m, 1H), 7,25-7,20 (m, 2H), 5,97 (s, 1H), 5,65-5,59 (m, 1H), 5,36 (d, 1H), 4,91-4,87 (m, 1H), 4,73 (dd, 1H), 4,37-4,05 (m, 3H), 3,30 (s, 3H), 2,84-2,47 (m, 3H), 2,38 (s, 3H), 2,40-2,16 (m, 1H), 1,90-0,87 (m, 16H).

Composto 66: MS: m/z 871,3 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,42 (s, 1H), 8,19-8,02 (m, 2H), 7,93 (s, 1H), 7,67 (s, 1H), 7,47-7,26 (m, 3H), 6,05 (s, 1H), 5,62 (q, 1H), 5,34 (d, 1H), 4,96-4,42 (m, 4H), 4,36-4,10 (m, 2H), 2,95-2,90 (m, 1H), 2,77 (s, 3H), 2,76-2,48 (m, 3H), 2,35 (s, 3H), 2,30-0,87 (m, 24H).

Composto 67: MS: m/z 875,3 ($M^+ + 1$).

Composto 68: TG-2379: MS: m/z 871,3 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,33 (s, 1H), 8,34 (d, 2H), 7,85 (d, 1H), 7,73 (s, 1H), 7,54-7,46 (m, 1H), 7,38-7,22 (m, 3H), 6,12 (s, 1H), 5,65 (q, 1H), 5,35 (d, 1H), 4,93 (dd, 1H), 4,78 (dd, 1H), 4,62-4,50 (m, 2H), 4,32-4,08 (m, 2H), 2,81-2,42 (m, 3H), 2,40 (s, 3H), 2,26 (q, 1H), 1,93-1,11 (m, 23H), 0,80 (s, 3H).

Composto 69: MS: m/z 861,3 ($M^+ + 1$).

Composto 70: MS: m/z 857,2 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,23 (s, 1H), 8,09 (s, H), 8,05 (s, 1H), 7,96 (dd, 1H), 7,58 (dd, 1H), 7,47-7,19 (m, 3H), 7,06 (d, 1H), 6,21 (s,

1H), 5,69 (q, 1H), 4,95 (dd, 1H), 4,81-4,60 (m, 2H), 4,35-4,17 (m, 2H), 3,94 (s, 3H), 2,92-2,41 (m, 3H), 2,23 (q, 1H), 1,92-0,82 (m, 17H).

Composto 71: MS: m/z 819,2 (M⁺+1); ¹H NMR (CDCl₃) δ 10,36 (s, 1H), 8,01-7,81 (m, 3H), 7,71 (d, 1H), 7,34-7,22 (m, 3H), 6,96 (d, 1H), 6,01 (s, 1H), 5,61 (q, 1H), 5,27 (dd, 1H), 4,90 (dd, 1H), 4,69 (dd, 1H), 4,38 (d, 1H), 4,22-4,03 (m, 2H), 3,87 (s, 3H), 3,28 (s, 3H), 2,86-2,42 (m, 3H), 2,20 (q, 1H), 1,97-0,88 (m, 16H).

Composto 72: MS: m/z 861,3 (M⁺+1); ¹H NMR (CDCl₃) δ 10,38 (s, 1H), 8,10-7,98 (m, 2H), 7,86 (d, 1H), 7,54-7,22 (m, 3H), 7,20 (s, 1H), 7,06 (d, 1H), 6,10 (s, 1H), 5,70 (q, 1H), 5,29 (d, 1H), 4,97 (dd, 1H), 4,79-4,67 (m, 2H), 4,18-4,04 (m, 2H), 3,94 (s, 3H), 2,95-2,57 (m, 3H), 2,28 (q, 1H), 1,91-0,87 (m, 25H).

Composto 73: MS: m/z 803,2 (M⁺+1); ¹H NMR (CDCl₃) δ 10,37 (s, 1H), 8,12-8,96 (m, 2H), 7,85 (d, 1H), 7,56-7,26 (m, 4H), 7,05 (d, 1H), 6,19-6,15 (m, 2H), 5,71 (q, 1H), 4,96 (dd, 1H), 4,74 (s, 1H), 4,53-4,42 (m, 2H), 4,19 (d, 1H), 3,93 (s, 3H), 2,91-2,20 (m, 4H), 2,10-0,82 (m, 19H).

Composto 74: MS: m/z 861,3 (M⁺+1); ¹H NMR (CDCl₃) δ 10,42 (s, 1H), 8,39 (d, 2H), 7,81 (d, 1H), 7,50-7,26 (m, 3H), 7,00 (d, 2H), 6,05 (s, 1H), 5,65 (q, 1H), 5,21 (d, 1H), 4,95 (dd, 1H), 4,84 (dd, 1H), 4,68 (d, 1H), 4,21-4,07 (m, 2H), 3,90 (s, 3H), 2,90-2,45 (m, 4H), 2,22 (q, 1H),

1,98-1,20 (m, 14H), 1,13 (s, 9H), 0,99-0,84 (m, 1H).

Composto 75: MS: m/z 887,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,33 (s, 1H), 8,38 (d, 2H), 7,82 (d, 1H), 7,61 (s, 1H),
7,59-7,43 (m, 1H), 7,35-7,20 (m, 1H), 7,01 (d, 2H), 6,07
(s, 1H), 5,68 (q, 1H), 5,42 (d, 1H), 4,98 (dd, 1H), 4,75
(dd, 1H), 4,58 (s, 1H), 4,38-4,13 (m, 3H), 3,88 (s, 3H),
2,86 (br, 2H), 2,59-2,11 (m, 2H), 1,96-1,20 (m, 22H), 0,92-
0,78 (m, 4H).

Composto 76: MS: m/z 903,3, 905,3 ($M^+ + 1$).

Composto 77: MS: m/z 887,3 ($M^+ + 1$).

Composto 78: MS: m/z 883,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,19 (s, 1H), 8,46 (d, 2H), 8,25 (d, 1H), 7,62 (m, 2H),
7,46 (m, 1H), 7,04 (d, 2H), 6,96 (s, 1H), 6,19 (s, 1H),
5,73 (q, 1H), 5,15 (d, 1H), 5,02 (dd, 1H), 4,77 (m, 1H),
4,58 (m, 2H), 4,30 (m, 1H), 4,15 (m, 3H), 2,79 (m, 2H),
2,54 (m, 1H), 2,26 (q, 1H), 1,92-0,83 (m, 26H), 0,83 (s,
3H).

Composto 79: MS: m/z 869,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,36 (s, 1H), 8,44 (d, 2H), 8,24 (d, 1H), 7,60 (m, 2H),
7,44 (m, 1H), 7,04 (s, 1H), 7,00 (d, 2H), 6,16 (s, 1H),
5,71 (q, 1H), 5,21 (d, 1H), 4,97 (dd, 1H), 4,74 (m, 1H),
4,57 (m, 2H), 4,30 (m, 1H), 4,15 (m, 3H), 2,91 (m, 1H),
2,75 (m, 2H), 2,56 (m, 1H), 2,26 (q, 1H), 1,92-0,83 (m,
26H).

Composto 80: MS: m/z 883,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,42 (s, 1H), 8,43 (d, 2H), 8,23 (d, 1H), 7,61-7,39 (m, 4H), 7,03 (d, 2H), 6,18 (s, 1H), 5,71 (q, 1H), 5,30 (d, 1H), 4,96 (dd, 1H), 4,79-4,57 (m, 4H), 4,41-4,22 (m, 1H), 4,15-4,08 (m, 1H), 2,96-2,67 (m, 3H), 2,57-2,42 (m, 1H), 2,25 (q, 1H), 1,98-0,87 (m, 29H).

Composto 81: MS: m/z 897,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,31 (s, 1H), 8,42 (d, 2H), 8,21 (d, 1H), 7,57-7,25 (m, 4H), 7,02 (d, 2H), 6,14 (s, 1H), 5,67-5,64 (m, 1H), 5,40 (d, 1H), 5,03-4,93 (m, 1H), 4,79-4,54 (m, 4H), 4,39-4,12 (m, 2H), 2,77-2,72 (m, 2H), 2,54 (br, 1H), 2,26 (q, 1H), 2,03-1,24 (m, 29H), 0,80 (s, 3H).

Composto 82: MS: m/z 915,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,29 (s, 1H), 8,38 (d, 2H), 7,74 (d, 1H), 7,57-7,24 (m, 3H), 7,27 (d, 2H), 6,14 (s, 1H), 5,66 (q, 1H), 5,32 (d, 1H), 4,98 (dd, 1H), 4,76 (dd, 1H), 4,71-4,48 (m, 3H), 4,39-4,08 (m, 2H), 2,85-2,42 (m, 3H), 2,31 (q, 1H), 2,03-1,24 (m, 29H), 0,80 (s, 3H).

Composto 83: MS: m/z 901,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,42 (s, 1H), 8,46 (d, 2H), 7,82 (d, 1H), 7,54 (dd, 1H), 7,42 (s, 1H), 7,32 (m, 1H), 6,98 (d, 2H), 6,14 (s, 1H), 5,65 (q, 1H), 5,33 (d, 1H), 4,97 (dd, 1H), 4,76 (dd, 1H), 4,71-4,50 (m, 3H), 4,41-4,08 (m, 2H), 2,93-2,42 (m, 4H), 2,31 (q, 1H), 2,03-0,80 (m, 29H).

Composto 84: MS: m/z 885,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,26 (s, 1H), 8,42 (d, 2H), 8,23 (d, 1H), 7,58 (m, 2H),
7,44 (dd, 1H), 7,22 (s, 1H), 7,01 (d, 2H), 6,17 (s, 1H),
5,67 (q, 1H), 5,16 (d, 1H), 4,98 (dd, 1H), 4,75 (dd, 1H),
4,62 (m, 2H), 4,38-4,08 (m, 2H), 2,80-2,42 (m, 3H), 2,32
(q, 1H), 1,96-1,20 (m, 21H), 1,13 (s, 9H), 0,81 (m, 3H).

Composto 85: MS: m/z 923,2 ($M^+ + 1$).

Composto 86: MS: m/z 883,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,41 (s, 1H), 8,19 (d, 1H), 8,06 (d, 1H), 7,95 (s, 1H),
7,61-7,41 (m, 4H), 6,92 (d, 1H), 6,12 (s, 1H), 6,04 (s,
2H), 5,67 (q, 1H), 5,35 (d, 1H), 4,97 (dd, 1H), 4,77 (dd,
1H), 4,58 (d, 1H), 4,36-4,11 (m, 2H), 2,85-2,43 (m, 3H),
2,27 (q, 1H), 1,98-1,21 (m, 24H), 0,81 (s, 3H).

Composto 87: MS: m/z 869,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,36 (s, 1H), 8,17 (d, 1H), 7,97 (d, 1H), 7,88 (s, 1H),
7,58-7,32 (m, 4H), 6,85 (d, 1H), 6,02 (s, 1H), 5,98 (s,
2H), 5,59 (q, 1H), 5,37 (d, 1H), 4,87 (d, 1H), 4,68 (dd,
1H), 4,52-4,02 (m, 3H), 2,90-2,38 (m, 4H), 2,23 (q, 1H),
1,91-0,88 (m, 24H).

Composto 88: MS: m/z 868,5 ($M^+ + 1$).

Composto 89: MS: m/z 882,5 ($M^+ + 1$).

Composto 90: MS: m/z 910,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,32 (s, 1H), 8,34 (d, 2H), 8,22 (d, 1H), 7,61-7,43 (m,

3H), 7,44 (dd, 1H), 6,76 (d, 2H), 6,14 (s, 1H), 5,62 (q, 1H), 5,39 (d, 1H), 4,96 (dd, 1H), 4,72 (dd, 1H), 4,63 (brs, 1H), 4,55 (d, 1H), 4,41-4,04 (m, 2H), 3,42 (q, 4H), 2,80-2,42 (m, 3H), 2,32 (q, 1H), 1,98-1,17 (m, 29H), 0,83 (s, 3H).

Composto 91: MS: m/z 896,3 (M^{+1}); ^1H NMR (CDCl_3) δ 10,46 (s, 1H), 8,33 (d, 2H), 8,21 (d, 1H), 7,62-7,43 (m, 3H), 7,43 (dd, 1H), 6,77 (d, 2H), 6,13 (s, 1H), 5,65 (q, 1H), 5,39 (d, 1H), 4,93 (dd, 1H), 4,73 (dd, 1H), 4,64 (brs, 1H), 4,53 (d, 1H), 4,43-4,05 (m, 2H), 3,43 (q, 4H), 2,94-2,42 (m, 4H), 2,29 (q, 1H), 2,14-0,83 (m, 29H).

Composto 92: MS: m/z 901,4, 903,4 (M^{+1}); ^1H NMR (CDCl_3) δ 10,40 (s, 1H), 8,36 (d, 2H), 8,23 (s, 1H), 7,58-7,26 (m, 5H), 6,15 (s, 1H), 5,65 (q, 1H), 5,19 (d, 1H), 4,96 (dd, 1H), 4,77 (dd, 1H), 4,62-4,52 (m, 2H), 4,33-4,08 (m, 2H), 3,01-2,42 (m, 5H), 2,25 (q, 1H), 1,96-0,89 (m, 29H).

Composto 93: MS: m/z 915,4, 917,4 (M^{+1}); ^1H NMR (CDCl_3) δ 10,27 (s, 1H), 8,38 (d, 2H), 8,22 (s, 1H), 7,59-7,34 (m, 5H), 6,13 (s, 1H), 5,70 (q, 1H), 5,29 (d, 1H), 4,98 (dd, 1H), 4,78 (dd, 1H), 4,62-4,55 (m, 2H), 4,35-4,08 (m, 2H), 3,04-2,96 (m, 1H), 2,80-2,43 (m, 3H), 2,25 (q, 1H), 1,97-1,20 (m, 29H), 0,81 (s, 3H).

Composto 94: MS: m/z 867,4 (M^{+1}).

Composto 95: MS: m/z 881,3 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,31 (s, 1H), 8,41 (d, 2H), 8,22 (d, 1H), 7,63-7,21 (m, 4H), 7,20 (d, 2H), 6,16 (s, 1H), 5,65 (q, 1H), 5,38 (d, 1H), 4,94 (dd, 1H), 4,80 (dd, 1H), 4,65-4,56 (m, 2H), 4,38-4,12 (m, 2H), 3,08-2,92 (m, 1H), 2,83-2,67 (m, 2H), 2,59-2,41 (m, 1H), 2,25 (q, 1H), 1,98-1,08 (m, 28H), 0,95-0,86 (m, 4H).

Composto 96: MS: m/z 881,4 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,47 (s, 1H), 8,40 (d, 2H), 8,23 (d, 1H), 7,76 (s, 1H), 7,62-7,41 (m, 5H), 6,13 (s, 1H), 5,65 (q, 1H), 5,33 (d, 1H), 5,03-4,87 (m, 2H), 4,78 (dd, 1H), 4,57 (d, 1H), 4,38-4,04 (m, 2H), 2,95-2,43 (m, 4H), 2,21 (q, 1H), 2,01-1,37 (m, 20H), 1,33 (s, 9H), 1,21-0,86 (m, 3H).

Composto 97: MS: m/z 895,4 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,30 (s, 1H), 8,40 (d, 2H), 8,23 (d, 1H), 7,59-7,43 (m, 5H), 6,98 (d, 1H), 6,16 (s, 1H), 5,65 (q, 1H), 5,41 (d, 1H), 4,98 (dd, 1H), 4,79 (q, 1H), 4,62-4,52 (m, 1H), 4,36-4,09 (m, 3H), 2,75 (brs, 2H), 2,59-2,56 (m, 1H), 2,28 (q, 1H), 1,91-1,18 (m, 31H), 0,89-0,78 (m, 4H).

Composto 98: MS: m/z 869,4 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,41 (s, 1H), 8,42 (d, 2H), 8,23 (d, 1H), 7,62-7,43 (m, 5H), 7,44 (dd, 1H), 6,17 (s, 1H), 5,64 (q, 1H), 5,17 (d, 1H), 4,97 (dd, 1H), 4,77-4,63 (m, 2H), 4,21-4,10 (m, 2H), 2,94-2,55 (m, 4H), 2,27 (q, 1H), 1,891,15 (m, 23H), 1,10 (s, 9H), 0,98-0,87 (m, 1H).

Composto 99: MS: m/z 925,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,28 (s, 1H), 8,37 (d, 2H), 8,03 (d, 1H), 7,50 (d, 2H),
7,48 (s, 1H), 7,01-6,92 (m, 2H), 6,13 (s, 1H), 5,65 (q,
1H), 5,39 (d, 1H), 4,98 (dd, 1H), 4,88 (dd, 1H), 4,64 (s,
1H), 4,53 (d, 1H), 4,41-4,23 (m, 1H), 4,19-4,11 (m, 1H),
3,88 (s, 3H), 2,78-2,42 (m, 3H), 2,26 (q, 1H), 2,04-1,18
(m, 31H), 0,89-0,78 (m, 4H).

Composto 100: MS: m/z 925,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,23 (s, 1H), 8,35 (d, 2H), 7,77 (d, 1H), 7,48 (d, 2H),
7,38-7,22 (m, 1H), 7,04-6,81 (m, 2H), 6,16 (s, 1H), 5,68
(q, 1H), 5,21 (d, 1H), 4,99 (dd, 1H), 4,78 (dd, 1H), 4,57
(d, 1H), 4,22-4,03 (m, 3H), 4,00 (s, 3H), 2,80-2,43 (m,
3H), 2,31 (q, 1H), 1,96-1,20 (m, 31H), 0,95-0,78 (m, 4H).

Composto 101: MS: m/z 827,3 ($M^+ + 1$).

Composto 102: MS: m/z 897,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,30 (s, 1H), 8,39 (d, 2H), 8,20 (d, 1H), 7,59-7,37 (m,
5H), 7,14 (s, 1H), 6,04 (s, 1H), 5,61 (q, 1H), 5,21 (d,
1H), 4,87 (dd, 1H), 4,77 (dd, 1H), 4,57 (d, 1H), 4,19-4,07
(m, 4H), 3,67-3,42 (m, 2H), 3,17-2,40 (m, 6H), 2,20 (q,
1H), 1,93-0,78 (m, 27H).

Composto 103: MS: m/z 866,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,45 (s, 1H), 8,31 (d, 2H), 8,12 (d, 1H), 7,51-7,42 (m,
5H), 7,32-7,25 (m, 1H), 6,09 (s, 1H), 5,61 (q, 1H), 4,90
(dd, 1H), 4,81 (dd, 1H), 4,59 (d, 1H), 4,50-4,36 (m, 2H),
4,13 (dd, 1H), 3,69-3,27 (m, 3H), 3,10 (brs, 4H), 2,90-2,41
(m, 4H), 2,19 (q, 1H), 1,98-0,78 (m, 25H).

Composto 104: MS: m/z 811,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,38 (s, 1H), 8,38 (d, 2H), 8,19 (d, 1H), 7,60-7,31 (m, 5H), 7,32-7,25 (m, 1H), 6,15 (s, 1H), 5,65 (q, 1H), 4,88 (dd, 1H), 4,70 (dd, 1H), 4,57 (dd, 1H), 4,40 (d, 1H), 4,21-4,05 (m, 2H), 2,95-2,41 (m, 4H), 2,22 (q, 1H), 2,01 (s, 3H), 1,98-0,79 (m, 24H).

Composto 105: MS: m/z 868,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,57 (s, 1H), 8,37 (d, 2H), 8,15 (d, 1H), 8,09 (s, 1H), 7,58-7,51 (m, 4H), 7,27 (dd, 1H), 6,09 (s, 1H), 5,61 (q, 1H), 4,98-4,79 (m, 4H), 4,44 (s, 1H), 4,10 (dd, 1H), 3,79-3,68 (m, 2H), 2,92-2,45 (m, 4H), 2,24 (q, 1H), 1,98-0,88 (m, 32H).

Composto 106: MS: m/z 882,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,37 (s, 1H), 8,35 (d, 2H), 8,16 (d, 1H), 7,56-7,48 (m, 2H), 7,42 (d, 2H), 7,36-7,33 (m, 1H), 7,30 (s, 1H), 6,09 (s, 1H), 5,63 (q, 1H), 4,97-4,86 (m, 2H), 4,76 (dd, 1H), 4,58 (d, 1H), 4,28-4,11 (m, 2H), 3,39-3,25 (m, 4H), 3,01-2,82 (m, 5H), 2,75-2,44 (m, 2H), 2,16 (q, 1H), 1,95-0,76 (m, 25H).

Composto 107: MS: m/z 863,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,34 (s, 1H), 8,33 (d, 2H), 8,32 (d, 1H), 7,59-7,40 (m, 6H), 7,37 (s, 1H), 6,81 (d, 1H), 6,65 (d, 1H), 6,25 (s, 1H), 6,13 (s, 1H), 5,62 (q, 1H), 4,87 (dd, 1H), 4,69-4,52 (m, 2H), 4,42 (d, 1H), 4,18 (dd, 1H), 2,95-2,40 (m, 4H), 2,24-0,78 (m, 25H).

Composto 108: MS: m/z 840,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,67 (s, 1H), 8,32 (d, 2H), 8,19 (d, 1H), 7,77 (s, 1H),
7,58-7,44 (m, 4H), 7,34-7,25 (m, 1H), 6,14 (s, 1H), 5,77
(q, 1H), 4,98 (dd, 1H), 4,78-4,71 (m, 2H), 4,44 (d, 1H),
4,29 (brs, 1H), 4,11-4,05 (m, 1H), 2,96-2,72 (m, 2H), 2,64
(s, 6H), 2,41 (br, 1H), 2,20 (q, 1H), 1,96-0,78 (m, 25H).

Composto 109: MS: m/z 837,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,49 (s, 1H), 8,35-8,25 (m, 3H), 7,71 (s, 1H), 7,55-7,41
(m, 4H), 7,26 (s, 1H), 6,19 (d, 1H), 6,01 (s, 1H), 5,63 (q,
1H), 4,88 (dd, 1H), 4,71 (brs, 1H), 4,56 (d, 1H), 4,39
(brs, 1H), 4,06 (d, 1H), 2,81-2,45 (m, 4H), 2,23 (q, 1H),
1,99-1,64 (m, 4H), 1,58-0,77 (m, 21H), 0,51 (brs, 4H).

Composto 110: MS: m/z 865,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,39 (s, 1H), 8,29 (d, 2H), 8,15 (d, 1H), 7,56-7,42 (m,
5H), 7,36-7,24 (m, 1H), 6,05 (s, 1H), 5,98 (d, 1H), 5,64
(q, 1H), 4,87 (dd, 1H), 4,69 (dd, 1H), 4,55 (d, 1H), 4,42
(dd, 1H), 4,04 (dd, 1H), 2,81-2,05 (m, 5H), 1,95-1,71 (m,
4H), 1,57-0,76 (m, 29H).

Composto 111: MS: m/z 881,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,29 (s, 1H), 8,33 (d, 2H), 8,30 (s, 1H), 7,58-7,41 (m,
4H), 7,39 (dd, 1H), 7,22 (s, 1H), 6,10 (s, 1H), 5,98 (d,
1H), 5,62 (q, 1H), 4,91 (dd, 1H), 4,68 (dd, 1H), 4,46-4,40
(m, 2H), 4,05 (dd, 1H), 3,79-3,62 (m, 2H), 3,21-3,09 (m,
2H), 2,88-2,40 (m, 3H), 2,22-1,72 (m, 6H), 1,47-0,78 (m,
25H).

Composto 112: MS: m/z 864,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,29 (s, 1H), 8,38 (d, 2H), 8,23 (d, 1H), 8,09 (s, 1H),
7,57-7,45 (m, 5H), 7,41 (dd, 1H), 7,28 (s, 1H), 6,42 (s,
1H), 6,15 (s, 1H), 5,62 (q, 1H), 4,86 (dd, 1H), 4,75-4,66
(m, 2H), 4,49 (d, 1H), 4,17 (dd, 1H), 2,83-2,43 (m, 3H),
2,25 (q, 1H), 1,99-0,78 (m, 25H).

Composto 113: MS: m/z 853,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,34 (s, 1H), 8,36 (d, 2H), 8,30 (d, 1H), 7,62-7,46 (m,
4H), 7,41-7,36 (m, 1H), 7,17 (s, 1H), 6,19 (s, 1H), 6,17
(d, 1H), 5,68 (q, 1H), 4,92 (dd, 1H), 4,73 (dd, 1H), 4,58-
4,43 (m, 2H), 4,19 (dd, 1H), 2,89-2,43 (m, 3H), 2,22 (q,
1H), 1,99-1,82 (m, 6H), 1,59-0,83 (m, 28H).

Composto 114: MS: m/z 907,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,30 (s, 1H), 8,39 (d, 2H), 8,21 (d, 1H), 7,56 (dd, 1H),
7,48 (d, 2H), 7,40 (dd, 1H), 7,24 (s, 1H), 7,18 (d, 2H),
7,03 (d, 2H), 6,92 (s, 1H), 6,06 (s, 1H), 5,74 (d, 1H),
5,61 (q, 1H), 4,87 (dd, 1H), 4,70 (dd, 1H), 4,42 (d, 1H),
4,31 (dd, 1H), 4,08 (dd, 1H), 2,84-2,79 (m, 1H), 2,65-2,43
(m, 2H), 2,23 (q, 1H), 1,88-1,62 (m, 6H), 1,49-0,78 (m,
19H).

Composto 115: MS: m/z 895,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,42 (s, 1H), 8,40 (d, 2H), 8,01 (s, 1H), 7,55 (d, 2H),
7,46-7,32 (m, 3H), 6,13 (s, 1H), 5,61 (q, 1H), 5,32 (brs,
1H), 5,01-4,87 (m, 1H), 4,89 (dd, 1H), 4,62-4,55 (m, 2H),

4,34-4,08 (m, 2H), 2,94-2,55 (m, 4H), 2,50 (s, 3H), 2,23 (q, 1H), 1,95-1,10 (m, 32H).

Composto 116: MS: m/z 909,4 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,29 (s, 1H), 8,40 (d, 2H), 8,01 (s, 1H), 7,55 (d, 2H),
7,47-7,26 (m, 3H), 6,14 (s, 1H), 5,69 (q, 1H), 5,37 (d,
1H), 4,99 (dd, 1H), 4,78 (dd, 1H), 4,60 (d, 1H), 4,40-4,05
(m, 3H), 2,80-2,51 (m, 3H), 2,50 (s, 3H), 2,29 (q, 1H),
1,98-1,12 (m, 32H), 0,82 (s, 3H).

Composto 117: MS: m/z 855,2 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,08 (s, 1H), 8,22 (d, 2H), 8,03 (d, 2H), 7,44-7,18 (m,
3H), 7,26-7,17 (m, 1H), 7,13 (d, 1H), 6,12 (s, 1H), 5,65
(q, 1H), 4,89 (dd, 1H), 4,77 (dd, 1H), 4,49 (d, 1H), 4,42-
4,36 (m, 1H), 4,13 (dd, 1H), 3,16 (s, 1H), 2,84-2,46 (m,
4H), 2,16 (q, 1H), 1,95-0,77 (m, 31H).

Composto 118: MS: m/z 895,4 (M^{+1}).

Composto 119: MS: m/z 895,4 (M^{+1}).

Composto 120: MS: m/z 840,2 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,26 (s, 1H), 8,38 (d, 2H), 8,20 (d, 1H), 8,00 (d, 1H),
7,61-7,54 (m, 2H), 7,50 (d, 2H), 7,41-7,35 (m, 1H), 7,15
(s, 1H), 6,72 (d, 1H), 6,10 (d, 1H), 5,63 (q, 1H), 5,27 (d,
1H), 4,89 (dd, 1H), 4,68 (dd, 1H), 4,51-4,42 (m, 2H), 4,12
(dd, 1H), 2,84-2,43 (m, 4H), 2,22 (q, 1H), 1,98-0,84 (m,
24H).

Composto 121: MS: m/z 829,3 ($M^+ + 1$).

Composto 122: MS: m/z 833,3 ($M^+ + 1$).

Composto 123: MS: m/z 821,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,27 (s, 1H), 7,90 (dd, 1H), 7,60 (s, 1H), 7,27 (dd, 1H), 7,32-7,20 (m, 2H), 6,91 (s, 1H), 6,53 (dd, 1H), 6,03 (s, 1H), 5,64 (q, 1H), 4,98-4,89 (m, 2H), 4,71-4,58 (m, 2H), 4,14-4,03 (m, 2H), 2,86-2,80 (m, 1H), 2,67-2,40 (m, 2H), 2,22 (q, 1H), 1,98-1,10 (m, 15H), 1,05 (s, 9H), 0,98-0,82 (m, 1H).

Composto 124: MS: m/z 779,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,31 (s, 1H), 7,93 (dd, 1H), 7,70 (s, 1H), 7,65-7,55 (dd, 1H), 7,41-7,26 (m, 2H), 7,04 (s, 1H), 6,61 (s, 1H), 6,15 (s, 1H), 5,72 (q, 1H), 5,37 (d, 1H), 5,01-4,91 (m, 1H), 4,77 (dd, 1H), 4,46 (d, 1H), 4,37-4,09 (m, 2H), 3,36 (s, 3H), 2,92-2,53 (m, 3H), 2,23 (q, 1H), 1,99-0,86 (m, 16H).

Composto 125: MS: m/z 817,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,28 (s, 1H), 7,98 (d, 1H), 7,66 (s, 1H), 7,60 (dd, 1H), 7,40-7,09 (m, 3H), 6,11 (s, 1H), 6,60 (s, 1H), 6,17 (s, 1H), 5,72 (q, 1H), 4,99 (dd, 1H), 4,76-4,67 (m, 2H), 4,31-4,18 (m, 2H), 2,91-2,75 (m, 2H), 2,45 (br, 1H), 2,22-0,84 (m, 17H).

Composto 126: MS: m/z 763,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,29 (s, 1H), 7,81 (dd, 1H), 7,60 (s, 1H), 7,52 (dd,

1H), 7,35-7,18 (m, 3H), 6,52 (d, 1H), 6,13-6,01 (m, 2H), 5,61 (q, 1H), 4,83 (dd, 1H), 4,62 (dd, 1H), 4,45 (dd, 1H), 4,38 (d, 1H), 4,17 (dd, 1H), 2,85-2,79 (m, 1H), 2,67 (d, 1H), 2,41 (m, 1H), 2,21-0,84 (m, 20H).

Composto 127: MS: m/z 821,3 (M^{+1}); ^1H NMR (CDCl_3) δ 10,37 (s, 1H), 8,15 (s, 1H), 7,79 (d, 1H), 7,45-7,42 (m, 3H), 7,35-7,25 (m, 1H), 7,01 (s, 1H), 5,89 (s, 1H), 5,54 (q, 1H), 5,19 (d, 1H), 4,85 (dd, 1H), 4,67 (dd, 1H), 4,54 (d, 1H), 4,20 (dd, 1H), 4,04 (d, 1H), 2,91-2,44 (m, 3H), 2,24 (q, 1H), 2,01-1,11 (m, 15H), 1,06 (s, 9H), 0,83-0,78 (m, 1H).

Composto 128: MS: m/z 833,3 (M^{+1}); ^1H NMR (CDCl_3) δ 10,37 (s, 1H), 8,07 (d, 1H), 7,56-7,22 (m, 5H), 6,89 (d, 1H), 5,96 (s, 1H), 5,57-5,49 (m, 1H), 5,21-5,17 (m, 1H), 4,96-4,83 (m, 1H), 4,72 (dd, 1H), 4,67 (d, 1H), 4,18-4,03 (m, 2H), 2,90-2,79 (m, 1H), 2,69 (s, 3H), 2,64-2,46 (m, 2H), 2,22 (q, 1H), 1,97-1,04 (m, 15H), 1,04 (s, 9H), 0,96-0,87 (m, 1H).

Composto 129: MS: m/z 836,3 (M^{+1}); ^1H NMR (CDCl_3) δ 10,29 (s, 1H), 7,88 (d, 1H), 7,53-7,50 (m, 1H), 7,49 (dd, 1H), 7,19 (s, 1H), 6,65 (s, 1H), 6,04 (s, 1H), 5,70-5,50 (m, 1H), 5,12-4,48 (m, 4H), 4,19-3,98 (m, 2H), 2,95-2,58 (m, 3H), 2,48 (s, 3H), 2,32-2,12 (m, 1H), 1,97-1,18 (m, 15H), 1,00 (s, 9H), 0,98-0,86 (m, 1H).

Composto 130: MS: m/z 832,2 (M^{+1}); ^1H NMR (CDCl_3)

δ 10,20 (s, 1H), 7,84 (dd, 1H), 7,52 (dd, 1H), 7,39 (, 1H), 7,38-7,26 (m, 2H), 6,62 (s, 1H), 6,05 (s, 1H), 5,60 (q, 1H), 4,83 (dd, 1H), 4,67 (dd, 1H), 4,55 (dd, 1H), 4,36 (d, 1H), 4,08 (dd, 1H), 2,81-2,50 (m, 3H), 2,48 (s, 3H), 2,45-2,37 (m, 1H), 2,18 (q, 1H), 1,99-0,87 (m, 15H).

Composto 131: MS: m/z 888,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,36 (s, 1H), 8,23 (d, 1H), 7,41 (s, 1H), 7,30 (m, 2H), 7,11 (s, 1H), 6,16 (s, 1H), 5,68 (q, 1H), 5,23 (d, 1H), 4,98 (dd, 1H), 4,75 (brs, 1H), 4,54 (d, 1H), 4,36-4,11 (m, 3H), 3,39-3,27 (m, 1H), 2,96-2,63 (m, 3H), 2,54 (s, 3H), 2,25 (q, 1H), 1,89-0,93 (m, 30H).

Composto 132: MS: m/z 888,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,24 (s, 1H), 8,37 (d, 1H), 7,74-7,51 (m, 2H), 7,48-7,42 (m, 1H), 7,22 (s, 1H), 7,12 (s, 1H), 6,17 (s, 1H), 5,70 (q, 1H), 5,28 (d, 1H), 4,99 (dd, 1H), 4,76 (dd, 1H), 4,58 (d, 1H), 4,52 (brs, 1H), 4,35-4,16 (m, 2H), 3,40-3,35 (m, 1H), 2,79-2,43 (m, 3H), 2,25 (q, 1H), 1,95-1,23 (m, 29H), 0,87-0,76 (m, 3H).

Composto 133: MS: m/z 887,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,37 (s, 1H), 8,59 (s, 1H), 8,22 (d, 1H), 7,81 (d, 1H), 7,58-7,42 (m, 3H), 6,95-6,89 (m, 2H), 6,09 (s, 1H), 5,68 (q, 1H), 5,32 (d, 1H), 4,99 (m, 1H), 4,74 (m, 1H), 4,54 (d, 1H), 4,39-4,22 (m, 1H), 4,14-4,11 (m, 1H), 2,90 (m, 1H), 2,78 (m, 2H), 2,55 (m, 1H), 2,27 (q, 1H), 1,90-1,10 (m, 21H), 1,45 (s, 9H), 0,94-0,83 (m, 2H).

Composto 134: MS: m/z 901,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,21 (s, 1H), 8,8,51 (s, 1H), 8,23 (d, 1H), 7,81 (d, 1H), 7,59-7,43 (m, 3H), 7,13 (s, 1H), 6,90 (d, 1H), 6,09 (s, 1H), 5,68 (q, 1H), 5,22 (d, 1H), 4,99 (dd, 1H), 4,76 (m, 1H), 4,55 (d, 1H), 4,39-4,22 (m, 1H), 4,14-4,11 (m, 1H), 2,78 (m, 2H), 2,55 (m, 1H), 2,27 (q, 1H), 1,90-0,83 (m, 23H), 1,46 (s, 9H).

Composto 135: MS: m/z 888,3 (M^{+1}).

Composto 136: MS: m/z 902,3 (M^{+1}).

Composto 137: MS: m/z 899,4 (M^{+1}).

Composto 138: MS: m/z 885,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,36 (s, 1H), 8,17 (d, 1H), 7,58 (m, 2H), 7,42-7,33 (m, 2H), 6,63 (m, 1H), 6,07 (s, 1H), 5,67 (q, 1H), 5,29 (d, 1H), 4,97 (dd, 1H), 4,77 (m, 1H), 4,57 (m, 1H), 4,42-4,03 (m, 3H), 2,89 (m, 1H), 2,75 (m, 5H), 2,52 (m, 1H), 2,27 (q, 1H), 1,91-0,82 (m, 32H).

Composto 139: MS: m/z 803,3 (M^{+1}).

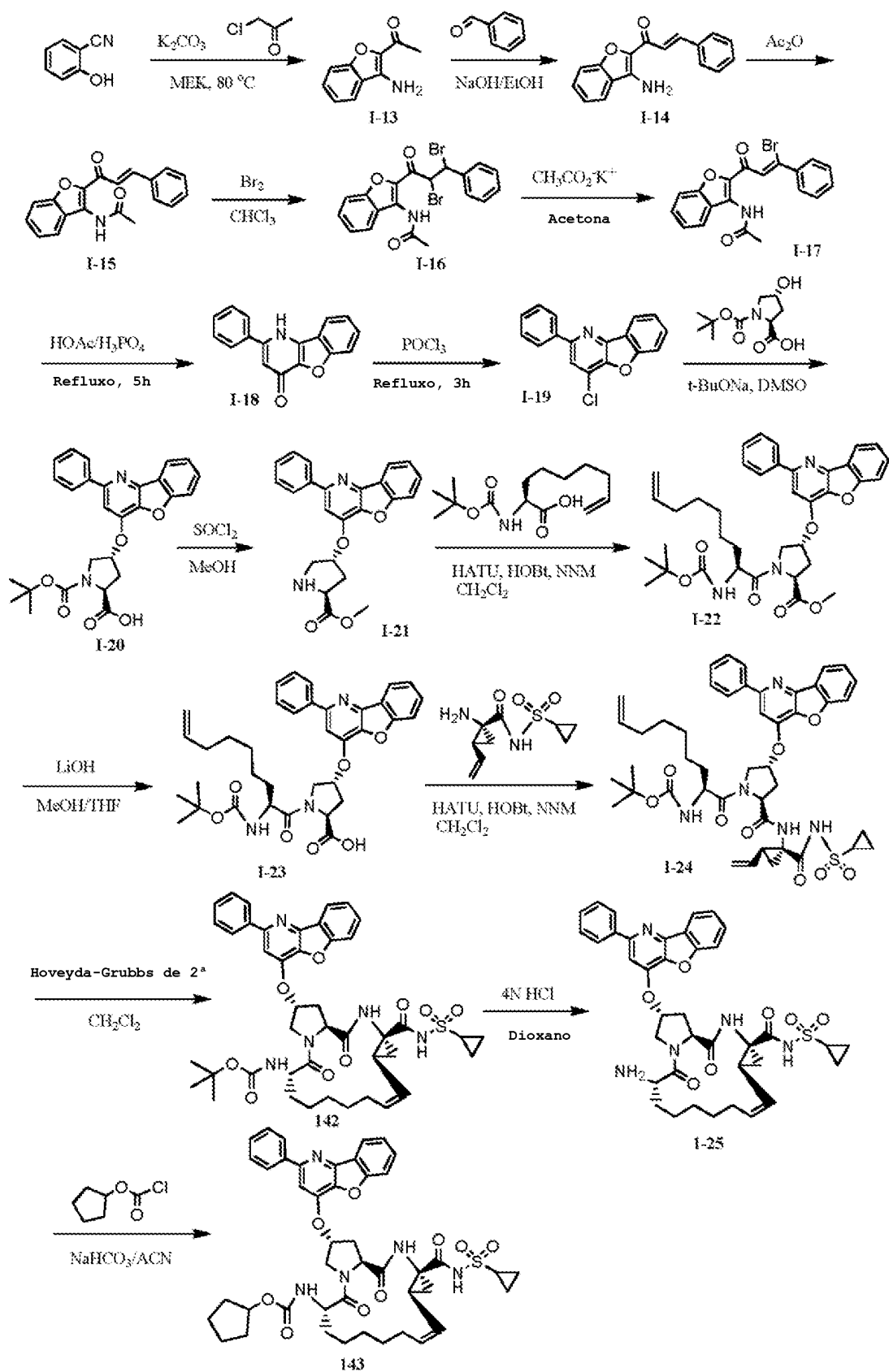
Composto 140: MS: m/z 817,3 (M^{+1}).

Composto 141: MS: m/z 831,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,33 (s, 1H), 8,05 (s, 1H), 7,56-7,48 (m, 3H), 6,06 (s, 1H), 5,62 (q, 1H), 5,15 (dd, 1H), 4,91 (dd, 1H), 4,75 (dd, 1H), 4,59 (d, 1H), 4,35-4,02 (m, 3H), 2,96-2,88 (m, 1H),

2,74-2,65 (m, 2H), 2,53 (s, 3H), 2,24 (q, 1H), 1,96-0,89 (m, 24H).

Exemplos 142 e 143: Síntese de Éster terc-butílico do ácido [4-ciclopropano-sulfonilaminocarbonil-2,15-dioxo-18-(2-fenil-benzo[4,5]furo[3,2-b]piridin-4-iloxi)-3,16-diaza-triciclo[14.3.0.04,6]nonadec-7-en-14-il]-carbâmico (Composto 142) e Éster ciclopentílico do ácido [4-ciclopropano-sulfonilaminocarbonil-2,15-dioxo-18-(2-fenil-benzo[4,5]furo[3,2-b]piridin-4-iloxi)-3,16-diaza-triciclo[14.3.0.04,6]nonadec-7-en-14-il]-carbâmico (Composto 143)

Os compostos 142 e 143 foram preparados através da via ilustrada abaixo:



A uma solução de 2-hidroxi-benzonitrilo (30 g, 251,6 mmol) em etil metil cetona (320 mL) adicionou-se carbonato de potássio (69,6 g, 755,5 mmol). Após se ter agitado à temperatura ambiente durante 30 min, adicionou-se cloroacetona (34,95 g, 377,8 mmol) à mistura resultante e, em seguida, aqueceu-se a solução a 100 °C durante a noite. Finalmente, removeu-se o solvente da reação sob pressão reduzida e lavou-se o sólido resultante com água e éter etílico para dar o I-13 (31 g, rendimento de 70,3%) MS: m/z 176,0 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 7,59 (d, 1H), 7,46 (dd, 1H), 7,41 (d, 1H), 7,24 (dd, 1H), 2,50 (s, 3H).

A uma solução de 2-acetil-3-aminobenzofurano I-13 (2,17 g, 12,38 mmol) e benzaldeído (1,31 g, 12,38 mmol) em etanol (30 mL) a 5~10 °C adicionou-se, gota a gota, uma solução aquosa de hidróxido de sódio (70%, 5 mL) sob agitação constante. Após se ter agitado durante a noite, suspendeu-se um sólido amarelo brilhante do produto bruto na solução reacional. O sólido foi filtrado, recolhido e re-cristalizado a partir de etanol para proporcionar umas agulhas sedosas de I-14 (2,7 g, 90%). MS: m/z 264,0 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 7,83 (d, 1H), 7,71 (dd, 2H), 7,64 (d, 1H), 7,62 (d, 1H), 7,58-7,39 (m, 5H), 7,29-7,24 (m, 1H), 5,83 (largo, 2H).

O intermediário I-14 (1,32 g, 5,0 mmol) foi suspenso em anidrido acético (10 ml) e agitado num banho de água aquecido. Após ter sido agitada durante a noite, a

mistura reaccional foi vertida sobre água gelada. O produto bruto suspenso foi separado e recolhido, e em seguida re-cristalizado a partir de etanol para dar o I-15 (1,52 g, 90%). MS: m/z 306,0 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 8,58 (d, 1H), 7,91 (d, 1H), 7,72 (m, 3H), 7,54-7,44 (m, 5H), 7,34-7,7,28 (m, 1H), 2,35 (s, 3H).

Adicionou-se, gota a gota e lentamente, uma solução do intermediário I-15 (1,22 g, 4,0 mmol) em CHCl_3 (20 ml) a uma solução de bromo (0,72 g 4,5 mmol) em CHCl_3 (15 mL). Depois de agitada durante a noite, a mistura reacional foi temperada com água gelada. O sólido suspenso foi separado, recolhido e re-cristalizado a partir de etanol/ H_2O para proporcionar I-16 (1,12 g, 60%). MS: m/z 465,9 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,22 (brs, 1H), 8,63 (d, 1H), 7,61-7,25 (m, 8H), 5,92 (d, 1H), 5,62 (d, 1H), 2,37 (s, 3H).

A uma solução de I-16 (0,93 g, 2,0 mmol) em acetona (25 ml) adicionou-se acetato de potássio anidro (0,2 g, 2,0 mmol). Depois de agitada durante a noite, a mistura reaccional foi vertida em água fria. O sólido suspenso foi separado, recolhido e re-cristalizado a partir de etanol para dar monobrometo do composto I-17 (0,46 g, 60%). MS: m/z 385,9 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,50 (brs, 1H), 8,54 (d, 1H), 8,48 (s, 1H), 7,93 (m, 2H), 7,56-7,46 (m, 5H), 7,36-7,31 (m, LH), 2,35 (s, 3H).

Colocou-se sob refluxo composto I-17 (0,35 g, 1,0

mmol) em ácido acético (5 mL) e ácido ortofosfórico (5 mL) durante 5 h. A mistura reacional foi arrefecida até à temperatura ambiente, vertida em água gelada e agitada durante mais 30 min. Um sólido suspenso foi separado, recolhido e re-cristalizado a partir de DMF para dar o I-18 (0,2 g, 80%). MS: m/z 262,0 (M^+1).

Colocou-se sob refluxo uma solução de I-18 (1,0 g, 3,8 mmol) e oxicloreto de fósforo (POCl_3) (10 mL) durante 2 horas. Depois da solução ter sido arrefecida e cuidadosamente concentrada, o resíduo resultante foi temperado com hidróxido de sódio a 10% e extraído com cloreto de metileno (20 ml \times 3). A camada orgânica foi recolhida, seca sobre sulfato de sódio, e concentrada. O produto bruto foi recristalizado a partir de CH_2Cl_2 e *n*-hexano para proporcionar I-19 (0,7 g, 75%). MS: m/z 279,9 (M^+1); ^1H NMR (CDCl_3) δ 8,45 (d, 1H), 8,09 (d, 2H), 7,84 (s, 1H), 7,71-7,64 (m, 2H), 7,56-7,47 (m, 4H).

A uma suspensão de Boc-trans-4-hidroxi-L-prolina (0,53 g, 2,3 mmol) em DMSO (10 mL) adicionou-se *t*-BuONa (0,49 g, 5,08 mmol) a 0 °C. Depois de se aquecer até à temperatura ambiente e agitar-se durante 1 h, adicionou-se lentamente o intermediário I-19 (0,64 g, 2,3 mmol) a 10 °C. A mistura reacional foi agitada durante 4 h e depois temperada com solução aquosa de HCl a 10% até pH de 6~7. O sólido bruto foi filtrado, lavado com água e seco sob vácuo para dar o I-20 (0,94 g, 86,3%). MS: m/z 475,1 (M^+1); ^1H NMR (CDCl_3) δ 8,27 (d, 1H), 7,97 (m, 2H), 7,86-7,76 (m,

3H), 7,66-7,44 (m, 4H), 5,81 (s, 1H), 4,47 (m, 1H), 4,03-3,89 (m, 2H), 2,81 (m, 1H), 2,50 (q, 1H).

A uma solução de I-20 (1,1 g, 2,3 mmol) em MeOH (20 mL) adicionou-se SOCl_2 (1,17 g, 9,9 mmol) à temperatura ambiente. Depois de se submeter a refluxo durante 1 hora, o solvente da reação foi removido sob vácuo para dar o composto bruto I-21, o qual foi utilizado no passo seguinte sem purificação adicional. MS: m/z 389,1 (M^+1).

A uma solução de I-21 (0,78 g, 2,0 mmol), 2-(1H-hexafluoro-fosfato de 7-azabenzotriazol-1-il)-1,1,3,3-tetrametilurônio metanamínio (HATU, 1,12 g, 3,0 mmol), N-Hidroxibenzotriazol (HOBT, 0,4 g, 3,0 mmol), e ácido 2-terc-butoxicarbonilamino-non 8-enóico (1,19 g, 5,2 mmol) em CH_2Cl_2 (20 mL) adicionou-se NMM (1,0 g, 9,9 mmol) à temperatura ambiente. Após a mistura ter sido agitada durante a noite, foi concentrada sob vácuo. O resíduo foi purificado por cromatografia em coluna de sílica gel para dar o composto I-22 (1,02 g, 80,7%). MS: m/z 642,3 (M^+1); ^1H NMR (CDCl_3) δ 8,24 (d, 1H), 8,05 (d, 2H), 7,58 (m, 2H), 7,56-7,41 (m, 4H), 7,28 (d, 1H), 5,83-5,76 (q, 1H), 5,71 (s, 1H), 5,24 (d, 1H), 5,01-4,82 (m, 2H), 4,76 (dd, 1H), 4,75-4,34 (m, 2H), 4,03 (m, 1H), 3,77 (s, 3H), 2,78 (m, 1H), 2,36 (q, 1H), 2,01 (m, 2H), 1,75 (m, 1H), 1,54 (m, 1H), 1,42 (m, 6H), 1,31 (s, 9H).

A uma solução de I-22 (1,0 g, 1,6 mmol) em THF (20 mL) adicionou-se LiOH 0,5 M (5,7 mL, 2,9 mmol) à

temperatura ambiente. Após a mistura reacional ter sido agitada durante a noite, foi acidificada por HCl a 10% até pH <7 e concentrada sob vácuo para dar um produto sólido, o qual foi filtrado e lavado com água para dar o I-23. MS: m/z 628,1 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 8,34 (brs, 1H), 8,04 (d, 2H), 7,62 (m, 2H), 7,60-7,41 (m, 4H), 7,28 (m, 2H), 5,81-5,72 (q, 1H), 5,70 (s, 1H), 5,29 (d, 1H), 5,00-4,87 (m, 3H), 4,48 (m, 2H), 4,01 (m, 1H), 2,77 (m, 2H), 1,98 (m, 2H), 1,72 (m, 1H), 1,61 (m, 1H), 1,44 (m, 6H), 1,33 (s, 9H).

Adicionou-se NMM (0,12 g, 1,2 mmol) a uma solução de composto I-23 (0,26 g, 0,41 mmol), HATU (0,31 g, 0,81 mmol), HOBT (0,084 g, 0,61 mmol), e ácido ciclopropano-sulfônico (1-amino-2-vinil-ciclopropanocarbonil)-amida (0,094 g, 0,41 mmol) em CH_2Cl_2 (10 mL) à temperatura ambiente. Após a mistura reacional ter sido agitada durante a noite, foi concentrada sob vácuo. O resíduo foi purificado por cromatografia em coluna de sílica gel para dar o composto I-24 (0,15 g, 45%). MS: m/z 804,3 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,22 (s, 1H), 8,35 (d, 1H), 8,01 (d, 2H), 7,59 (d, 2H), 7,48-7,30 (m, 5H), 7,04 (s, 1H), 5,78 (m, 3H), 5,35 (d, 1H), 5,23 (d, 1H), 5,15 (d, 1H), 4,93 (m, 2H), 4,53 (dd, 1H), 4,41-4,30 (m, 2H), 4,05 (m, 1H), 2,91 (m, 1H), 2,61 (m, 2H), 2,14 (dd, 1H), 2,04 (m, 3H), 1,91-1,52 (m, 3H), 1,45-1,22 (18H), 1,21 (m, 2H).

A uma solução de composto I-24 (100 mg, 0,12 mmol) em CH_2Cl_2 adicionou-se catalisador de Hoveyda-Grubbs

de 2ª geração (35 mg, 0,056 mmol) sob N₂ à temperatura ambiente, e em seguida a mistura reaccional foi aquecida a 40 °C e agitada durante 24 horas. A mistura reaccional foi concentrada e purificada por coluna para dar o composto 142 (30 mg, 31%). MS: m/z 812,3 (M⁺+1); ¹H NMR (CDCl₃) δ 10,29 (s, 1H), 8,28 (d, 1H), 8,04 (d, 2H), 7,61-7,41 (m, 7H), 7,00 (s, 1H), 5,69 (m, 2H), 5,19 (d, 1H), 4,97 (dd, 1H), 4,67 (m, 2H), 4,31 (m, 1H), 4,05 (m, 1H), 2,89 (m, 1H), 2,70 (m, 2H), 2,55 (m, 1H), 2,29 (q, 1H), 1,89-1,11 (m, 13H), 1,19 (s, 9H), 0,97-0,86 (m, 2H).

A uma solução de composto 142 (0,1 g, 0,14 mmol) em CH₂Cl₂ (5 mL) adicionou-se uma quantidade em excesso de solução 4 N de HCl em dioxano (2 mL) à temperatura ambiente. Depois de se agitar durante 4 horas, removeu-se HCl, dioxano e CH₂Cl₂ por evaporação para dar o composto bruto I-25, o qual foi utilizado no passo seguinte sem purificação adicional. MS: m/z 712,3 (M⁺+1).

Dissolveu-se I-25 em acetonitrilo (2 mL) e depois adicionou-se NaHCO₃ saturado (1 mL). Agitou-se a mistura reaccional durante 10 min. Adicionou-se cloroformato de ciclopentilo (0,02 g, 0,15 mmol) à mistura reaccional à temperatura ambiente. Após ter sido agitada durante 2 horas adicionais, a mistura reaccional foi temperada por NaHCO₃ saturado e extraída com CH₂Cl₂. O resíduo foi purificado por cromatografia em coluna de sílica gel para dar o composto 143 (0,1 g, 87%). MS: m/z 824,3 (M⁺+1); ¹H NMR (CDCl₃) δ 10,26 (s, 1H), 8,29 (d, 1H), 8,07 (d, 2H), 7,62-

7,32 (m, 7H), 7,00 (s, 1H), 5,75 (s, 1H), 5,70 (q, 1H), 5,22 (d, 1H), 4,99 (dd, 1H), 4,75 (m, 2H), 4,56 (d, 1H), 4,32 (m, 1H), 4,05 (m, 1H), 2,89 (m, 1H), 2,70 (m, 2H), 2,52 (m, 1H), 2,29 (q, 1H), 1,91-0,85 (m, 23H).

Exemplos 144-253: Sínteses dos Compostos 144-253

Cada um dos Compostos 144-253 foi preparado de um modo semelhante ao descrito nos Exemplos 142 e 143.

Composto 144: MS: m/z 7887,3 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,36 (s, 1H), 8,40 (s, 1H), 8,21 (d, 1H), 8,08 (dd, 1H), 7,56-7,11 (m, 7H), 6,80 (s, 1H), 5,63 (m, 2H), 4,93 (m, 1H), 4,79 (m, 1H), 4,31 (m, 2H), 4,05 (m, 1H), 3,45 (s, 3H), 2,87 (m, 1H), 2,70 (m, 2H), 2,52 (m, 1H), 2,25 (q, 1H), 1,91-0,84 (m, 15H).

Composto 145: MS: m/z 872,3 ($M^+ + 1$).

Composto 146: MS: m/z 770,3 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,35 (s, 1H), 8,25 (d, 1H), 8,00 (d, 2H), 7,56-7,25 (m, 7H), 6,66 (s, 1H), 5,69 (m, 2H), 5,45 (d, 1H), 4,95 (dd, 1H), 4,70 (m, 1H), 4,40-4,28 (m, 2H), 4,05 (m, 1H), 3,52 (s, 3H), 2,88 (m, 1H), 2,70 (m, 2H), 2,51 (m, 1H), 2,30 (q, 1H), 1,87-1,09 (m, 13H), 0,97-0,84 (m, 2H).

Composto 147: MS: m/z 697,2 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,37 (s, 1H), 8,24 (d, 1H), 8,04 (d, 2H), 7,56-7,31 (m, 8H), 5,63 (m, 2H), 4,97 (dd, 1H), 4,63 (m, 1H), 4,09 (m,

1H), 3,96 (m, 1H), 2,84 (m, 1H), 2,62 (m, 2H), 2,6-2,03 (m, 4H), 1,95-0,84 (m, 15H).

Composto 148: MS: m/z 872,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,29 (s, 1H), 8,09 (dd, 1H), 7,69 (d, 1H), 7,48-7,14 (m, 7H), 5,71 (m, 2H), 5,31 (d, 1H), 4,98 (dd, 1H), 4,74 (m, 1H), 4,55 (d, 1H), 4,36 (m, 1H), 4,05 (m, 2H), 3,96 (s, 3H), 2,89 (m, 1H), 2,68 (m, 2H), 2,52 (m, 1H), 2,28 (q, 1H), 2,00-0,88 (m, 23H).

Composto 149: MS: m/z 818,2 (M^{+1}).

Composto 150: MS: m/z 802,2 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,23 (s, 1H), 8,08 (dd, 1H), 7,68 (d, 1H), 7,49 (d, 1H), 7,39-7,13 (m, 6H), 6,10 (d, 1H), 5,72 (m, 2H), 4,95 (dd, 1H), 4,63 (m, 2H), 4,17 (d, 1H), 4,06 (m, 1H), 3,92 (s, 3H), 2,89 (m, 1H), 2,69 (m, 2H), 2,46 (m, 1H), 2,26 (q, 1H), 1,94-0,86 (m, 15H), 1,91 (s, 3H).

Composto 151: MS: m/z 854,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,26 (s, 1H), 8,27 (d, 1H), 8,03 (d, 2H), 7,59 (m, 3H), 7,45 (dd, 1H), 7,01 (d, 2H), 6,88 (m, 1H), 5,74 (m, 2H), 5,19 (d, 1H), 4,96 (m, 2H), 4,75 (s, 1H), 4,53 (d, 1H), 4,32 (m, 1H), 4,04 (m, 1H), 3,87 (s, 3H), 2,89 (m, 1H), 2,69 (m, 2H), 2,46 (m, 1H), 2,27 (q, 1H), 1,90-1,12 (m, 21H), 0,92-0,87 (m, 2H).

Composto 152: MS: m/z 842,3 (M^{+1}).

Composto 153: MS: m/z 854,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,31 (s, 1H), 8,58 (s, 1H), 8,43 (m, 1H), 7,85 (d, 1H),
7,59 (m, 2H), 7,37 (m, 3H), 7,12 (dd, 1H), 7,01 (d, 1H),
5,65 (m, 2H), 5,31 (d, 1H), 4,94 (dd, 1H), 4,72 (m, 2H),
4,53 (d, 1H), 4,37 (m, 1H), 4,07 (m, 1H), 3,87 (s, 3H),
2,88 (m, 1H), 2,66 (m, 2H), 2,50 (m, 1H), 2,28 (q, 1H),
1,88-0,82 (m, 23H).

Composto 154: MS: m/z 854,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,29 (s, 1H), 8,50 (s, 1H), 8,29 (d, 1H), 7,63 (s, 1H),
7,56 (m, 3H), 7,43 (m, 2H), 7,28 (m, 1H), 7,11 (s, 1H),
6,98 (dd, 1H), 5,74 (s, 1H), 5,69 (q, 1H), 5,29 (d, 1H),
4,94 (dd, 1H), 4,73 (m, 1H), 4,57 (d, 1H), 4,34 (m, 1H),
4,04 (m, 1H), 3,92 (s, 3H), 2,88 (m, 1H), 2,68 (m, 2H),
2,51 (m, 1H), 2,29 (q, 1H), 1,87-0,84 (m, 23H).

Composto 155: MS: m/z 842,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,28 (s, 1H), 8,28 (d, 1H), 7,85 (d, 1H), 7,57 (m, 2H),
7,40 (m, 3H), 7,14 (dd, 1H), 7,01 (d, 2H), 5,68 (q, 1H),
5,58 (s, 1H), 5,19 (d, 1H), 4,92 (dd, 1H), 4,67 (m, 2H),
4,33 (m, 1H), 4,03 (m, 1H), 3,87 (s, 3H), 2,89 (m, 1H),
2,68 (m, 2H), 2,54 (m, 1H), 2,28 (q, 1H), 1,90-1,11 (m,
13H), 1,21 (s, 9H), 0,97-0,87 (m, 2H).

Composto 156: MS: m/z 854,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,24 (s, 1H), 8,59 (s, 1H), 8,04 (m, 2H), 7,84 (d, 1H),
7,49-7,28 (m, 4H), 7,08 (d, 1H), 6,91 (s, 1H), 5,72 (s,
1H), 5,68 (q, 1H), 5,21 (d, 1H), 4,97 (dd, 1H), 4,71-4,67
(m, 2H), 4,56 (d, 1H), 4,36 (m, 1H), 4,05 (s, 3H), 4,04 (m,

1H), 2,90 (m, 1H), 2,69 (m, 2H), 2,54 (m, 1H), 2,31 (q, 1H), 1,96-1,06 (m, 21H), 0,95-0,83 (m, 2H).

Composto 157: MS: m/z 838,3 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,30 (s, 1H), 8,59 (s, 1H), 8,27 (d, 1H), 7,92 (d, 2H),
7,57 (m, 2H), 7,44 (m, 1H), 7,26-7,17 (m, 3H), 5,68 (s,
1H), 5,64 (q, 1H), 5,37 (d, 1H), 4,96 (m, 1H), 4,76 (m,
1H), 4,67 (m, 1H), 4,56 (d, 1H), 4,36 (m, 1H), 4,04 (m,
1H), 2,89 (m, 1H), 2,69 (m, 2H), 2,53 (m, 1H), 2,40 (s,
3H), 2,31 (q, 1H), 1,94-1,07 (m, 21H), 0,95-0,83 (m, 2H).

Composto 158: MS: m/z 842,3 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,31 (s, 1H), 8,26 (d, 1H), 8,05 (m, 2H), 7,58 (m, 2H),
7,43 (m, 1H), 7,25-7,19 (m, 4H), 5,72 (s, 1H), 5,68 (q,
1H), 5,35 (d, 1H), 4,96 (dd, 1H), 4,75-4,69 (m, 2H), 4,56
(d, 1H), 4,36 (m, 1H), 4,04 (m, 1H), 2,87 (m, 1H), 2,67 (m,
2H), 2,50 (m, 1H), 2,28 (q, 1H), 1,91-1,07 (m, 21H), 0,97-
0,84 (m, 2H).

Composto 159: MS: m/z 872,3 (M⁺+1).

Composto 160: MS: m/z 872,1 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,48 (s, 1H), 8,02 (m, 2H), 7,68 (d, 1H), 7,47 (d, 1H),
7,23-7,17 (m, 4H), 5,74 (m, 2H), 5,68 (q, 1H), 5,23 (d,
1H), 4,97 (dd, 1H), 4,76 (s, 1H), 4,67 (m, 1H), 4,54 (d,
1H), 4,33 (m, 1H), 4,04 (m, 1H), 3,93 (s, 3H), 2,89 (m,
1H), 2,67 (m, 2H), 2,52 (m, 1H), 2,27 (q, 1H), 1,92-1,06
(m, 21H), 0,97-0,84 (m, 2H).

Composto 161: MS: m/z 860,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,34 (s, 1H), 8,01 (m, 2H), 7,67 (d, 1H), 7,47 (d, 1H),
7,29-7,16 (m, 5H), 5,68 (m, 2H), 5,23 (d, 1H), 4,95 (dd,
1H), 4,69-4,63 (m, 2H), 4,31 (m, 1H), 4,04 (m, 1H), 3,92
(s, 3H), 2,88 (m, 1H), 2,67 (m, 2H), 2,54 (m, 1H), 2,27 (q,
1H), 1,92-0,83 (m, 15H), 1,20 (s, 9H).

Composto 162: MS: m/z 856,1 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,23 (s, 1H), 8,03 (m, 2H), 7,66 (d, 1H), 7,48 (d, 1H),
7,32 (s, 1H), 7,29-7,15 (m, 5H), 5,73 (m, 2H), 4,92 (dd,
1H), 4,69 (m, 2H), 4,31 (d, 1H), 4,06 (m, 1H), 3,91 (s,
3H), 2,85 (m, 1H), 2,68 (m, 2H), 2,44 (m, 1H), 2,20 (q,
1H), 1,93-0,83 (m, 15H).

Composto 163: MS: m/z 854,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,30 (s, 1H), 8,60 (s, 1H), 8,01 (m, 2H), 7,68 (d, 1H),
7,46 (m, 4H), 7,15 (m, 2H), 5,71 (s, 1H), 5,68 (q, 1H),
5,37 (d, 1H), 4,96 (dd, 1H), 4,67 (s, 1H), 4,64 (m, 1H),
4,55 (d, 1H), 4,36 (m, 1H), 4,03 (m, 1H), 3,93 (s, 3H),
2,88 (m, 1H), 2,68 (m, 2H), 2,52 (m, 1H), 2,28 (q, 1H),
1,94-1,07 (m, 21H), 0,97-0,84 (m, 2H).

Composto 164: MS: m/z 830,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,33 (s, 1H), 8,25 (d, 1H), 8,04 (m, 2H), 7,57 (m, 2H),
7,42 (m, 1H), 7,25-7,14 (m, 4H), 5,68 (m, 2H), 5,25 (d,
1H), 4,92 (dd, 1H), 4,66 (m, 2H), 4,32 (m, 1H), 4,05 (m,
1H), 2,87 (m, 1H), 2,68 (m, 2H), 2,55 (m, 1H), 2,28 (q,
1H), 1,91-1,06 (m, 13H), 1,20 (s, 9H), 0,97-0,84 (m, 2H).

Composto 165: MS: m/z 868,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,29 (s, 1H), 8,53 (s, 1H), 8,13 (d, 1H), 7,91 (m, 2H),
7,58 (m, 1H), 7,19 (m, 1H), 7,00 (m, 3H), 5,72 (s, 1H),
5,68 (q, 1H), 5,28 (d, 1H), 4,95 (dd, 1H), 4,79 (s, 1H),
4,68 (m, 1H), 4,53 (d, 1H), 4,37 (m, 1H), 4,05 (m, 1H),
3,91 (s, 3H), 2,88 (m, 1H), 2,66 (m, 2H), 2,50 (m, 1H),
2,40 (s, 3H), 2,25 (q, 1H), 1,90-1,06 (m, 21H), 0,97-0,83
(m, 2H).

Composto 166: MS: m/z 868,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,30 (s, 1H), 8,59 (s, 1H), 7,98 (m, 2H), 7,71 (s, 1H),
7,46 (d, 1H), 7,27 (m, 2H), 7,15 (m, 2H), 5,71 (s, 1H),
5,68 (q, 1H), 5,29 (d, 1H), 4,94 (dd, 1H), 4,78 (s, 1H),
4,67 (m, 1H), 4,54 (d, 1H), 4,36 (m, 1H), 4,04 (m, 1H),
3,93 (s, 3H), 2,88 (m, 1H), 2,68 (m, 2H), 2,53 (m, 1H),
2,40 (s, 3H), 2,28 (q, 1H), 1,92-1,08 (m, 21H), 0,97-0,83
(m, 2H).

Composto 167: MS: m/z 872,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,29 (s, 1H), 8,51 (s, 1H), 8,08 (d, 1H), 8,01 (m, 2H),
7,15 (d, 2H), 7,04 (m, 3H), 5,73 (s, 1H), 5,69 (q, 1H),
5,30 (d, 1H), 4,95 (dd, 1H), 4,79 (s, 1H), 4,65 (m, 1H),
4,53 (d, 1H), 4,37 (m, 1H), 4,04 (m, 1H), 3,91 (s, 3H),
2,88 (m, 1H), 2,66 (m, 2H), 2,50 (m, 1H), 2,28 (q, 1H),
1,90-1,05 (m, 21H), 0,97-0,83 (m, 2H).

Composto 168: MS: m/z 826,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,23 (s, 1H), 8,28 (d, 1H), 7,94 (d, 2H), 7,56 (m, 2H),
7,42 (m, 1H), 7,28 (m, 3H), 7,03 (s, 1H), 5,68 (m, 2H),

5,21 (d, 1H), 4,94 (dd, 1H), 4,67 (m, 2H), 4,32 (m, 1H), 4,05 (m, 1H), 2,89 (m, 1H), 2,68 (m, 2H), 2,55 (m, 1H), 2,55 (s, 3H), 2,35 (q, 1H), 1,94-1,07 (m, 13H), 1,20 (s, 9H), 0,97-0,84 (m, 2H).

Composto 169: MS: m/z 858,3, 859,3 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,35 (s, 1H), 8,58 (s, 1H), 8,24 (d, 1H), 8,00 (d, 2H), 7,57 (m, 2H), 7,45 (m, 3H), 7,25 (s, 1H), 5,71 (s, 1H), 5,66 (q, 1H), 5,41 (d, 1H), 4,96 (dd, 1H), 4,75 (m, 2H), 4,55 (d, 1H), 4,35 (m, 1H), 4,04 (m, 1H), 2,87 (m, 1H), 2,69 (m, 2H), 2,57 (m, 1H), 2,28 (q, 1H), 1,92-0,83 (m, 23H).

Composto 170: MS: m/z 772,2 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,31 (s, 1H), 8,22 (d, 1H), 8,00 (m, 2H), 7,59 (m, 2H), 7,41 (m, 1H), 7,20-7,10 (m, 4H), 6,12 (d, 1H), 5,72 (m, 2H), 4,96 (dd, 1H), 4,64 (m, 1H), 4,55 (m, 1H), 4,40 (d, 1H), 4,01 (m, 1H), 2,88 (m, 1H), 2,66 (m, 2H), 2,50 (m, 1H), 2,26 (q, 1H), 1,92-1,05 (m, 13H), 1,91 (s, 3H), 0,97-0,85 (m, 2H).

Composto 171: MS: m/z 768,2 ($M^+ + 1$); ^1H NMR (CDCl_3) δ 10,29 (s, 1H), 8,26 (d, 1H), 7,93 (d, 2H), 7,57 (m, 2H), 7,42 (m, 1H), 7,27 (m, 4H), 6,16 (d, 1H), 5,69 (m, 2H), 4,94 (dd, 1H), 4,67 (m, 1H), 4,57 (m, 1H), 4,40 (d, 1H), 4,05 (m, 1H), 2,89 (m, 1H), 2,68 (m, 2H), 2,51 (m, 1H), 2,39 (s, 3H), 2,30 (q, 1H), 1,94-1,05 (m, 13H), 1,92 (s, 3H), 0,97-0,84 (m, 2H).

Composto 172: MS: m/z 788,2 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,32 (s, 1H), 8,22 (d, 1H), 8,01 (m, 2H), 7,57 (m, 2H),
7,42 (m, 1H), 7,22-7,11 (m, 4H), 5,72 (m, 2H), 5,39 (d,
1H), 4,96 (dd, 1H), 4,71 (m, 1H), 4,39 (m, 2H), 4,04 (m,
1H), 3,54 (s, 3H), 2,89 (m, 1H), 2,71 (m, 2H), 2,54 (m,
1H), 2,25 (q, 1H), 1,91-1,06 (m, 13H), 0,93-0,83 (m, 2H).

Composto 173: MS: m/z 822,2 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,15 (s, 1H), 8,27 (d, 1H), 7,91 (d, 2H), 7,59 (m, 2H),
7,44 (m, 1H), 7,27 (m, 3H), 7,15 (d, 1H), 7,07 (s, 1H),
5,75 (s, 1H), 5,69 (q, 1H), 4,91 (dd, 1H), 4,68 (m, 2H),
4,32 (d, 1H), 4,06 (m, 1H), 2,89 (m, 1H), 2,68 (m, 2H),
2,41 (m, 1H), 2,39 (s, 3H), 2,21 (q, 1H), 1,96-1,08 (m,
13H), 0,96-0,83 (m, 2H).

Composto 174: MS: m/z 826,2 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,21 (s, 1H), 8,22 (d, 1H), 8,02 (m, 2H), 7,59 (m, 2H),
7,41 (m, 1H), 7,24-7,13 (m, 5H), 5,73 (s, 1H), 5,67 (q,
1H), 4,89 (dd, 1H), 4,72 (m, 2H), 4,31 (d, 1H), 4,05 (m,
1H), 2,87 (m, 1H), 2,69 (m, 2H), 2,47 (m, 1H), 2,24 (q,
1H), 1,93-1,04 (m, 13H), 0,93-0,82 (m, 2H).

Composto 175: MS: m/z 842,3 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,30 (s, 1H), 8,58 (s, 1H), 8,26 (d, 1H), 8,10 (dd, 1H),
7,61-7,14 (m, 7H), 6,91 (s, 1H), 5,67 (m, 2H), 5,38 (d,
1H), 4,96 (dd, 1H), 4,70 (m, 1H), 4,56 (d, 1H), 4,36 (m,
1H), 4,06 (m, 1H), 2,88 (m, 1H), 2,69 (m, 2H), 2,51 (m,
1H), 2,28 (q, 1H), 1,87-0,88 (m, 23H).

Composto 176: MS: m/z 844,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,28 (s, 1H), 8,00 (m, 3H), 7,42 (d, 1H), 7,37 (d, 1H),
7,19 (m, 3H), 6,98 (s, 1H), 5,68 (m, 2H), 5,19 (d, 1H),
4,96 (dd, 1H), 4,66 (m, 2H), 4,30 (m, 1H), 4,04 (m, 1H),
2,89 (m, 1H), 2,67 (m, 2H), 2,52 (s, 3H), 2,51 (m, 1H),
2,26 (q, 1H), 1,94-1,05 (m, 13H), 1,20 (s, 9H), 0,98-0,83
(m, 2H).

Composto 177: MS: m/z 840,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,25 (s, 1H), 8,00 (m, 3H), 7,42 (d, 1H), 7,35-7,11 (m,
6H), 5,73 (s, 1H), 5,69 (q, 1H), 4,93 (dd, 1H), 4,66 (m,
2H), 4,32 (d, 1H), 4,04 (m, 1H), 2,89 (m, 1H), 2,70 (m,
2H), 2,51 (s, 3H), 2,48 (m, 1H), 2,23 (q, 1H), 1,95-1,04
(m, 13H), 0,96-0,82 (m, 2H).

Composto 178: MS: m/z 784,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,33 (s, 1H), 8,27 (d, 1H), 7,92 (d, 2H), 7,55 (m, 2H),
7,41 (m, 1H), 7,27 (m, 4H), 5,70 (m, 2H), 5,45 (d, 1H),
4,95 (dd, 1H), 4,67 (m, 1H), 4,36 (m, 2H), 4,06 (m, 1H),
3,49 (s, 3H), 2,89 (m, 1H), 2,69 (m, 2H), 2,51 (m, 1H),
2,39 (s, 3H), 2,26 (q, 1H), 1,96-1,06 (m, 13H), 0,97-0,83
(m, 2H).

Composto 179: MS: m/z 856,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,28 (s, 1H), 7,92 (d, 2H), 7,69 (d, 1H), 7,44 (d, 1H),
7,29 (d, 2H), 7,15 (s, 1H), 7,05 (dd, 1H), 6,97 (s, 1H),
5,68 (m, 2H), 5,22 (d, 1H), 4,95 (dd, 1H), 4,62 (m, 2H),
4,30 (m, 1H), 4,03 (m, 1H), 3,93 (s, 3H), 2,87 (m, 1H),
2,66 (m, 2H), 2,54 (m, 1H), 2,41 (s, 3H), 2,29 (q, 1H),
1,94-0,82 (m, 15H), 1,21 (s, 9H).

Composto 180: MS: m/z 814,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,35 (s, 1H), 7,92 (d, 2H), 7,63 (d, 1H), 7,42 (d, 1H),
7,33-7,21 (m, 4H), 7,10 (dd, 1H), 5,66 (m, 2H), 5,41 (d,
1H), 4,94 (dd, 1H), 4,65 (m, 1H), 4,37 (m, 2H), 4,03 (m,
1H), 3,91 (s, 3H), 3,50 (s, 3H), 2,87 (m, 1H), 2,66 (m,
2H), 2,51 (m, 1H), 2,41 (s, 3H), 2,25 (q, 1H), 1,94-1,07
(m, 13H), 0,93-0,83 (m, 2H).

Composto 181: MS: m/z 852,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,19 (s, 1H), 7,91 (d, 2H), 7,71 (d, 1H), 7,48 (d, 1H),
7,30-7,15 (m, 5H), 7,13 (dd, 1H), 5,66 (s, 1H), 5,64 (q,
1H), 4,94 (dd, 1H), 4,65 (m, 2H), 4,30 (d, 1H), 4,03 (m,
1H), 3,93 (s, 3H), 2,84 (m, 1H), 2,67 (m, 2H), 2,46 (m,
1H), 2,40 (s, 3H), 2,22 (q, 1H), 1,95-0,84 (m, 15H).

Composto 182: MS: m/z 798,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,33 (s, 1H), 7,92 (d, 2H), 7,72 (d, 1H), 7,43 (d, 1H),
7,39 (s, 1H), 7,21 (m, 3H), 7,11 (dd, 1H), 6,18 (d, 1H),
5,70 (q, 1H), 5,64 (s, 1H), 4,94 (dd, 1H), 4,66 (dd, 1H),
4,56 (m, 1H), 4,39 (d, 1H), 4,02 (m, 1H), 3,93 (s, 3H),
2,84 (m, 1H), 2,68 (m, 2H), 2,47 (m, 1H), 2,39 (s, 3H),
2,25 (q, 1H), 1,95-0,83 (m, 15H), 1,91 (s, 3H).

Composto 183: MS: m/z 802,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,39 (s, 1H), 7,96 (m, 3H), 7,44 (m, 2H), 7,35 (m, 1H),
7,14 (m, 3H), 5,66 (m, 2H), 5,41 (d, 1H), 4,92 (dd, 1H),
4,61 (m, 1H), 4,30 (m, 2H), 4,00 (m, 1H), 3,50 (s, 3H),
2,89 (m, 1H), 2,72 (m, 2H), 2,51 (s, 3H), 2,50 (m, 1H),
2,26 (q, 1H), 1,93-1,06 (m, 13H), 0,97-0,83 (m, 2H).

Composto 184: MS: m/z 786,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,36 (s, 1H), 7,96 (m, 3H), 7,42 (m, 2H), 7,32 (m, 1H),
7,15 (m, 3H), 6,12 (d, 1H), 5,69 (q, 1H), 5,65 (s, 1H),
4,94 (dd, 1H), 4,64 (m, 1H), 4,54 (m, 1H), 4,38 (d, 1H),
3,98 (m, 1H), 2,88 (m, 1H), 2,71 (m, 2H), 2,50 (m, 1H),
2,49 (s, 3H), 2,27 (q, 1H), 1,92-0,82 (m, 15H), 1,91 (s,
3H).

Composto 185: MS: m/z 812,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,37 (s, 1H), 7,96 (m, 3H), 7,41 (d, 1H), 7,36 (d, 1H),
7,25 (m, 1H), 7,10 (m, 3H), 6,19 (d, 1H), 5,71 (q, 1H),
5,64 (s, 1H), 4,95 (dd, 1H), 4,66 (m, 1H), 4,48 (m, 2H),
3,99 (m, 1H), 2,89 (m, 1H), 2,70 (m, 2H), 2,51 (m, 1H),
2,50 (s, 3H), 2,27 (q, 1H), 1,91-1,10 (m, 14H), 0,97-0,80
(m, 2H), 0,80-0,68 (m, 4H).

Composto 186: MS: m/z 856,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,28 (s, 1H), 8,00 (m, 3H), 7,42 (d, 1H), 7,37 (d, 1H),
7,25-7,13 (m, 3H), 7,04 (s, 1H), 5,72 (s, 1H), 5,69 (q,
1H), 5,23 (d, 1H), 4,97 (dd, 1H), 4,77 (s, 1H), 4,67 (m,
1H), 4,55 (d, 1H), 4,35 (m, 1H), 4,04 (m, 1H), 2,89 (m,
1H), 2,68 (m, 2H), 2,52 (s, 3H), 2,51 (m, 1H), 2,25 (q,
1H), 1,93-1,06 (m, 21H), 0,97-0,83 (m, 2H).

Composto 187: MS: m/z 830,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,29 (s, 1H), 8,01 (d, 2H), 7,93 (d, 1H), 7,50 (m, 4H),
7,29 (m, 2H), 7,07 (s, 1H), 5,67 (m, 2H), 5,19 (d, 1H),
4,94 (dd, 1H), 4,67 (m, 2H), 4,30 (m, 1H), 4,04 (m, 1H),

2,89 (m, 1H), 2,69 (m, 2H), 2,52 (m, 1H), 2,28 (q, 1H),
1,94-1,05 (m, 13H), 1,19 (s, 9H), 0,97-0,84 (m, 2H).

Composto 188: MS: m/z 842,2 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,27 (s, 1H), 8,02 (d, 2H), 7,93 (d, 1H), 7,52 (m, 4H),
7,32 (s, 1H), 7,26 (m, 1H), 7,08 (s, 1H), 5,68 (s, 1H),
5,66 (q, 1H), 5,22 (d, 1H), 4,92 (dd, 1H), 4,71 (m, 2H),
4,57 (d, 1H), 4,33 (m, 1H), 4,05 (m, 1H), 2,89 (m, 1H),
2,68 (m, 2H), 2,53 (m, 1H), 2,28 (q, 1H), 1,95-0,83 (m,
23H).

Composto 189: MS: m/z 882,4 (M^{+1}).

Composto 190: MS: m/z 884,2 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,29 (s, 1H), 7,96 (m, 3H), 7,54 (m, 1H), 7,36-7,26 (m,
5H), 5,70 (m, 2H), 5,27 (d, 1H), 4,95 (dd, 1H), 4,74 (m,
1H), 4,53 (d, 1H), 4,32 (m, 1H), 4,05 (m, 2H), 2,95 (m,
2H), 2,69 (m, 2H), 2,52 (m, 1H), 2,28 (q, 1H), 1,94-0,83
(m, 23H), 1,29 (d, 6H).

Composto 191: MS: m/z 898,2 (M^{+1}).

Composto 192: MS: m/z 880,2 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,31 (s, 1H), 8,28 (d, 1H), 7,95 (d, 2H), 7,50 (m, 4H),
7,42 (dd, 1H), 7,27 (s, 1H), 7,21 (s, 1H), 5,68 (s, 1H),
5,65 (q, 1H), 5,35 (d, 1H), 4,94 (dd, 1H), 4,72 (m, 2H),
4,57 (d, 1H), 4,35 (m, 1H), 4,04 (m, 1H), 2,88 (m, 1H),
2,68 (m, 2H), 2,53 (m, 1H), 2,28 (q, 1H), 1,93-1,05 (m,
21H), 1,36 (s, 9H), 0,97-0,82 (m, 2H).

Composto 193: MS: m/z 894,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,21 (s, 1H), 8,28 (d, 1H), 7,95 (d, 2H), 7,52 (m, 4H),
7,41 (dd, 1H), 7,34 (s, 1H), 7,26 (s, 1H), 5,70 (s, 1H),
5,65 (q, 1H), 5,41 (d, 1H), 4,95 (dd, 1H), 4,75 (m, 2H),
4,57 (d, 1H), 4,36 (m, 1H), 4,05 (m, 1H), 2,70 (m, 2H),
2,50 (m, 1H), 2,29 (q, 1H), 1,93-0,82 (m, 23H), 1,46 (s,
3H), 1,36 (s, 9H).

Composto 194: MS: m/z 857,3 ($M^+ + 1$).

Composto 195: MS: m/z 857,3 ($M^+ + 1$).

Composto 196: MS: m/z 784,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,20 (s, 1H), 8,27 (d, 1H), 7,88 (d, 1H), 7,57 (m, 2H),
7,39 (m, 3H), 7,13 (dd, 1H), 7,01 (d, 2H), 6,14 (d, 1H),
5,68 (q, 1H), 5,62 (s, 1H), 4,97 (dd, 1H), 4,64 (m, 2H),
4,41 (d, 1H), 4,07 (m, 1H), 3,87 (s, 3H), 2,87 (m, 1H),
2,67 (m, 2H), 2,45 (m, 1H), 2,25 (q, 1H), 1,93-0,85 (m,
15H), 1,92 (s, 3H).

Composto 197: MS: m/z 856,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,34 (s, 1H), 8,03 (s, 1H), 8,00 (d, 2H), 7,45 (d, 1H),
7,35 (d, 1H), 7,16 (m, 2H), 7,00 (d, 2H), 5,71 (s, 1H),
5,69 (q, 1H), 5,23 (d, 1H), 4,95 (dd, 1H), 4,62 (m, 2H),
4,30 (m, 1H), 4,03 (m, 1H), 3,86 (s, 3H), 2,88 (m, 1H),
2,66 (m, 2H), 2,51 (s, 3H), 2,50 (m, 1H), 2,31 (q, 1H),
1,91-0,82 (m, 15H), 1,22 (s, 9H).

Composto 198: MS: m/z 784,2 (M^{+1})

Composto 199: MS: m/z 798,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,37 (s, 1H), 7,96 (m, 3H), 7,58 (s, 1H), 7,43 (d, 1H),
7,32 (d, 1H), 7,16 (s, 1H), 6,97 (d, 2H), 6,24 (d, 1H),
5,69 (q, 1H), 5,64 (s, 1H), 4,96 (dd, 1H), 4,66 (m, 1H),
4,55 (m, 1H), 4,40 (d, 1H), 4,02 (m, 1H), 3,84 (s, 3H),
2,87 (m, 1H), 2,68 (m, 2H), 2,49 (s, 3H), 2,50 (m, 1H),
2,28 (q, 1H), 1,91-0,83 (m, 15H), 1,91 (s, 3H).

Composto 200: MS: m/z 852,2 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,26 (s, 1H), 8,03 (s, 1H), 7,96 (d, 2H), 7,52 (s, 1H),
7,45 (d, 1H), 7,34 (d, 1H), 7,23 (s, 1H), 6,98 (d, 2H),
5,67 (s, 1H), 5,64 (q, 1H), 5,21 (m, 1H), 4,93 (dd, 1H),
4,67 (m, 2H), 4,30 (d, 1H), 4,04 (m, 1H), 3,85 (s, 3H),
2,87 (m, 1H), 2,66-2,40 (m, 3H), 2,51 (s, 3H), 2,22 (q,
1H), 1,95-0,82 (m, 15H).

Composto 201: MS: m/z 814,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,41 (s, 1H), 7,98 (m, 3H), 7,60 (s, 1H), 7,43 (d, 1H),
7,33 (d, 1H), 7,16 (s, 1H), 6,98 (d, 2H), 5,64 (m, 2H),
5,29 (m, 2H), 4,93 (dd, 1H), 4,69 (m, 1H), 4,36 (m, 1H),
4,01 (m, 1H), 3,84 (s, 3H), 3,42 (s, 3H), 2,87 (m, 1H),
2,66 (m, 2H), 2,50 (m, 1H), 2,49 (s, 3H), 2,25 (q, 1H),
1,94-0,82 (m, 15H).

Composto 202: MS: m/z 838,2 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,23 (s, 1H), 8,26 (d, 1H), 8,00 (d, 2H), 7,60 (m, 2H),
7,44 (m, 2H), 7,23 (m, 2H), 7,01 (d, 2H), 5,73 (s, 1H),

5,67 (q, 1H), 4,94 (dd, 1H), 4,68 (m, 2H), 4,32 (d, 1H), 4,07 (m, 1H), 3,86 (s, 3H), 2,86 (m, 1H), 2,67 (m, 2H), 2,41 (m, 1H), 2,23 (q, 1H), 1,94-1,08 (m, 13H), 0,94-0,87 (m, 2H).

Composto 203: MS: m/z 842,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,30 (s, 1H), 8,28 (d, 1H), 7,63 (s, 1H), 7,57 (m, 3H), 7,42 (m, 2H), 7,25 (m, 1H), 7,08 (s, 1H), 6,97 (dd, 1H), 5,71 (m, 2H), 5,22 (d, 1H), 4,92 (dd, 1H), 4,64 (m, 2H), 4,31 (m, 1H), 4,00 (m, 1H), 3,91 (s, 3H), 2,89 (m, 1H), 2,69 (m, 2H), 2,55 (m, 1H), 2,29 (q, 1H), 1,85-0,83 (m, 15H), 1,19 (s, 9H).

Composto 204: MS: m/z 784,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,28 (s, 1H), 8,26 (d, 1H), 7,62 (s, 1H), 7,58 (m, 3H), 7,41 (m, 2H), 7,25 (m, 2H), 6,96 (dd, 1H), 6,13 (d, 1H), 5,71 (q, 1H), 5,68 (s, 1H), 4,95 (dd, 1H), 4,63 (t, 1H), 4,59 (m, 1H), 4,41 (d, 1H), 4,04 (m, 1H), 3,90 (s, 3H), 2,88 (m, 1H), 2,71 (m, 2H), 2,52 (m, 1H), 2,29 (q, 1H), 1,92-1,1,05 (m, 13H), 1,91 (s, 3H), 0,97-0,84 (m, 2H).

Composto 205: MS: m/z 801,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,34 (s, 1H), 8,25 (d, 1H), 7,61 (s, 1H), 7,57 (m, 3H), 7,39-7,25 (m, 4H), 6,93 (dd, 1H), 5,70 (m, 2H), 5,44 (d, 1H), 4,94 (dd, 1H), 4,70 (m, 1H), 4,39 (d, 1H), 4,32 (m, 1H), 4,03 (m, 1H), 3,90 (s, 3H), 3,48 (s, 3H), 2,88 (m, 1H), 2,70 (m, 2H), 2,52 (m, 1H), 2,26 (q, 1H), 1,89-0,82 (m, 15H).

Composto 206: MS: m/z 838,2 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,19 (s, 1H), 8,27 (d, 1H), 7,62 (s, 1H), 7,58 (m, 3H),
7,41 (m, 2H), 7,25 (m, 3H), 6,97 (dd, 1H), 5,71 (s, 1H),
5,63 (q, 1H), 4,92 (dd, 1H), 4,64 (m, 2H), 4,33 (d, 1H),
4,05 (m, 1H), 3,90 (s, 3H), 2,88 (m, 1H), 2,69 (m, 2H),
2,46 (m, 1H), 2,23 (q, 1H), 1,94-1,1,03 (m, 13H), 0,95-0,84
(m, 2H).

Composto 207: MS: m/z 800,2 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,24 (s, 1H), 8,27 (d, 1H), 7,86 (d, 1H), 7,55 (m, 2H),
7,42 (m, 3H), 7,12 (m, 2H), 7,00 (d, 1H), 5,68 (q, 1H),
5,62 (s, 1H), 5,47 (d, 1H), 4,92 (dd, 1H), 4,68 (m, 1H),
4,40 (m, 2H), 4,04 (m, 1H), 3,87 (s, 3H), 3,50 (s, 3H),
2,89 (m, 1H), 2,68 (m, 2H), 2,50 (m, 1H), 2,25 (q, 1H),
1,91-1,03 (m, 13H), 0,98-0,82 (m, 2H).

Composto 208: MS: m/z 838,2 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,19 (s, 1H), 8,27 (d, 1H), 7,82 (d, 1H), 7,57 (m, 2H),
7,39 (m, 5H), 7,12 (dd, 1H), 7,02 (d, 1H), 5,63 (q, 1H),
5,60 (s, 1H), 4,90 (dd, 1H), 4,70 (m, 2H), 4,32 (d, 1H),
4,03 (m, 1H), 3,85 (s, 3H), 2,86 (m, 1H), 2,71-2,52 (m,
2H), 2,39 (m, 1H), 2,20 (q, 1H), 1,94-0,84 (m, 15H).

Composto 209: MS: m/z 896,4 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,20 (s, 1H), 8,31 (d, 1H), 7,99 (d, 2H), 7,58 (m, 2H),
7,42 (m, 1H), 7,30-7,22 (m, 2H), 7,01 (d, 2H), 5,68 (s,
1H), 5,66 (q, 1H), 5,37 (d, 1H), 4,96 (dd, 1H), 4,78-4,51
(m, 4H), 4,37 (m, 1H), 4,06 (m, 1H), 2,69 (m, 2H), 2,51 (m,
1H), 2,28 (q, 1H), 1,94-0,83 (m, 23H), 1,46 (s, 3H), 1,37
(d, 6H).

Composto 210: MS: m/z 882,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,24 (s, 1H), 8,27 (d, 1H), 7,98 (d, 2H), 7,58 (m, 2H),
7,42 (m, 1H), 7,24 (m, 1H), 7,01 (d, 2H), 6,89 (s, 1H),
5,68 (s, 1H), 5,66 (q, 1H), 5,22 (d, 1H), 4,97 (dd, 1H),
4,78-4,52 (m, 4H), 4,36 (m, 1H), 4,04 (m, 1H), 2,88 (m,
1H), 2,68 (m, 2H), 2,54 (m, 1H), 2,29 (q, 1H), 1,94-1,05
(m, 21H), 1,37 (d, 6H), 0,97-0,83 (m, 2H).

Composto 211: MS: m/z 922,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,13 (s, 1H), 8,26 (d, 1H), 8,10 (d, 2H), 7,59 (m, 2H),
7,42 (m, 1H), 7,35-7,25 (m, 3H), 7,03 (s, 1H), 5,77 (s,
1H), 5,66 (q, 1H), 5,20 (d, 1H), 4,99 (dd, 1H), 4,71 (m,
2H), 4,56 (d, 1H), 4,35 (m, 1H), 4,03 (m, 1H), 2,70 (m,
2H), 2,50 (m, 1H), 2,29 (q, 1H), 1,90-0,84 (m, 23H), 0,85
(s, 3H).

Composto 212: MS: m/z 892,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,36 (s, 1H), 8,59 (s, 1H), 8,25 (d, 1H), 8,18 (d, 2H),
7,73 (d, 2H), 7,58 (m, 2H), 7,45 (m, 1H), 7,34 (s, 1H),
5,74 (s, 1H), 5,68 (q, 1H), 5,39 (d, 1H), 4,94 (dd, 1H),
4,72 (m, 2H), 4,55 (d, 1H), 4,31 (m, 1H), 4,04 (m, 1H),
2,86 (m, 1H), 2,67 (m, 2H), 2,49 (m, 1H), 2,26 (q, 1H),
1,91-1,05 (m, 23H).

Composto 213: MS: m/z 880,4 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,36 (s, 1H), 8,26 (d, 1H), 8,16 (d, 2H), 7,74 (d, 2H),
7,59 (m, 2H), 7,45 (m, 1H), 7,30 (m, 2H), 5,71 (s, 1H),
5,66 (q, 1H), 5,25 (d, 1H), 4,95 (dd, 1H), 4,71 (m, 1H),

4,65 (d, 1H), 4,28 (m, 1H), 4,03 (m, 1H), 2,87 (m, 1H),
2,70 (m, 2H), 2,51 (m, 1H), 2,27 (q, 1H), 1,92-1,06 (m,
13H), 1,19 (s, 9H), 0,97-0,82 (m, 2H).

Composto 214: MS: m/z 780,2 (M^{+1}).

Composto 215: MS: m/z 822,2 (M^{+1}).

Composto 216: MS: m/z 910,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,30 (s, 1H), 8,15 (d, 2H), 7,75 (d, 2H), 7,61 (s, 1H),
7,47 (d, 1H), 7,25-7,15 (m, 3H), 5,72 (s, 1H), 5,68 (q,
1H), 5,18 (d, 1H), 4,98 (dd, 1H), 4,67 (m, 2H), 4,28 (m,
1H), 4,04 (m, 1H), 3,93 (s, 3H), 2,89 (m, 1H), 2,69 (m,
2H), 2,52 (m, 1H), 2,28 (q, 1H), 1,91-0,85 (m, 15H), 1,20
(s, 9H).

Composto 217: MS: m/z 922,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,28 (s, 1H), 8,17 (m, 3H), 7,74 (d, 2H), 7,26 (m, 1H),
7,17 (s, 1H), 7,02 (m, 2H), 5,77 (s, 1H), 5,69 (q, 1H),
5,20 (d, 1H), 4,96 (dd, 1H), 4,77 (s, 1H), 4,69 (m, 1H),
4,54 (d, 1H), 4,33 (m, 1H), 4,04 (m, 1H), 3,92 (s, 3H),
2,89 (m, 1H), 2,71 (m, 2H), 2,52 (m, 1H), 2,28 (q, 1H),
1,90-1,05 (m, 21H), 0,97-0,83 (m, 2H).

Composto 218: MS: m/z 892,4 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,29 (s, 1H), 8,35 (s, 1H), 8,28 (d, 1H), 8,24 (d, 1H),
7,59 (m, 4H), 7,44 (m, 1H), 7,33 (s, 1H), 7,15 (s, 1H),
5,80 (s, 1H), 5,67 (q, 1H), 5,27 (d, 1H), 4,95 (dd, 1H),
4,70 (m, 2H), 4,58 (d, 1H), 4,30 (m, 1H), 4,06 (m, 1H),

2,88 (m, 1H), 2,70 (m, 2H), 2,54 (m, 1H), 2,28 (q, 1H),
1,92-0,83 (m, 23H).

Composto 219: MS: m/z 880,2 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,31 (s, 1H), 8,34 (s, 1H), 8,28 (d, 1H), 8,20 (d, 1H),
7,60 (m, 4H), 7,45 (m, 1H), 7,29 (s, 1H), 7,13 (s, 1H),
5,77 (s, 1H), 5,67 (q, 1H), 5,19 (m, 1H), 4,94 (dd, 1H),
4,67 (m, 2H), 4,26 (m, 1H), 4,05 (m, 1H), 2,88 (m, 1H),
2,71 (m, 2H), 2,53 (m, 1H), 2,29 (q, 1H), 1,90-0,83 (m,
15H), 1,18 (s, 9H).

Composto 220: MS: m/z 892,2 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,29 (s, 1H), 8,39 (d, 1H), 8,06 (d, 2H), 7,88 (s, 1H),
7,71 (d, 1H), 7,45 (m, 3H), 7,36 (s, 1H), 7,18 (s, 1H),
5,68 (s, 1H), 5,65 (q, 1H), 5,33 (d, 1H), 4,93 (dd, 1H),
4,72 (m, 2H), 4,67 (d, 1H), 4,36 (m, 1H), 4,05 (m, 1H),
2,88 (m, 1H), 2,70 (m, 2H), 2,53 (m, 1H), 2,28 (q, 1H),
1,92-0,84 (m, 23H).

Composto 221: MS: m/z 880,4 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,30 (s, 1H), 8,39 (d, 1H), 8,04 (d, 2H), 7,87 (s, 1H),
7,69 (d, 1H), 7,48 (m, 3H), 7,33 (s, 1H), 7,25 (s, 1H),
5,67 (m, 2H), 5,21 (d, 1H), 4,94 (dd, 1H), 4,68 (m, 2H),
4,30 (m, 1H), 4,04 (m, 1H), 2,88 (m, 1H), 2,69 (m, 2H),
2,52 (m, 1H), 2,28 (q, 1H), 1,93-0,84 (m, 15H), 1,17 (s,
9H).

Composto 222: MS: m/z 814,3 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,29 (s, 1H), 8,46 (s, 1H), 8,27 (d, 1H), 7,47 (m, 3H),

7,41 (m, 1H), 7,33 (s, 1H), 7,16 (d, 1H), 7,05 (s, 1H),
6,56 (d, 1H), 5,69 (m, 2H), 5,24 (d, 1H), 4,95 (dd, 1H),
4,66 (m, 1H), 4,58 (d, 1H), 4,38 (m, 1H), 4,05 (m, 1H),
2,89 (m, 1H), 2,70 (m, 2H), 2,34 (m, 1H), 2,29 (q, 1H),
1,90-1,06 (m, 21H), 0,96-0,83 (m, 2H).

Composto 223: MS: m/z 802,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,30 (s, 1H), 8,28 (d, 1H), 7,54 (m, 3H), 7,42 (m, 1H),
7,29 (s, 1H), 7,20 (d, 1H), 7,08 (s, 1H), 6,56 (d, 1H),
5,66 (m, 2H), 5,15 (d, 1H), 4,95 (dd, 1H), 4,69 (m, 2H),
4,30 (m, 1H), 4,05 (m, 1H), 2,89 (m, 1H), 2,68 (m, 2H),
2,35 (m, 1H), 2,29 (q, 1H), 1,89-1,04 (m, 13H), 1,19 (s,
9H), 0,97-0,83 (m, 2H).

Composto 224: MS: m/z 848,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,30 (s, 1H), 8,08 (d, 1H), 7,58 (d, 1H), 7,39 (d, 1H),
7,14 (s, 1H), 7,12-6,95 (m, 4H), 5,70 (m, 2H), 5,20 (d,
1H), 4,95 (dd, 1H), 4,66 (m, 1H), 4,59 (d, 1H), 4,33 (m,
1H), 4,03 (m, 1H), 3,91 (s, 3H), 2,90 (m, 1H), 2,66 (m,
2H), 2,52 (m, 1H), 2,28 (q, 1H), 1,89-1,06 (m, 13H), 1,24
(s, 9H), 0,94-0,83 (m, 2H).

Composto 225: MS: m/z 760,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,35 (s, 1H), 8,25 (d, 1H), 7,55 (m, 3H), 7,40 (m, 1H),
7,27 (m, 2H), 7,16 (d, 1H), 6,54 (d, 1H), 5,66 (m, 2H),
5,42 (d, 1H), 4,94 (dd, 1H), 4,67 (m, 1H), 4,46 (d, 1H),
4,35 (m, 1H), 4,04 (m, 1H), 3,50 (s, 3H), 2,89 (m, 1H),
2,66 (m, 2H), 2,33 (m, 1H), 2,26 (q, 1H), 1,92-0,83 (m,
15H).

Composto 226: MS: m/z 798,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,20 (s, 1H), 8,25 (d, 1H), 7,55 (m, 3H), 7,41 (m, 1H),
7,27 (m, 3H), 7,16 (d, 1H), 6,56 (d, 1H), 5,66 (m, 2H),
4,94 (dd, 1H), 4,67 (m, 2H), 4,35 (d, 1H), 4,05 (m, 1H),
2,88 (m, 1H), 2,66 (m, 2H), 2,43 (m, 1H), 2,26 (q, 1H),
1,96-0,83 (m, 15H).

Composto 227: MS: m/z 744,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,31 (s, 1H), 8,21 (d, 1H), 7,55 (m, 3H), 7,39 (m, 1H),
7,33-7,25 (m, 2H), 7,12 (d, 1H), 6,56 (d, 1H), 6,16 (d,
1H), 5,66 (q, 1H), 5,62 (s, 1H), 4,94 (dd, 1H), 4,62 (m,
1H), 4,59 (m, 1H), 4,41 (d, 1H), 4,06 (m, 1H), 2,87 (m,
1H), 2,68 (m, 2H), 2,50 (m, 1H), 2,26 (q, 1H), 1,95-0,83
(m, 15H), 1,90 (s, 3H).

Composto 228: MS: m/z 857,3 ($M^+ + 1$).

Composto 229: MS: m/z 830,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,25 (s, 1H), 8,26 (d, 1H), 7,59 (m, 2H), 7,43 (m, 2H),
7,25 (m, 2H), 7,19 (m, 1H), 7,06 (m, 1H), 5,76 (s, 1H),
5,72 (q, 1H), 5,18 (m, 1H), 4,97 (dd, 1H), 4,68 (m, 2H),
4,56 (d, 1H), 4,30 (m, 1H), 4,04 (m, 1H), 2,90 (m, 1H),
2,70 (m, 2H), 2,39 (m, 1H), 2,27 (q, 1H), 1,90-0,80 (m,
3H).

Composto 230: MS: m/z 860,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,28 (s, 1H), 8,10 (d, 1H), 7,58 (d, 1H), 7,39 (d, 1H),
7,18 (s, 1H), 7,09-6,97 (m, 4H), 5,72 (s, 1H), 5,68 (q,

1H), 5,24 (d, 1H), 4,95 (dd, 1H), 4,80 (s, 1H), 4,65 (m, 1H), 4,54 (d, 1H), 4,32 (m, 1H), 4,03 (m, 1H), 3,91 (s, 3H), 2,94 (m, 1H), 2,68 (m, 2H), 2,54 (m, 1H), 2,28 (q, 1H), 1,90-1,05 (m, 21H), 0,95-0,84 (m, 2H).

Composto 231: MS: m/z 848,2 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,26 (s, 1H), 7,64 (d, 1H), 7,60 (d, 1H), 7,48 (d, 1H), 7,40 (d, 1H), 7,20 (s, 1H), 7,15 (m, 2H), 6,88 (s, 1H), 5,65 (m, 2H), 5,10 (d, 1H), 4,96 (dd, 1H), 4,63 (m, 2H), 4,31 (m, 1H), 4,04 (m, 1H), 3,94 (s, 3H), 2,86 (m, 1H), 2,68 (m, 2H), 2,56 (m, 1H), 2,29 (q, 1H), 1,94-0,83 (m, 15H), 1,22 (s, 9H).

Composto 232: MS: m/z 836,2 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,29 (s, 1H), 7,89 (dd, 1H), 7,60 (d, 1H), 7,50 (dd, 1H), 7,40 (d, 1H), 7,22 (m, 2H), 7,10 (m, 1H), 7,00 (s, 1H), 5,68 (m, 2H), 5,18 (d, 1H), 4,95 (dd, 1H), 4,66 (m, 2H), 4,29 (m, 1H), 4,04 (m, 1H), 2,88 (m, 1H), 2,67 (m, 2H), 2,53 (m, 1H), 2,26 (q, 1H), 1,92-0,83 (m, 15H), 1,20 (s, 9H).

Composto 233: MS: m/z 806,2 (M⁺+1); ¹H NMR (CDCl₃)
δ 10,36 (s, 1H), 8,05 (d, 1H), 7,59 (d, 1H), 7,38 (m, 2H), 7,14-6,97 (m, 4H), 5,70 (m, 2H), 5,64 (d, 1H), 4,96 (dd, 1H), 4,65 (m, 1H), 4,58 (m, 2H), 4,04 (m, 1H), 3,90 (s, 3H), 3,58 (s, 3H), 2,89 (m, 1H), 2,68 (m, 2H), 2,53 (m, 1H), 2,25 (q, 1H), 1,88-0,82 (m, 15H).

Composto 234: MS: m/z 860,2 (M⁺+1); ¹H NMR (CDCl₃)

δ 10,31 (s, 1H), 7,63 (d, 1H), 7,60 (d, 1H), 7,45 (d, 1H), 7,40 (d, 1H), 7,20 (m, 2H), 7,10 (m, 2H), 5,69 (s, 1H), 5,67 (q, 1H), 5,30 (d, 1H), 4,94 (dd, 1H), 4,78 (s, 1H), 4,64 (m, 1H), 4,55 (d, 1H), 4,36 (m, 1H), 4,04 (m, 1H), 3,94 (s, 3H), 2,89 (m, 1H), 2,68 (m, 2H), 2,53 (m, 1H), 2,26 (q, 1H), 1,93-1,04 (m, 21H), 0,97-0,82 (m, 2H).

Composto 235: MS: m/z 844,2 (M^{+1}); ^1H NMR (CDCl_3)

δ 10,24 (s, 1H), 8,04 (d, 1H), 7,58 (d, 1H), 7,39 (d, 1H), 7,31 (m, 2H), 7,18 (s, 1H), 7,08 (m, 3H), 5,70 (s, 1H), 5,67 (q, 1H), 4,86 (dd, 1H), 4,64 (m, 2H), 4,26 (d, 1H), 4,02 (m, 1H), 3,90 (s, 3H), 2,84 (m, 1H), 2,65 (m, 2H), 2,44 (m, 1H), 2,20 (q, 1H), 1,91-0,83 (m, 15H).

Composto 236: MS: m/z 832,2 (M^{+1}); ^1H NMR (CDCl_3)

δ 10,27 (s, 1H), 8,22 (d, 1H), 7,58 (m, 2H), 7,44 (m, 1H), 7,29 (m, 1H), 7,10 (s, 1H), 6,94 (d, 1H), 6,90 (s, 1H), 5,69 (m, 2H), 5,18 (d, 1H), 4,93 (dd, 1H), 4,67 (m, 2H), 4,28 (m, 1H), 4,05 (m, 1H), 2,85 (m, 1H), 2,68 (m, 2H), 2,55 (s, 3H), 2,54 (m, 1H), 2,28 (q, 1H), 1,91-0,83 (m, 15H), 1,19 (s, 9H).

Composto 237: MS: m/z 844,3 (M^{+1}); ^1H NMR (CDCl_3)

δ 10,23 (s, 1H), 8,22 (d, 1H), 7,58 (m, 2H), 7,40 (m, 1H), 7,29 (m, 2H), 6,96 (d, 1H), 6,84 (s, 1H), 5,69 (s, 1H), 5,66 (q, 1H), 5,20 (d, 1H), 4,94 (dd, 1H), 4,73 (s, 1H), 4,67 (m, 1H), 4,58 (d, 1H), 4,35 (m, 1H), 4,05 (m, 1H), 2,89 (m, 1H), 2,68 (m, 2H), 2,56 (s, 3H), 2,54 (m, 1H), 2,26 (q, 1H), 1,91-0,83 (m, 23H).

Composto 238: MS: m/z 844,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,26 (s, 1H), 8,22 (d, 1H), 7,55 (m, 2H), 7,43 (m, 2H),
7,18 (m, 1H), 6,93 (s, 1H), 6,75 (s, 1H), 5,70 (m, 2H),
5,21 (d, 1H), 4,94 (dd, 1H), 4,78 (s, 1H), 4,63 (m, 1H),
4,53 (d, 1H), 4,35 (m, 1H), 4,05 (m, 1H), 2,89 (m, 1H),
2,67 (m, 2H), 2,53 (s, 3H), 2,52 (m, 1H), 2,26 (q, 1H),
1,92-1,04 (m, 21H), 0,95-0,83 (m, 2H).

Composto 239: MS: m/z 790,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,34 (s, 1H), 8,20 (d, 1H), 7,54 (m, 2H), 7,38 (m, 2H),
7,28 (s, 1H), 7,14 (s, 1H), 6,73 (s, 1H), 5,68 (m, 2H),
5,43 (d, 1H), 4,94 (dd, 1H), 4,65 (m, 1H), 4,39 (m, 2H),
4,04 (m, 1H), 3,58 (s, 3H), 2,89 (m, 1H), 2,68 (m, 2H),
2,51 (s, 3H), 2,50 (m, 1H), 2,28 (q, 1H), 1,93-1,06 (m,
13H), 0,94-0,82 (m, 2H).

Composto 240: MS: m/z 828,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,18 (s, 1H), 8,22 (d, 1H), 7,56 (m, 2H), 7,40 (m, 2H),
7,20 (s, 2H), 7,08 (s, 1H), 6,76 (d, 1H), 5,71 (s, 1H),
5,66 (q, 1H), 4,94 (dd, 1H), 4,66 (m, 2H), 4,29 (d, 1H),
4,04 (m, 1H), 2,88 (m, 1H), 2,65 (m, 2H), 2,53 (s, 3H),
2,45 (m, 1H), 2,23 (q, 1H), 1,96-1,05 (m, 13H), 0,95-0,83
(m, 2H).

Composto 241: MS: m/z 778,1 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,38 (s, 1H), 7,89 (dd, 1H), 7,58 (d, 2H), 7,44 (dd,
1H), 7,35 (d, 1H), 7,24 (m, 2H), 7,05 (m, 1H), 6,18 (d,
1H), 5,71 (q, 1H), 5,62 (s, 1H), 4,95 (dd, 1H), 4,63 (m,
1H), 4,50 (m, 1H), 4,40 (d, 1H), 4,00 (m, 1H), 2,88 (m,

1H), 2,66 (m, 2H), 2,53 (m, 1H), 2,22 (q, 1H), 1,96-0,82 (m, 15H), 1,91 (s, 3H).

Composto 242: MS: m/z 846,4 (M^{+1}).

Composto 243: MS: m/z 858,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,28 (s, 1H), 8,24 (d, 1H), 7,57 (m, 2H), 7,42 (m, 2H),
7,19 (s, 1H), 7,08 (s, 1H), 6,79 (d, 1H), 5,66 (m, 2H),
5,24 (d, 1H), 4,96 (m, 1H), 4,78 (s, 1H), 4,67 (m, 1H),
4,55 (d, 1H), 4,35 (m, 1H), 4,03 (m, 1H), 2,85 (m, 3H),
2,67 (m, 2H), 2,53 (m, 1H), 2,28 (q, 1H), 1,94-0,84 (m,
26H).

Composto 244: MS: m/z 872,3 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,13 (s, 1H), 8,24 (d, 1H), 7,53 (m, 2H), 7,41 (m, 2H),
7,19 (s, 1H), 6,99 (s, 1H), 6,79 (d, 1H), 5,69 (m, 2H),
5,23 (d, 1H), 4,98 (dd, 1H), 4,77 (s, 1H), 4,65 (m, 1H),
4,55 (d, 1H), 4,35 (m, 1H), 4,04 (m, 1H), 2,87 (q, 2H),
2,68 (m, 2H), 2,53 (m, 1H), 2,29 (q, 1H), 1,94-0,84 (m,
26H), 0,83 (s, 3H).

Composto 245: MS: m/z 831,2 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,21 (s, 1H), 8,26 (d, 1H), 7,90 (d, 2H), 7,58 (m, 2H),
7,46 (d, 2H), 7,00 (s, 1H), 5,69 (m, 2H), 5,09 (d, 1H),
4,99 (dd, 1H), 4,62 (m, 3H), 4,27 (m, 1H), 4,05 (m, 1H),
2,89 (m, 1H), 2,70 (m, 2H), 2,56 (m, 1H), 2,29 (q, 1H),
1,94-0,84 (m, 23H).

Composto 246: MS: m/z 761,4 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,21 (s, 1H), 8,17 (d, 1H), 7,80 (d, 3H), 7,56 (m, 2H),

7,41 (d, 2H), 6,58 (s, 1H), 5,61 (m, 2H), 5,21 (d, 1H), 4,65 (m, 2H), 4,24 (m, 1H), 4,05 (m, 1H), 2,89 (m, 1H), 2,70 (m, 2H), 2,56-2,21 (m, 2H), 1,94-0,84 (m, 15H), 1,87 (s, 3H).

Composto 247: MS: m/z 803,4 (M^{+1}).

Composto 248: MS: m/z 845,3 (M^{+1}).

Composto 249: MS: m/z 917,2 (M^{+1}); ^1H NMR (CDCl_3) δ 10,22 (s, 1H), 8,08 (d, 1H), 7,78 (s, 1H), 7,40 (s, 1H), 7,06 (s, 1H), 6,97 (m, 2H), 5,64 (m, 2H), 5,32 (d, 1H), 4,94 (dd, 1H), 4,70 (m, 2H), 4,54 (d, 1H), 4,34 (dd, 1H), 4,08 (m, 1H), 3,83 (s, 3H), 3,18 (m, 1H), 2,73-2,43 (m, 2H), 2,33 (q, 1H), 2,15-1,20 (m, 30H), 0,83 (s, 3H).

Composto 250: MS: m/z 905,4 (M^{+1}).

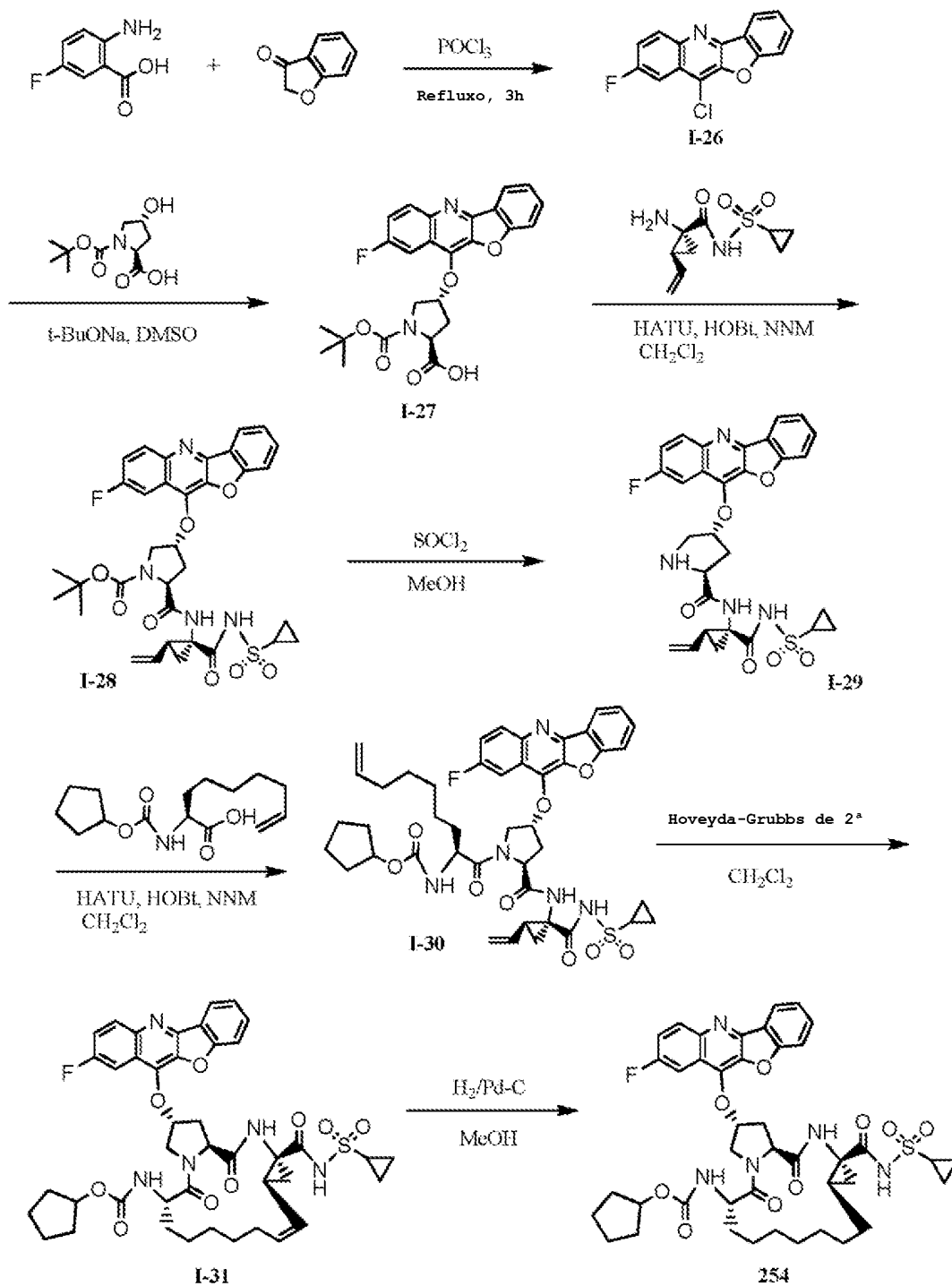
Composto 251: MS: m/z 901,3 (M^{+1}).

Composto 252: MS: m/z 917,4 (M^{+1}).

Composto 253: MS: m/z 903,3 (M^{+1}).

Exemplo 254: Síntese de Éster ciclopentílico do ácido [4-ciclopropano-sulfonilaminocarbonil-18-(2-fluoro-benzo[4,5]furo[3,2-b]quinolin-11-iloxi)-2,15-dioxo-3,16-diaza-triciclo[14.3.0.04,6]nonadec-14-il]-carbâmico (Composto 254)

O Composto 254 foi preparado através da via ilustrada abaixo.



A uma suspensão de Boc-trans-4-hidroxi-L-prolina (0,53 g, 2,30 mmol) em DMSO (10 mL) adicionou-se *t*-BuONa (0,49 g, 5,08 mmol) a 0 °C. Depois de se aquecer até à temperatura ambiente e agitar-se durante mais 1 hora, adicionou-se lentamente o intermediário I-26 (0,62 g, 2,31 mmol) a 10 °C. A mistura reacional foi agitada durante 4 h e em seguida temperada com solução aquosa de HCl a 10% até pH 6~7. O sólido bruto em suspensão foi filtrado, lavado com água e seco sob vácuo para dar o I-27 (0,92 g, 86%). MS: m/z 467,1 (M^+1).

A uma solução de I-27 (0,90 g, 1,93 mmol), HATU (58,9 g, 1,55 mmol), HOBT (7,0 g, 0,52 mmol) e NMM (38,3 g, 3,86 mmol) em CH₂Cl₂ (10 mL) adicionou-se gota a gota uma mistura de ácido ciclopropano-sulfónico (1-amino-2-vinil-ciclopropanocarbonil)-amida (54,0 g, 2,03 mmol) e NMM (0,19 g, 1,93 mmol) dissolvido em CH₂Cl₂ a 5 °C. Após ter sido aquecida até à temperatura ambiente e agitada durante mais 16 h, a mistura reaccional foi filtrada, concentrada e purificada por cromatografia em coluna de sílica gel para proporcionar um produto bruto I-28 (0,89 g, rendimento de 80%). MS: m/z 679,1 (M^+1).

Dissolveu-se o composto I-28 (1,20 g, 1,77 mmol) em MeOH (18 mL) à temperatura ambiente e em seguida arrefeceu-se a solução utilizando-se um banho de gelo. À mistura reaccional adicionou-se gota a gota cloreto de tionilo (0,39 mL, 5,30 mmoles). Após remoção do banho de

gelo, aqueceu-se a mistura reaccional a 65 °C durante 1 h. A solução resultante foi arrefecida a 40 °C, filtrada e lavada com MeOH frio e éter para proporcionar um pó amarelo claro que deu pó branco de I-29 o qual foi utilizado sem purificação adicional no passo reaccional seguinte. MS: m/z 579,1 (M^+1).

A uma solução de ácido 2-ciclopentiloxi-carbonilamino-non-8-enóico (0,87 g, 2,34 mmol), HATU (1,16 g, 3,05 mmol) e HOBt (0,14 g, 1,02 mmol) em CH_2Cl_2 (10 mL) adicionou-se gota a gota uma mistura de I-29 (1,18 g, 2,03 mmol) e NMM (0,49 g, 4,87 mmol) dissolvido em DMF (10 mL) a 5 °C. Depois de se aquecer até à temperatura ambiente e agitar-se durante mais 16 h, adicionou-se HCl a 10% (1 mL) e concentrou-se a mistura reaccional. O resíduo foi arrefecido até 5 °C e lavado sequencialmente com HCl (aq) a 5% (10 mL \times 2) e NaHCO_3 (aq) (10 mL \times 2) para dar um sólido amarelo claro. O sólido foi dissolvido em MeOH (10 mL) e adicionalmente precipitado por adição lenta de uma pequena porção de éter para proporcionar o I-30 (1,51 g, rendimento de 88%). MS: m/z 844,3 (M^+1).

Desgaseificou-se uma solução do composto I-30 (0,50 g, 0,59 mmol) em CH_2Cl_2 (120 mL) por borbulhamento de azoto durante 1 h. Adicionou-se catalisador de 2^a geração de Hoveyda-Grubb (48 mg, 0,076 mmol), e, em seguida, aqueceu-se a mistura reaccional a 40 °C durante 16 h. Após a reação ter sido completa, conforme indicado por HPLC, a mistura reaccional foi arrefecida a 30 °C, concentrada e

purificada por cromatografia em coluna de sílica gel para dar o produto I-31 (0,30 g, rendimento de 62%). MS: m/z 816,3 (M^{+1}); ^1H NMR (CDCl_3) δ 10,33 (s, 1H), 8,30 (d, 1H), 8,11 (dd, 1H), 7,88 (dd, 1H), 7,67-7,56 (m, 2H), 7,46 (dd, 1H), 7,43-7,30 (m, 2H), 6,12 (s, 1H), 5,64 (q, 1H), 5,22 (d, 1H), 4,92 (dd, 1H), 4,77 (d, 1H), 4,66 (dd, 1H), 4,32-4,22 (m, 1H), 4,04 (dd, 1H), 2,93-2,46 (m, 3H), 2,31 (q, 1H), 1,92-0,80 (m, 25H).

A uma solução do composto I-31 (50 mg, 0,061 mmol) em MeOH (10 mL) adicionou-se 5% Pd-C (5 mg) à temperatura ambiente sob N_2 . Em seguida, agitou-se a mistura reaccional em atmosfera de hidrogénio sob uma pressão de 60 psi à temperatura ambiente durante 4 h. A mistura reaccional foi filtrada e purificada por cromatografia em coluna para dar o composto 254 (27,6 mg, 55%). MS: m/z 818,3 (M^{+1}); ^1H NMR (CDCl_3) δ 10,50 (s, 1H), 8,28 (d, 1H), 8,13 (dd, 1H), 7,80 (dd, 1H), 7,65-7,57 (m, 2H), 7,45 (dd, 1H), 7,39-7,30 (m, 2H), 6,11 (s, 1H), 5,25 (d, 1H), 4,96 (brs, 1H), 4,68 (dd, 1H), 4,60 (d, 1H), 4,37 (dd, 1H), 4,14 (dd, 1H), 3,02-2,57 (m, 3H), 1,92-0,80 (m, 29H).

Exemplos 255-281: Sínteses dos Compostos 255-281

Cada um dos compostos 255-281 foi preparado de um modo semelhante ao descrito no Exemplo 254.

Composto 255: MS: m/z 764,2 (M^{+1}); ^1H NMR (CDCl_3)

δ 10,47 (s, 1H), 7,88-7,84 (m, 3H), 7,70 (s, 1H), 7,56 (dd, 1H), 7,37 (m, 1H), 7,18 (m, 1H), 6,20 (d, 1H), 5,97 (s, 1H), 5,64 (q, 1H), 4,94 (dd, 1H), 4,68 (m, 1H), 4,61 (d, 1H), 4,44 (m, 1H), 4,02 (m, 1H), 2,85 (m, 2H), 2,70 (m, 1H), 2,58 (m, 1H), 2,25 (q, 1H), 1,92 (s, 3H), 1,90-1,03 (m, 15H).

Composto 256: MS: m/z 815,6 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,31 (s, 1H), 8,32 (d, 1H), 8,25 (m, 1H), 7,81 (dd, 1H), 7,64 (m, 2H), 7,46 (dd, 1H), 7,23-7,12 (m, 2H), 6,20 (s, 1H), 5,66 (q, 1H), 5,16 (d, 1H), 4,98 (dd, 1H), 4,75-4,64 (m, 3H), 4,31 (m, 1H), 4,08 (m, 1H), 2,88 (m, 1H), 2,78 (m, 2H), 2,55 (m, 1H), 2,29 (q, 1H), 1,92-0,84 (m, 23H).

Composto 257: MS: m/z 804,1 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,52 (s, 1H), 8,29 (d, 1H), 8,03-7,97 (m, 2H), 7,82 (dd, 1H), 7,63-7,42 (m, 3H), 7,21 (m, 1H), 5,97 (s, 1H), 5,60 (q, 1H), 5,44 (d, 1H), 4,85 (dd, 1H), 4,66 (m, 2H), 4,29 (m, 1H), 4,02 (m, 1H), 3,88-3,62 (m, 2H), 2,87-2,58 (m, 5H), 2,33 (q, 1H), 1,90-0,78 (m, 15H), 0,97 (s, 6H).

Composto 258: MS: m/z 806,1 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,36 (s, 1H), 8,28 (d, 1H), 8,07 (m, 1H), 7,84 (s, 1H), 7,62 (m, 3H), 7,44 (m, 2H), 7,18 (m, 1H), 6,06 (s, 1H), 5,67 (q, 1H), 4,96 (dd, 1H), 4,80 (d, 1H), 4,60 (m, 1H), 4,41 (m, 1H), 4,10 (m, 2H), 3,66 (m, 1H), 3,39 (m, 2H), 3,22 (s, 3H), 2,91-2,58 (m, 4H), 2,20 (q, 1H), 1,90-0,86 (m, 15H).

Composto 259: MS: m/z 788,1 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,51 (s, 1H), 8,28 (d, 1H), 7,94 (m, 1H), 7,86 (s, 1H),
7,64 (d, 1H), 7,60-7,43 (m, 4H), 7,16 (m, 1H), 6,00 (s,
1H), 5,85 (m, 1H), 5,62 (m, 2H), 5,30-5,19 (m, 2H), 4,93
(dd, 1H), 4,66 (m, 1H), 4,58-4,36 (m, 3H), 4,02 (m, 1H),
2,87-2,56 (m, 4H), 2,26 (q, 1H), 1,86-0,86 (m, 15H).

Composto 260: MS: m/z 762,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,63 (s, 1H), 8,26 (d, 1H), 8,10 (s, 1H), 7,88 (d, 1H),
7,67-7,44 (m, 4H), 6,84 (s, 1H), 5,89 (s, 1H), 5,68 (q,
1H), 5,38 (d, 1H), 4,97 (dd, 1H), 4,76 (m, 1H), 4,58 (d,
1H), 4,21 (m, 1H), 3,96 (m, 1H), 3,66 (s, 3H), 2,91-2,60
(m, 4H), 2,25 (q, 1H), 1,89-0,89 (m, 15H).

Composto 261: MS: m/z 704,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 9,26 (s, 1H), 8,47 (d, 1H), 8,26 (m, 1H), 8,15 (dd, 1H),
7,97-7,82 (m, 3H), 7,66 (m, 1H), 6,54 (s, 1H), 5,74 (q,
1H), 5,13 (dd, 1H), 4,60 (d, 1H), 4,35 (m, 2H), 3,72-3,58
(m, 2H), 2,97-2,81 (m, 3H), 2,51 (m, 1H), 2,33 (q, 1H),
1,99-1,06 (m, 15H).

Composto 262: MS: m/z 818,3 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,42 (s, 1H), 8,30 (d, 1H), 8,12 (m, 1H), 7,86 (m, 1H),
7,49-7,33 (m, 5H), 6,10 (s, 1H), 5,66 (m, 2H), 5,08-4,66
(m, 4H), 4,28 (m, 1H), 4,03 (m, 1H), 3,86-3,58 (m, 4H),
2,86-2,57 (m, 4H), 2,34 (q, 1H), 2,03-0,87 (m, 17H).

Composto 263: MS: m/z 780,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,60 (s, 1H), 8,04-7,92 (m, 3H), 7,78 (m, 1H), 7,56 (dd,

1H), 7,38 (m, 1H), 6,94 (m, 1H), 5,89 (s, 1H), 5,67 (q, 1H), 5,40 (d, 1H), 4,95 (dd, 1H), 4,76 (m, 1H), 4,57 (d, 1H), 4,20 (m, 1H), 3,97 (m, 1H), 3,64 (s, 3H), 2,94-2,63 (m, 4H), 2,23 (q, 1H), 1,88-1,09 (m, 15H).

Composto 264: MS: m/z 931,3 (M⁺+1); ¹H NMR (CDCl₃) δ 10,43 (s, 1H), 8,30 (d, 1H), 8,10 (m, 1H), 7,86 (d, 1H), 7,62-7,34 (m, 5H), 6,08 (s, 1H), 5,60 (q, 1H), 5,38 (s, 1H), 4,90-4,62 (m, 4H), 4,26 (m, 1H), 4,03 (m, 1H), 3,64 (m, 2H), 3,15 (m, 2H), 2,85-2,55 (m, 4H), 2,33 (q, 1H), 1,83-0,86 (m, 19H), 1,44 (s, 9H).

Composto 265: MS: m/z 780,2 (M⁺+1); ¹H NMR (CDCl₃) δ 10,45 (s, 1H), 8,29 (d, 1H), 8,05 (m, 1H), 7,78 (d, 1H), 7,63-7,25 (m, 4H), 6,04 (m, 2H), 5,63 (q, 1H), 4,91 (dd, 1H), 4,72-4,63 (m, 3H), 4,43-4,32 (m, 2H), 4,02 (m, 1H), 3,78-3,58 (m, 1H), 2,85-2,35 (m, 6H), 2,03-0,86 (m, 15H).

Composto 266: MS: m/z 776,3 (M⁺+1); ¹H NMR (CDCl₃) δ 10,56 (s, 1H), 8,24 (d, 1H), 8,00 (s, 1H), 7,87-7,79 (m, 2H), 7,61-7,42 (m, 4H), 7,06 (m, 1H), 5,93 (s, 1H), 5,61 (q, 1H), 5,44 (m, 1H), 4,91 (dd, 1H), 4,68 (m, 1H), 4,25-3,96 (m, 4H), 2,86-2,57 (m, 4H), 2,29 (q, 1H), 1,81-0,88 (m, 18H).

Composto 267: MS: m/z 812,2 (M⁺+1); ¹H NMR (CDCl₃) δ 10,47 (s, 1H), 8,27 (d, 1H), 7,90 (m, 1H), 7,81 (m, 2H), 7,76-7,43 (m, 4H), 7,17 (m, 1H), 6,03-5,85 (m, 2H), 5,61 (q, 1H), 4,88 (dd, 1H), 4,72-4,61 (m, 2H), 4,25-3,98 (m, 4H), 2,86-2,58 (m, 4H), 2,30 (q, 1H), 1,84-0,88 (m, 15H).

Composto 268: MS: m/z 832,2 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,50 (s, 1H), 8,35-8,29 (m, 1H), 8,15-8,01 (m, 1H),
7,84-7,32 (m, 5H), 7,13-7,03 (m, 1H), 6,10 (s, 1H), 5,54
(m, 1H), 5,36 (d, 1H), 5,05-4,83 (m, 2H), 4,74-4,65 (m,
1H), 4,36 (m, 1H), 4,14-4,05 (m, 1H), 2,88-2,51 (m, 4H),
2,12-0,88 (m, 24H).

Composto 269: MS: m/z 834,3 (M^{+1}).

Composto 270: MS: m/z 792,2 (M^{+1}).

Composto 271: MS: m/z 822,2 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,38 (s, 1H), 8,09 (m, 1H), 7,99 (dd, 1H), 7,83 (dd,
1H), 7,58 (dd, 1H), 7,41-7,25 (m, 3H), 6,15 (s, 1H), 5,59
(q, 1H), 5,16 (d, 1H), 4,89 (dd, 1H), 4,78-4,67 (m, 2H),
4,25 (m, 1H), 4,07 (m, 1H), 2,77-2,70 (m, 3H), 2,57 (m,
1H), 2,30 (q, 1H), 1,90-0,82 (m, 15H), 1,23 (s, 9H).

Composto 272: MS: m/z 822,2 (M^{+1}); ^1H NMR (CDCl_3)
 δ 10,37 (s, 1H), 8,10 (m, 1H), 7,98 (dd, 1H), 7,83 (dd,
1H), 7,58 (dd, 1H), 7,42-7,27 (m, 2H), 7,19 (s, 1H), 6,16
(s, 1H), 5,62 (q, 1H), 5,11 (d, 1H), 4,92 (dd, 1H), 4,78-
4,67 (m, 2H), 4,24 (m, 1H), 4,07 (m, 1H), 2,86-2,77 (m,
3H), 2,56 (m, 1H), 2,32 (q, 1H), 1,90-0,82 (m, 15H), 1,23
(s, 9H).

Composto 273: MS: m/z 850,3, 852,3 (M^{+1}).

Composto 274: MS: m/z 834,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,43 (s, 1H), 8,08 (m, 1H), 7,95 (dd, 1H), 7,91 (dd, 1H), 7,56 (dd, 1H), 7,50 (s, 1H), 7,37-7,31 (m, 2H), 6,05 (s, 1H), 5,58 (q, 1H), 5,39 (d, 1H), 4,72-4,67 (m, 4H), 4,27 (m, 1H), 4,03 (m, 1H), 2,89-2,67 (m, 3H), 2,55 (m, 1H), 2,29 (q, 1H), 1,90-0,87 (m, 23H).

Composto 275: MS: m/z 780,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,61 (s, 1H), 8,06-7,92 (m, 3H), 7,75 (m, 1H), 7,55 (dd, 1H), 7,39 (m, 1H), 6,90 (m, 1H), 5,89 (s, 1H), 5,66 (q, 1H), 5,44 (d, 1H), 4,94 (dd, 1H), 4,77 (m, 1H), 4,58 (d, 1H), 4,20 (m, 1H), 3,96 (m, 1H), 3,65 (s, 3H), 2,93-2,67 (m, 4H), 2,24 (q, 1H), 1,87-1,09 (m, 15H).

Composto 276: MS: m/z 818,1 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,35 (s, 1H), 8,05 (m, 1H), 7,96 (dd, 1H), 7,75 (dd, 1H), 7,57-7,52 (m, 2H), 7,39-7,32 (m, 3H), 6,06 (s, 1H), 5,60 (q, 1H), 4,85-4,73 (m, 2H), 4,55-4,48 (m, 2H), 4,06 (m, 1H), 2,83 (m, 2H), 2,69 (m, 1H), 2,50 (m, 1H), 2,23 (q, 1H), 1,85-1,05 (m, 15H).

Composto 277: MS: m/z 856,3 ($M^+ + 1$).

Composto 278: MS: m/z 764,2 ($M^+ + 1$); ^1H NMR (CDCl_3)
 δ 10,49 (s, 1H), 7,94-7,82 (m, 3H), 7,72 (s, 1H), 7,55 (dd, 1H), 7,38 (m, 1H), 7,17 (m, 1H), 6,21 (d, 1H), 5,99 (s, 1H), 5,62 (q, 1H), 4,94 (dd, 1H), 4,68 (m, 1H), 4,61 (d, 1H), 4,45 (m, 1H), 4,02 (m, 1H), 2,85 (m, 2H), 2,71 (m, 1H), 2,56 (m, 1H), 2,27 (q, 1H), 1,92 (s, 3H), 1,90-1,03 (m, 15H).

Composto 279: MS: m/z 834,3 (M^+1); ^1H NMR (CDCl_3) δ 10,43 (s, 1H), 8,05 (m, 1H), 7,96 (dd, 1H), 7,91 (dd, 1H), 7,55 (dd, 1H), 7,48 (s, 1H), 7,37-7,32 (m, 2H), 6,05 (s, 1H), 5,57 (q, 1H), 5,39 (d, 1H), 4,79-4,67 (m, 4H), 4,28 (m, 1H), 4,03 (m, 1H), 2,87-2,67 (m, 3H), 2,54 (m, 1H), 2,29 (q, 1H), 1,90-0,87 (m, 23H).

Composto 280: MS: m/z 818,2 (M^+1); ^1H NMR (CDCl_3) δ 10,36 (s, 1H), 8,02 (m, 1H), 7,94 (dd, 1H), 7,71 (dd, 1H), 7,60 (s, 1H), 7,54-7,51 (dd, 1H), 7,42 (d, 1H), 7,36-7,30 (m, 2H), 6,03 (s, 1H), 5,60 (q, 1H), 4,86-4,72 (m, 2H), 4,56-4,48 (m, 2H), 4,05 (m, 1H), 2,84 (m, 2H), 2,68 (m, 1H), 2,48 (m, 1H), 2,23 (q, 1H), 1,88-1,05 (m, 15H).

O composto 281 foi preparado de modo semelhante ao procedimento descrito no Exemplo 1: Composto 281: MS: m/z 901,2 (M^+1); ^1H NMR (CDCl_3) δ 10,25 (s, 1H), 8,48 (d, 1H), 7,59 (dd, 1H), 7,39 (d, 1H), 7,32 (dd, 1H), 7,15 (s, 1H), 7,04 (s, 1H), 6,14 (s, 1H), 5,69 (ddd, 1H), 5,04 (m, 2H), 4,72 (m, 1H), 4,56 (m, 2H), 4,24-4,15 (m, 2H), 3,97 (s, 3H), 3,34 (tt, 1H), 2,55 (m, 1H), 2,24-2,26 (m, 1H), 2,01-0,69 (m, 34H).

Exemplo 282: Inibição de Protease NS3/4A

Expressão e purificação de proteína

Transformou-se um plasmídeo contendo um gene que

codifica o NS4A₍₂₁₋₃₂₎-GSGS-NS3₍₃₋₁₈₁₎ marcado com His₆ com N-terminal em estirpe de *E. coli* BL21 (DE3) pLysS (Novagen) para sobre-expressão da proteína. Cultivou-se colônia única de BL21 (DE3) pLysS transformada em 200 mL de meio de Lauria-Bertani (LB) com Canamicina e Cloranfenicol a 37°C durante a noite. Transferiu-se a cultura bacteriana para 6 L de meio LB (Difco) contendo antibióticos e incubou-se com vibração a 22 °C. Após a absorvância a 600 nm atingir 0,6, induziu-se a cultura com isopropil-1-tio-β-D-galactopiranosido (IPTG) 1 mM a 22 °C durante 5 horas. A cultura foi subsequentemente recolhida por centrifugação (6.000 ×g durante 15 minutos a 4 °C). Suspenderam-se novamente pellets celulares em 150 mL de tampão A (HEPES 50 mM, pH 7,4, NaCl 0,3 M, CHAPS 0,1% (p/v), imidazol 10 mM, glicerol 10% (v/v)). Após a mistura ter sido interrompida por quatro passagens através de um Microfluidizador operado a 30 psi, removeram-se os detritos celulares por centrifugação (58.250 ×g durante 30 minutos a 4 °C). Carregou-se o lisado celular contendo proteínas marcadas com His₆ a 3 mL/min numa coluna de 25 mL Ni-NTA (Qiagen) na presença de imidazol 10 mM usando-se um sistema gradiFrac (Pharmacia). Lavou-se a coluna com 10 volumes de coluna de tampão de lise. O NS4A₍₂₁₋₃₂₎-GSGS-NS3₍₃₋₁₈₁₎ ligado foi eluído com 8 volumes de coluna de tampão A suplementado com imidazol 300 mM. As frações reunidas foram adicionalmente purificadas por coluna Q-Sepharose equilibrada com tampão B (HEPES 50 mM, pH 7,4, CHAPS 0,1% (p/v), glicerol 10% (v/v), ditiotreititol 5 mM (DTT) e NaCl 1 M. O eluente contendo NS4A₍₂₁₋₃₂₎-GSGS-NS3₍₃₋₁₈₁₎ foi recolhido e adicionalmente purificado por cromatografia de exclusão por tamanho a um

caudal de 0,5 mL/min usando-se a coluna sephacryl-75 (16 × 100 cm, Pharmacia) pré-equilibrada com tampão C (HEPES 50 mM, pH 7,4, CHAPS 0,1% (p/v), DTT 5 mM, glicerol 10% (v/v)). A proteína purificada foi congelada e armazenada a -80 °C antes de ser usada.

Ensaio de HPLC Microbore

Preparou-se uma solução contendo Tris 50 mM, pH 7,4, NaCl 100 mM, glicerol 20%, CHAPS 0,012%, DTT 10 mM, substrato Ac-Asp-Glu-Asp(EDANS)-Glu-Glu-Abu-Ψ-[COOAla]-Ser-Lys(DABCYL)-NH₂ 5 μM (RET S1, ANASPEC), e composto de ensaio 10 μM. Adicionaram-se 80 μL da solução a cada poço de uma placa de 96 poços. Iniciou-se a reação por adição de 20 μL de protease NS3/4A 10 nM num tampão contendo tampão Tris 50 mM, pH 7,4, NaCl 100 mM, glicerol 20%, e CHAPS 0,012%. A concentração final da protease NS3/4A foi 2 nM, a qual era inferior ao Km do substrato RET S1.

Incubou-se a solução de ensaio durante 30 minutos a 30 °C. A reação foi em seguida extinta por adição de 100 μL de TFA a 1%. Transferiu-se uma alíquota de 200 μL para cada poço de placas de 96 poços Agilent.

Analisaram-se os produtos da reação utilizando-se HPLC de fase reversa descrita abaixo. O sistema de HPLC incluía: Agilent 1100, Desgaseificador G1379A, Bomba binária G1312A, Auto-amostrador G1367A, Câmara com coluna termostaticada G1316A, Detetor de díodos G1315B, Coluna: Agilent, ZORBAX Eclipse XDB-C18, 4,6 mm, 5 μm, P/N 993967-

902, Termostato da coluna: temperatura ambiente, volume de injeção: 100 µL, Solvente A = água de grau HPLC + TFA 0,09%, Solvente B = acetonitrilo de grau HPLC + TFA 0,09%. O tempo total de operação do HPLC foi de 7,6 minutos com um gradiente linear de 25 a 50% de solvente B durante 4 minutos, 50% de solvente B durante 30 segundos, e um gradiente de 50 a 25% de solvente B durante mais 30 segundos. A coluna foi reequilibrada com 25% de solvente B durante 2,6 minutos antes da amostra seguinte ser injetada. O valor de IC₅₀ (a concentração à qual se observou 50% de inibição de atividade de NS3/4A) foi calculado para cada composto de ensaio com base nos resultados de HPLC.

Os compostos 1-281 foram testados no ensaio de inibição anterior. Os resultados mostraram que 274 compostos apresentaram valores de IC₅₀ inferiores a 20 nM e 7 compostos apresentaram valores de IC₅₀ na gama de 20-100 nM.

Além disso, verificou-se que certos compostos desta invenção inibem, inesperadamente, de uma forma eficaz mutantes da protease de HCV resistentes a uma ou mais outras drogas de HCV.

Exemplo 283: Protocolo de Ensaio de Células replicação de HCV

Mantiveram-se células que contêm o replicação de HCV em DMEM contendo soro fetal de bovino (FBS) a 10%, 1,0 mg/ml de G418, e os suplementos apropriados (meio A).

No dia 1, a monocamada de células replicação foi tratada com uma mistura de tripsina/EDTA, removida e diluída com o meio A até uma concentração final de 48.000 células/ml. Adicionou-se a solução (1 ml) a cada poço de uma placa de cultura de tecidos de 24 poços e cultivou-se durante a noite numa incubadora de cultura de tecidos a 37 °C com 5% de CO₂.

No dia 2, diluiu-se um composto de ensaio (em 100% de DMSO) em série através de DMEM contendo 10% de FBS e suplementos apropriados (meio B). Manteve-se a concentração final de DMSO a 0,2% durante a série de diluições.

Removeu-se o meio na monocamada de células replicação e em seguida adicionou-se meio B contendo várias concentrações de compostos. Adicionou-se meio B sem qualquer composto a outros poços como controlos sem composto.

Incubaram-se as células com um composto ou com 0,2% de DMSO em meio B durante 72 horas numa incubadora de cultura de tecidos com 5% de CO₂ a 37°C. Em seguida, removeu-se o meio e lavou-se a monocamada de células replicação uma vez com PBS. Adicionaram-se imediatamente reagentes de extração de RNA de kits RNeasy ou reagentes Trizol às células para se evitar a degradação do RNA. Extraíu-se o RNA total de acordo com as instruções fornecidas pelo fabricante com modificações para se melhorar a eficiência da extração e a consistência.

Finalmente, eluíu-se o RNA celular total, incluindo o RNA replicação de VHC, e armazenou-se a -80°C até processamento posterior.

Instalou-se um ensaio TaqMan® de quantificação de RT-PCR em tempo real com dois conjuntos de iniciadores específicos: um para HCV e o outro para ACTB (beta-actina). Adicionou-se o RNA total às reações PCR para a quantificação de ambos, HCV e RNA ACTB, no mesmo poço de PCR. A falha experimental foi marcada e rejeitada com base no nível de RNA ACTB em cada poço. O nível de RNA HCV em cada poço foi calculado de acordo com uma curva padrão obtida na mesma placa de PCR. A percentagem de inibição do nível de RNA HCV pelo tratamento com composto foi calculada usando-se o controlo de DMSO ou sem composto como 0% de inibição. A EC₅₀ (concentração à qual foi atingida 50% de inibição do nível de RNA HCV) foi calculada a partir da curva de titulação de qualquer composto.

Testaram-se os compostos 1-281 no ensaio de células replicação de HCV. Os resultados mostraram que 274 compostos apresentaram valores de EC₅₀ inferiores a 20 nM e 7 compostos apresentaram valores de EC₅₀ na gama de 20-100 nM.

Exemplo 284: Estudo farmacocinético

Implantaram-se cirurgicamente ratos Sprague-Dawley machos (300-400 g) com uma cânula de polietileno na veia jugular para amostragem de sangue, sob anestesia com

pentobarbital, no dia antes da fase em vida. Mantiveram-se os ratos em jejum durante a noite com água *ad libitum* e dosearam-se, no dia seguinte, com um composto de teste por sonda oral (PO). Recolheram-se amostras sanguíneas periódicas dos animais até 48 horas após a dose e recuperou-se o plasma heparinizado após centrifugação. Extraíu-se o composto de teste no plasma sanguíneo e determinou-se por análise de espectrometria de massa-cromatografia líquida (LC-MS/MS).

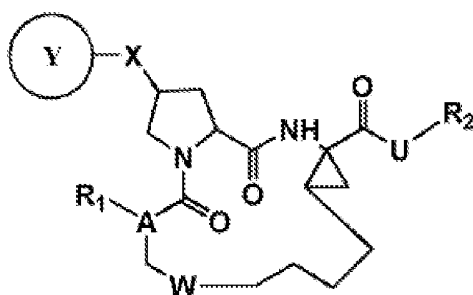
Avaliaram-se os parâmetros farmacocinéticos padrões por análise não compartimental utilizando-se WinNonlin (Versão 4,0, Pharsight, CA, EUA). O máximo da curva de concentração do composto de teste no plasma sanguíneo em função do tempo é representado por C_{max} . Calcularam-se as eliminações de fase terminal aparente ($t_{1/2}$) como $\ln(2)/\lambda_z$, onde λ_z é uma constante de velocidade de eliminação. Calculou-se a área sob a curva de concentração em função do tempo desde o momento da dosagem até infinito ($AUC_{(0-\infty)}$) de acordo com a regra dos trapézios linear.

Certos compostos desta invenção mostraram uma meia vida prolongada e grandes valores de AUC.

Lisboa, 24 de agosto de 2016

REIVINDICAÇÕES

1. Um composto com a seguinte fórmula:



em que

R_1 é -H, -OH, alquilo C_{1-6} , alcoxilo C_{1-6} , cicloalquilo C_{3-10} , heterocicloalquilo C_{1-10} , arilo, heteroarilo ou -NH-Z-R; em que R é H ou é uma metade selecionada de alquilo C_{1-6} , cicloalquilo C_{3-10} , heterocicloalquilo C_{1-10} , arilo e heteroarilo, sendo cada uma das quais opcionalmente mono-, di- ou tri-substituída com halo, nitro, ciano, amino, alquilo C_{1-6} , alcoxilo C_{1-6} , alcenilo C_{2-6} , alquinilo C_{2-6} , arilo ou heteroarilo; e Z é -C(O)-, -C(O)O-, -C(O)C(O)O-, -C(O)C(O)NH-, -C(O)NR'-, -OC(S)-, -C(S)NR'- ou -C(NH)O-, sendo R' H, alquilo C_{1-6} , cicloalquilo C_{3-10} , heterocicloalquilo C_{1-10} , arilo ou heteroarilo;

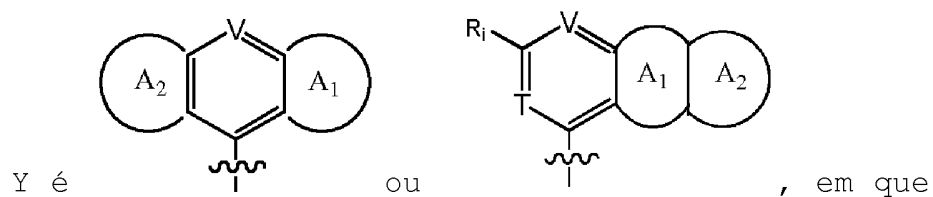
R_2 é H ou uma metade selecionada de alquilo C_{1-6} , cicloalquilo C_{3-10} , heterocicloalquilo C_{1-10} , arilo e heteroarilo, sendo cada uma das quais opcionalmente mono-, di- ou tri-substituída com halo, nitro, ciano, amino, alquilo C_{1-6} , alcoxilo C_{1-6} , alcenilo C_{2-6} , alquinilo C_{2-6} , arilo ou heteroarilo;

A é N ou CH;

U é -O-, -NH-, -NH(CO)-, -NHSO- ou -NH₂SO₂-;

W é -(CH₂)_m-, -NH(CH₂)_n-, -(CH₂)_nNH-, -O(CH₂)_n-,
-(CH₂)_nO-, -S(CH₂)_n-, -(CH₂)_nS-, -SO-, -SO(CH₂)_n-, -(CH₂)_nSO-,
-SO₂(CH₂)_n- ou -(CH₂)_nSO₂-, sendo m 1, 2, ou 3 e sendo n 0, 1
ou 2;

X é -O-, -S-, ou -NH- e

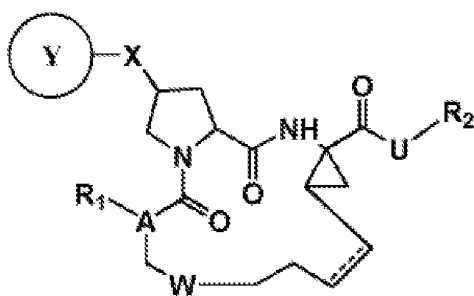


cada um de V e T é, independentemente, -CH- ou -N-; cada um de A₁ e A₂ é, independentemente, uma metade selecionada de cicloalquilo C₄₋₁₀, heterocicloalquilo C₁₋₁₀, arilo e heteroarilo, sendo cada uma das quais opcionalmente mono-, di- ou tri-substituída com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, arilo ou heteroarilo, ou opcionalmente fundida com cicloalquilo C₃₋₁₀, heterocicloalquilo C₂₋₁₀, arilo ou heteroarilo; e R₁ é H, halo, nitro, ciano ou amino, ou é uma metade selecionada de alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo e heteroarilo, sendo cada um de alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆ e alquinilo C₂₋₆

opcionalmente mono-, di- ou tri-substituído com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo, e sendo cada um de cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo e heteroarilo opcionalmente mono-, di- ou tri-substituído com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo, ou opcionalmente fundido com cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo.

2. O composto da reivindicação 1, em que A é CH e W é -CH₂CH₂-, -OCH₂-, -SCH₂-, ou -SOCH₂-.

3. Um composto com a seguinte fórmula:



em que

R₁ é -H, -OH, alquilo C₁₋₆, alcoxilo C₁₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo,

heteroarilo ou -Z-R; em que R é H, ou é uma metade selecionada de alquilo C₁₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo e heteroarilo, sendo cada uma das quais é opcionalmente mono-, di- ou tri-substituída com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, arilo ou heteroarilo; e Z é -C(O)-, -C(O)O-, -C(O)C(O)O-, -C(O)C(O)NH-, -C(O)NR'-, -OC(S)-, -C(S)NR'- ou -C(NH)O-, sendo R' H, alquilo C₁₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo;

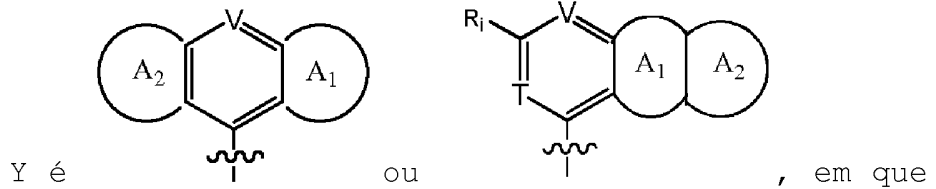
R₂ é H, ou é uma metade selecionada de alquilo C₁₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo e heteroarilo, sendo cada uma das quais opcionalmente mono-, di- ou tri-substituída com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, arilo ou heteroarilo;

A é CH ou N;

U é -O-, -NH-, -NH(CO)-, -NHSO- ou -NHSO₂-;

W é -(CH₂)_m-, -NH(CH₂)_n-, -(CH₂)_nNH-, -O(CH₂)_n-, -(CH_{2n})O-, -S(CH₂)_n-, -(CH₂)_nS-, -SO-, -SO(CH₂)_n-, -(CH₂)_nSO-, -SO₂(CH₂)_n- ou -(CH₂)_nSO₂-, sendo m 1, 2, ou 3 e sendo n 0, 1 ou 2;

X é -O-, -S- ou -NH-;



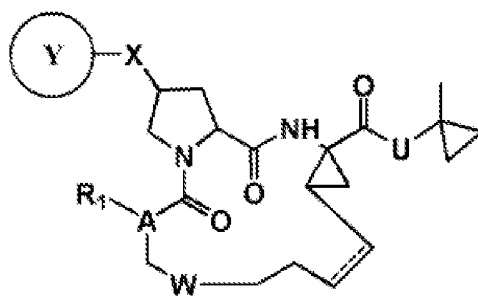
cada um de V e T é, independentemente, -CH- ou -N-; cada um de A₁ e A₂ é, independentemente, uma metade selecionada de cicloalquilo C₄₋₁₀, heterocicloalquilo C₂₋₁₀, arilo e heteroarilo, sendo cada uma das quais opcionalmente mono-, di- ou tri-substituída com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, arilo ou heteroarilo, ou opcionalmente fundida com cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo; e R₁ é H, halo, nitro, ciano ou amino, ou é uma metade selecionada de alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo e heteroarilo, sendo cada um de alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆ e alquinilo C₂₋₆ opcionalmente mono-, di- ou tri-substituído com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo, e sendo cada um de cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo e heteroarilo mono-, di- ou tri-substituído com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo, ou opcionalmente fundido com cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo;

e

\equiv é uma ligação simples ou uma ligação dupla.

4. O composto da reivindicação 3, em que W é $-\text{CH}_2-\text{CH}_2-$, $-\text{OCH}_2-$, $-\text{SCH}_2-$ ou $-\text{SOCH}_2-$; e \equiv é uma ligação dupla.

5. Um composto com a seguinte fórmula:



em que

R_1 é $-\text{H}$, $-\text{OH}$, alquilo C_{1-6} , alcoxilo C_{1-6} , cicloalquilo C_{3-10} , heterocicloalquilo C_{1-10} , arilo, heteroarilo, $-\text{Z}-\text{R}$ ou $-\text{NH}-\text{Z}-\text{R}$; em que R é H, ou é uma metade selecionada de alquilo C_{1-6} , cicloalquilo C_{3-10} , heterocicloalquilo C_{1-10} , arilo e heteroarilo, sendo cada uma das quais opcionalmente mono-, di- ou tri-substituída com halo, nitro, ciano, amino, alquilo C_{1-6} , alcoxilo C_{1-6} , alcenilo C_{2-6} , alquinilo C_{2-6} , arilo ou heteroarilo; e Z é $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{C}(\text{O})\text{NH}-$, $-\text{C}(\text{O})\text{NR}'-$, $-\text{OC}(\text{S})-$, $-\text{C}(\text{S})\text{NR}'-$ ou $-\text{C}(\text{NH})\text{O}-$, sendo R' H, alquilo C_{1-6} ,

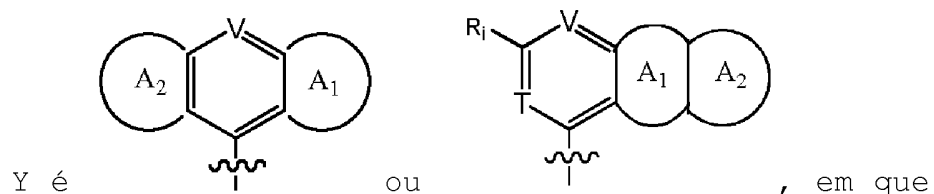
cicloalquilo C_{3-10} , heterocicloalquilo C_{1-10} , arilo ou heteroarilo;

A é N ou CH;

U é -O-, -NH-, -NH(CO)-, -NHSO- ou -NH₂SO₂-;

W é $-(CH_2)_m-$, $-NH(CH_2)_n-$, $-(CH_2)_nNH-$, $-O(CH_2)_n-$, $-(CH_2)_nO-$, $-S(CH_2)_n-$, $-(CH_2)_nS-$, -SO-, -SO(CH₂)_n-, -(CH₂)_nSO-, -SO₂(CH₂)_n- ou -(CH₂)_nSO₂-, sendo m 1, 2, ou 3 e sendo n 0, 1 ou 2;

X é -O-, -S- ou -NH-;



cada um de V e T é, independentemente, -CH- ou -N-; cada um de A₁ e A₂ é, independentemente, uma metade selecionada de cicloalquilo C_{4-10} , heterocicloalquilo C_{2-10} , arilo e heteroarilo, sendo cada uma das quais opcionalmente mono-, di- ou tri-substituída com halo, nitro, ciano, amino, alquilo C_{1-6} , alcoxilo C_{1-6} , alcenilo C_{2-6} , alquinilo C_{2-6} , arilo ou heteroarilo, ou opcionalmente fundida com cicloalquilo C_{3-10} , heterocicloalquilo C_{1-10} , arilo ou heteroarilo; e R_i é H, halo, nitro, ciano ou amino, ou é uma metade selecionada de alquilo C_{1-6} , alcoxilo C_{1-6} ,

alcenilo C₂₋₆, alquinilo C₂₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo e heteroarilo, sendo cada um de alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆ e alquinilo C₂₋₆ opcionalmente mono-, di- ou tri-substituído com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo, e cada um de cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo e heteroarilo opcionalmente mono-, di- ou tri-substituído com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆, alquinilo C₂₋₆, cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo, ou opcionalmente fundido com cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo;

e

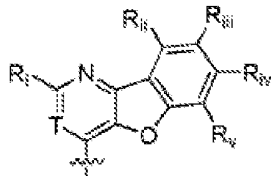
--- é uma ligação simples ou uma ligação dupla.

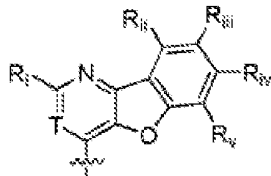
6. O composto da reivindicação 5, em que A é CH; W é -CH₂-CH₂-, -OCH₂-, -SCH₂- ou -SOCH₂-; e --- é uma ligação dupla.

7. O composto de qualquer das reivindicações 1 a 6, em que X é O.

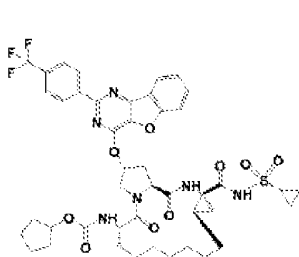
8. O composto de qualquer das reivindicações 1 a 7, em que U é -NHSO₂-.

9. O composto de qualquer das reivindicações 1

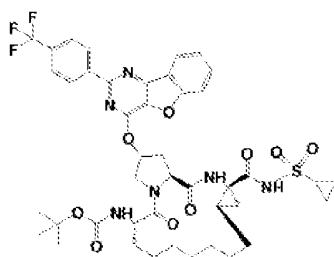


a 8, em que Y é , em que T é CH ou N e cada um de R_i, R_{ii}, R_{iii}, R_{iv} e R_v é, independentemente, H, halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo C₂₋₆ ou alquinilo C₂₋₆, ou é uma metade selecionada de cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo e heteroarilo, sendo cada um das quais opcionalmente mono-, di- ou tri-substituída com halo, nitro, ciano, amino, alquilo C₁₋₆, alcoxilo C₁₋₆, alcenilo, C₂₋₆, alquinilo C₂₋₆, arilo ou heteroarilo, ou opcionalmente fundida com cicloalquilo C₃₋₁₀, heterocicloalquilo C₁₋₁₀, arilo ou heteroarilo.

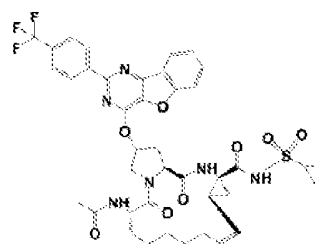
10. Um composto, em que o composto é um dos seguintes compostos:



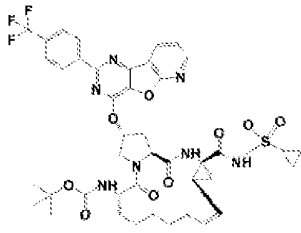
Composto 1



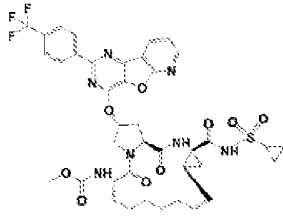
Composto 2



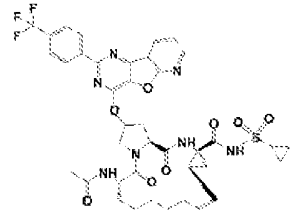
Composto 3



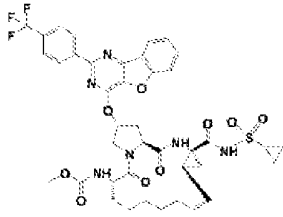
Composto 4



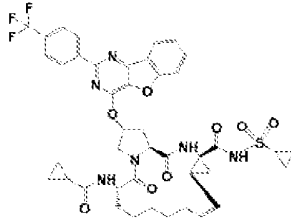
Composto 5



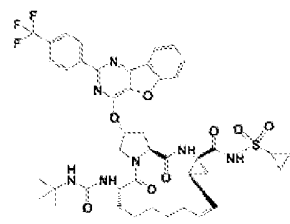
Composto 6



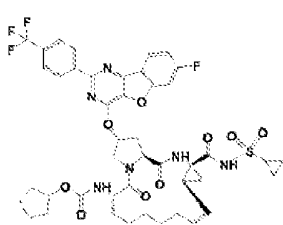
Composto 7



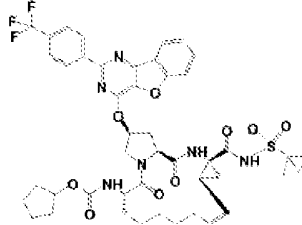
Composto 8



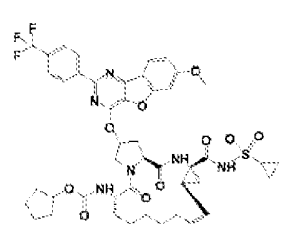
Composto 9



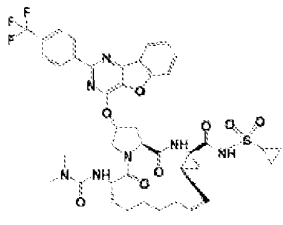
Composto 10



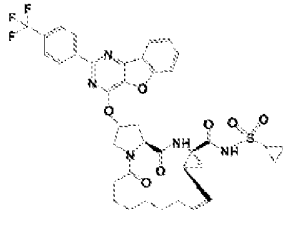
Composto 11



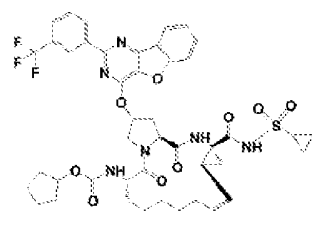
Composto 12



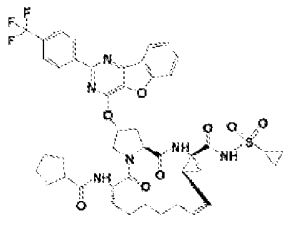
Composto 13



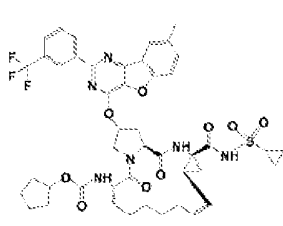
Composto 14



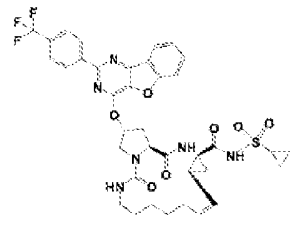
Composto 15



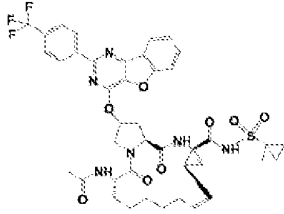
Composto 16



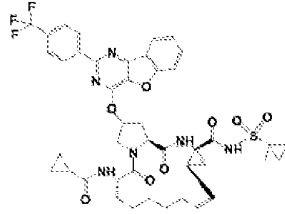
Composto 17



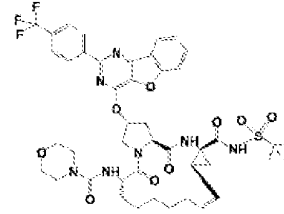
Composto 18



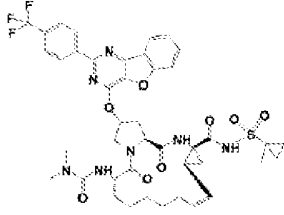
Composto 37



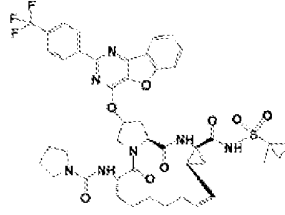
Composto 38



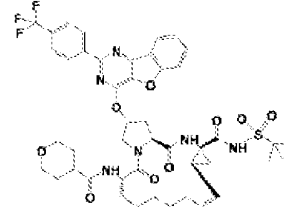
Composto 39



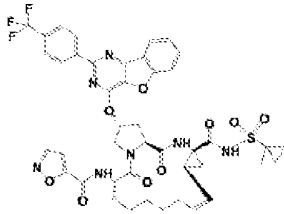
Composto 40



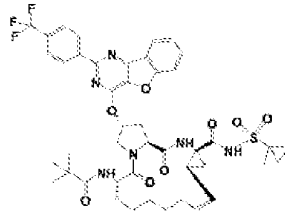
Composto 41



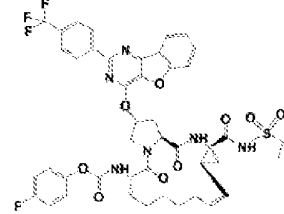
Composto 42



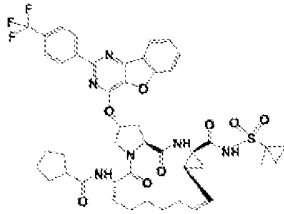
Composto 43



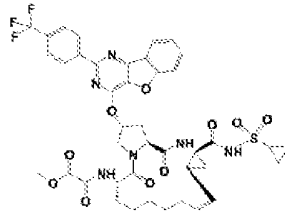
Composto 44



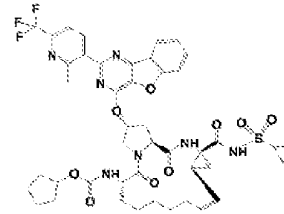
Composto 45



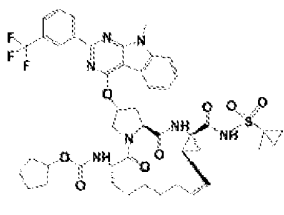
Composto 46



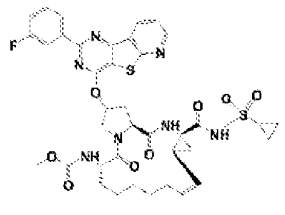
Composto 47



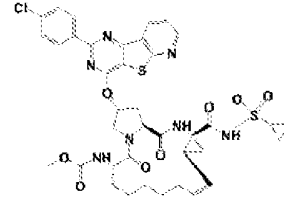
Composto 48



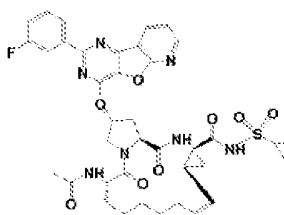
Composto 49



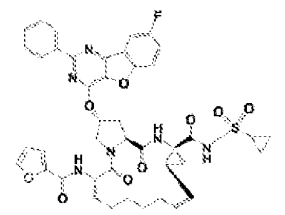
Composto 50



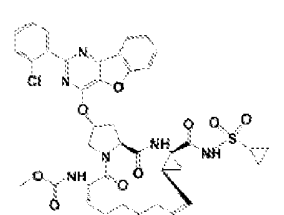
Composto 51



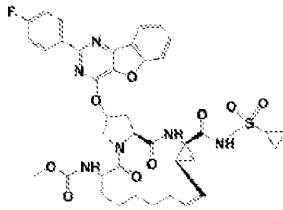
Composto 52



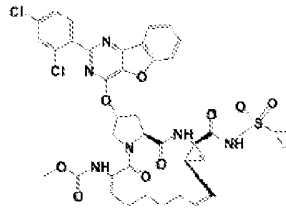
Composto 53



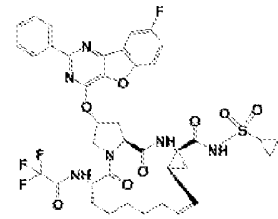
Composto 54



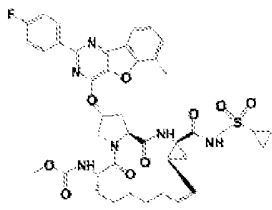
Composto 55



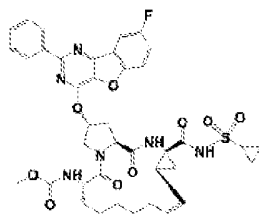
Composto 56



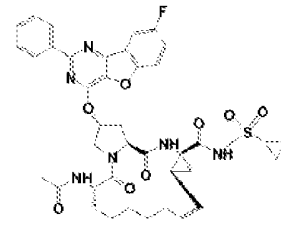
Composto 57



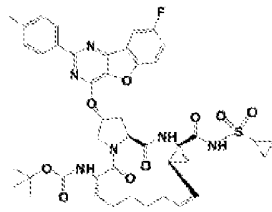
Composto 58



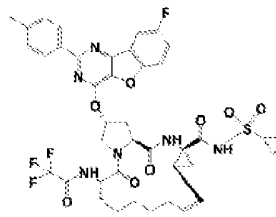
Composto 59



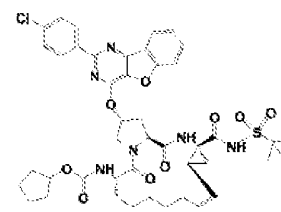
Composto 60



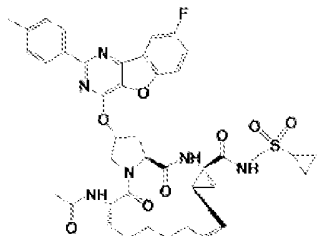
Composto 61



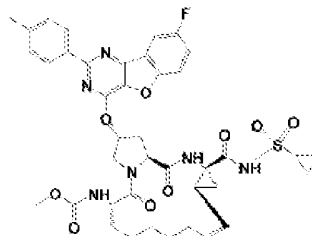
Composto 62



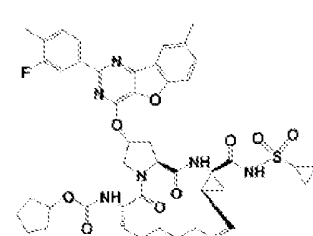
Composto 63



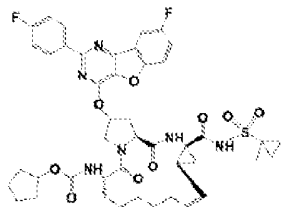
Composto 64



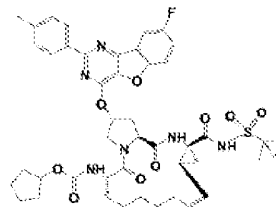
Composto 65



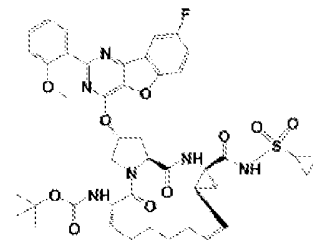
Composto 66



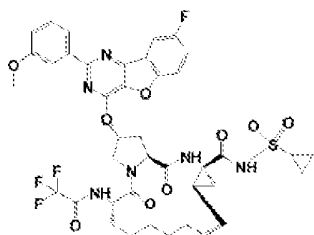
Composto 67



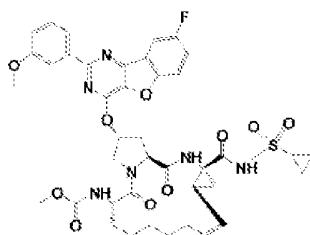
Composto 68



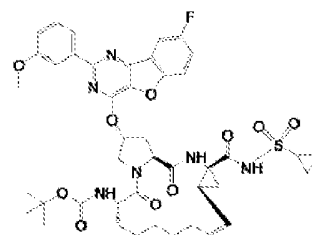
Composto 69



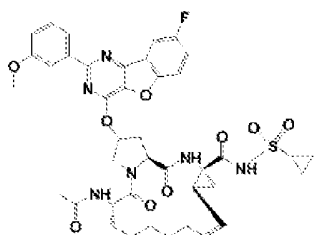
Composto 70



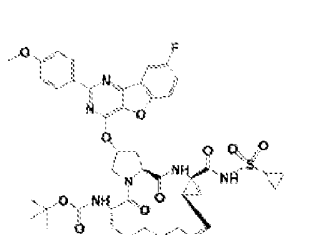
Composto 71



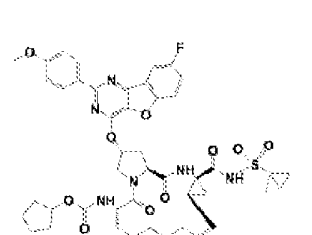
Composto 72



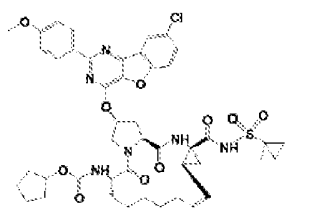
Composto 73



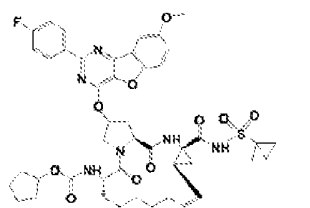
Composto 74



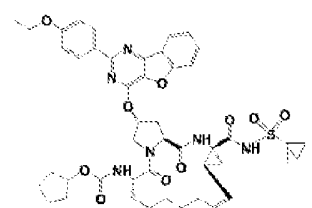
Composto 75



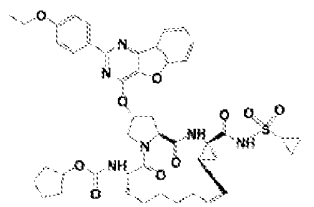
Composto 76



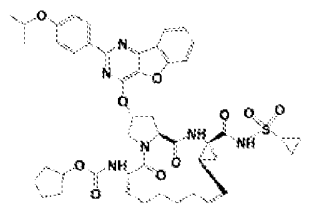
Composto 77



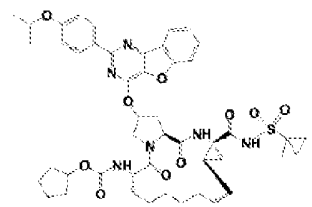
Composto 78



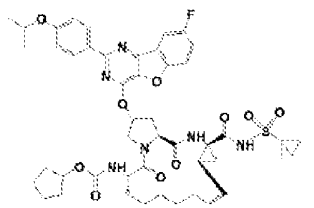
Composto 79



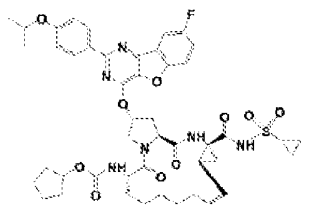
Composto 80



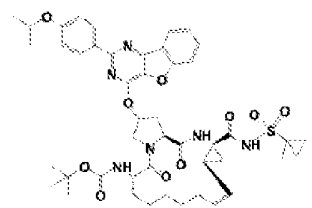
Composto 81



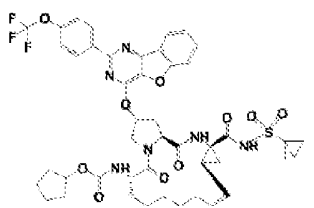
Composto 82



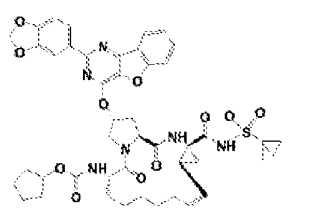
Composto 83



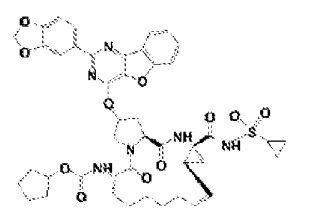
Composto 84



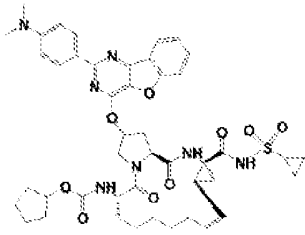
Composto 85



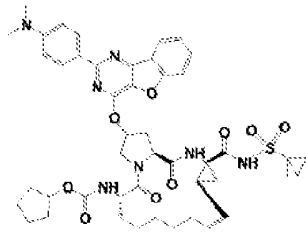
Composto 86



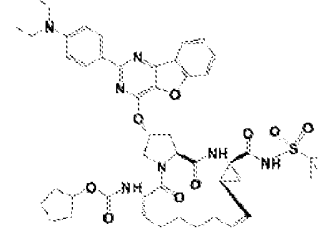
Composto 87



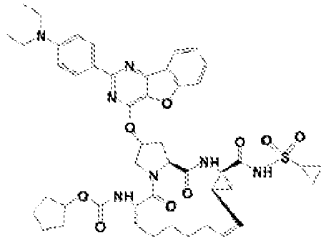
Composto 88



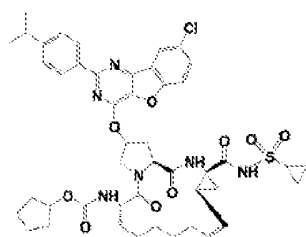
Composto 89



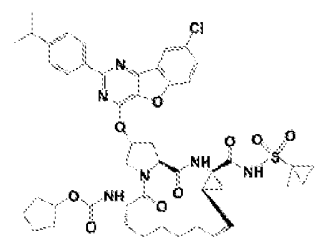
Composto 90



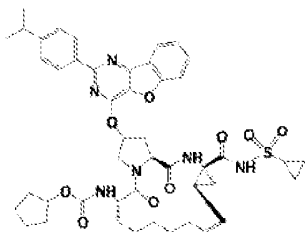
Composto 91



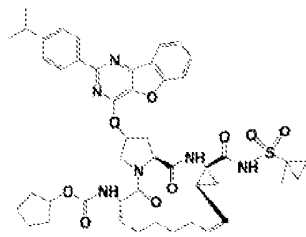
Composto 92



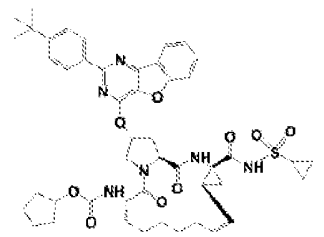
Composto 93



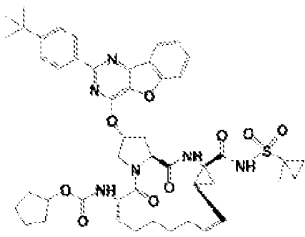
Composto 94



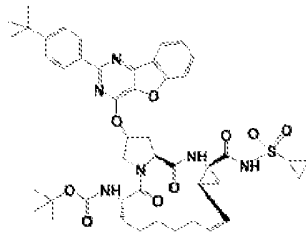
Composto 95



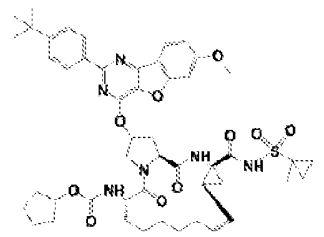
Composto 96



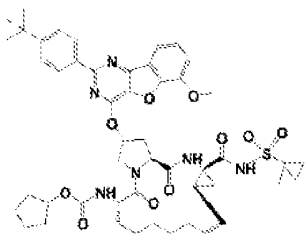
Composto 97



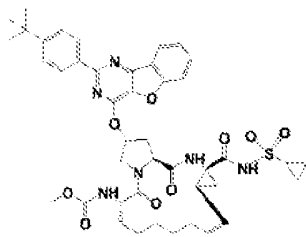
Composto 98



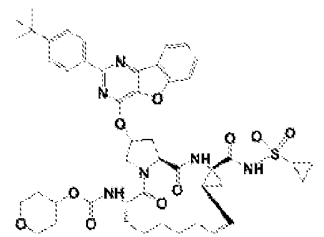
Composto 99



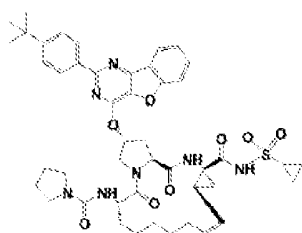
Composto 100



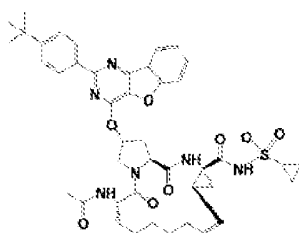
Composto 101



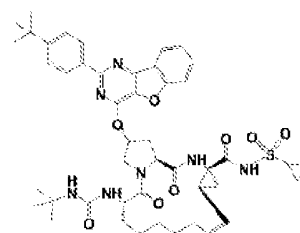
Composto 102



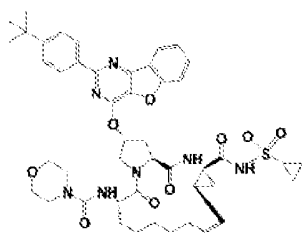
Composto 103



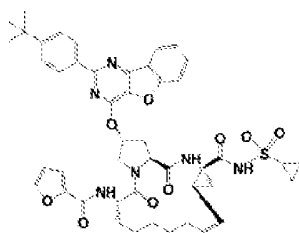
Composto 104



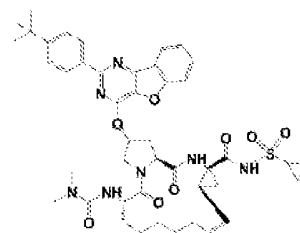
Composto 105



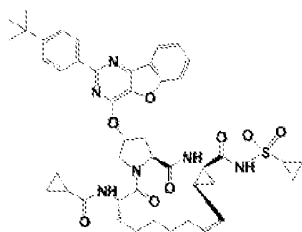
Composto 106



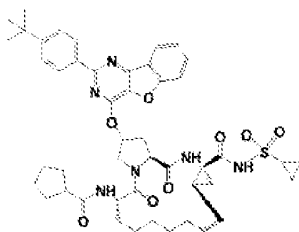
Composto 107



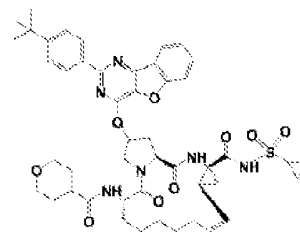
Composto 108



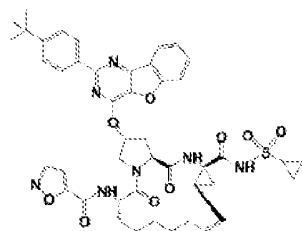
Composto 109



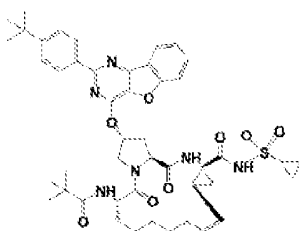
Composto 110



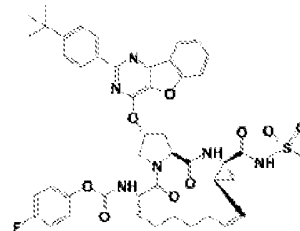
Composto 111



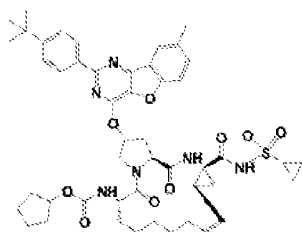
Composto 112



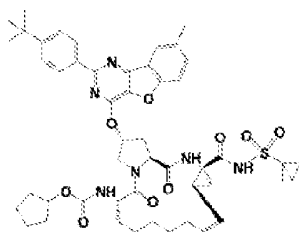
Composto 113



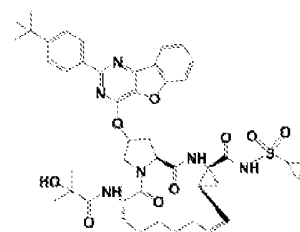
Composto 114



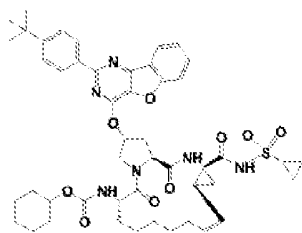
Composto 115



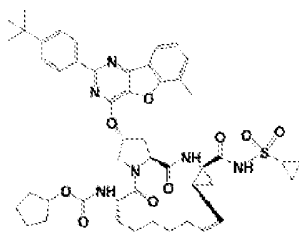
Composto 116



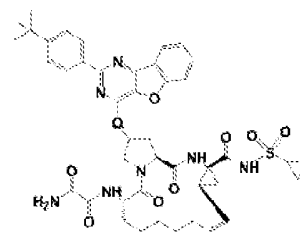
Composto 117



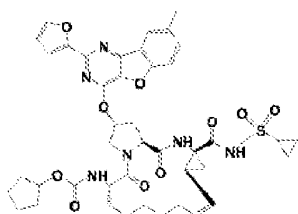
Composto 118



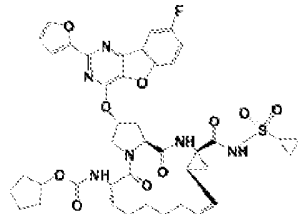
Composto 119



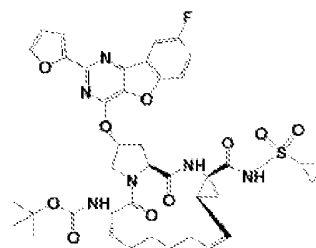
Composto 120



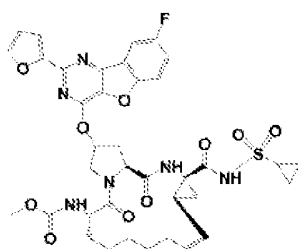
Composto 121



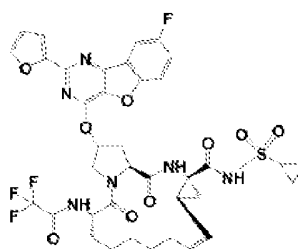
Composto 122



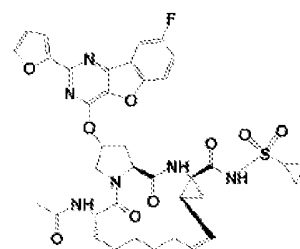
Composto 123



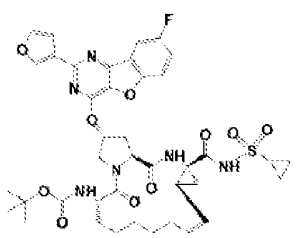
Composto 124



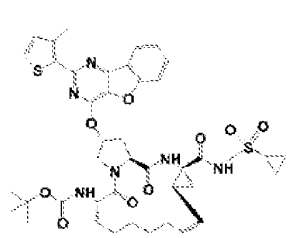
Composto 125



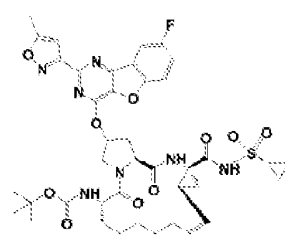
Composto 126



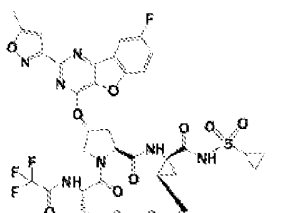
Composto 127



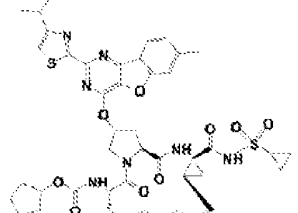
Composto 128



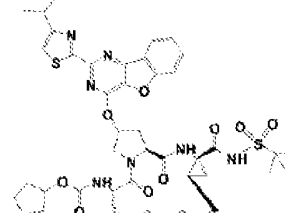
Composto 129



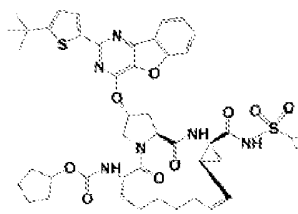
Composto 130



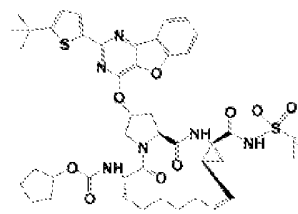
Composto 131



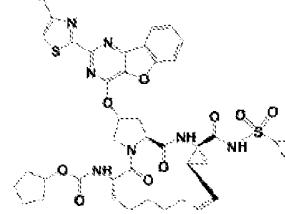
Composto 132



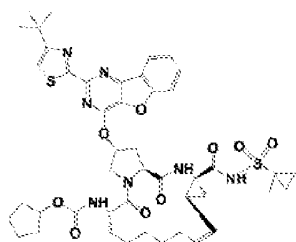
Composto 133



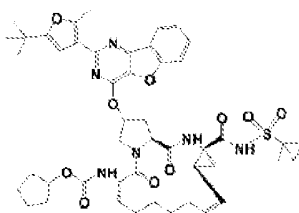
Composto 134



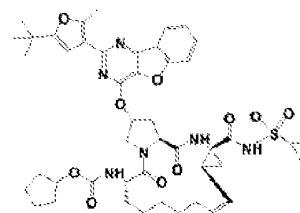
Composto 135



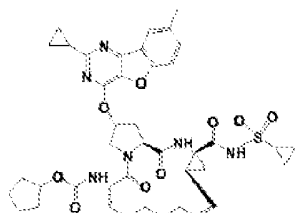
Composto 136



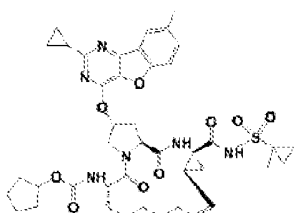
Composto 137



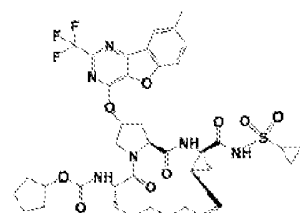
Composto 138



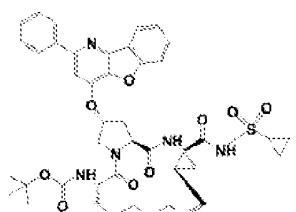
Composto 139



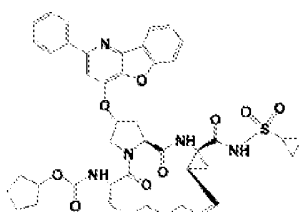
Composto 140



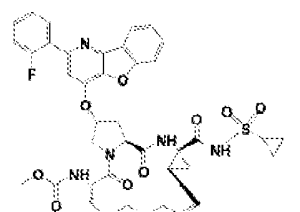
Composto 141



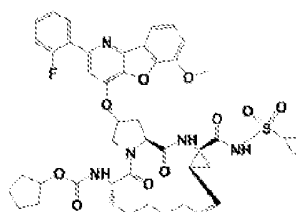
Composto 142



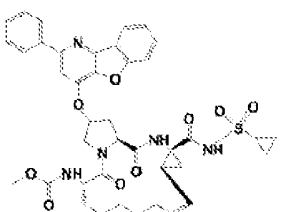
Composto 143



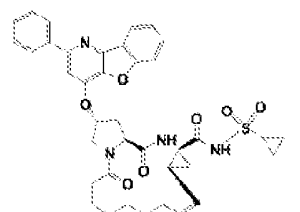
Composto 144



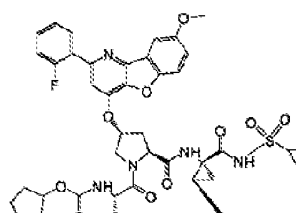
Composto 145



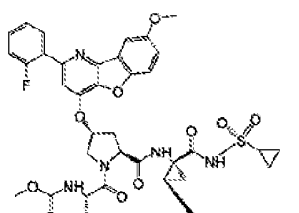
Composto 146



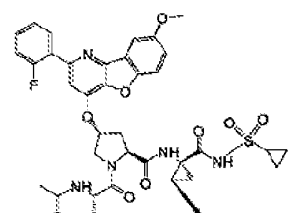
Composto 147



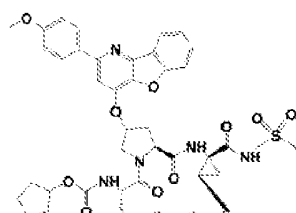
Composto 148



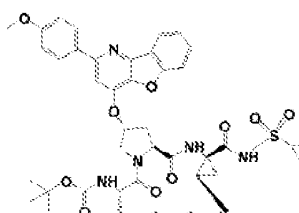
Composto 149



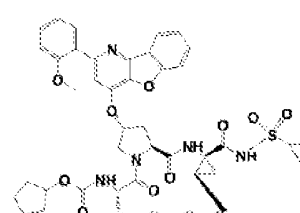
Composto 150



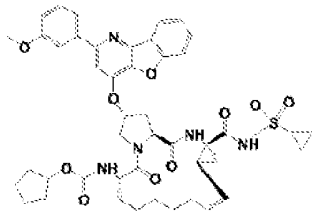
Composto 151



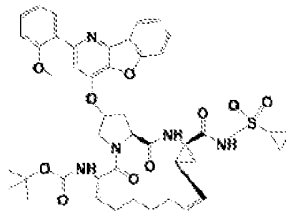
Composto 152



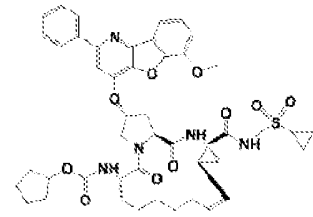
Composto 153



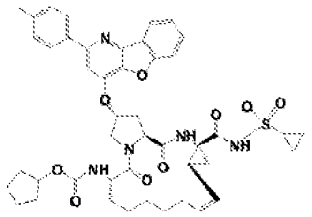
Composto 154



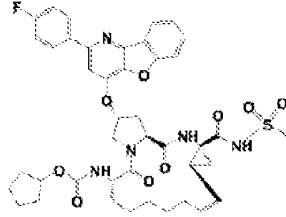
Composto 155



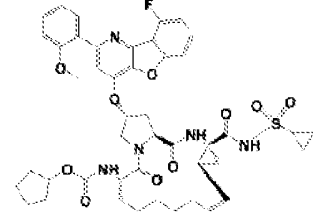
Composto 156



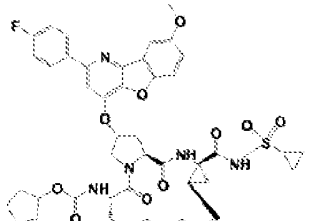
Composto 157



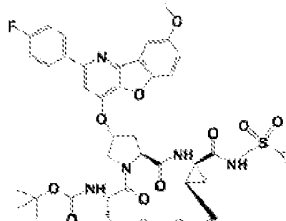
Composto 158



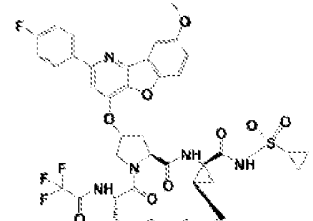
Composto 159



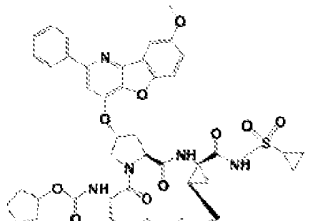
Composto 160



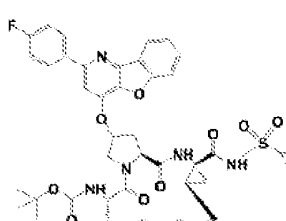
Composto 161



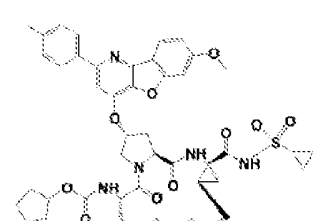
Composto 162



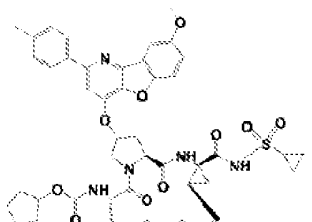
Composto 163



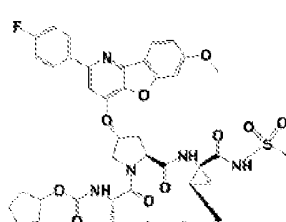
Composto 164



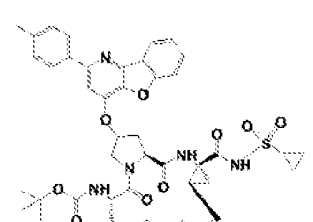
Composto 165



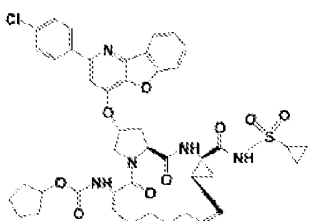
Composto 166



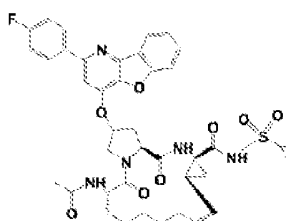
Composto 167



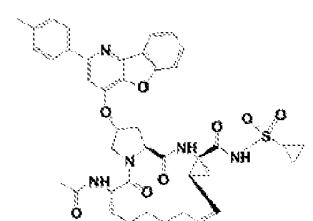
Composto 168



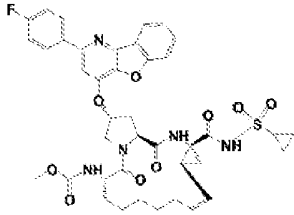
Composto 169



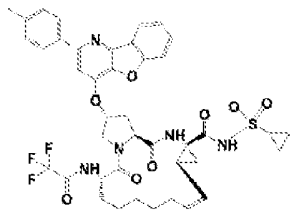
Composto 170



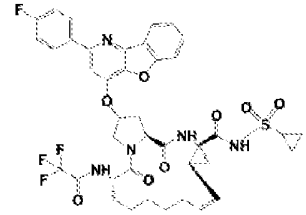
Composto 171



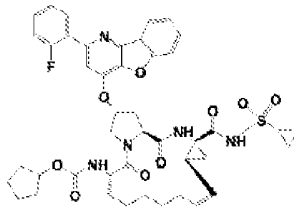
Composto 172



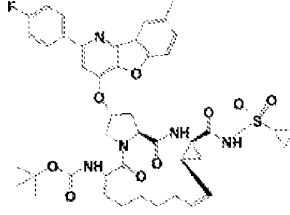
Composto 173



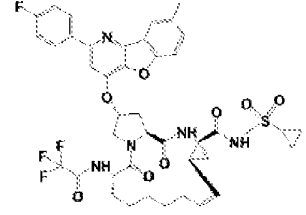
Composto 174



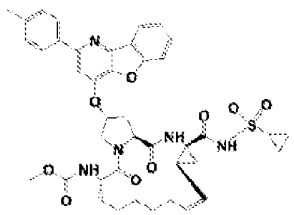
Composto 175



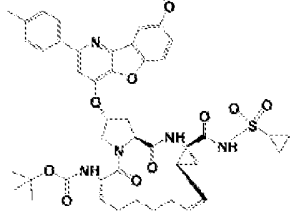
Composto 176



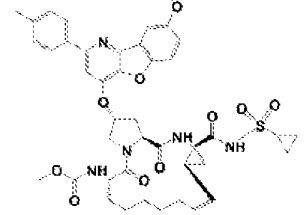
Composto 177



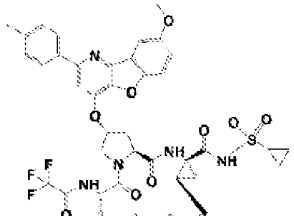
Composto 178



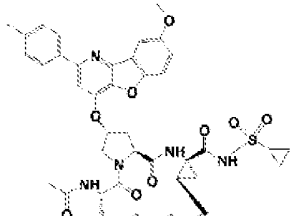
Composto 179



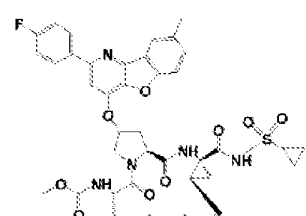
Composto 180



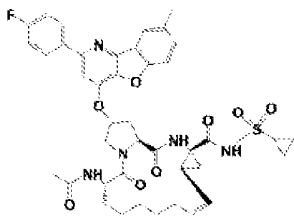
Composto 181



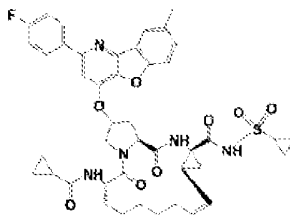
Composto 182



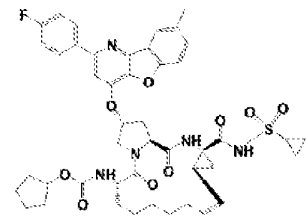
Composto 183



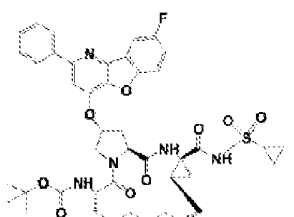
Composto 184



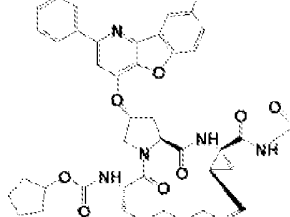
Composto 185



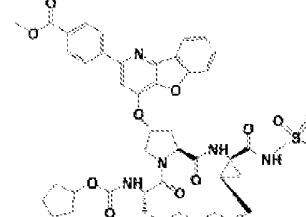
Composto 186



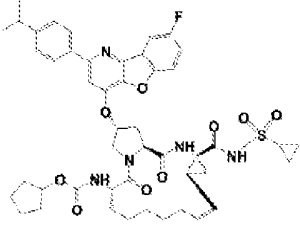
Composto 187



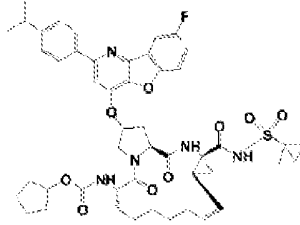
Composto 188



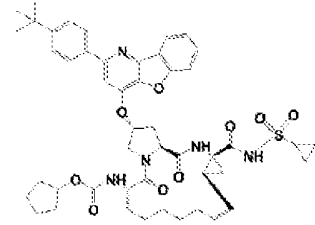
Composto 189



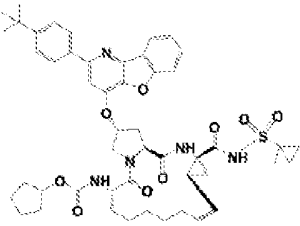
Composto 190



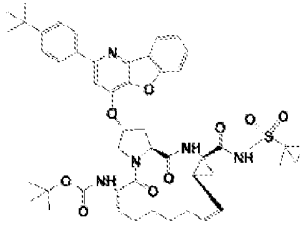
Composto 191



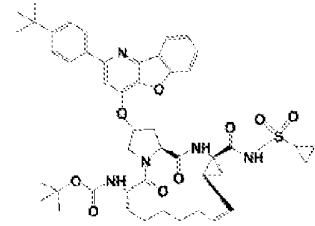
Composto 192



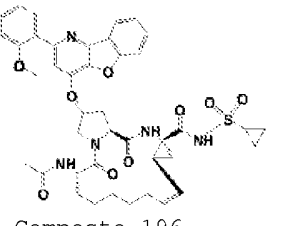
Composto 193



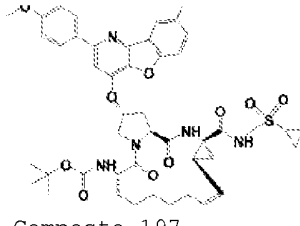
Composto 194



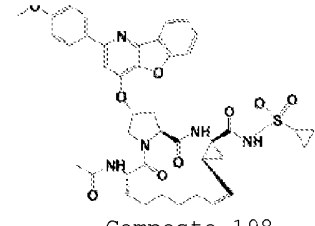
Composto 195



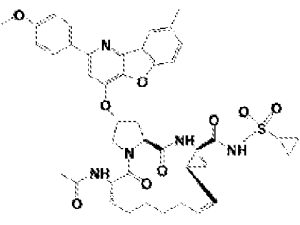
Composto 196



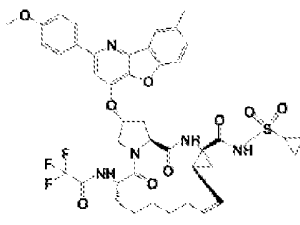
Composto 197



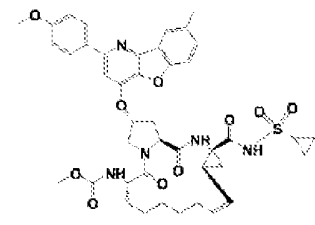
Composto 198



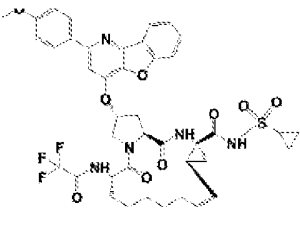
Composto 199



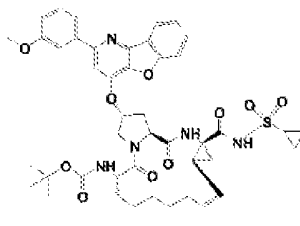
Composto 200



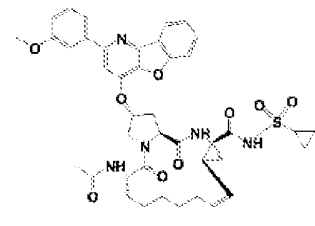
Composto 201



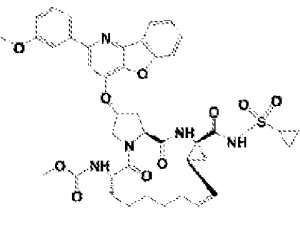
Composto 202



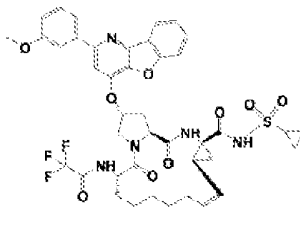
Composto 203



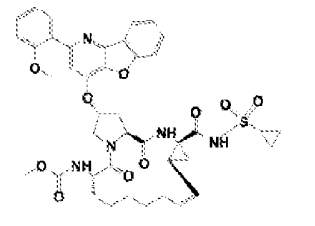
Composto 204



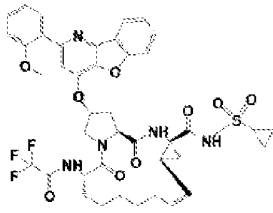
Composto 205



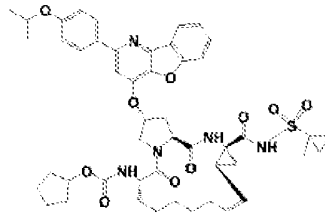
Composto 206



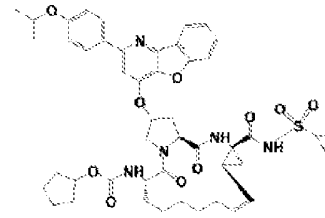
Composto 207



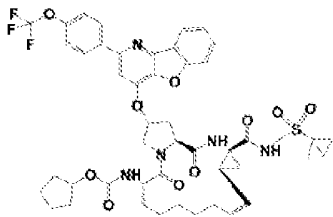
Composto 208



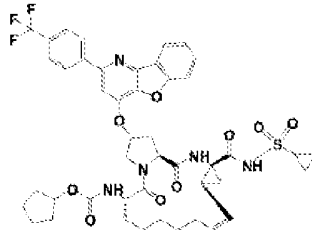
Composto 209



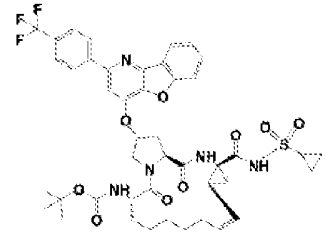
Composto 210



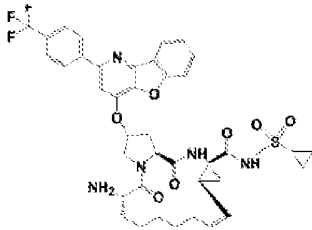
Composto 211



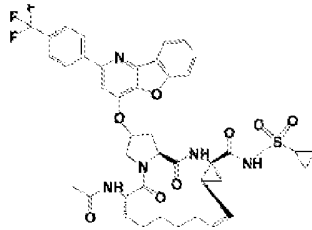
Composto 212



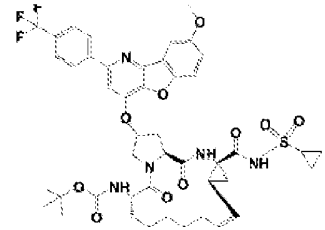
Composto 213



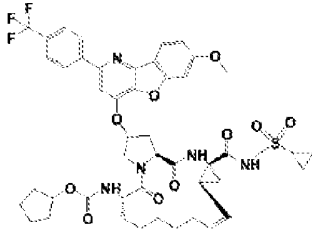
Composto 214



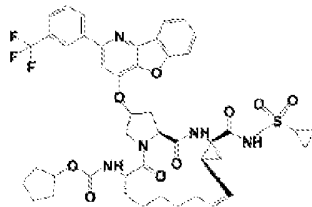
Composto 215



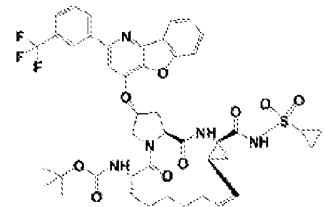
Composto 216



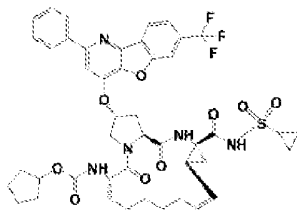
Composto 217



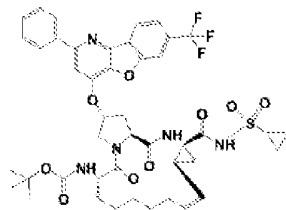
Composto 218



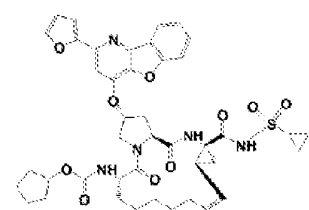
Composto 219



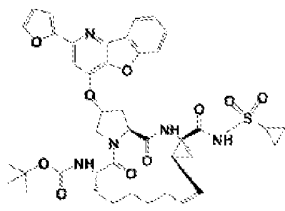
Composto 220



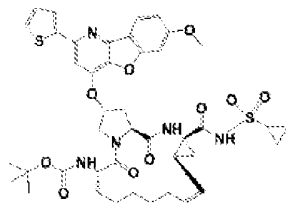
Composto 221



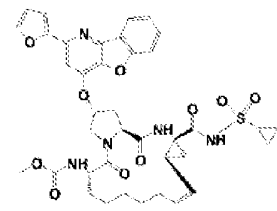
Composto 222



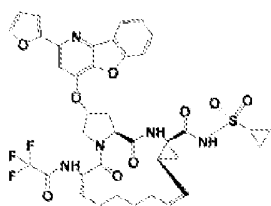
Composto 223



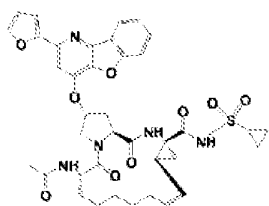
Composto 224



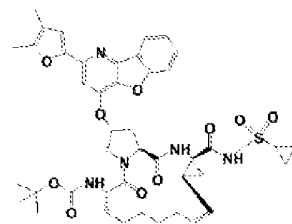
Composto 225



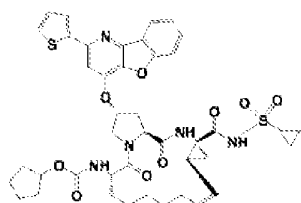
Composto 226



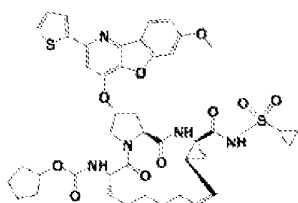
Composto 227



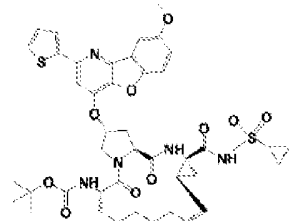
Composto 228



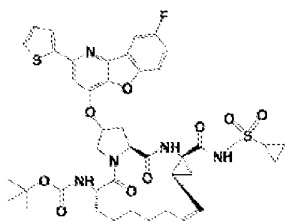
Composto 229



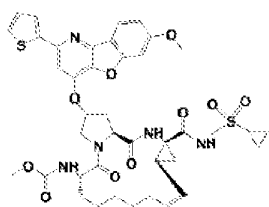
Composto 230



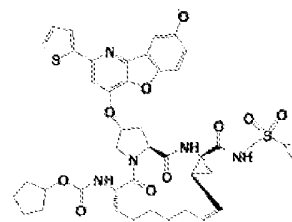
Composto 231



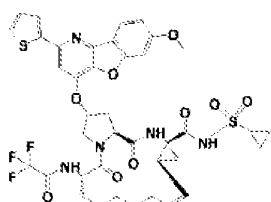
Composto 232



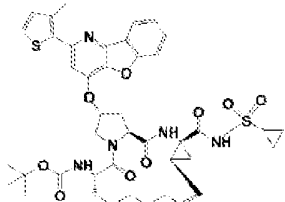
Composto 233



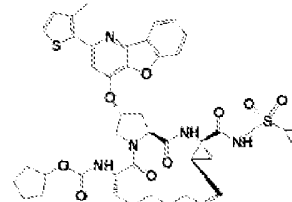
Composto 234



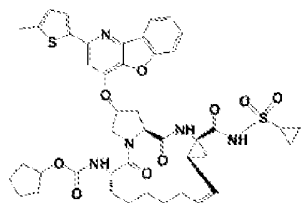
Composto 235



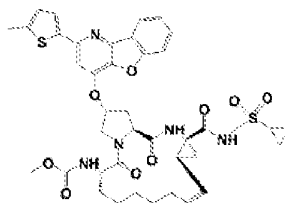
Composto 236



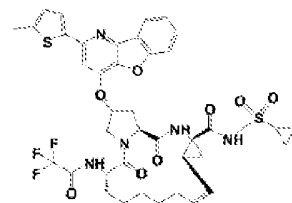
Composto 237



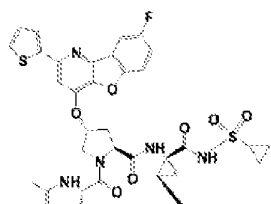
Composto 238



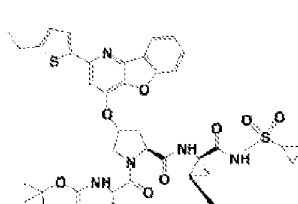
Composto 239



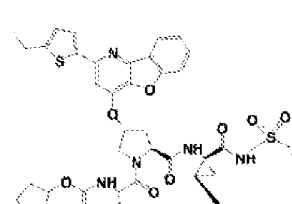
Composto 240



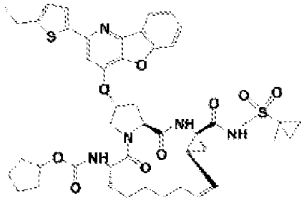
Composto 241



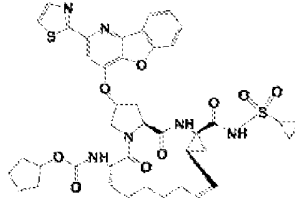
Composto 242



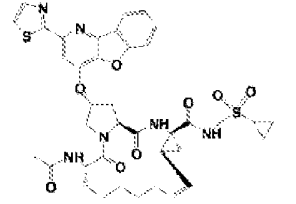
Composto 243



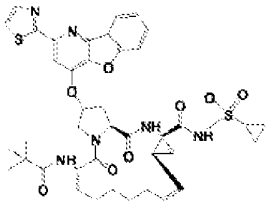
Composto 244



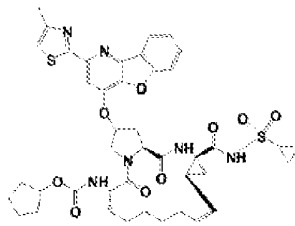
Composto 245



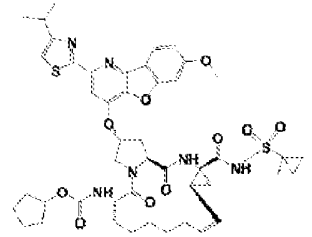
Composto 246



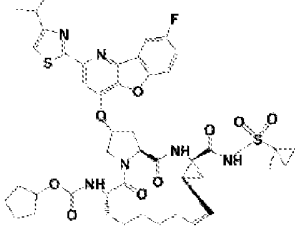
Composto 247



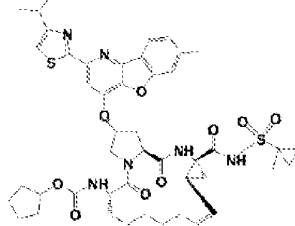
Composto 248



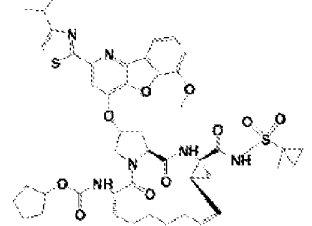
Composto 249



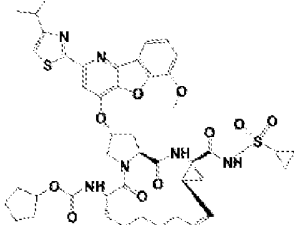
Composto 250



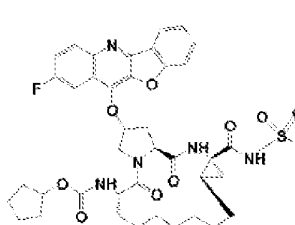
Composto 251



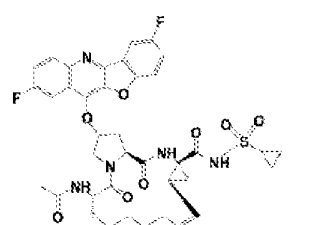
Composto 252



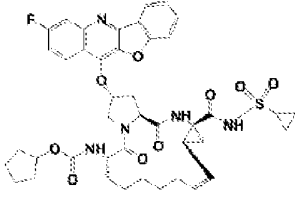
Composto 253



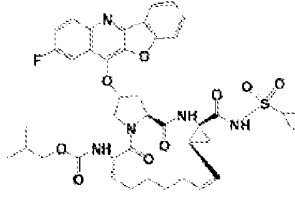
Composto 254



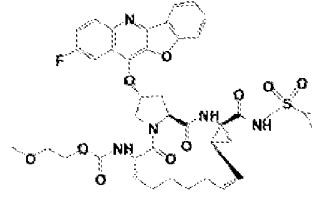
Composto 255



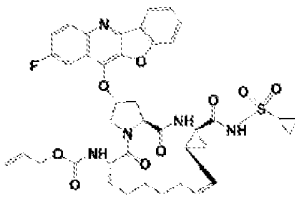
Composto 256



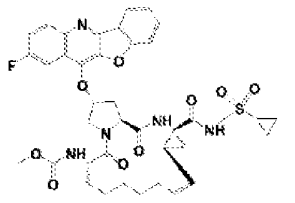
Composto 257



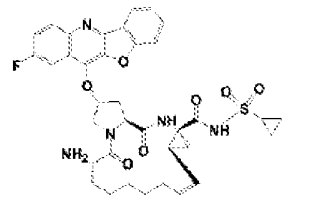
Composto 258



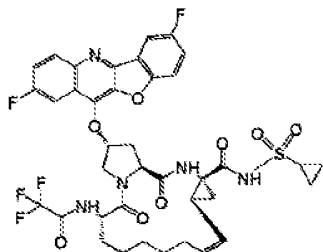
Composto 259



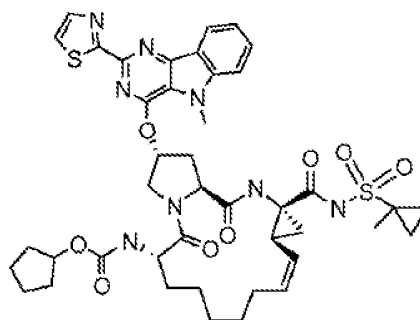
Composto 260



Composto 261

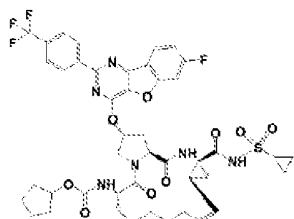


Composto 280

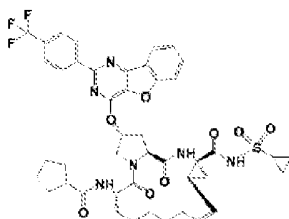


Composto 281.

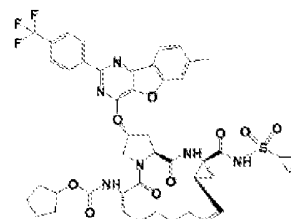
11. Um composto, em que o composto é um dos seguintes compostos:



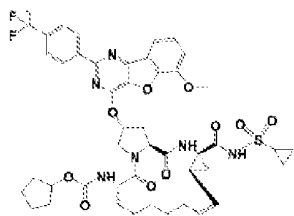
Composto 10



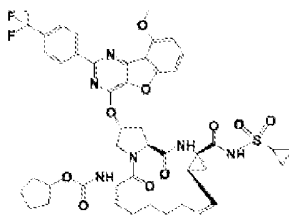
Composto 16



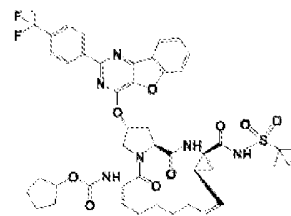
Composto 23



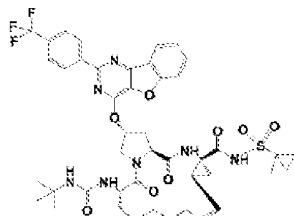
Composto 25



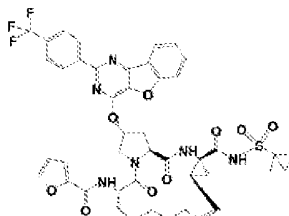
Composto 26



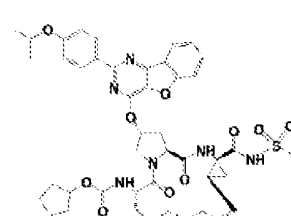
Composto 30



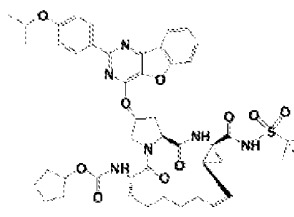
Composto 35



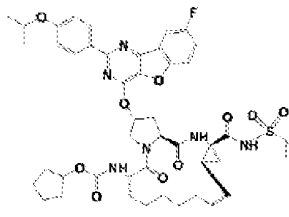
Composto 36



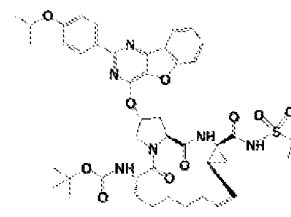
Composto 80



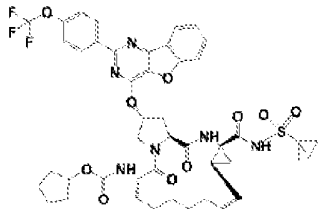
Composto 81



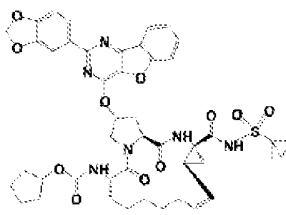
Composto 82



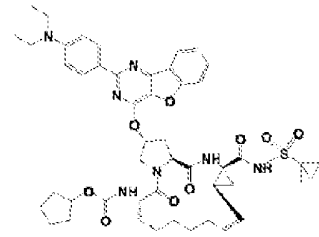
Composto 84



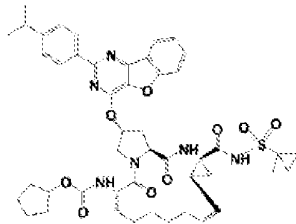
Composto 85



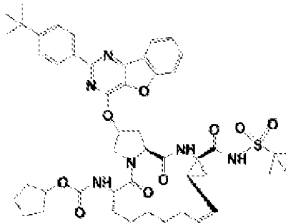
Composto 86



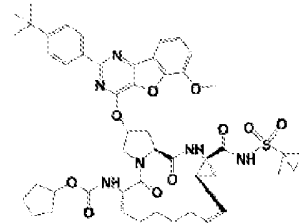
Composto 90



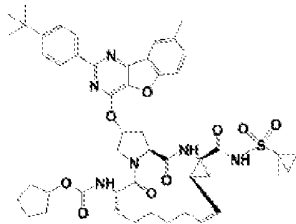
Composto 95



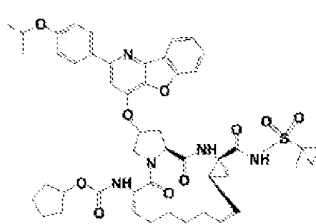
Composto 97



Composto 100



Composto 116



Composto 209.

12. Uma composição farmacêutica compreendendo um composto de qualquer uma das reivindicações 1-11 e um portador farmacêuticamente aceitável.

13. Um composto de qualquer uma das reivindicações 1-11 para uso no tratamento de infecção por vírus da hepatite C.

14. Um composto de acordo com a reivindicação 13 para uso no tratamento de infecção por vírus da hepatite C, em que o composto é para ser administrado oralmente a um indivíduo necessitado do tratamento.

15. Um composto de acordo com a reivindicação 13 ou 14 para uso no tratamento de infeção por vírus da hepatite C, em que o composto é para ser administrado uma vez por dia.

Lisboa, 24 de agosto de 2016

REFERÊNCIAS CITADAS NA DESCRIÇÃO

Esta lista de referências citadas pelo requerente é apenas para conveniência do leitor. A mesma não faz parte do documento da patente europeia. Ainda que tenha sido tomado o devido cuidado ao compilar as referências, podem não estar excluídos erros ou omissões e o IEP declina quaisquer responsabilidades a esse respeito.

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