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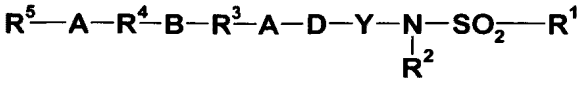
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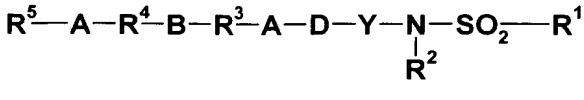
(87) Publicação Internacional: WO 2008/022945de 28/02/2008

(57) Resumo: ARILSULFONAMIDAS, SAIS FISIOLOGICAMENTE TOLERÁVEIS DAS MESMAS, SEU USO, MEDICAMENTO QUE AS COMPREENDE E PROCESSO DE PRODUÇÃO DO REFERIDO MEDICAMENTO. A presente invenção refere-se a compostos da fórmula geral (I), (I) na qual A, B, D, Y, R^1, R^2, R^3, R^4 e R^5 são como definidos na reivindicação 1, seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos, os quais apresentam valiosas propriedades, sua preparação, os medicamentos contendo os compostos farmacologicamente eficazes, sua produção e seu uso.



Relatório Descritivo da Patente de Invenção para **"ARILSULFONAMIDAS COM EFEITO ANALGÉSICO".**

A presente invenção refere-se a compostos da fórmula geral **I**



, (I)

na qual **A**, **B**, **D**, **Y**, R^1, R^2, R^3, R^4 e R^5 são definidos tal como na reivindicação 1, seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos, os quais apresentam propriedades valiosas, sua preparação, os medicamentos contendo os compostos farmacologicamente eficazes, sua produção e seu uso.

Descrição Detalhada da Invenção

Na fórmula geral **I** acima, em uma primeira forma de concretização, representam

A uma ligação, C_{1-4}-alquileno ou $-CH_2-C(O)-$,

B uma ligação, C_{1-3}-alquileno, -O- ou $-C(O)-$,

D um grupo das fórmulas gerais **II**



Y um grupo C_{1-6}-alquileno eventualmente substituído pelo radical R^2, no qual um grupo metileno pode ser adicionalmente substituído por Y^1 e

Y^1 representa –O-, -S-, -S(O)-, -N(R^2)-, -N(R^2)-C(O)-, -C(O)-N(R^2)-, -C(O)-, -CH(arila)-, C_{3-6}-cicloalquileno ou $-S(O)_2-$,

R^1 C_{3-7}-cicloalquila ou aril-, heteroaril- ou aril-C_{1-3}-alquila, que em cada caso podem ser substituídos por um, dois, três ou quatro radicais $R^{1.1}$, em que os radicais $R^{1.1}$ podem ser iguais ou diferentes e

$R^{1.1}$ representa H, F, Cl, Br, I, C_{1-3}-alquila, F_3C-, HO-, C_{1-3}-alquila-O- ou C_{1-3}-alquil-O-C_{2-4}-alquileno-O-,

R^2 H ou C_{1-3}-alquila, em que cada grupo metileno pode ser substituído com até dois e cada grupo metila com até três átomos de flúor ou também $H_3C-C(O)-$,

$\mathbf{R^3}$ a) C_{1-6}-alquileno,

b) um grupo C_{3-6}-cicloalquileno substituído uma, duas ou três vezes por $\mathbf{R^{3.1}}$

c) um grupo C_{5-7}-cicloalquenileno substituído uma ou duas vezes por $\mathbf{R^{3.1}}$, que é condensado com um anel fenila através da ligação insaturada,

d) $-N(\mathbf{R^2})$,

e) um grupo arileno substituído uma ou duas vezes por $\mathbf{R^{3.1}}$,

f) um grupo heteroarileno substituído uma ou duas vezes por $\mathbf{R^{3.1}}$,

g) um anel heterocíclico saturado com 4 a 7 membros substituído uma ou duas vezes por $\mathbf{R^{3.1}}$,

h) um anel heterocíclico insaturado com 4 a 7 membros substituído uma ou duas vezes por $\mathbf{R^{3.1}}$, que é condensado com um ou dois anéis fenila através das ligações insaturadas, ou

i) um aza-heterobiciclo saturado com 8 a 10 membros substituído uma ou duas vezes por $\mathbf{R^{3.1}}$,

em que os radicais $\mathbf{R^{3.1}}$ em cada caso podem ser iguais ou diferentes e

$\mathbf{R^{3.1}}$ representa H, F, Cl, Br, I, C_{1-3}-alquila-, HO-, C_{1-3}-alquila-O- ou C_{1-3}-alquil-O-C_{2-4}-alquileno-O- ou

$\mathbf{R^3}$ também representa –O-, quando **B** não representa o grupo –O-,

$\mathbf{R^4}$ a) –O-,

b) –C(O)O-,

c) $-C(O)N\mathbf{R^2}$-,

d) $-N\mathbf{R^2}$-,

e) $-N\mathbf{R^2}$-$N\mathbf{R^2}$-,

f) C_{3-7}-cicloalquileno,

g) C_{1-6}-alquileno,

h) um grupo arileno substituído uma ou duas vezes por $\mathbf{R^{4.1}}$,

i) um grupo heteroarileno substituído uma ou duas vezes por $\mathbf{R^{4.1}}$,

j) um anel heterocíclico saturado com 4 a 7 membros substituído

uma ou duas vezes por **R$^{4.1}$**,

k) um diaza-heterobiciclo saturado com 8 a 10 membros substituído uma ou duas vezes por **R$^{4.1}$**,

l) um anel heterocíclico insaturado com 5 a 7 membros substituído uma ou duas vezes por **R$^{4.1}$**, que é condensado com um ou dois anéis fenila através de ligações insaturadas ou

m) um diaza-spirociclo saturado com 9 a 11 membros,

em que os radicais **R$^{4.1}$** em cada caso podem ser iguais ou diferentes e

R$^{4.1}$ representa H, F, Cl, Br, I, C_{1-3}-alquila-, HO-, C_{1-3}-alquila-O- ou C_{1-3}-alquila-O-C_{2-4}-alquileno-O-,

R^5 H, HO-, C_{1-8}-alquila, um grupo C_{3-7}-cicloalquila eventualmente substituído por C_{1-3}-alquila, H_2N, C_{1-4}-alquila-NH, (C_{3-6}-cicloalquil)-NH, (C_{1-4}-alquil)$_2$N, (C_{1-4}-alquil)(C_{3-6}-cicloalquil)N, (ciclopropilmetil)(metil)N, H_2N-C(O), um grupo fenila substituído uma ou duas vezes por **R$^{5.1}$**, um grupo heteroarila substituído uma ou duas vezes por **R$^{5.1}$** ou um anel heterocíclico saturado com 4 a 7 membros substituído uma ou duas vezes por **R$^{5.1}$**, em que os radicais **R$^{5.1}$** em cada caso podem ser iguais ou diferentes e

R$^{5.1}$ representa H, F, Cl, Br, I, C_{1-3}-alquila-, HO-, C_{1-3}-alquila-O-, (C_{1-3}-alquila)$_2$N ou C_{1-3}-alquil-O-C_{2-4}-alquileno-O-,

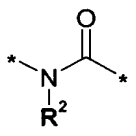
seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos.

Uma segunda forma de concretização da presente invenção, consiste nos compostos da fórmula geral **I** acima, nos quais

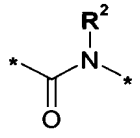
A representa uma ligação ou C_{1-4}-alquileno,

B representa uma ligação, C_{1-3}-alquileno, -O- ou –C(O)-,

D representa um grupo das fórmulas gerais **II**



ou



,

Y representa um grupo C_{1-4}-alquileno eventualmente substituído pelo radical **R^2**, em que um grupo metileno pode ser adicionalmente substituído por **Y^1** e

$\mathbf{Y^1}$ representa –O-, -S-, -S(O)-, -N($\mathbf{R^2}$)-, -N($\mathbf{R^2}$)-C(O)-, -C(O)-N($\mathbf{R^2}$)-, -C(O)-, -CH(arila)- ou –$S(O)_2$-,

$\mathbf{R^1}$ representa C_{3-7}-cicloalquila ou arila, heteroarila ou aril-C_{1-3}-alquila, que em cada caso podem ser substituídas por um, dois, três ou quatro radicais $\mathbf{R^{1.1}}$, em que os radicais $\mathbf{R^{1.1}}$ podem ser iguais ou diferentes e

$\mathbf{R^{1.1}}$ representa H, F, Cl, Br, I, C_{1-3}-alquila, HO, C_{1-3}-alquila-O ou C_{1-3}-alquil-O-C_{2-4}-alquileno-O,

$\mathbf{R^2}$ representa H ou C_{1-3}-alquila, em que cada grupo metileno pode ser substituído com até dois e cada grupo metila com até três átomos de flúor ou também H_3C-C(O)-,

$\mathbf{R^3}$ representa C_{1-6}-alquileno, um grupo arileno substituído uma ou duas vezes por $\mathbf{R^{3.1}}$, um grupo heteroarileno substituído uma ou duas vezes por $\mathbf{R^{3.1}}$, um anel heterocíclico saturado com 4 a 7 membros substituído uma ou duas vezes por $\mathbf{R^{3.1}}$ ou um anel heterocíclico insaturado com 4 a 7 membros substituído uma ou duas vezes por $\mathbf{R^{3.1}}$, e que os radicais $\mathbf{R^{3.1}}$ em cada caso podem ser iguais ou diferentes e

$\mathbf{R^{3.1}}$ representa H, F, Cl, Br, I, C_{1-3}-alquila-, HO-, C_{1-3}-alquila-O- ou C_{1-3}-alquila-O-C_{2-4}-alquileno-O-,

$\mathbf{R^4}$ representa –O-, -C(O)O-, -C(O)N$\mathbf{R^2}$, - N$\mathbf{R^2}$, -N$\mathbf{R^2}$-N$\mathbf{R^2}$, C_{3-7}-cicloalquileno, C_{1-6}-alquileno, um grupo arileno substituído uma ou duas vezes por $\mathbf{R^{4.1}}$, um grupo heteroarileno substituído uma ou duas vezes por $\mathbf{R^{4.1}}$, um anel heterocíclico saturado com 4 a 7 membros substituído uma ou duas vezes por $\mathbf{R^{4.1}}$ ou um anel heterocíclico insaturado com 4 a 7 membros substituído uma ou duas vezes por $\mathbf{R^{4.1}}$, em que os radicais $\mathbf{R^{4.1}}$ em cada caso podem ser iguais ou diferentes e

$\mathbf{R^{4.1}}$ representa H, F, Cl, Br, I, C_{1-3}-alquila-, HO-, C_{1-3}-alquila-O- ou C_{1-3}-alquila-O-C_{2-4}-alquileno-O-,

$\mathbf{R^5}$ representa H, C_{1-8}-alquila, um grupo C_{3-7}-cicloalquila eventualmente substituído por C_{1-3}-alquila, H_2N, C_{1-4}-alquila-NH, (C_{1-4}-alquila)$_2$N, H_2N-C(O), um grupo heteroarila substituído uma ou duas vezes por $\mathbf{R^{5.1}}$ ou um anel heterocíclico saturado com 4 a 7 membros substituído uma ou duas vezes por $\mathbf{R^{5.1}}$, em que os radicais $\mathbf{R^{5.1}}$ em cada caso podem ser iguais ou diferentes e

$R^{5.1}$ representa H, F, Cl, Br, I, C_{1-3}-alquila-, HO-, C_{1-3}-alquila-O- ou C_{1-3}-alquila-O-C_{2-4}-alquileno-O-,

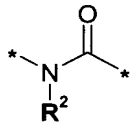
seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos.

Uma terceira forma de concretização da presente invenção, consiste nos compostos da fórmula geral **I** acima, nos quais

A representa uma ligação, C_{1-4}-alquileno ou $-CH_2-C(O)-$,

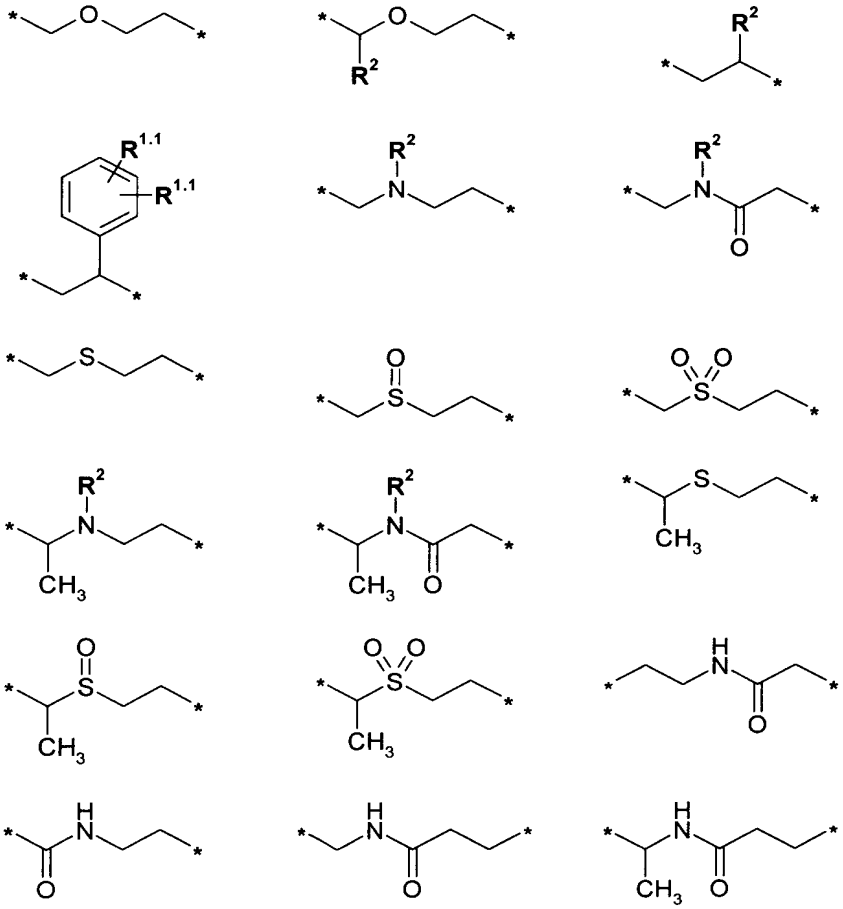
B representa uma ligação, C_{1-2}-alquileno, -O- ou $-C(O)-$,

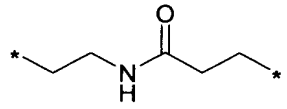
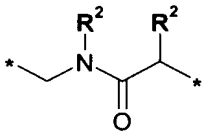
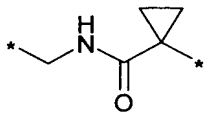
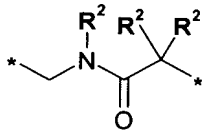
D representa um grupo da fórmula geral **II**



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Y representa C_{1-4}-alquileno ou um grupo selecionado de



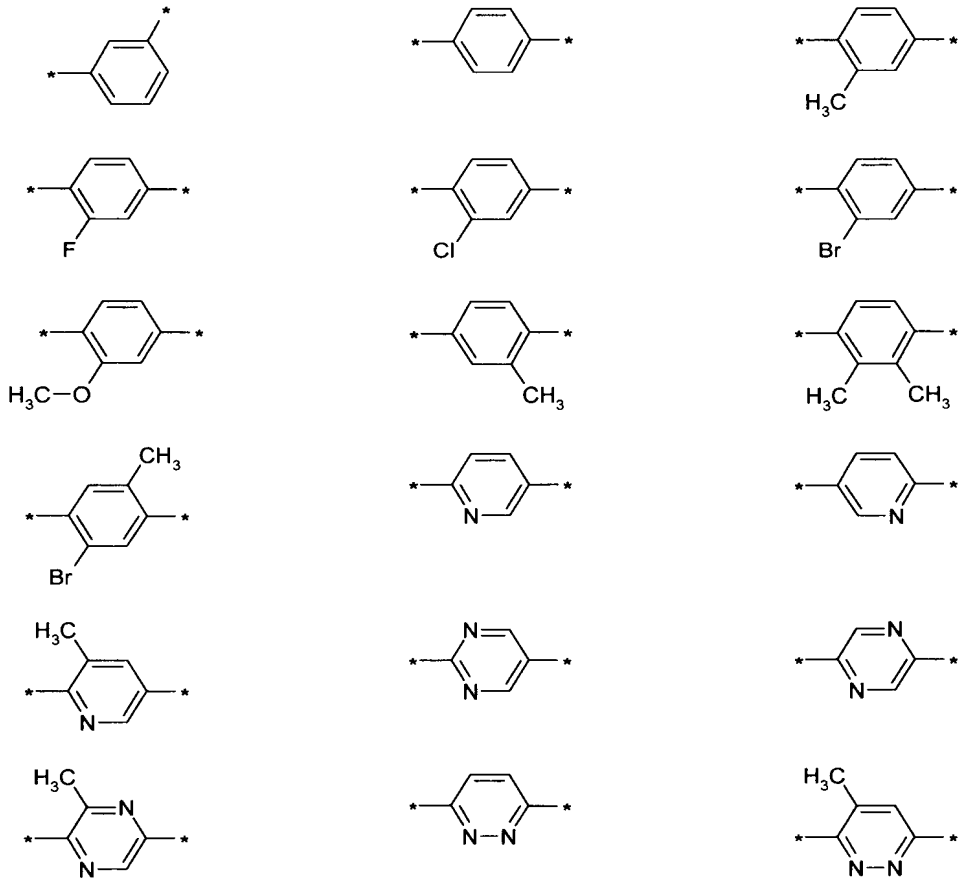





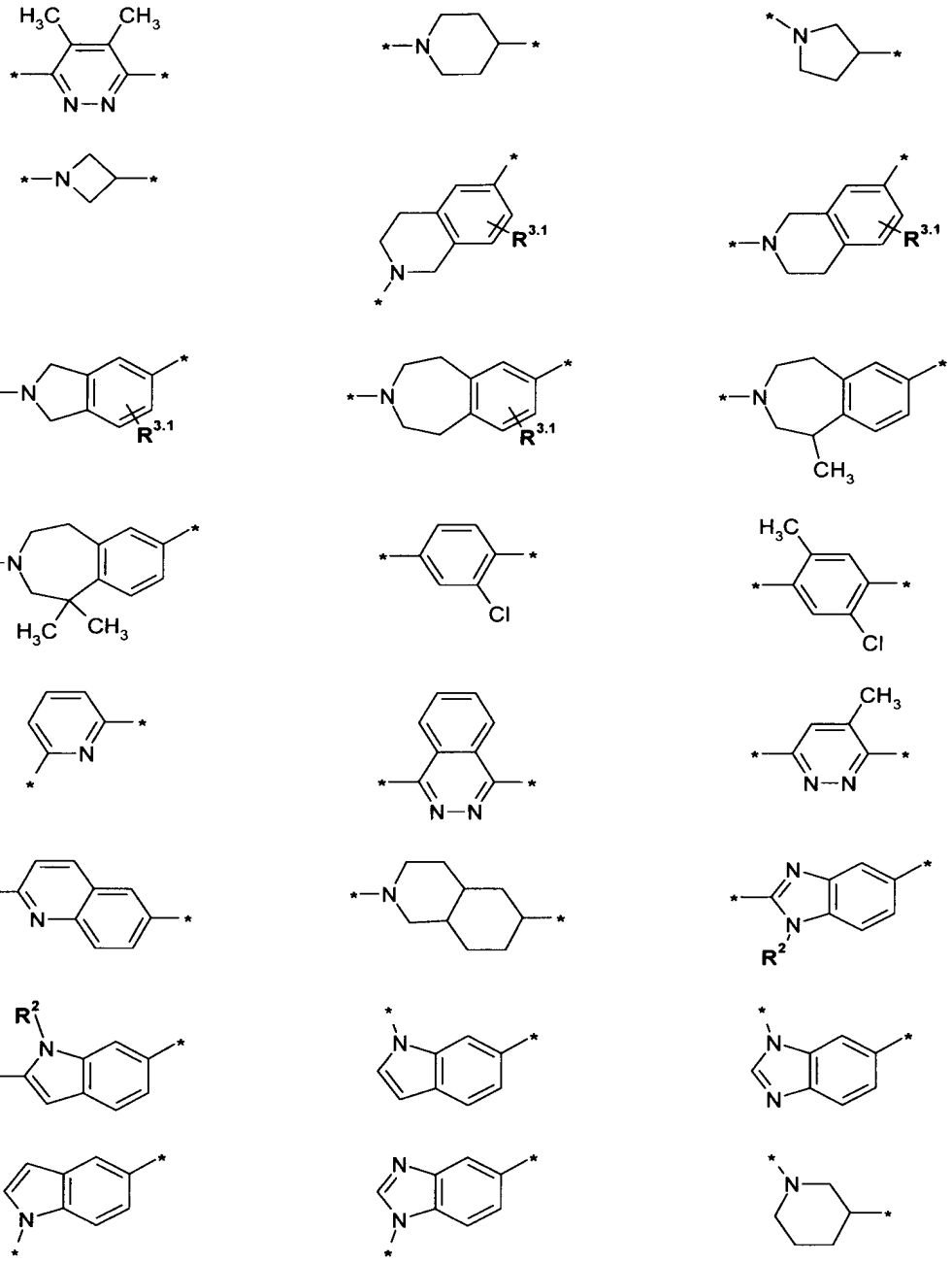
R^{1} representa arila ou heteroarila, que em cada caso podem ser substituídas por um, dois, três ou quatro radicais **R**$^{1.1}$, em que os radicais **R**$^{1.1}$ podem ser iguais ou diferentes e

R$^{1.1}$ representa H, F, Cl, Br, I, C_{1-3}-alquila, F_3C-, HO-, C_{1-3}-alquila-O- ou C_{1-3}-alquil-O-C_{2-4}-alquileno-O-,

R^{2} representa H, H_3C, H_5C_2, isopropila, F_3C-CH_2, F_2CH-CH_2 ou FH_2C-H_2C,

R^{3} representa C_{1-4}-alquileno, -N(**R**^{2}) ou um grupo selecionado de



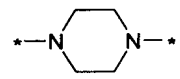
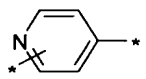
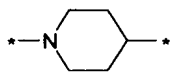


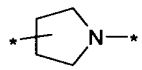
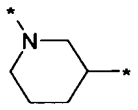
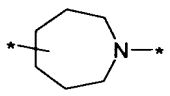
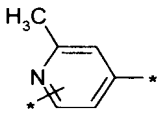
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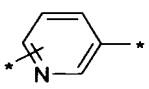
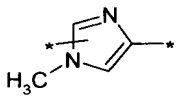
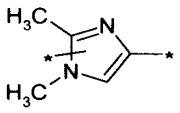
$R^{3.1}$ representa H, F, Cl, Br, I, C_{1-3}-alquila-, HO-, C_{1-3}-alquila-O- ou C_{1-3}-alquil-O-C_{2-4}-alquileno-O- ou

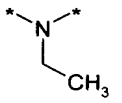
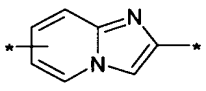
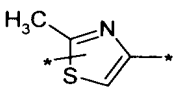
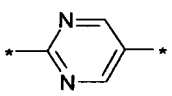
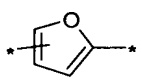
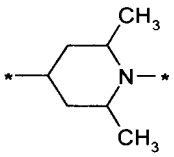
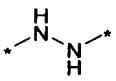
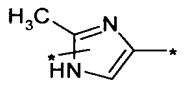
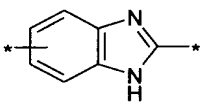
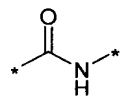
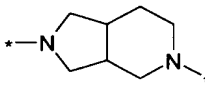
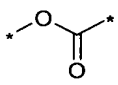
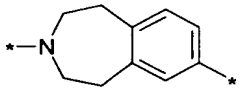
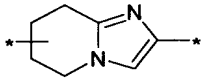
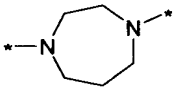
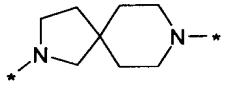
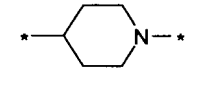
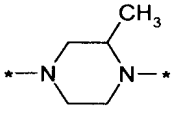
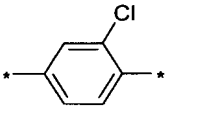
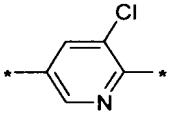
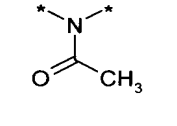
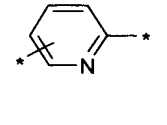
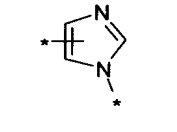
R^3 também representa –O-, quando **B** não representa o grupo –O-,

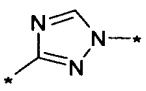
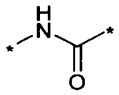
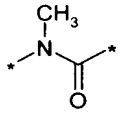
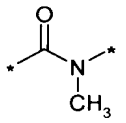
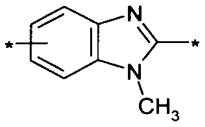
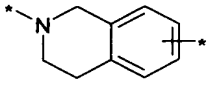
R^4 representa C_{1-4}-alquileno, C_{3-7}-cicloalquileno, -O- ou um grupo selecionado de

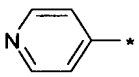
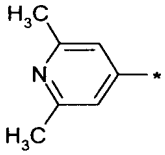
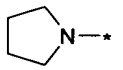
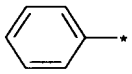
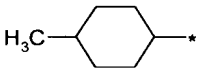
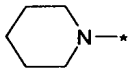
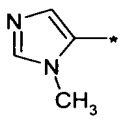
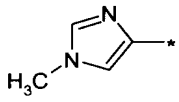
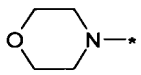
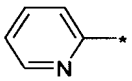
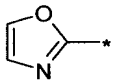
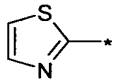
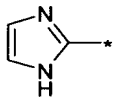
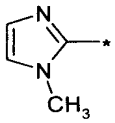
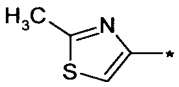
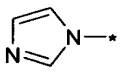
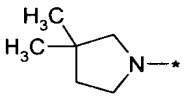
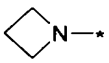
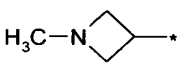
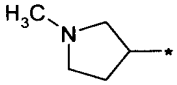
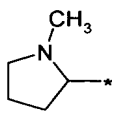
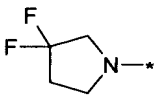
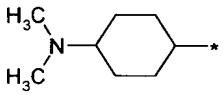
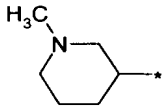
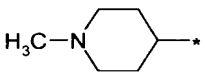
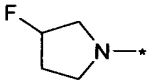
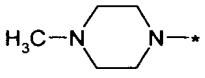




R^5 representa H, C_{1-8}-alquila, grupo C_{3-7}-cicloalquila, HO, (C_{1-3}-alquila)-O, (C_{1-4}-alquila)-NH, (C_{3-6}-cicloalquila)-NH, (C_{1-4}-alquila)$_2$N, (C_{1-4}-alquila)(C_{3-6}-cicloalquila)N, (ciclopropilmetil)(metila)N, H_2N-C(O) ou

R^5 representa um grupo selecionado de

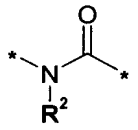
seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos.

Uma quarta forma de concretização da presente invenção, consiste nos compostos da fórmula geral **I** acima, nos quais

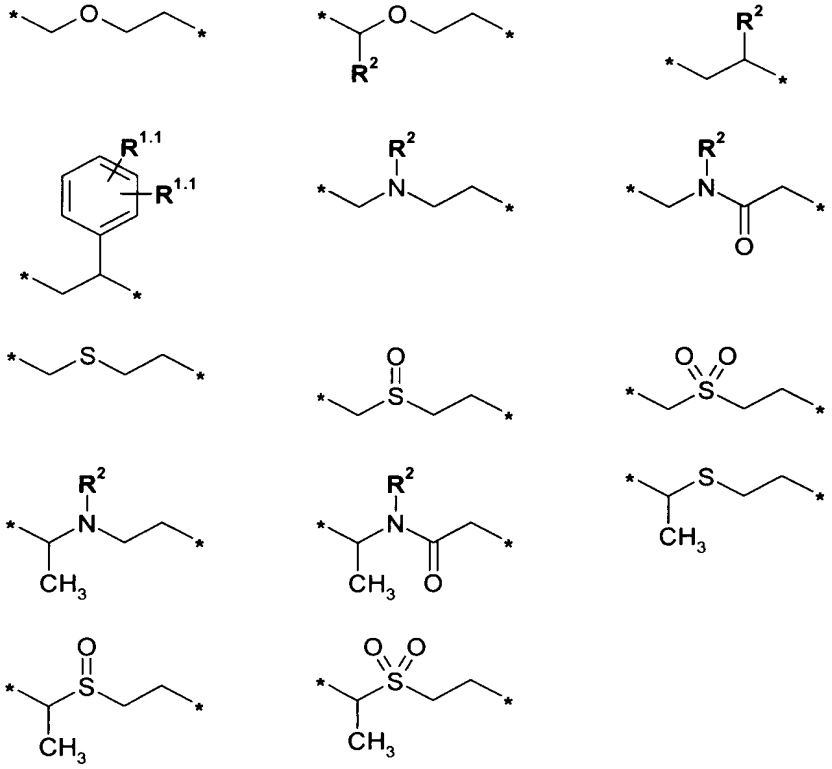
A representa uma ligação ou C_{1-4}-alquileno,

B representa uma ligação, C_{1-2}-alquileno, -O- ou –C(O)-,

D representa um grupo das fórmulas gerais **II**



Y representa C_{1-4}-alquileno ou um grupo selecionado de

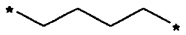
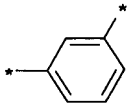
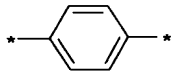
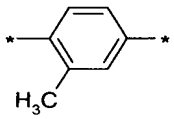
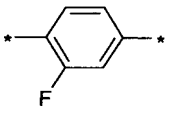
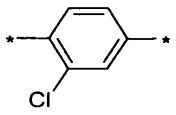
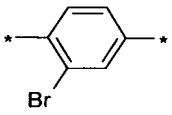
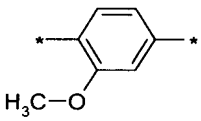
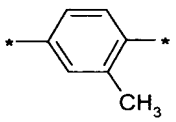
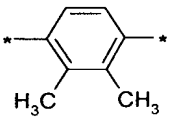
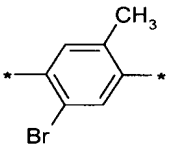
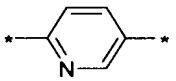
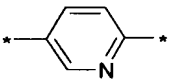
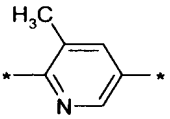
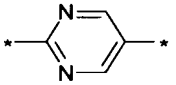
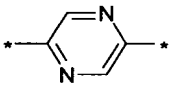
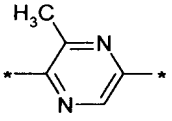
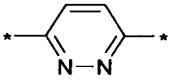
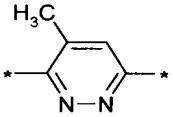


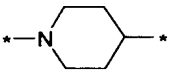
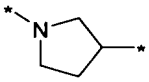
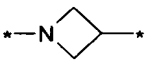
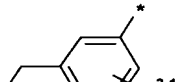
$\mathbf{R^1}$ representa arila ou heteroarila, que em cada caso podem ser substituídas por um, dois, três ou quatro radicais $\mathbf{R^{1.1}}$, em que os radicais $\mathbf{R^{1.1}}$ podem ser iguais ou diferentes e

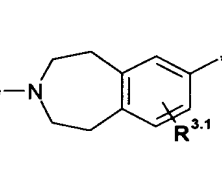
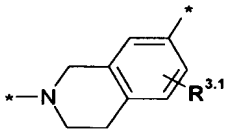
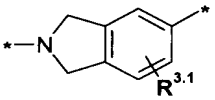
$\mathbf{R^{1.1}}$ representa H, F, Cl, Br, I, C_{1-3}-alquila, HO, C_{1-3}-alquila-O ou C_{1-3}-alquil-O-C_{2-4}-alquileno-O,

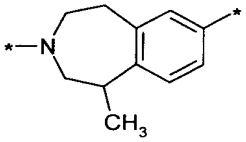
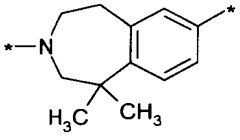
R² representa H, H_3C, H_5C_2, isopropila, F_3C-CH_2, F_2CH-CH_2 ou FH_2C-H_2C,

R³ representa C_{1-4}-alquileno ou um grupo selecionado de

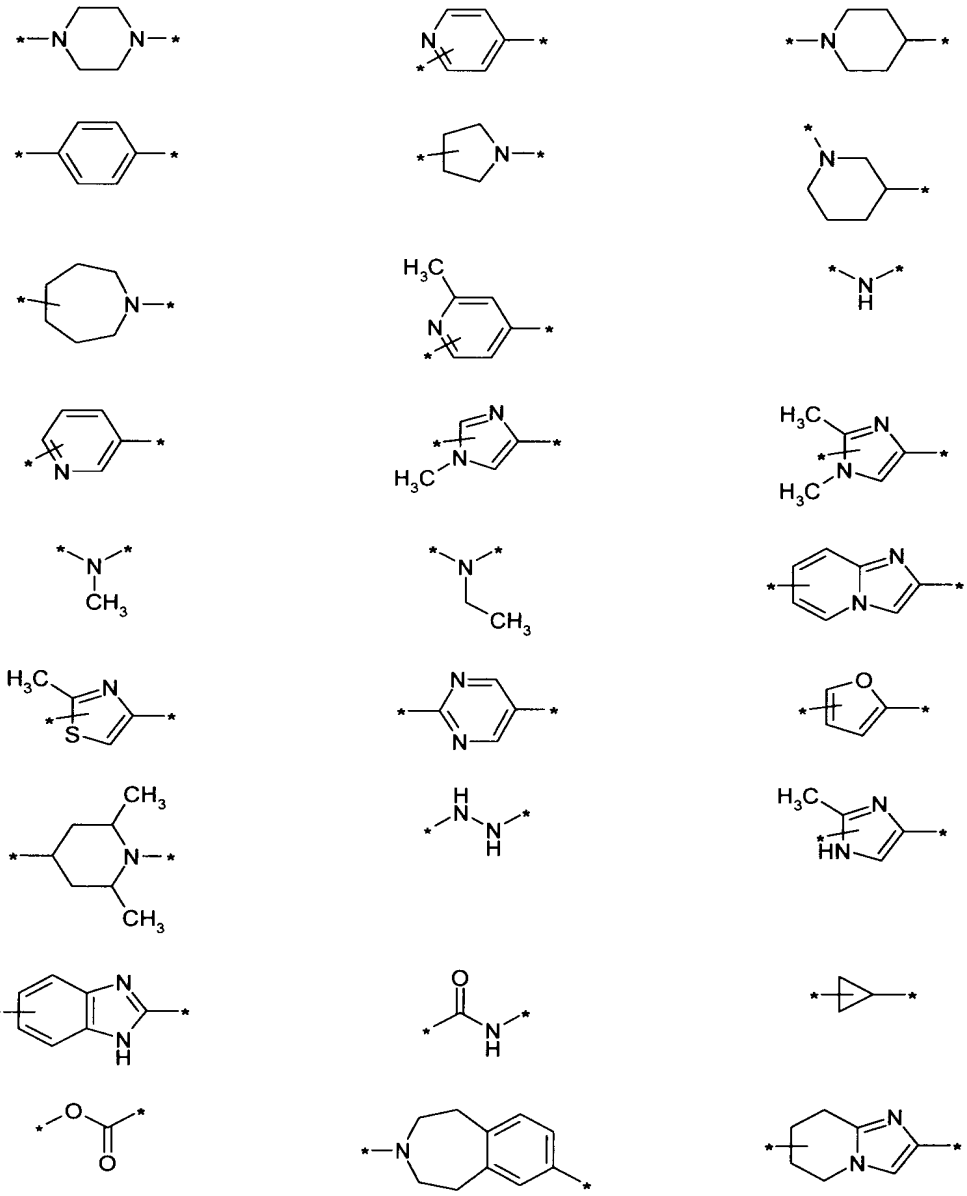




nas quais

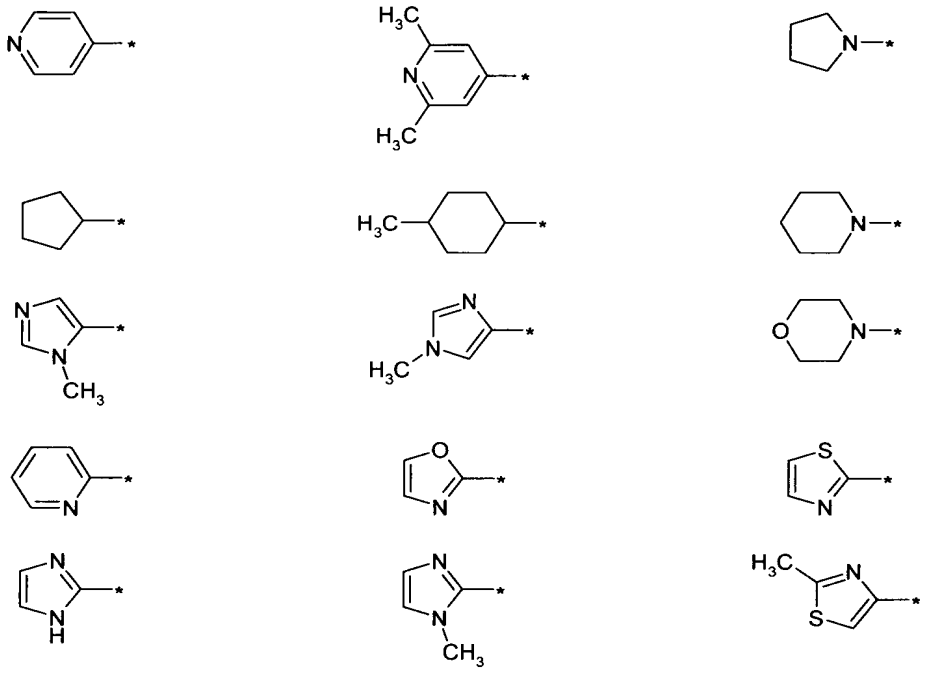
$R^{3.1}$ representa H, F, Cl, Br, I, C_{1-3}-alquila, HO, C_{1-3}-alquila-O ou C_{1-3}-alquil-O-C_{2-4}-alquileno-O,

R^4 representa C_{1-4}-alquileno, -O- ou um grupo selecionado de



R^5 representa H, C_{1-8}-alquila, C_{3-7}-cicloalquila, (C_{1-4}-alquila)-NH-, (C_{1-4}-alquila)$_2$N-, H_2N-C(O)-, ou

R^5 representa um grupo selecionado de



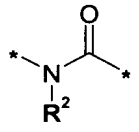
seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos.

Uma quinta forma de concretização da presente invenção consiste nos compostos da fórmula geral **I** acima, nos quais

A representa uma ligação, C_{1-3}-alquileno ou $-CH_2-C(O)-$,

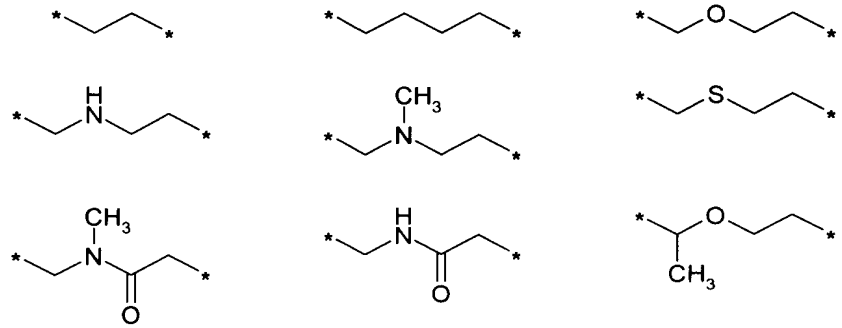
B representa uma ligação, C_{1-2}-alquileno, -O- ou $-C(O)-$,

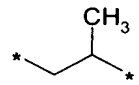
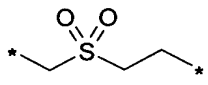
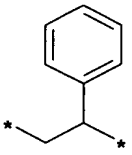
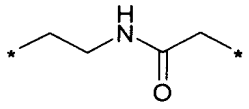
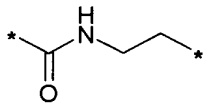
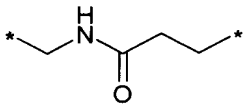
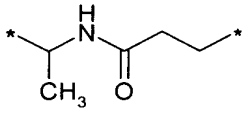
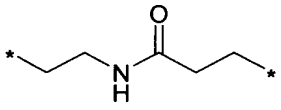
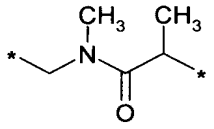
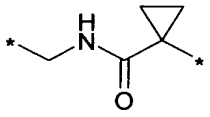
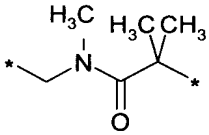
D representa um grupo da fórmula geral **II**

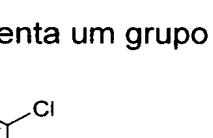
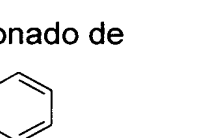


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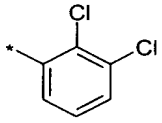
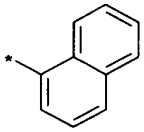
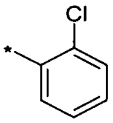
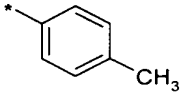
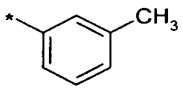
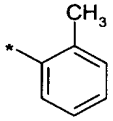
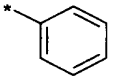
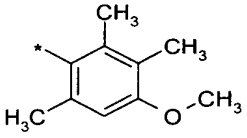
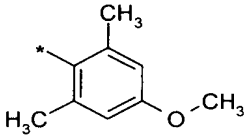
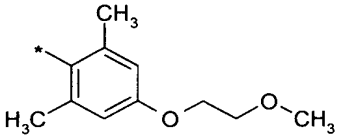
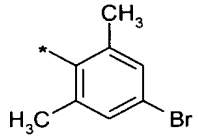
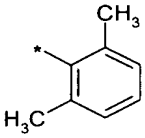
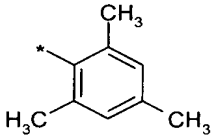
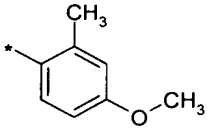
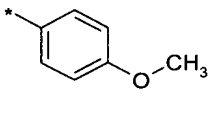
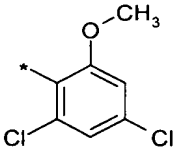
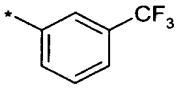
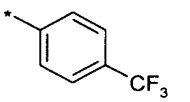
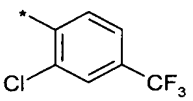
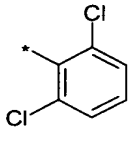
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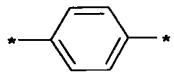
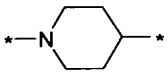
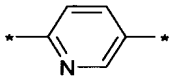
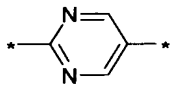
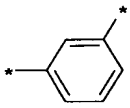
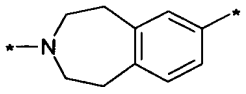
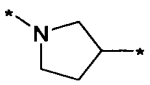



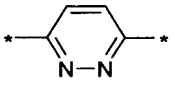
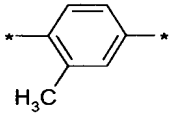
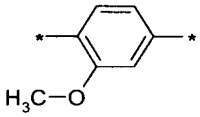
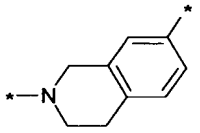
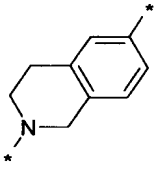
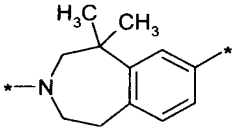
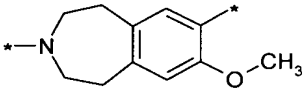
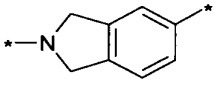
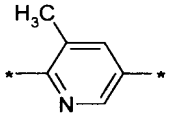
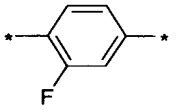
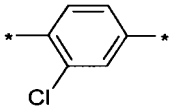
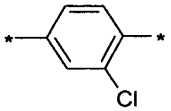
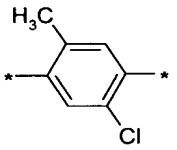
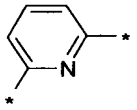
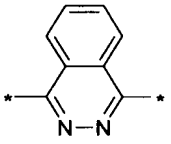
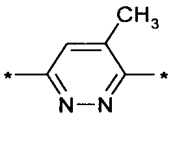
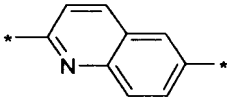
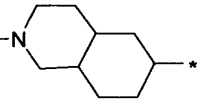
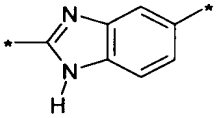
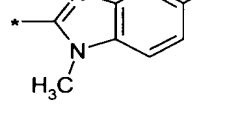
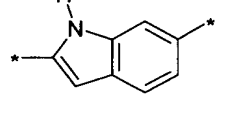
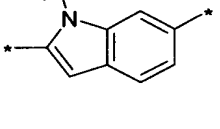
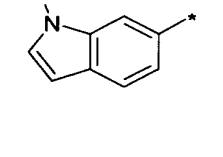
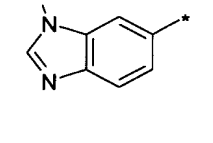
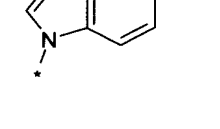
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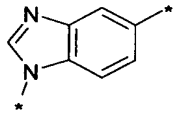
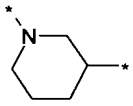





















R[2] representa H, H_3C, H_5C_2 ou FH_2C-H_2C,

R[3] representa C_{1-4}-alquileno, -NH-, -N(CH_3) ou um grupo selecionado de

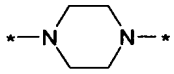
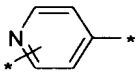
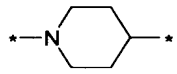
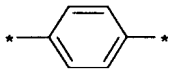
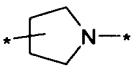
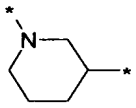
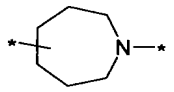
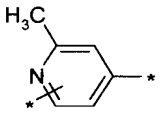


























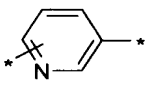
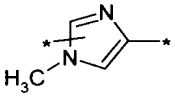
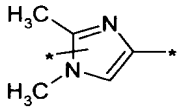



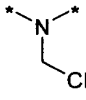
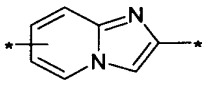
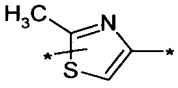
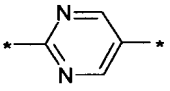
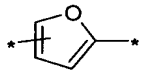
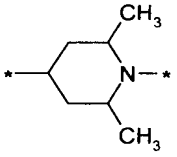
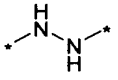
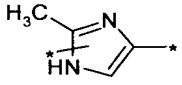
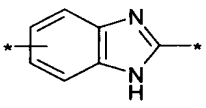
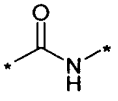
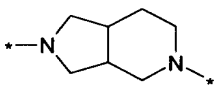
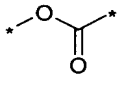
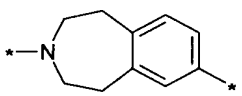
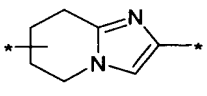
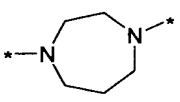
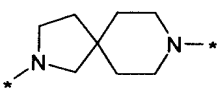
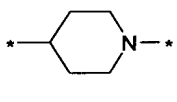
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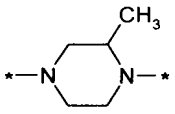
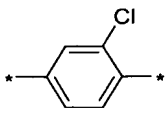
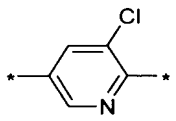
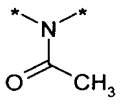
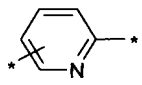
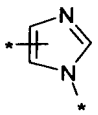
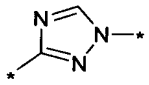
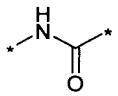
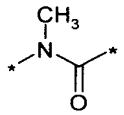
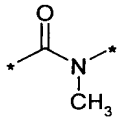
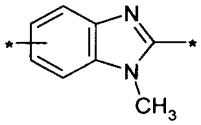
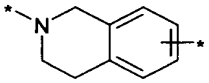
R^3 representa também –O-, quando **B** não representa o grupo –O-,

R^4 representa C_{1-4}-alquileno, C_{3-7}-alquileno, -O- ou um grupo selecionado de

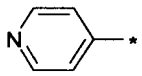
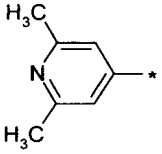
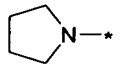
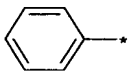
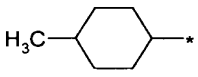
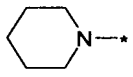
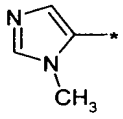
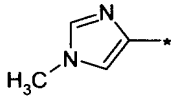
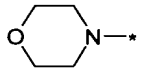
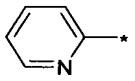
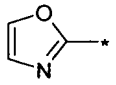
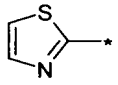
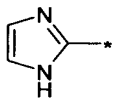
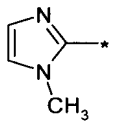
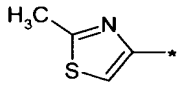
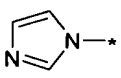
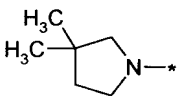
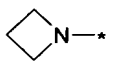




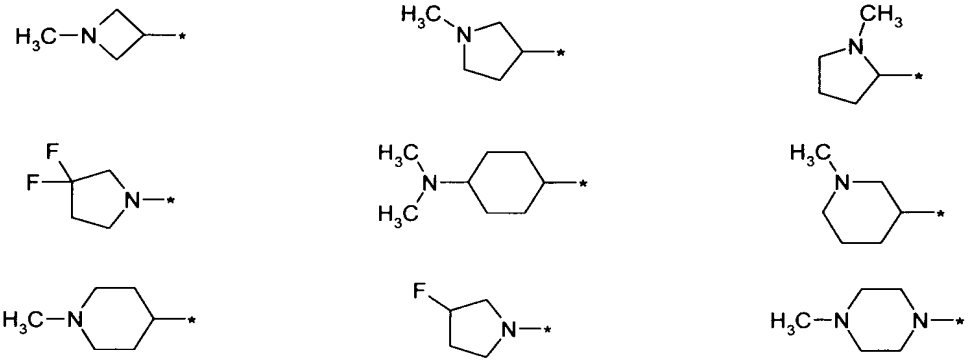


















R^{5} representa H, HO-, C_{1-5}-alquila, C_{3-5}-cicloalquila, H_2N-, (C_{1-2}-alquila)-NH-, (C_{3-6}-cicloalquila)-NH-, (C_{1-2}-alquila)$_2$N-, (C_{1-4}-alquil)(C_{3-6}-cicloalquila)N-, (ciclopropilmetil)(metila)N-, H_2N-C(O)-, ou

R^{5} representa um grupo selecionado de



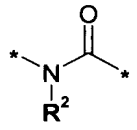
seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos e inorgânicos.

Uma sexta forma de concretização da presente invenção, consiste nos compostos da fórmula geral **I** acima, nos quais

A representa uma ligação ou C_{1-3}-alquileno,

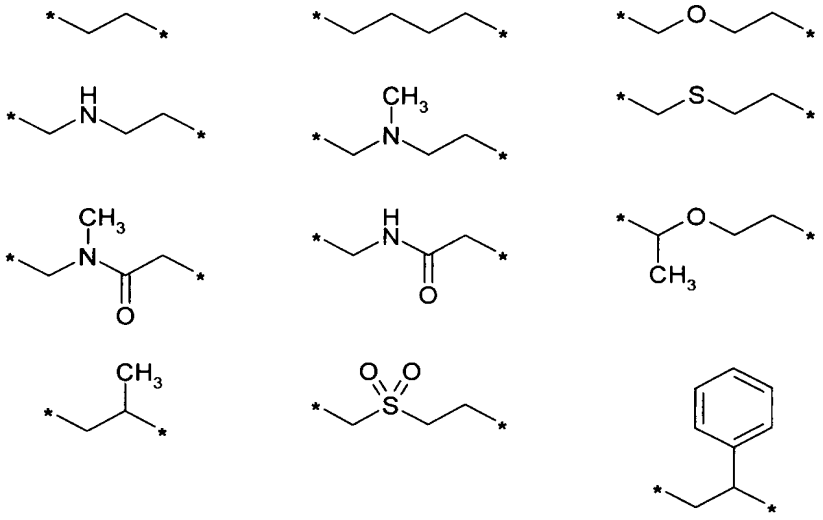
B representa uma ligação, C_{1-2}-alquileno, -O- ou –C(O)-,

D representa um grupo da fórmula geral **II**

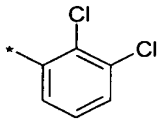
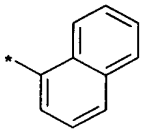
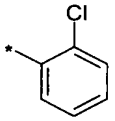
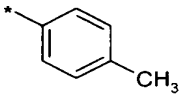
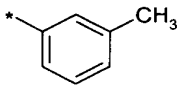
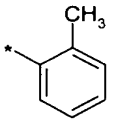
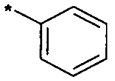
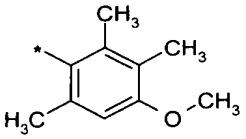
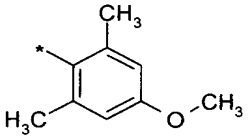
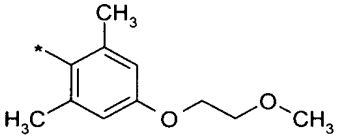
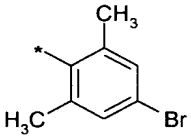
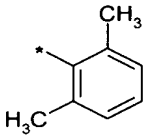
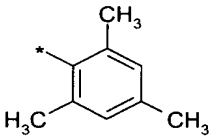
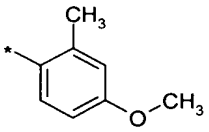
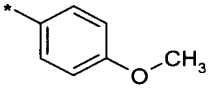


,

Y representa um grupo selecionado de

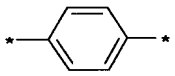
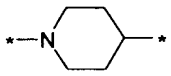
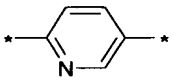
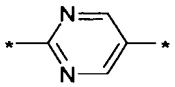
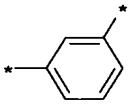
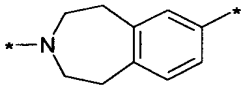
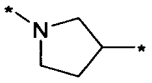
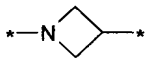
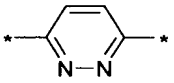
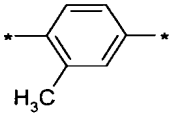
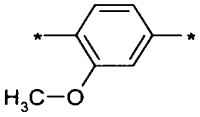
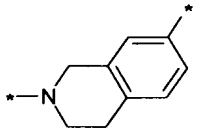
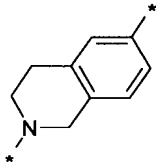
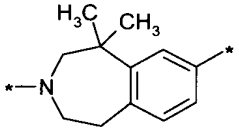
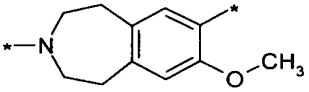
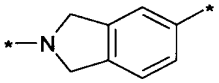
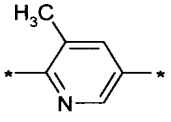
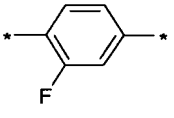


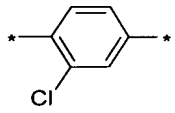
R^1 representa um grupo selecionado de

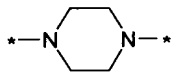
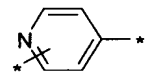
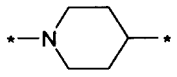
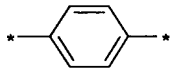
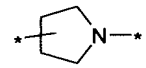
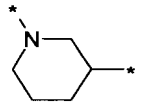
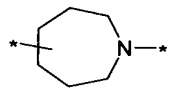
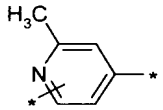
R² representa H, H_3C-, H_5C_2- ou FH_2C-H_2C-,

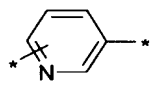
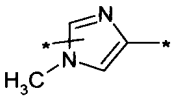
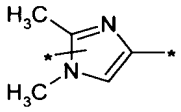
R³ representa C_{1-4}-alquileno ou um grupo selecionado de

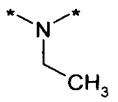
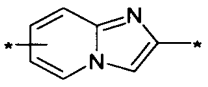
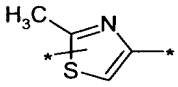
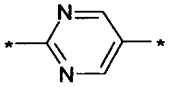
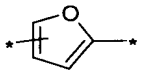
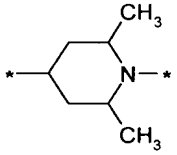
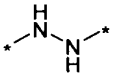
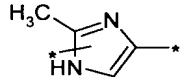
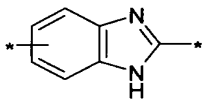
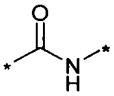
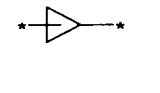
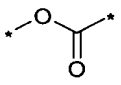
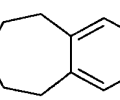
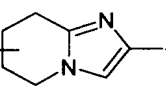



















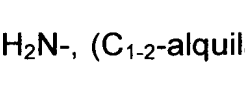
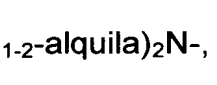


R^4 representa C_{1-4}-alquileno, -O- ou um grupo selecionado de

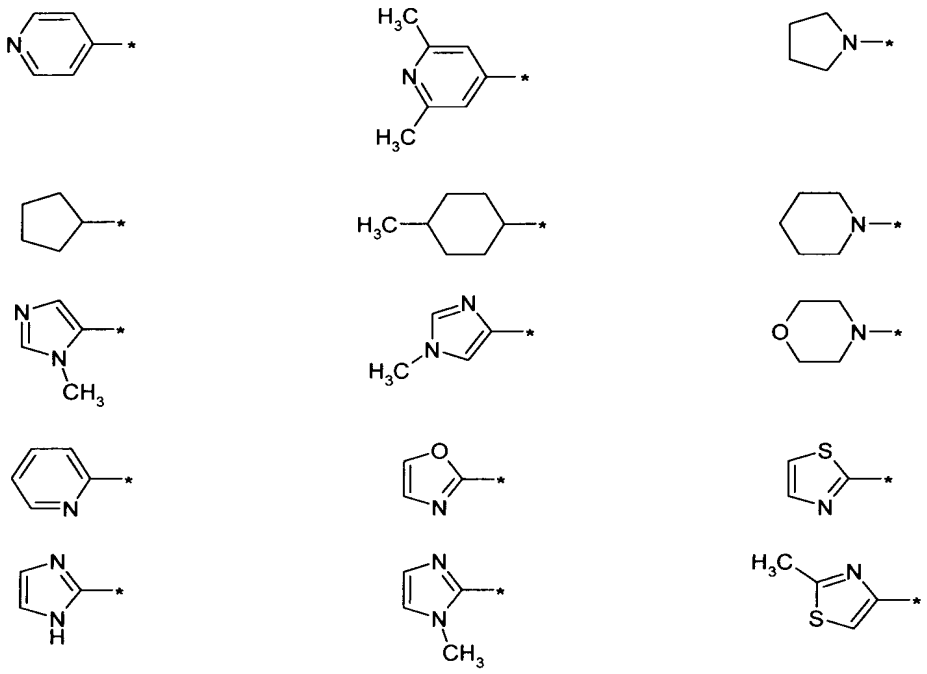




R^5 representa H, C_{1-5}-alquila, H_2N-, (C_{1-2}-alquila)-NH-, (C_{1-2}-alquila)$_2$N-, H_2N-C(O)- ou

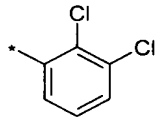
R^5 representa um grupo selecionado de



seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos.

Uma sétima forma de concretização da presente invenção, consiste nos compostos da fórmula geral **I** acima, nos quais **A**, **B**, **D**, **Y**, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$ e $\mathbf{R^5}$ são definidos tal como acima sob a primeira até sexta forma de concretização e

$\mathbf{R^1}$ representa o grupo

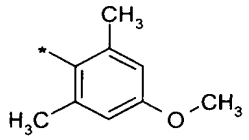


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seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos.

Uma oitava forma de concretização da presente invenção, consiste nos compostos da fórmula geral **I** acima, nos quais **A**, **B**, **D**, **Y**, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$ e $\mathbf{R^5}$ são definidos tal como acima sob a primeira até sexta forma de concretização e

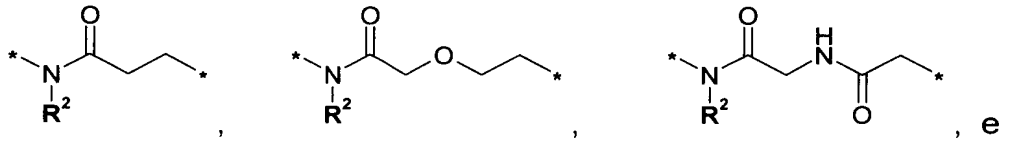
$\mathbf{R^1}$ representa o grupo



seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos.

Uma nona forma de concretização da presente invenção, consiste nos compostos da fórmula geral **I** acima, nos quais **A**, **B**, R^1, R^3, R^4 e R^5 são definidos tal como acima sob a primeira até oitava forma de concretização e

-D-Y- juntos representam um grupo selecionado de



R^2 representa H ou C_{1-3}-alquila,

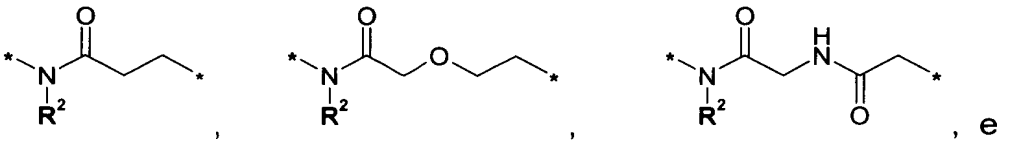
seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos.

Uma décima forma de concretização da presente invenção, consiste nos compostos da fórmula geral **I** acima, nos quais

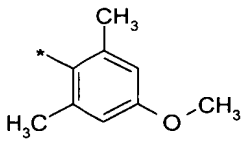
A representa uma ligação,

B representa uma ligação,

-D-Y- juntos representam um grupo selecionado de



R^1 representa o grupo



R^2 representa H ou C_{1-3}-alquila, em que cada grupo metileno pode ser substituído com até dois e cada grupo metila com até três átomos de flúor,

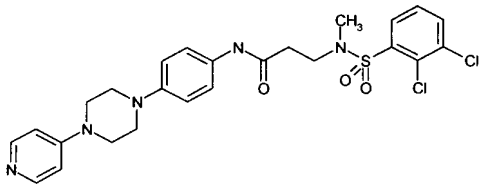
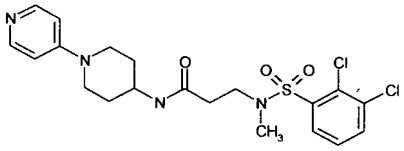
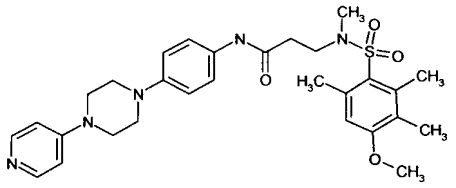
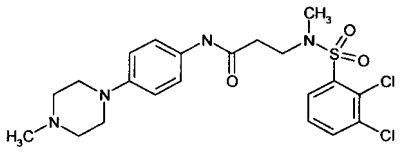
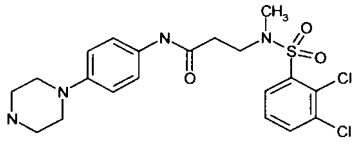
R^3 representa um grupo C_{4-6}-cicloalquileno,

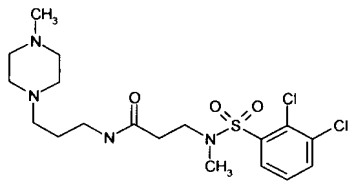
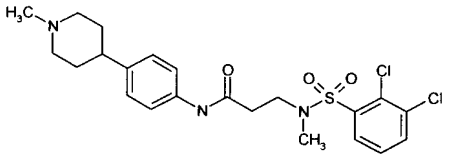
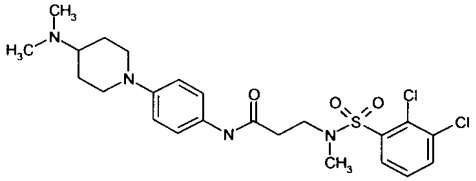
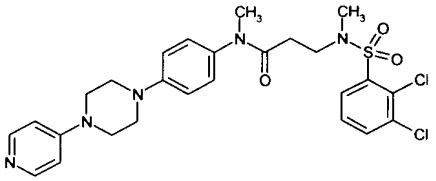
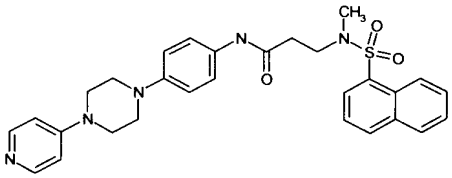
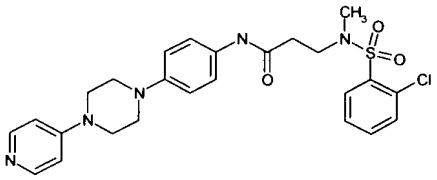
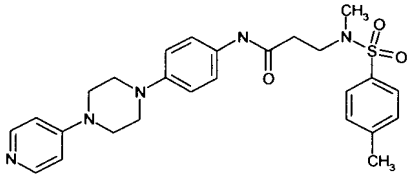
R^4 representa um diaza-heterociclo saturado com 6 ou 7 membro e

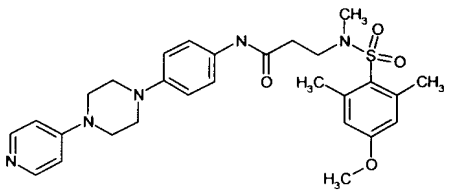
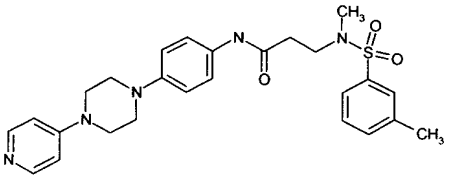
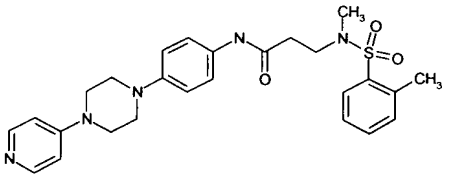
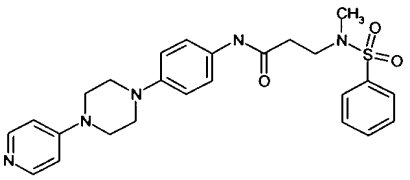
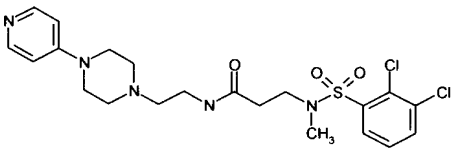
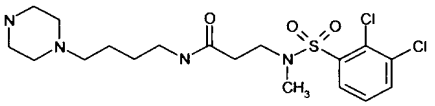
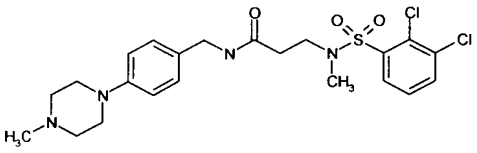
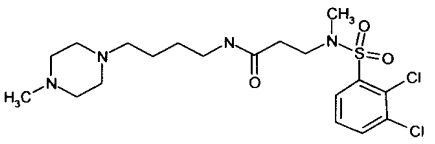
R^5 representa C_{1-3}-alquila ou C_{3-5}-cicloalquila,

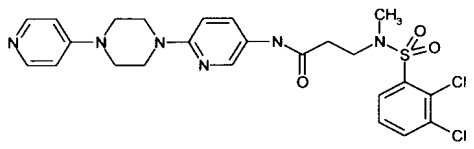
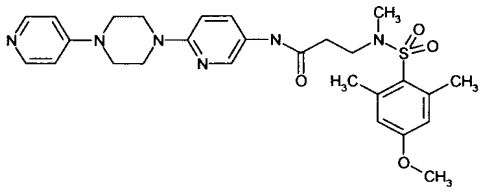
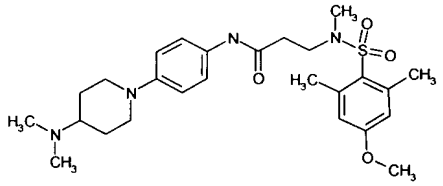
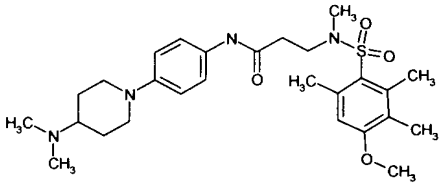
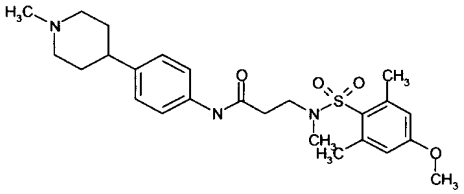
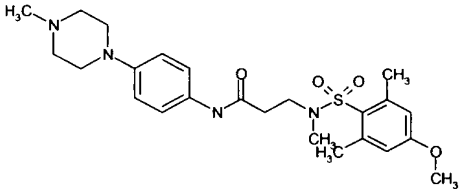
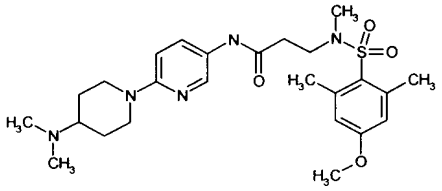
seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos.

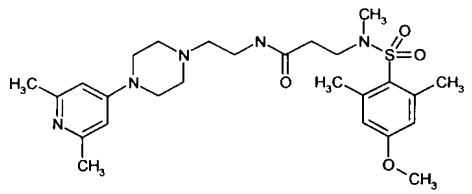
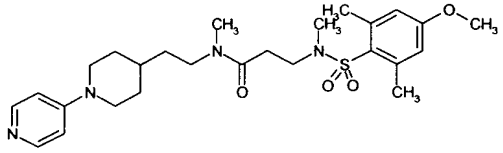
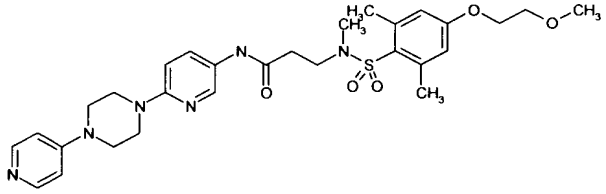
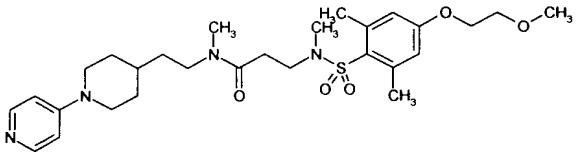
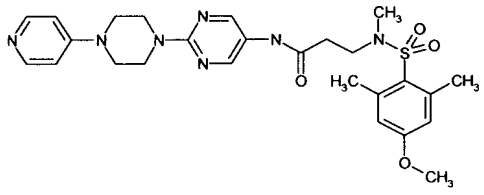
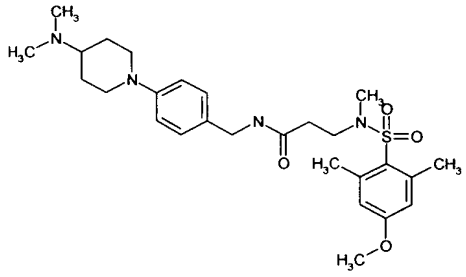
Como compostos muito particularmente preferidos da fórmula geral I acima, sejam mencionados, por exemplo, os seguintes:

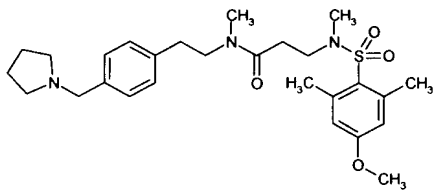
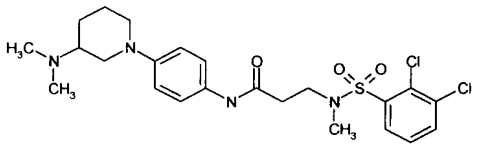
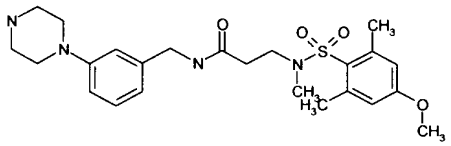
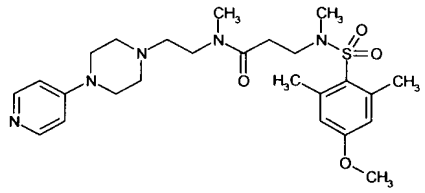
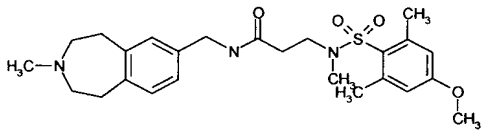
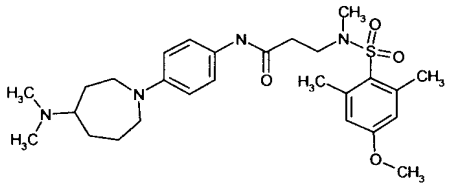
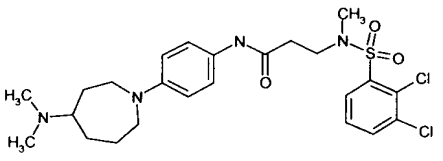
Exemplo	Estrutura
(1)	
(2)	
(3)	
(4)	
(5)	

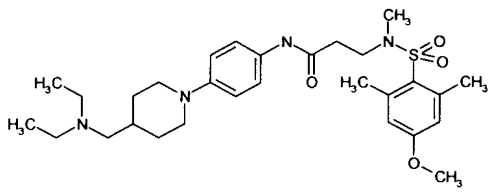
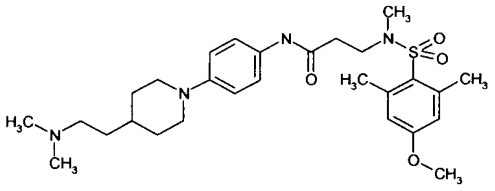
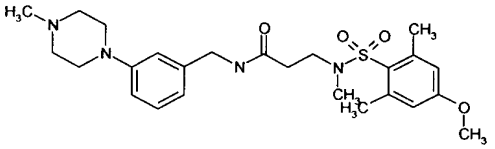
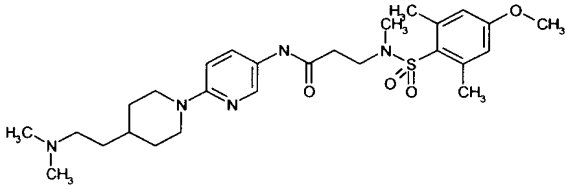
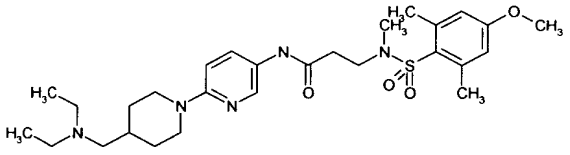
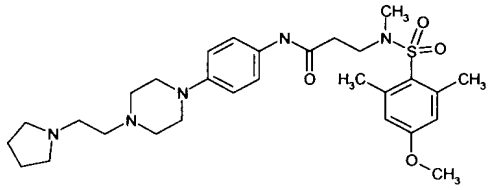
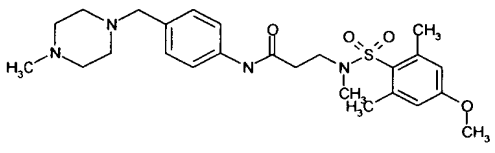
Exemplo	Estrutura
(6)	
(7)	
(8)	
(9)	
(10)	
(11)	
(12)	

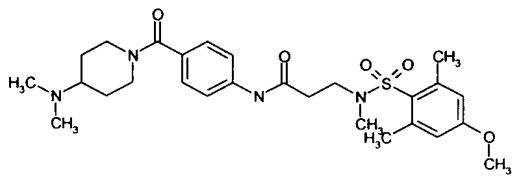
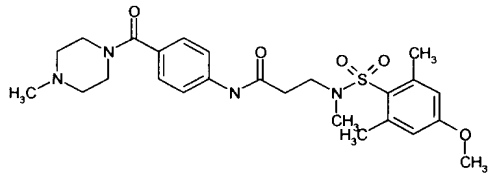
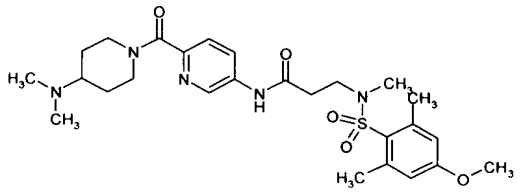
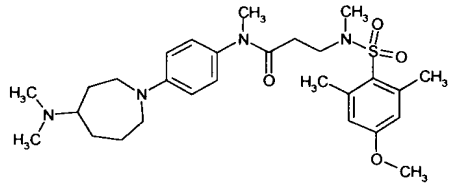
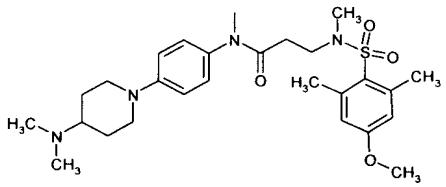
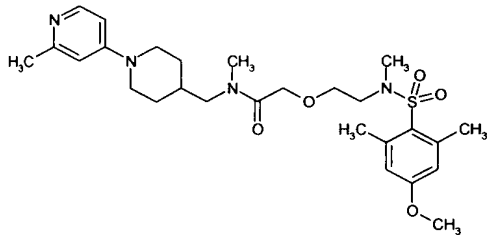
Exemplo	Estrutura
(13)	
(14)	
(15)	
(16)	
(17)	
(18)	
(19)	
(20)	

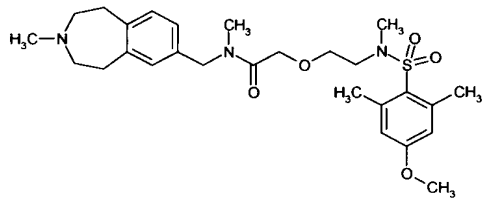
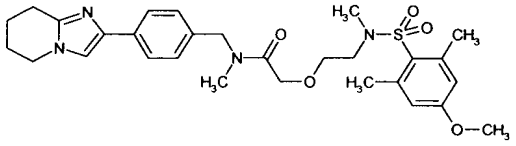
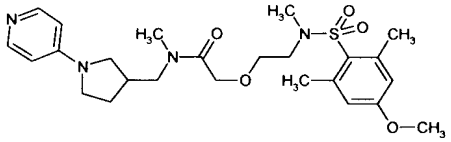
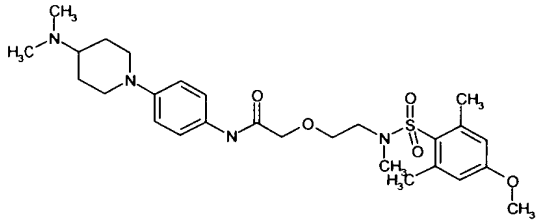
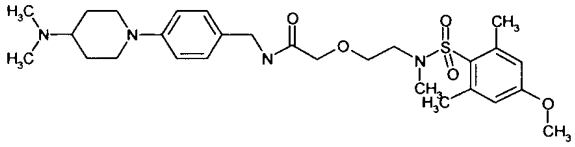
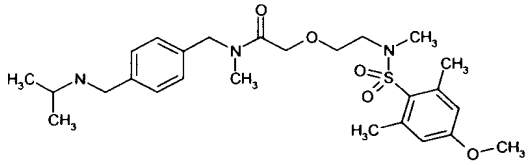
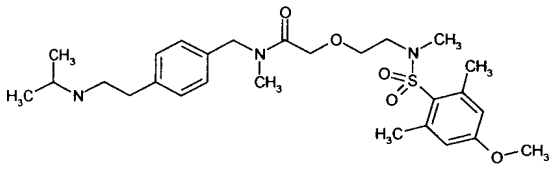
Exemplo	Estrutura
(21)	
(22)	
(23)	
(24)	
(25)	
(26)	
(27)	

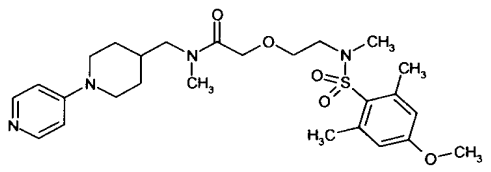
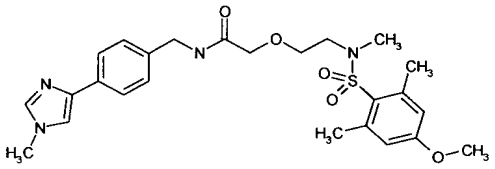
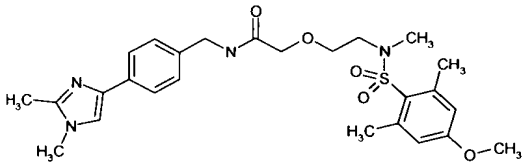
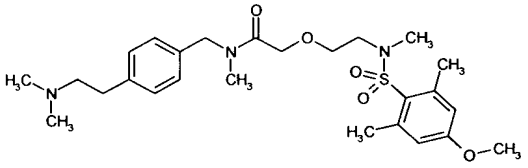
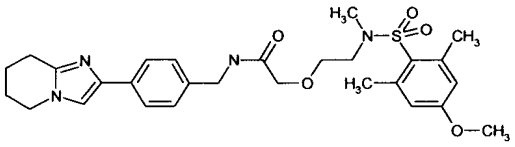
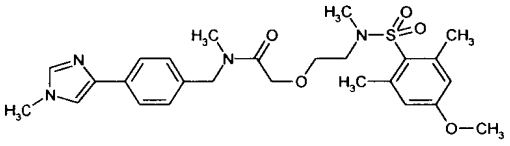
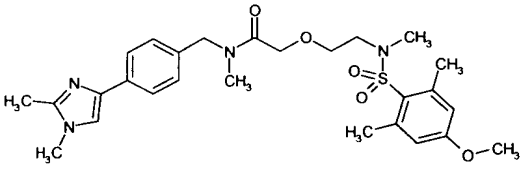
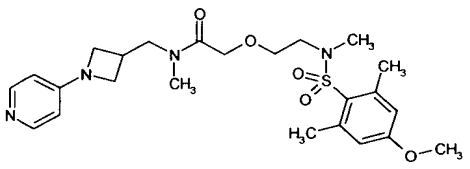
Exemplo	Estrutura
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(29)	
(30)	
(31)	
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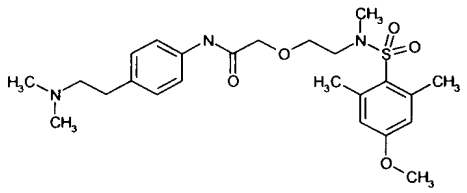
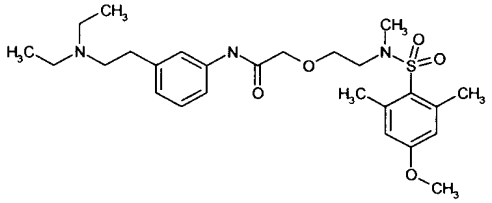
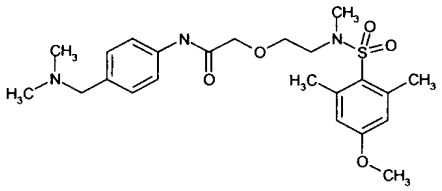
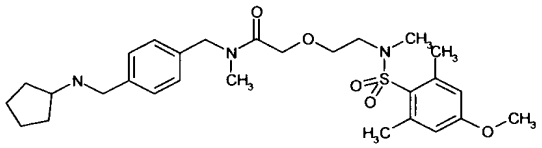
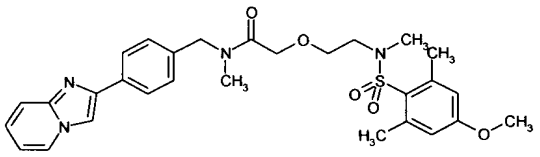
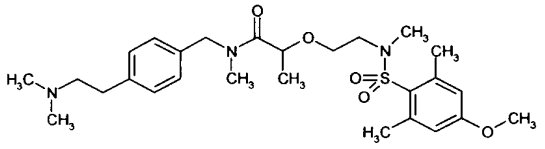
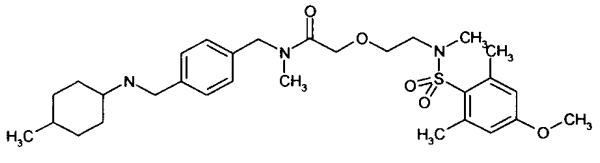
Exemplo	Estrutura
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(35)	
(36)	
(37)	
(38)	
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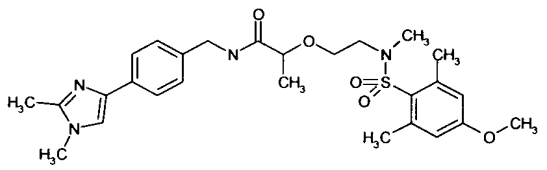
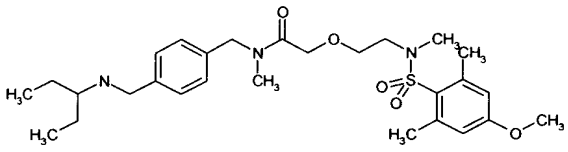
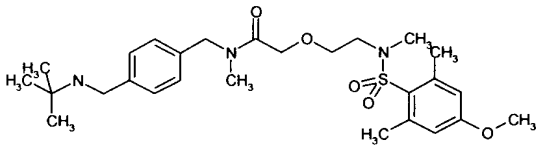
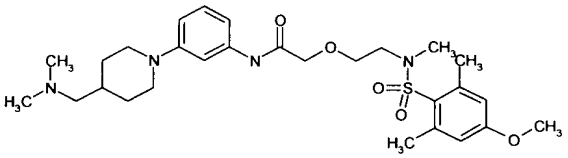
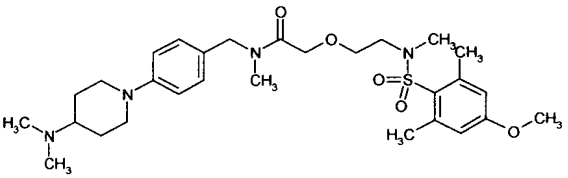
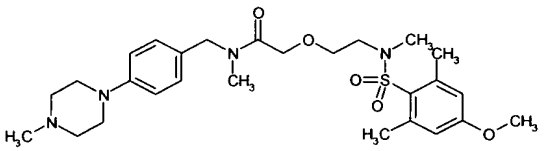
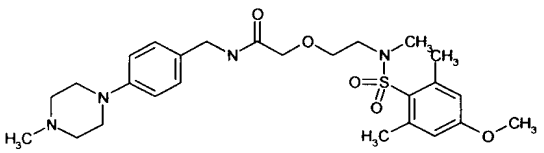
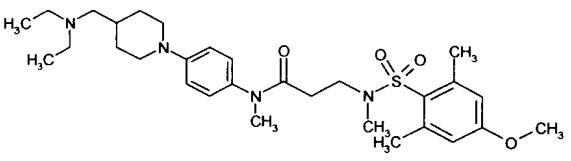
Exemplo	Estrutura
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(42)	
(43)	
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(45)	
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(47)	

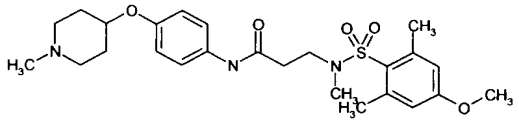
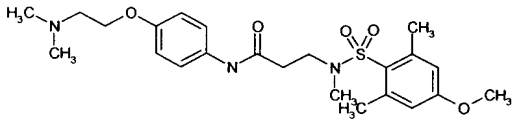
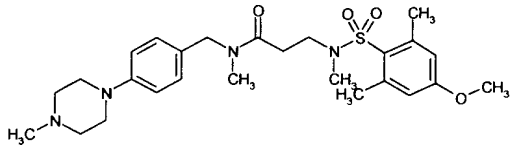
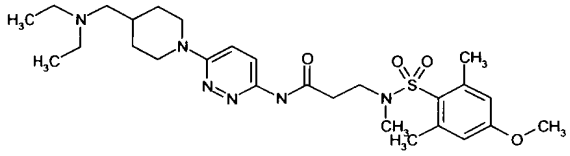
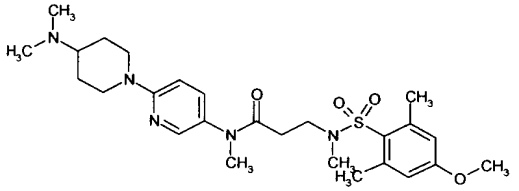
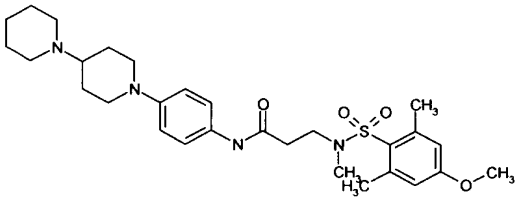
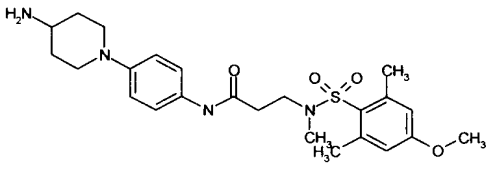
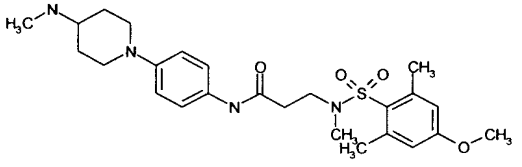
Exemplo	Estrutura
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(49)	
(50)	
(51)	
(52)	
(53)	

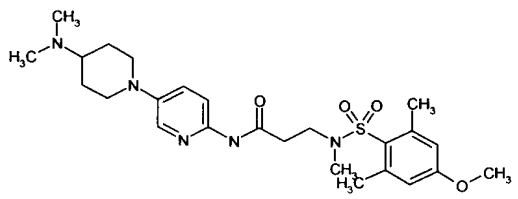
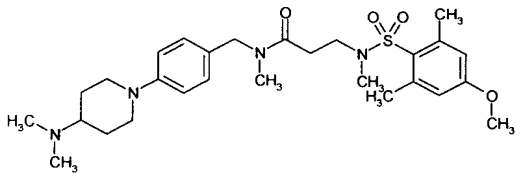
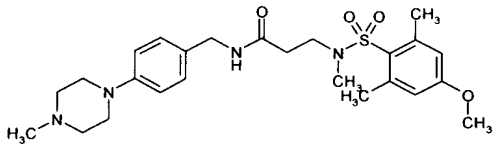
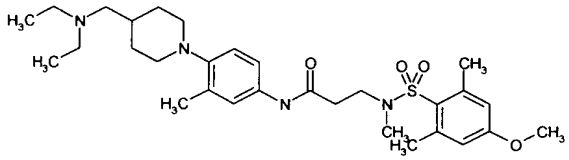
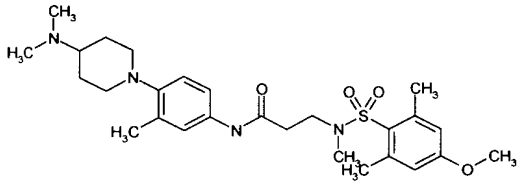
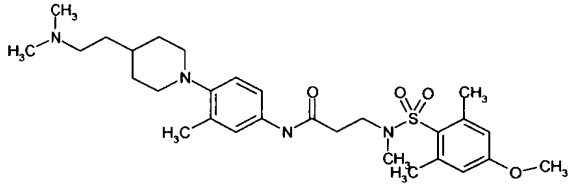
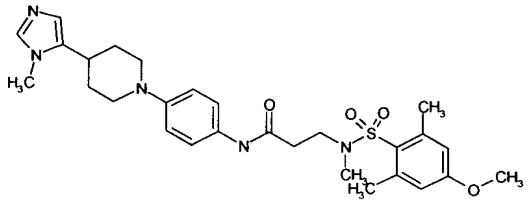
Exemplo	Estrutura
(54)	
(55)	
(56)	
(57)	
(58)	
(59)	
(60)	

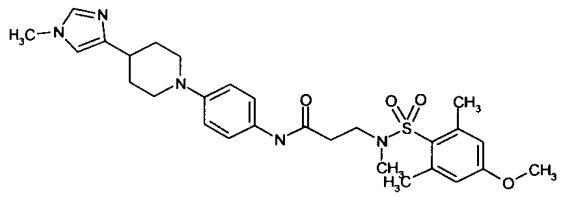
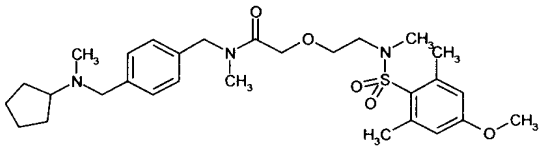
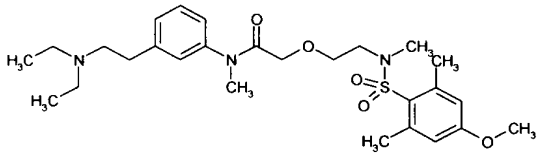
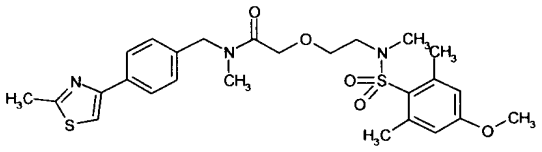
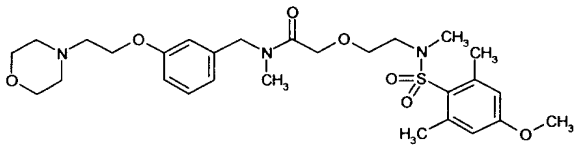
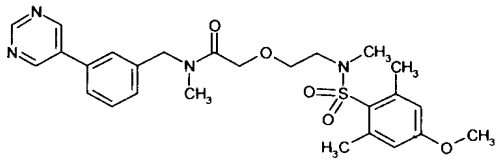
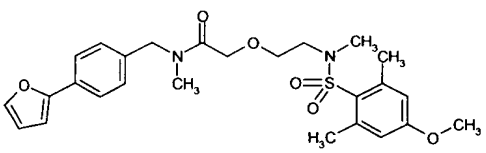
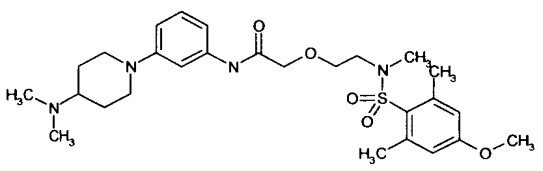
Exemplo	Estrutura
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(62)	
(63)	
(64)	
(65)	
(66)	
(67)	
(68)	

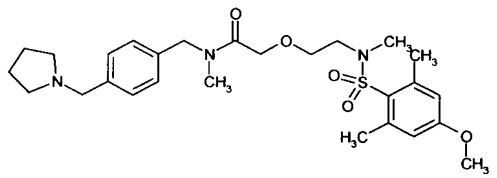
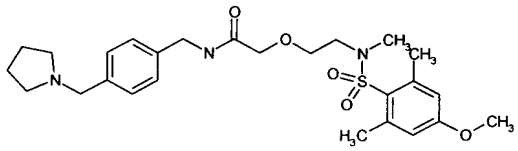
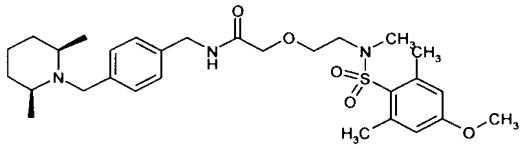
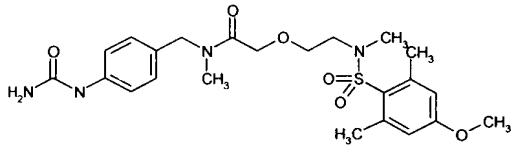
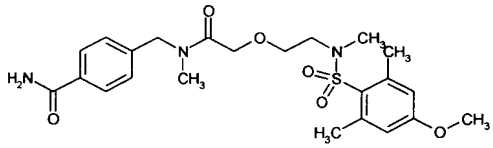
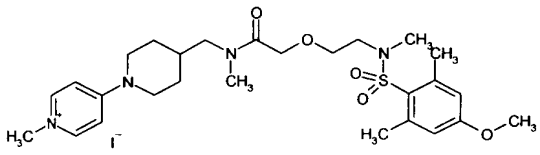
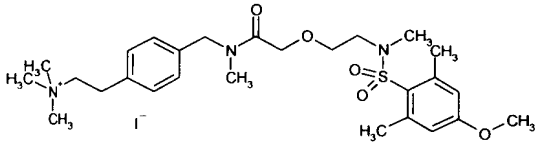
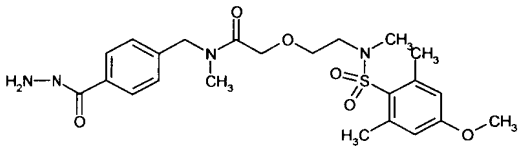
Exemplo	Estrutura
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(70)	
(71)	
(72)	
(73)	
(74)	
(75)	

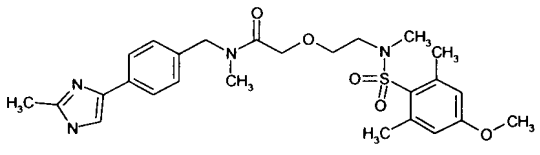
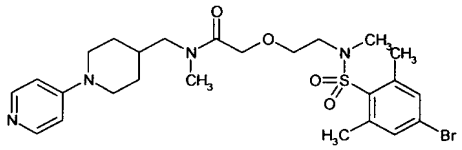
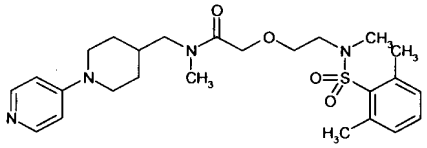
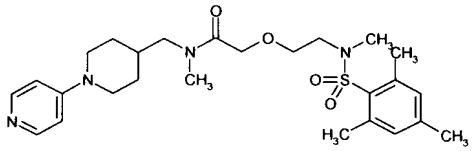
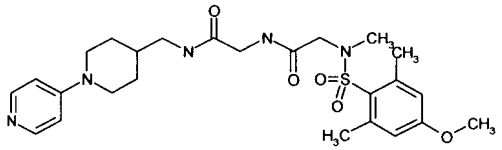
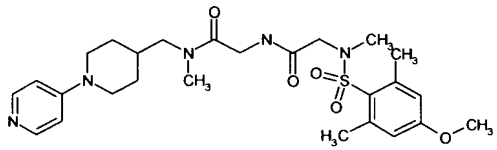
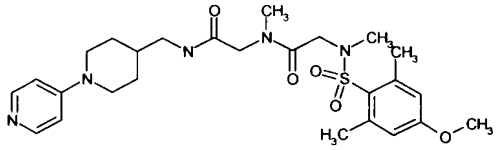
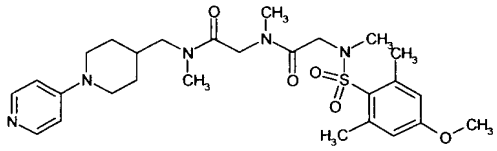
Exemplo	Estrutura
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(77)	
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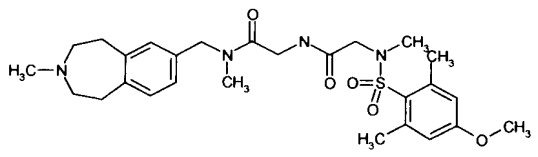
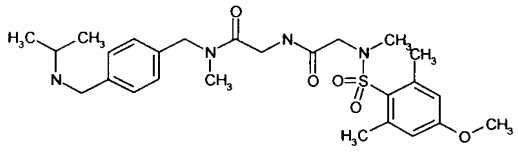
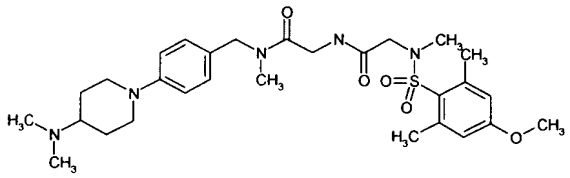
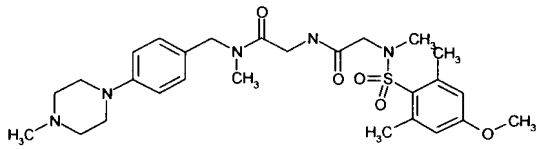
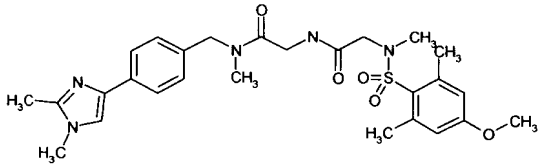
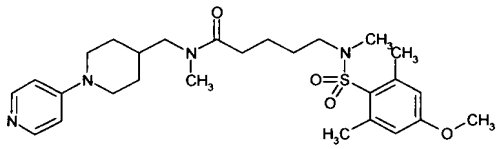
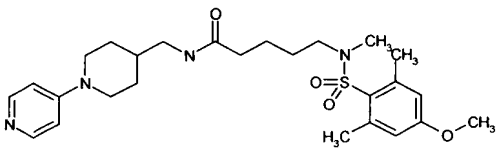
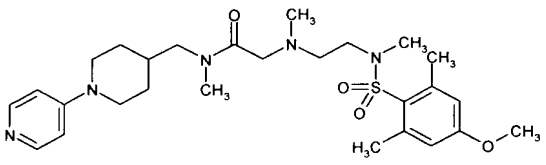
Exemplo	Estrutura
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(85)	
(86)	
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(91)	

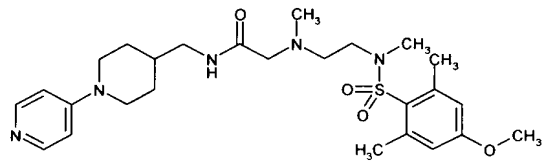
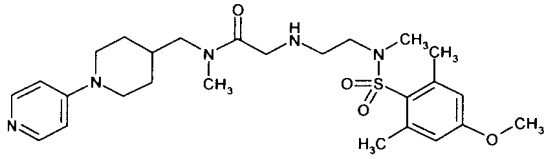
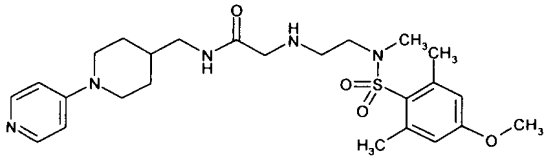
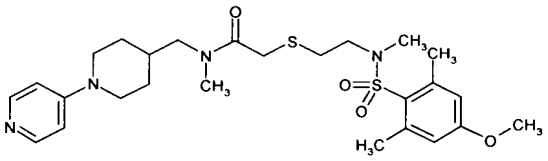
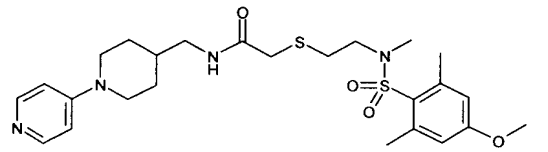
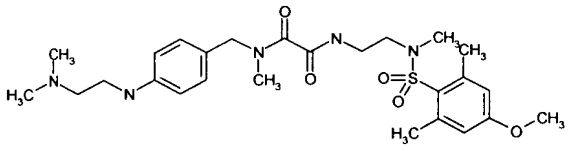
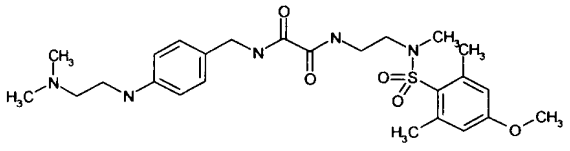
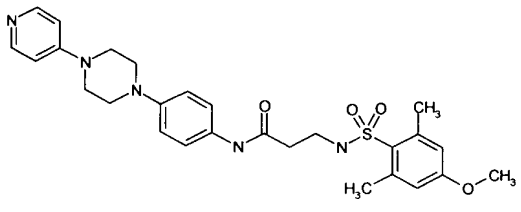
Exemplo	Estrutura
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(93)	
(94)	
(95)	
(96)	
(97)	
(98)	

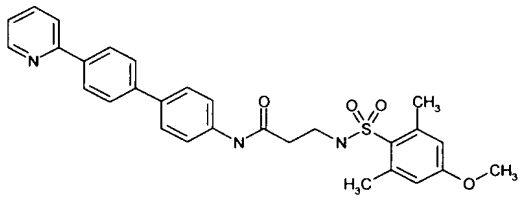
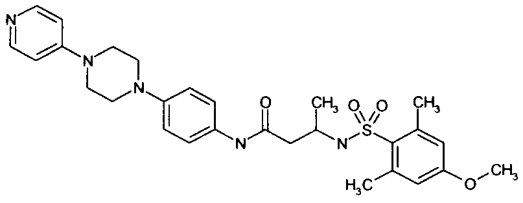
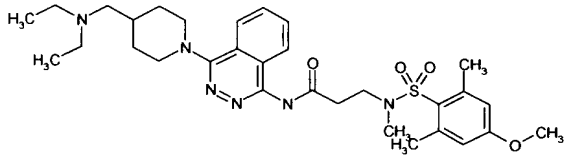
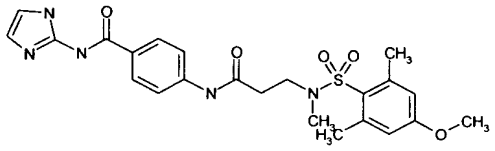
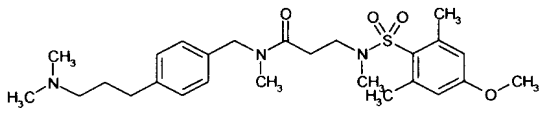
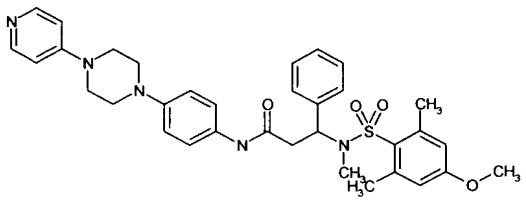
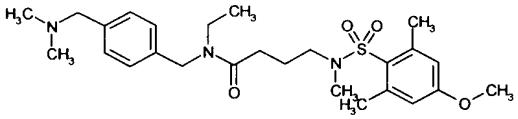
Exemplo	Estrutura
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(100)	
(101)	
(102)	
(103)	
(104)	
(105)	
(106)	

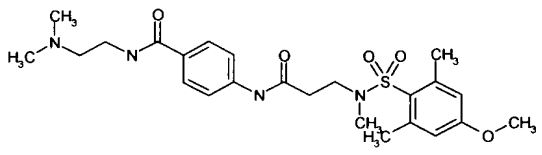
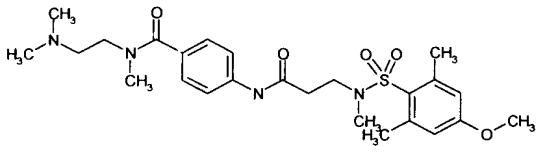
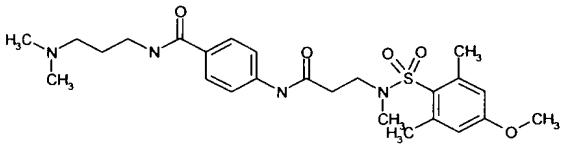
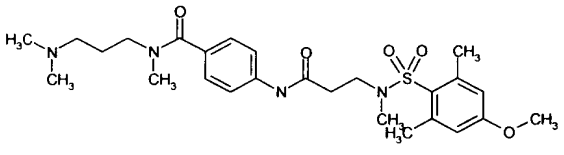
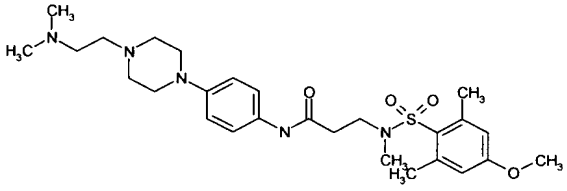
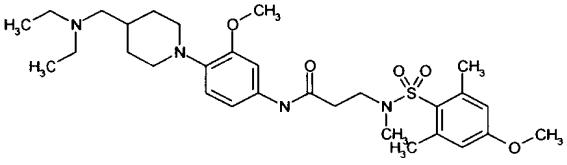
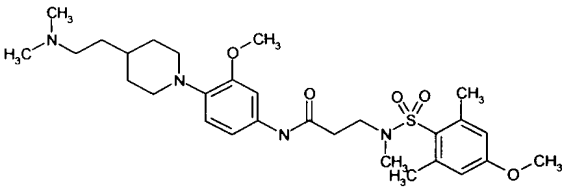
Exemplo	Estrutura
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(108)	
(109)	
(110)	
(111)	
(112)	
(113)	
(114)	

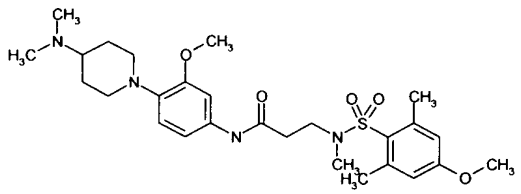
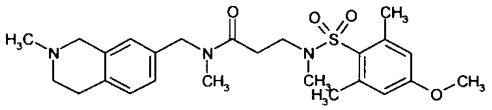
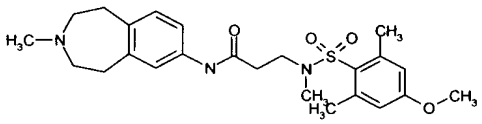
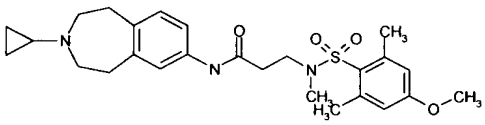
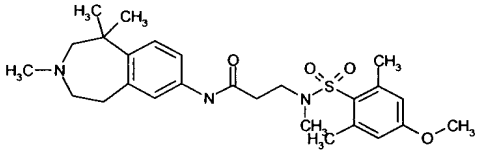
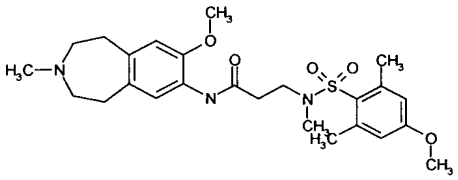
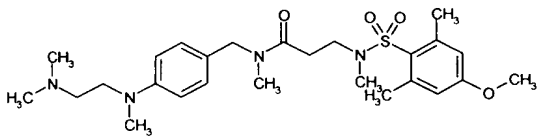
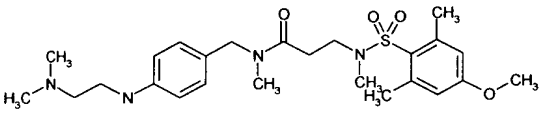
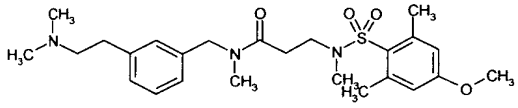
Exemplo	Estrutura
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(116)	
(117)	
(118)	
(119)	
(120)	
(121)	
(122)	

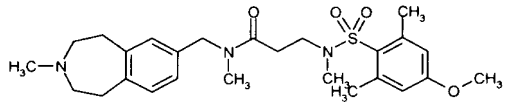
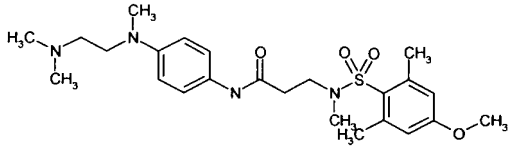
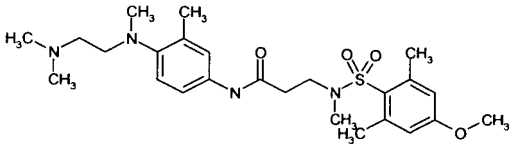
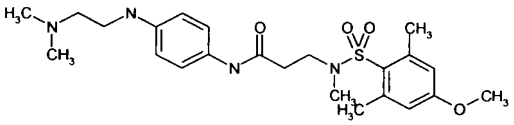
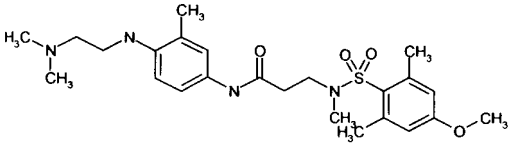
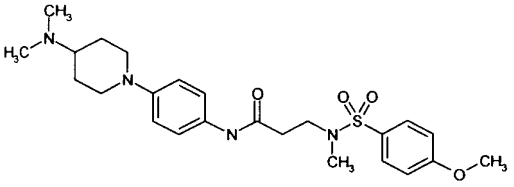
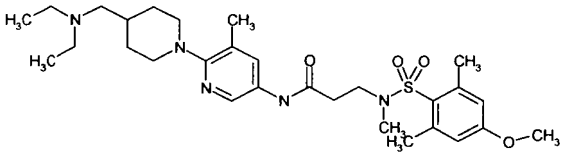
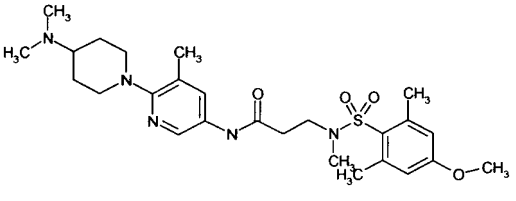
Exemplo	Estrutura
(123)	
(124)	
(125)	
(126)	
(127)	
(128)	
(129)	
(130)	

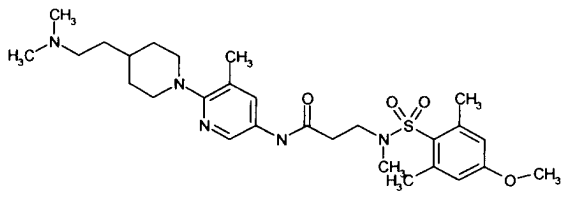
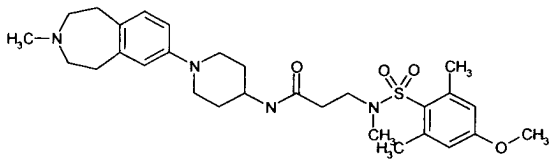
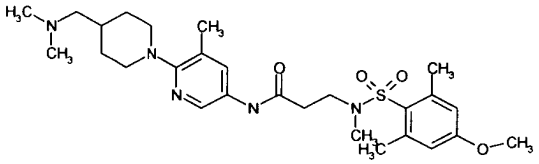
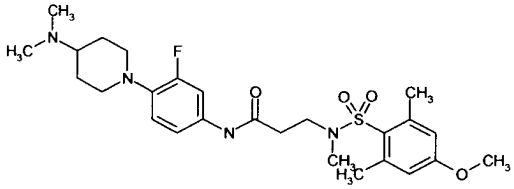
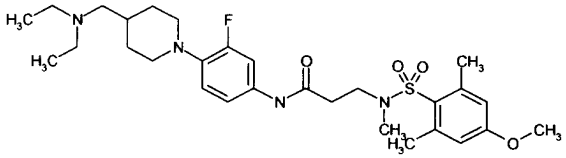
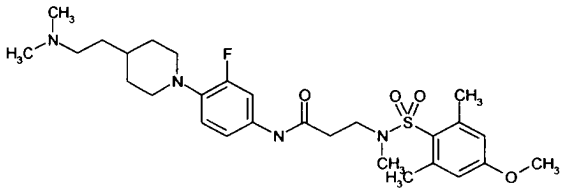
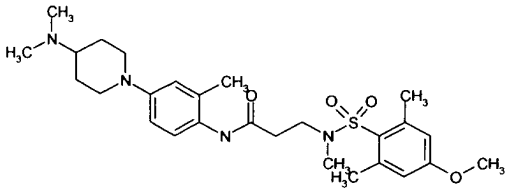
Exemplo	Estrutura
(131)	
(132)	
(133)	
(134)	
(135)	
(136)	
(137)	
(138)	

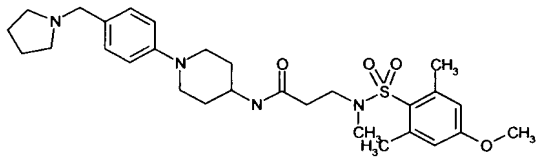
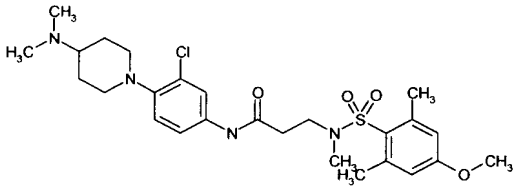
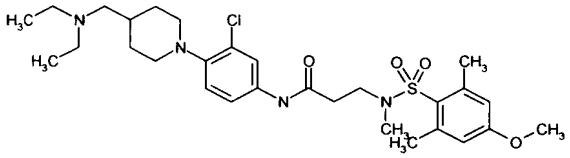
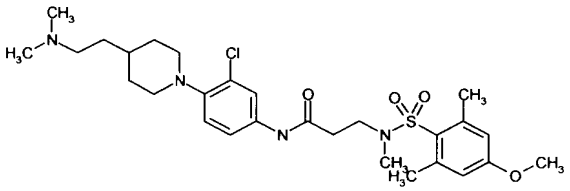
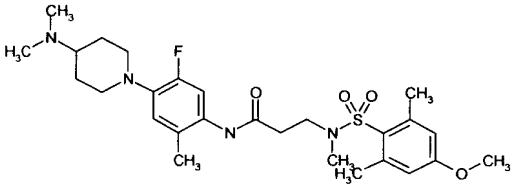
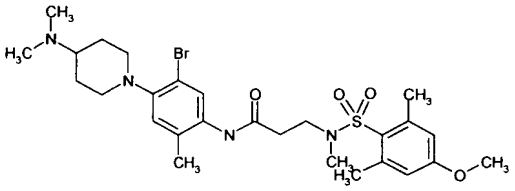
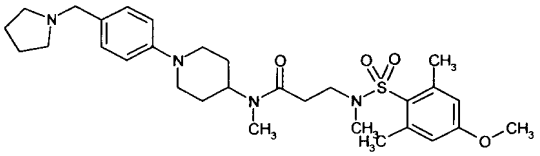
Exemplo	Estrutura
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(143)	
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(145)	

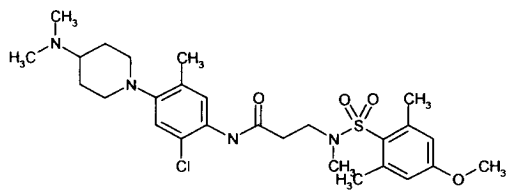
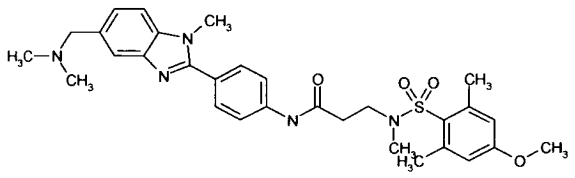
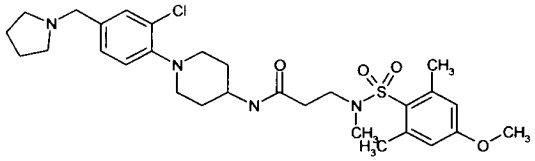
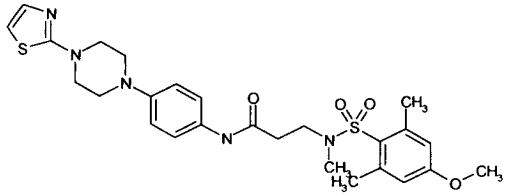
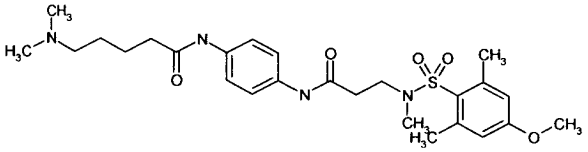
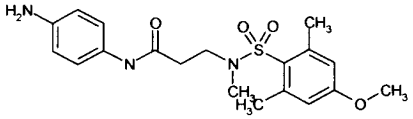
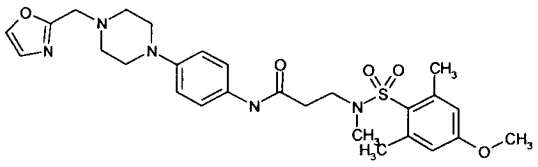
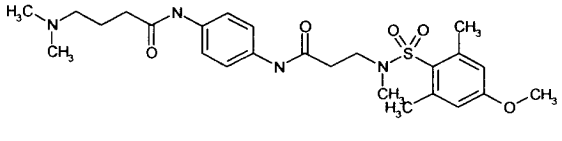
Exemplo	Estrutura
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(147)	
(148)	
(149)	
(150)	
(151)	
(152)	

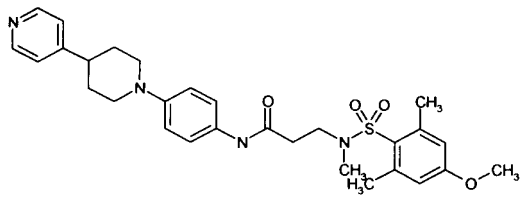
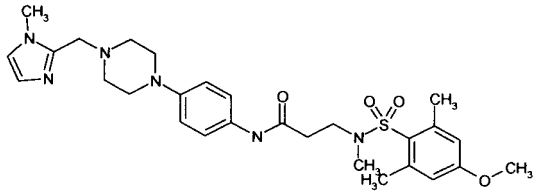
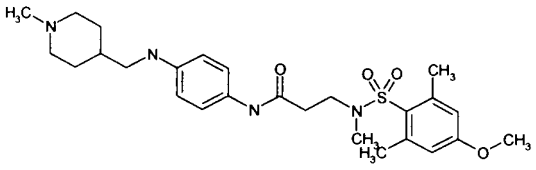
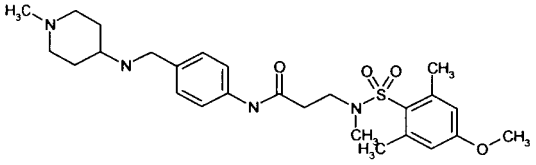
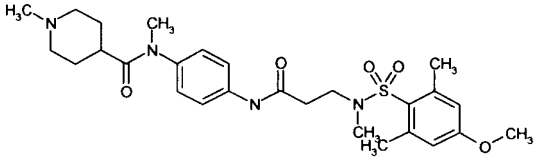
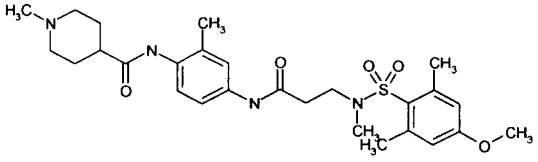
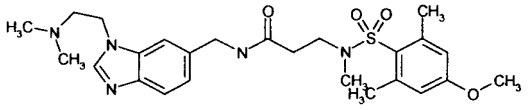
Exemplo	Estrutura
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(154)	
(155)	
(156)	
(157)	
(158)	
(159)	
(160)	
(161)	

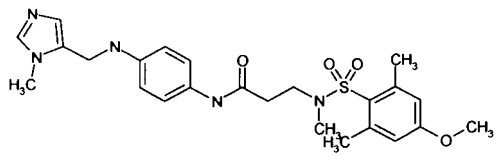
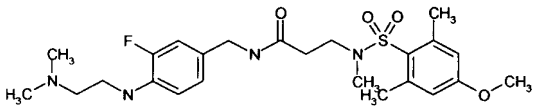
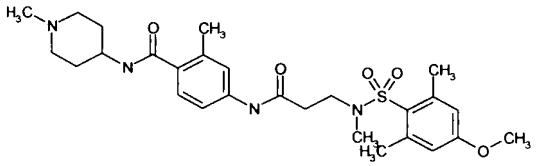
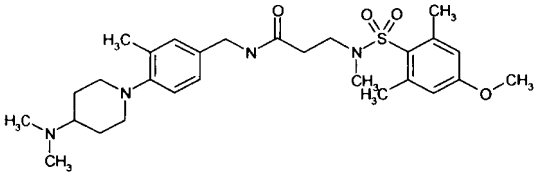
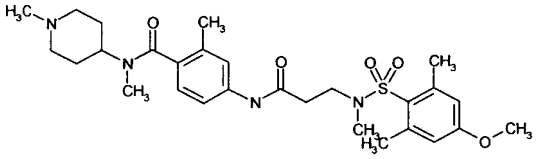
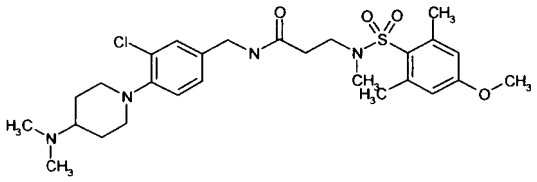
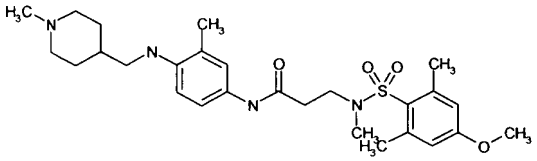
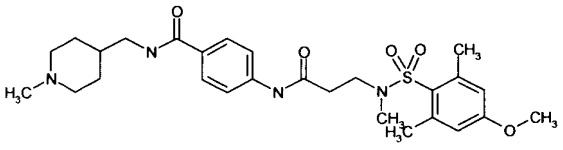
Exemplo	Estrutura
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(163)	
(164)	
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(166)	
(167)	
(168)	
(169)	

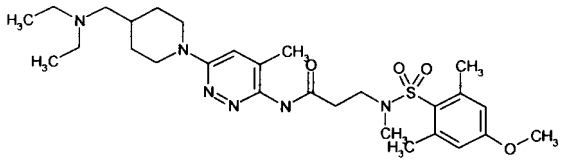
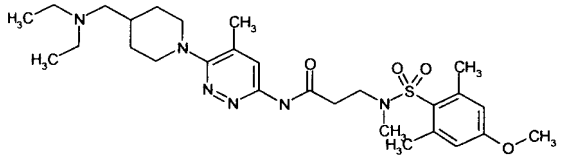
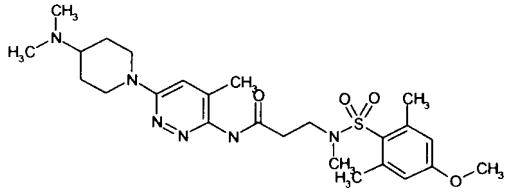
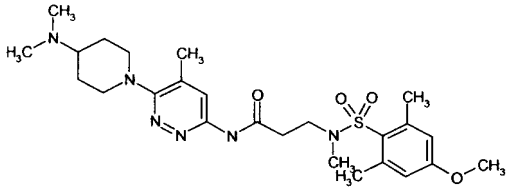
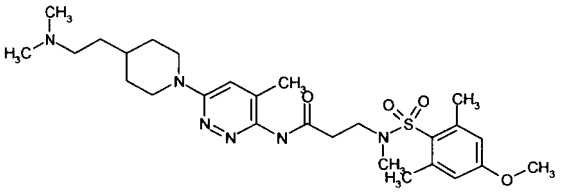
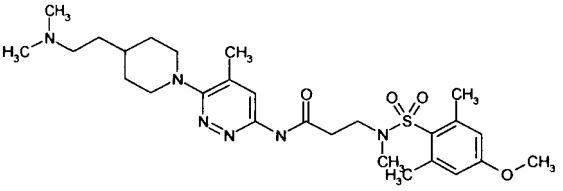
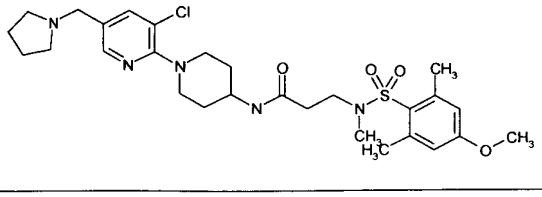
Exemplo	Estrutura
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(172)	
(173)	
(174)	
(175)	
(176)	

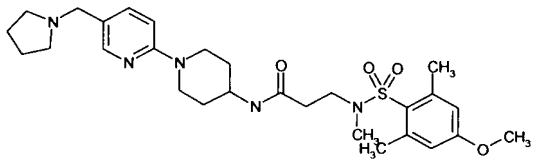
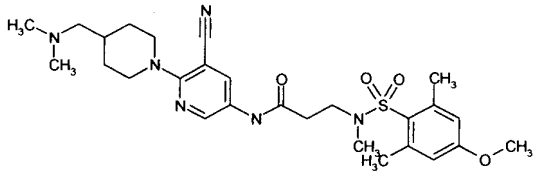
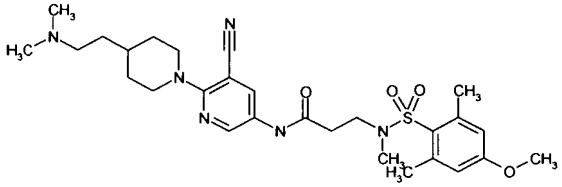
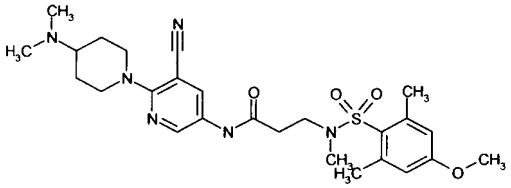
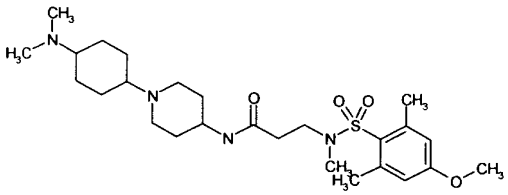
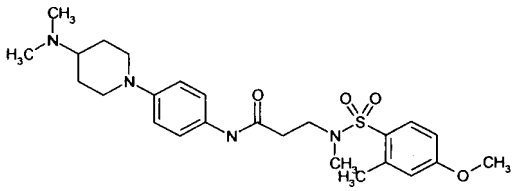
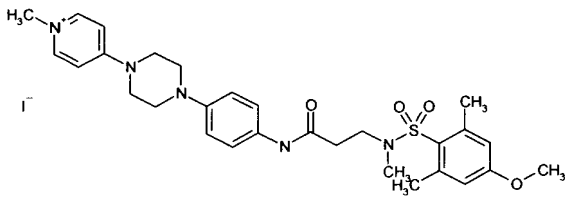
Exemplo	Estrutura
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(179)	
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(181)	
(182)	
(183)	

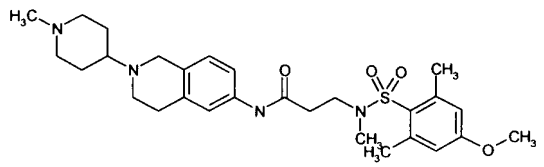
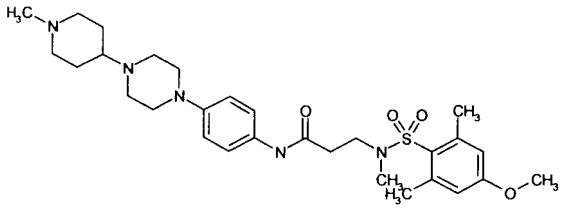
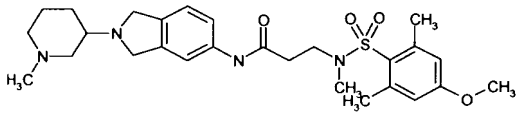
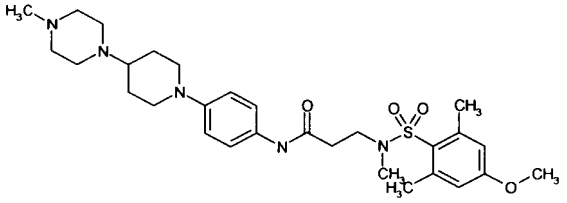
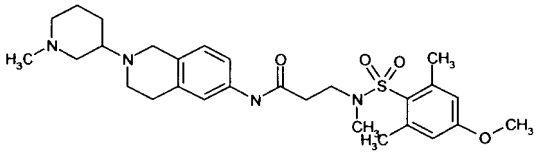
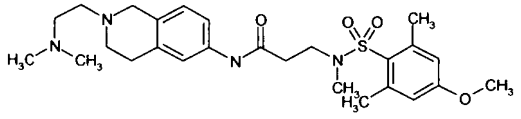
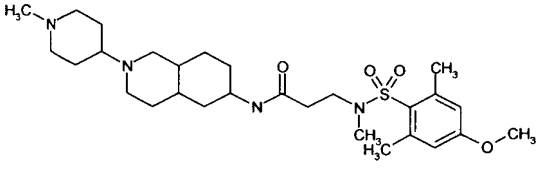
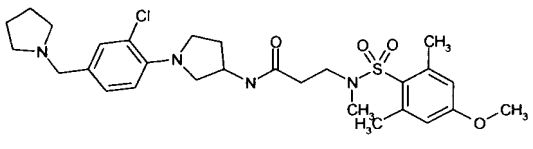
Exemplo	Estrutura
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(186)	
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(188)	
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(190)	
(191)	

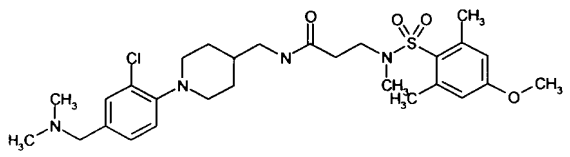
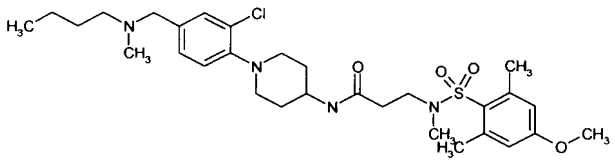
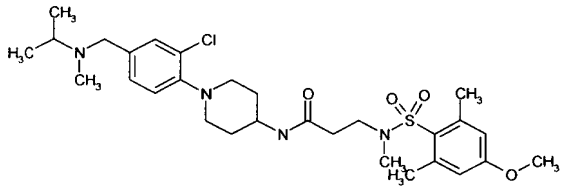
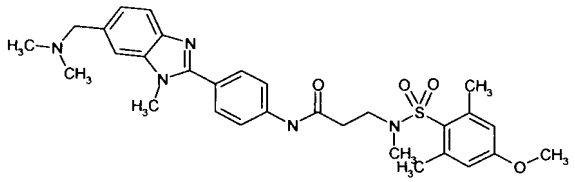
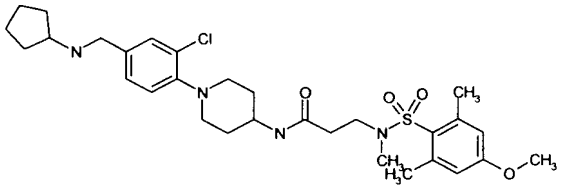
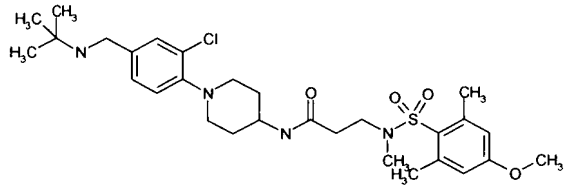
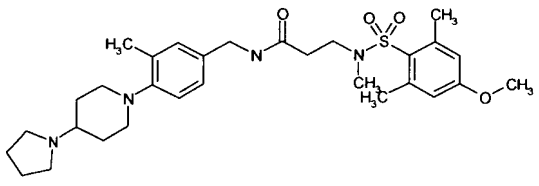
Exemplo	Estrutura
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(193)	
(194)	
(195)	
(196)	
(197)	
(198)	

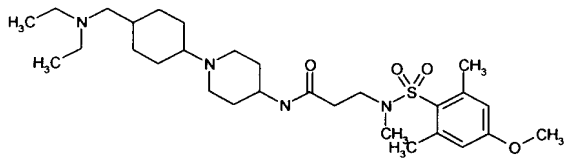
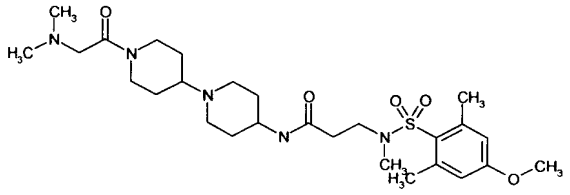
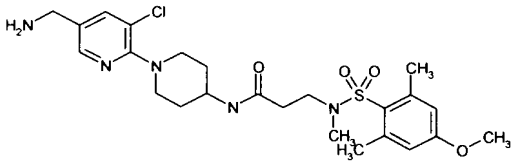
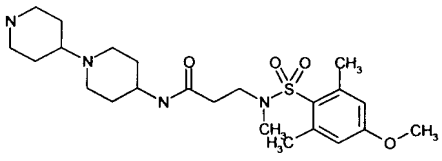
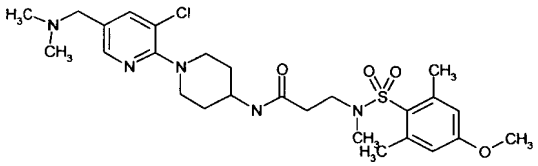
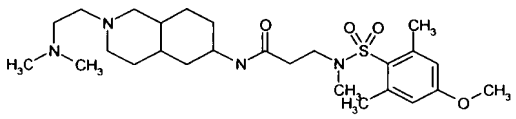
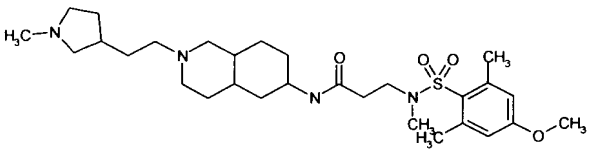
Exemplo	Estrutura
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(203)	
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(205)	
(206)	

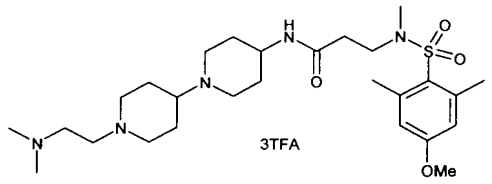
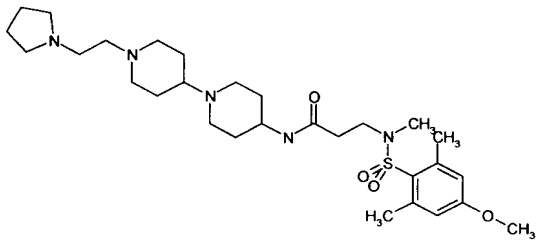
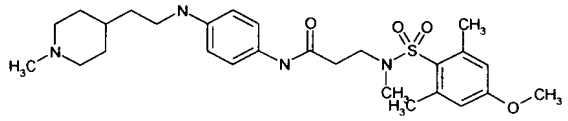
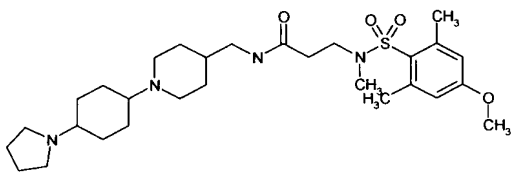
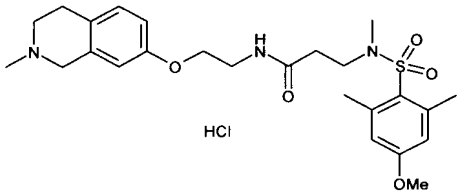
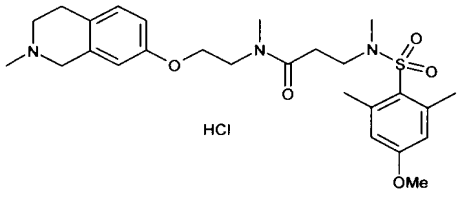
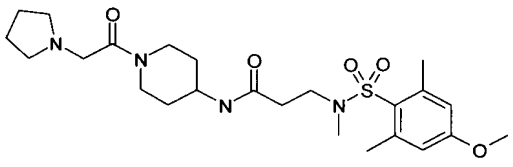
Exemplo	Estrutura
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(208)	
(209)	
(210)	
(211)	
(212)	
(213)	

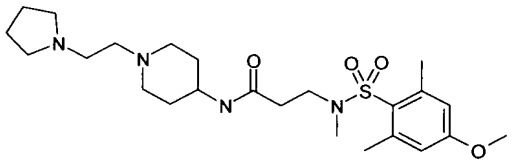
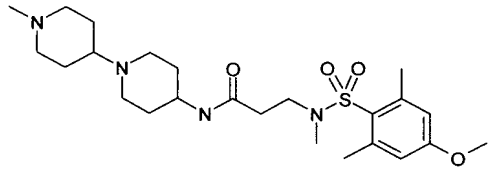
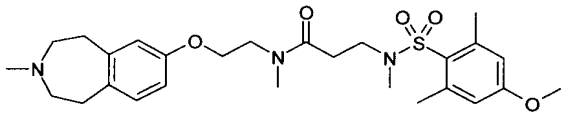
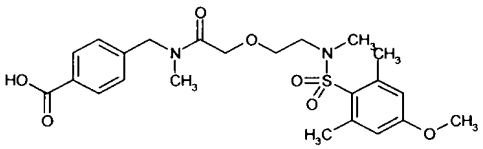
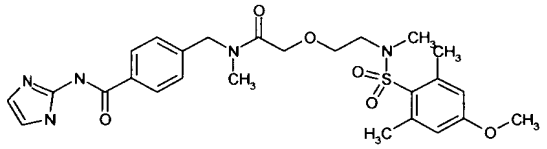
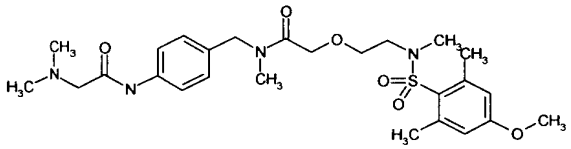
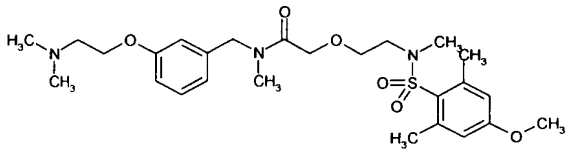
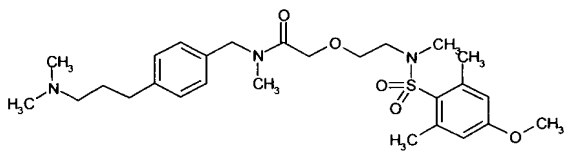
Exemplo	Estrutura
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(215)	
(216)	
(217)	
(218)	
(219)	
(220)	

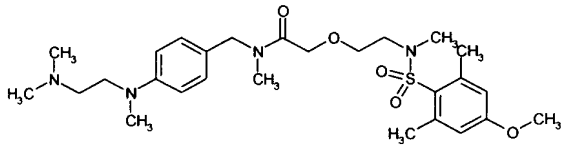
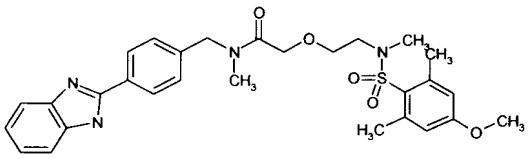
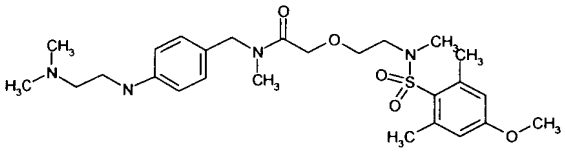
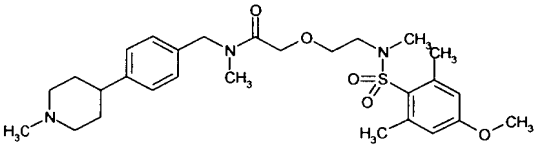
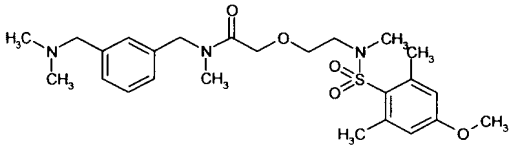
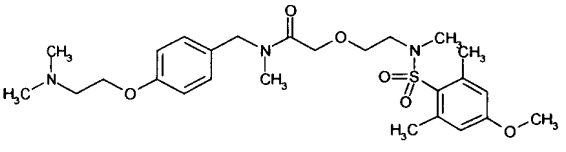
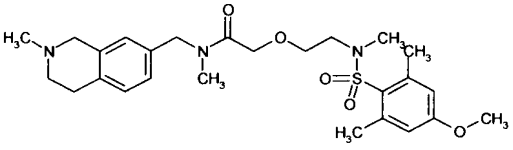
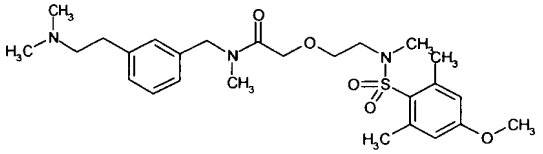
Exemplo	Estrutura
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(222)	
(223)	
(224)	
(225)	
(226)	
(227)	
(228)	

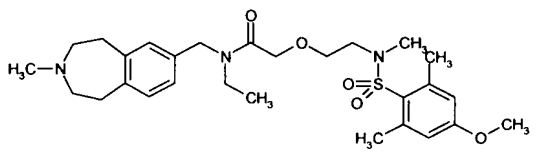
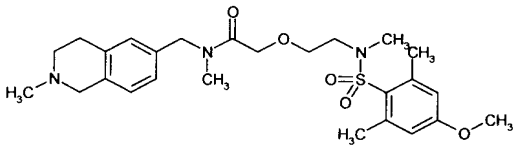
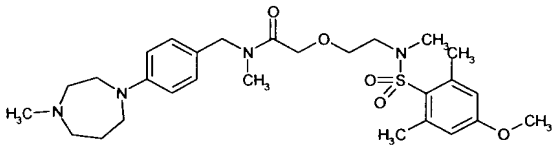
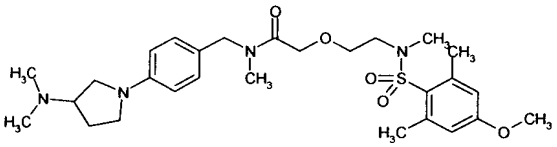
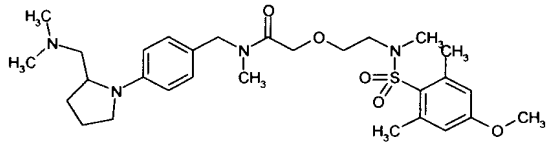
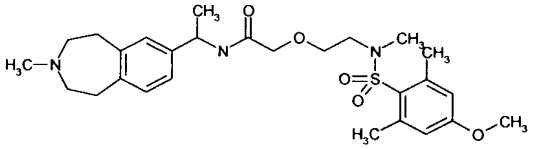
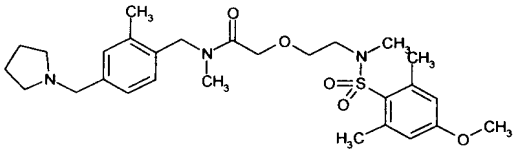
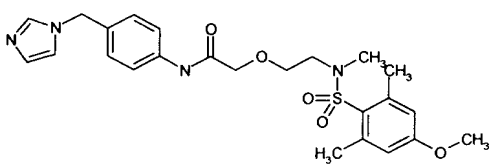
Exemplo	Estrutura
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(233)	
(234)	
(235)	

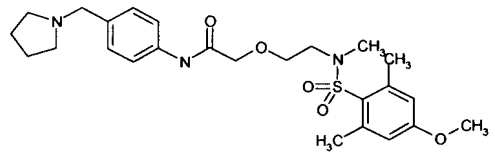
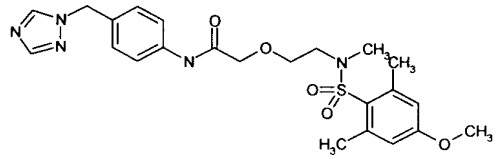
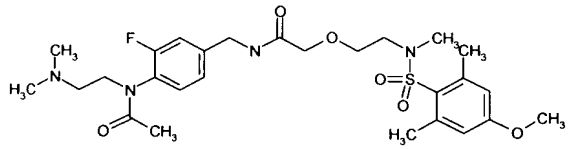
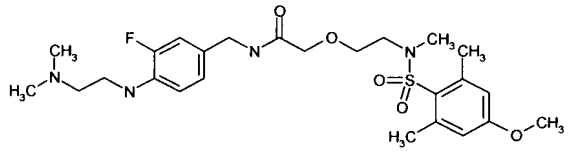
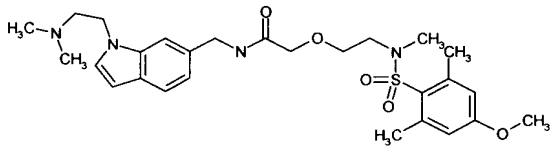
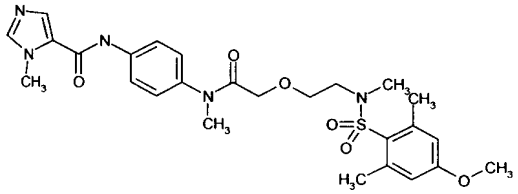
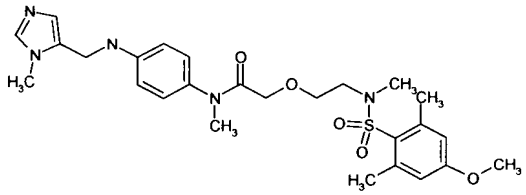
Exemplo	Estrutura
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(237)	
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(240)	
(241)	
(242)	

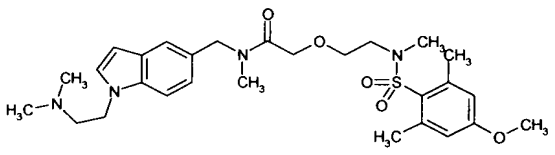
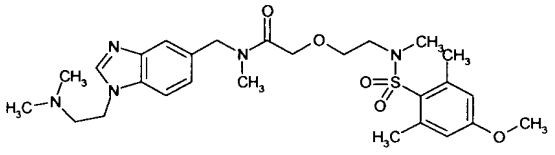
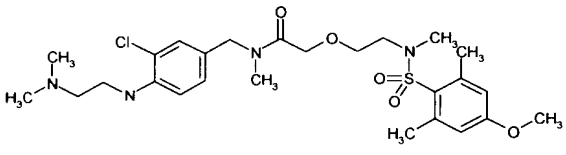
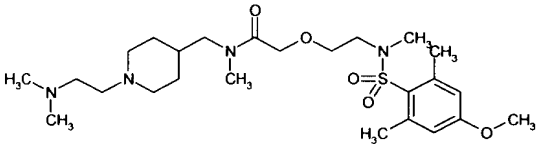
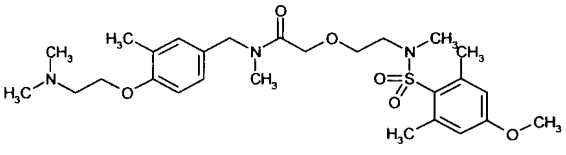
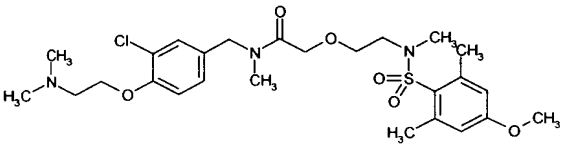
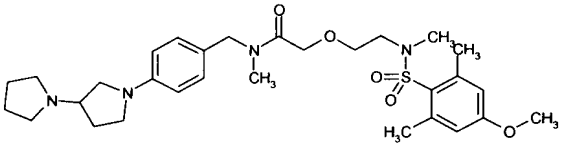
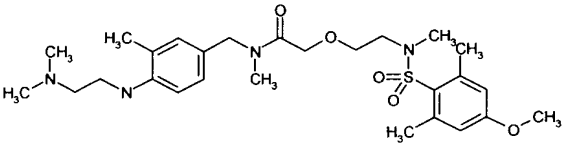
Exemplo	Estrutura
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(244)	
(245)	
(246)	
(247)	
(248)	
(249)	

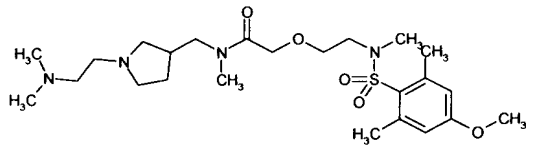
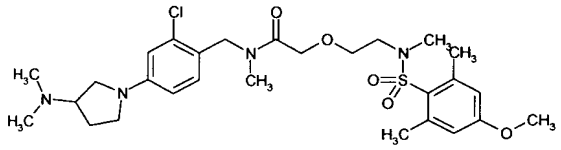
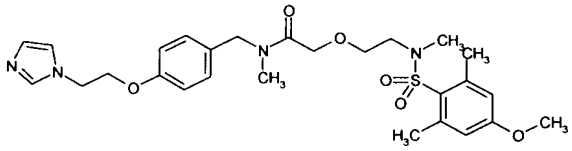
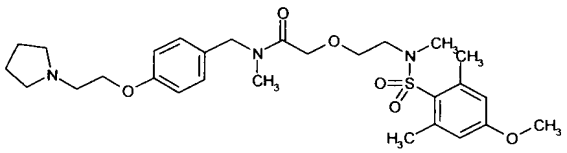
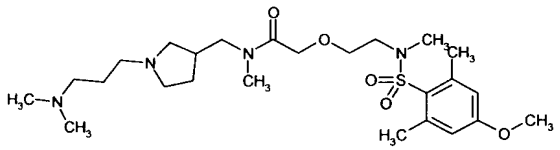
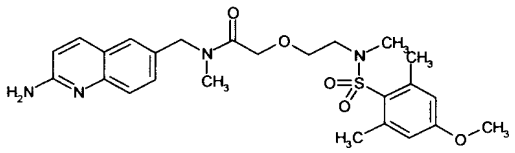
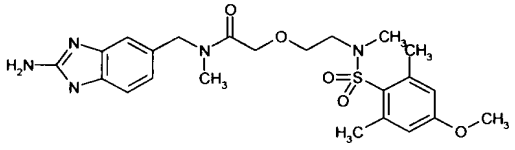
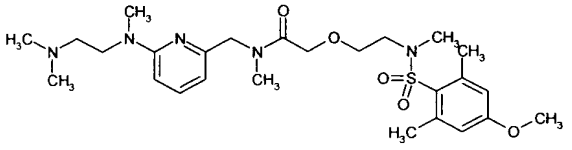
Exemplo	Estrutura
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(257)	

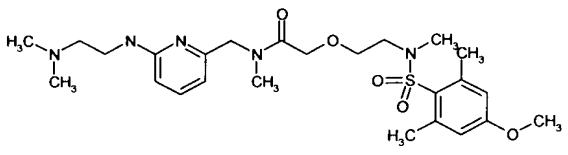
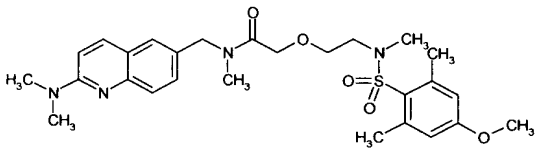
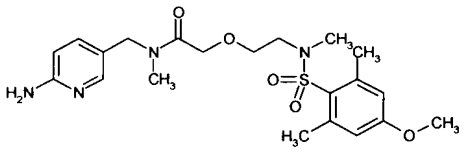
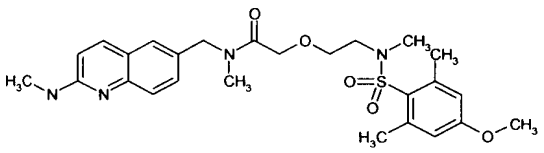
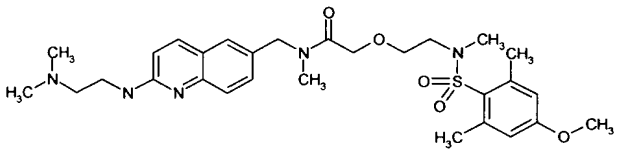
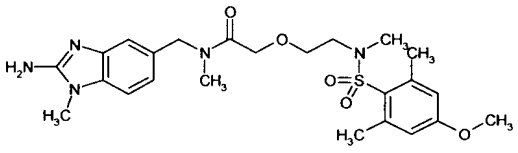
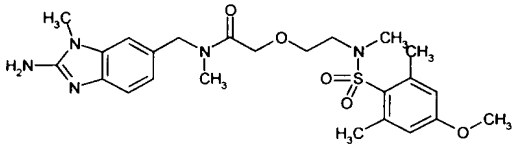
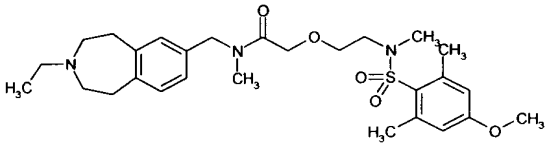
Exemplo	Estrutura
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(265)	

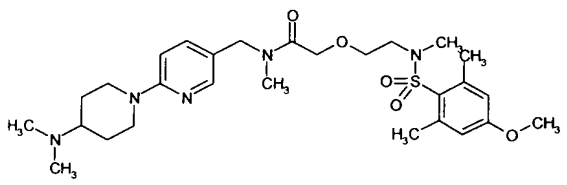
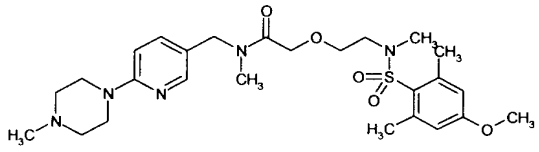
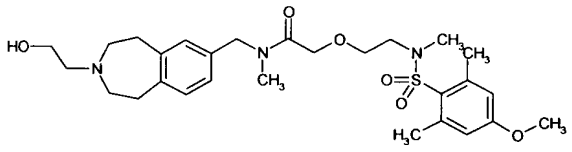
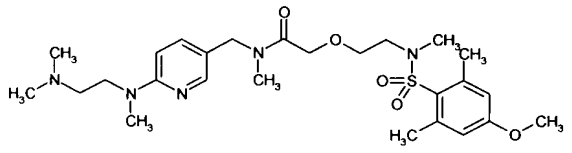
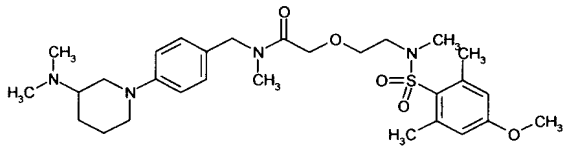
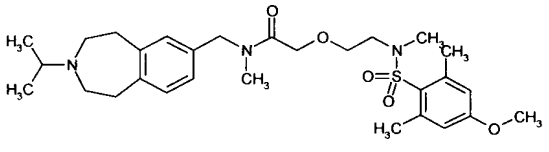
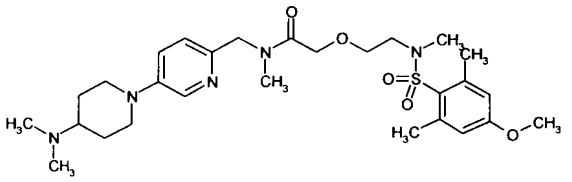
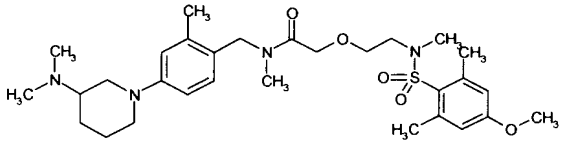
Exemplo	Estrutura
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(267)	
(268)	
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(270)	
(271)	
(272)	
(273)	

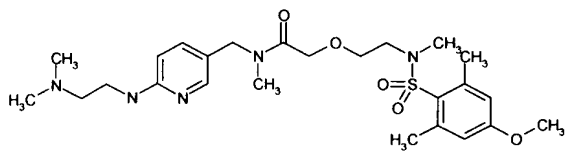
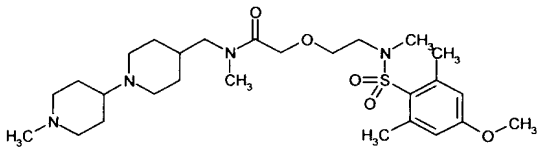
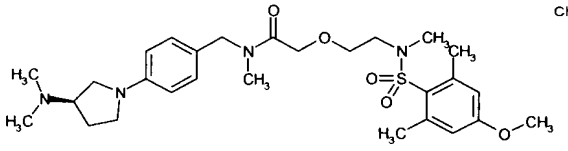
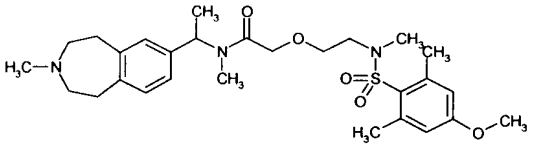
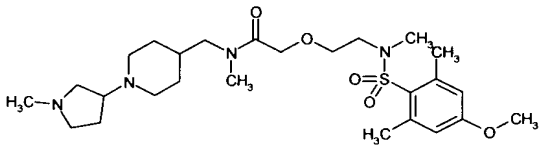
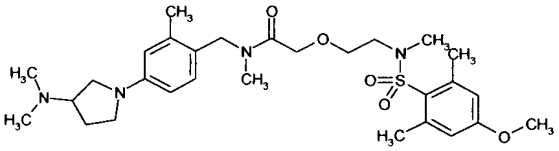
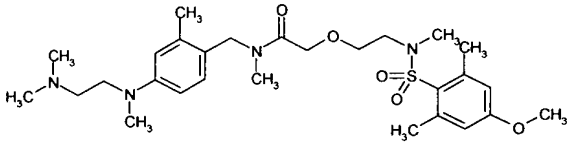
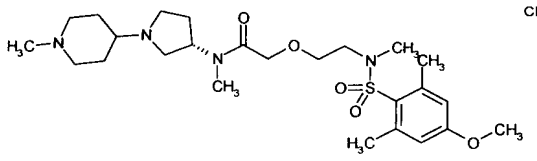
Exemplo	Estrutura
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(278)	
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(280)	

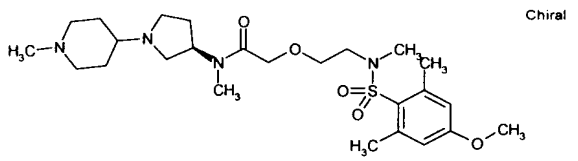
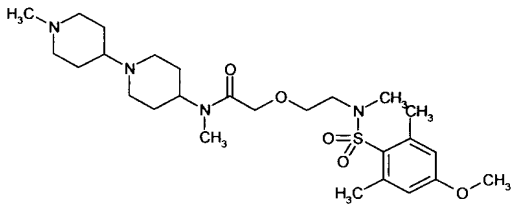
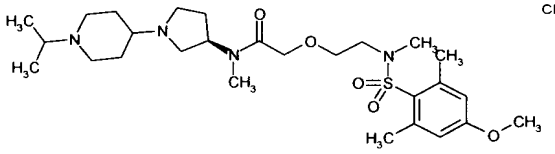
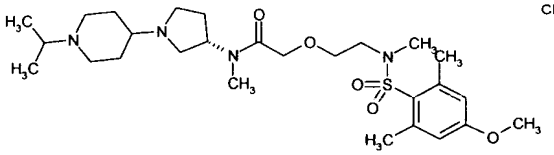
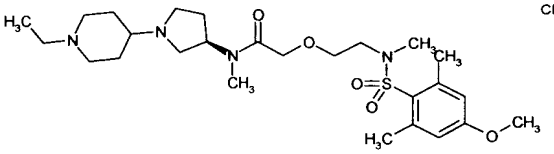
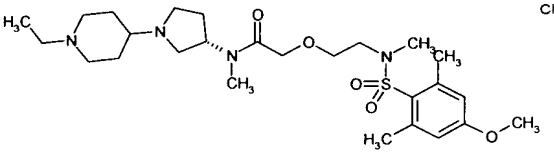
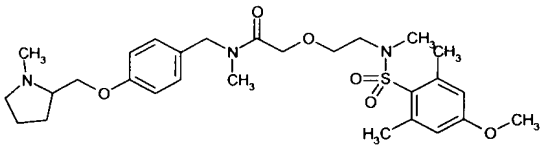
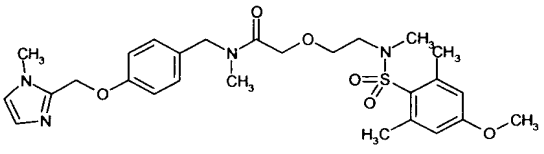
Exemplo	Estrutura
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(287)	
(288)	

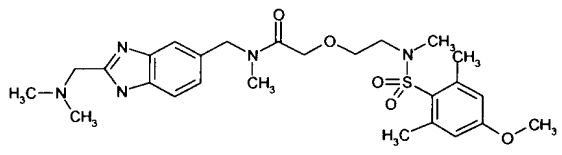
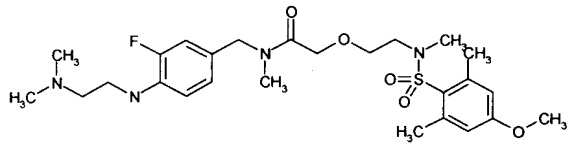
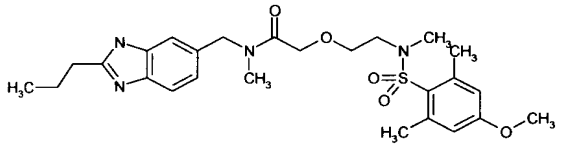
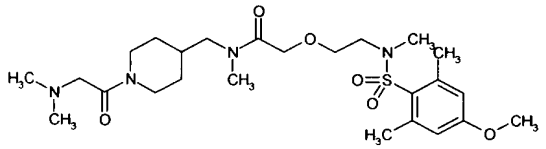
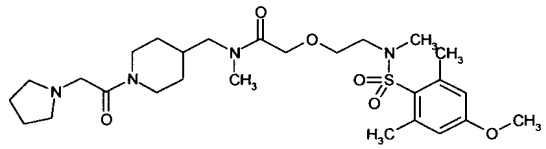
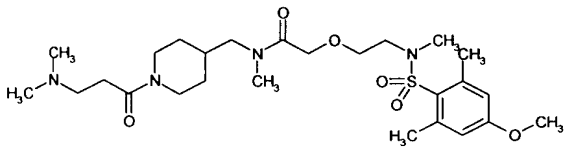
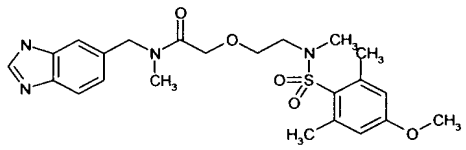
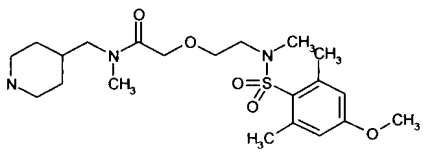
Exemplo	Estrutura
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(295)	
(296)	

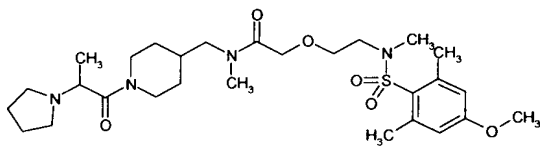
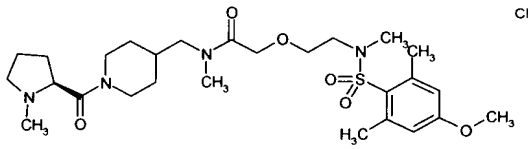
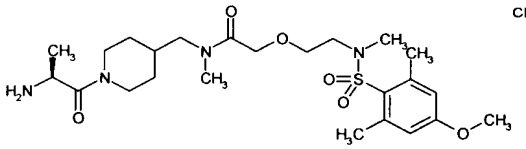
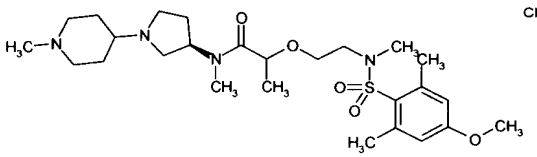
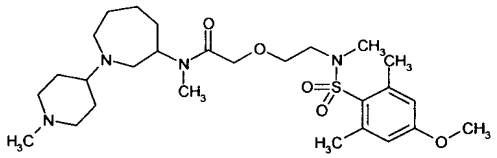
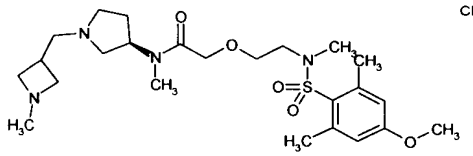
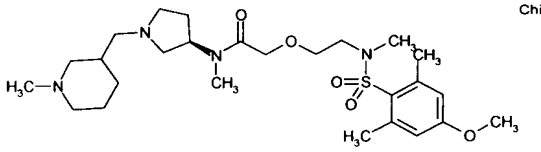
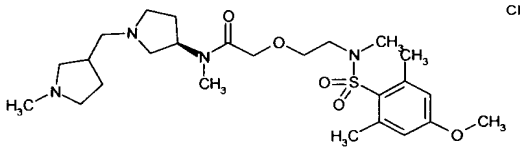
Exemplo	Estrutura
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(303)	
(304)	

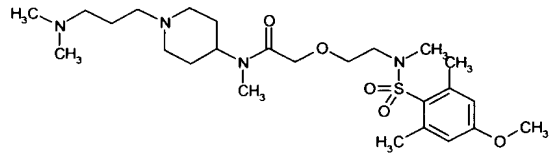
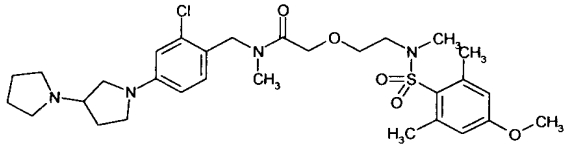
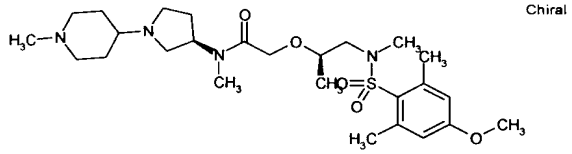
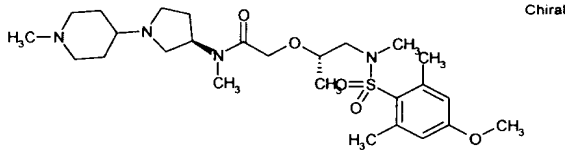
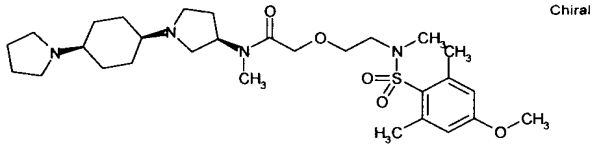
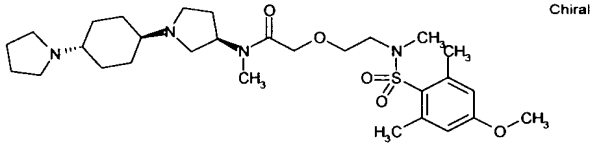
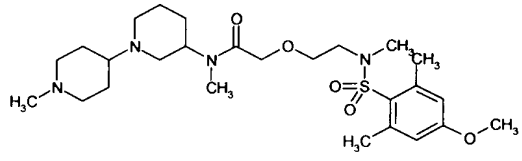
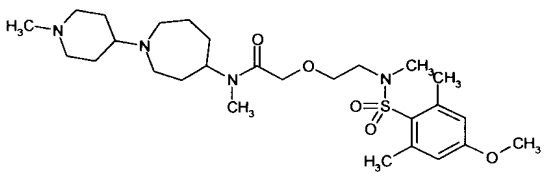
Exemplo	Estrutura
(305)	
(306)	
(307)	
(308)	
(309)	
(310)	
(311)	
(312)	

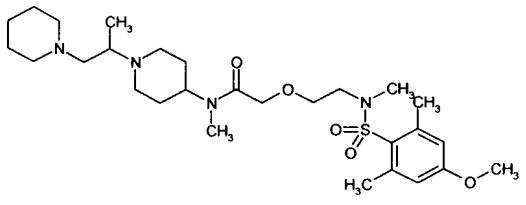
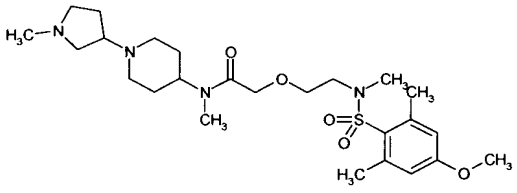
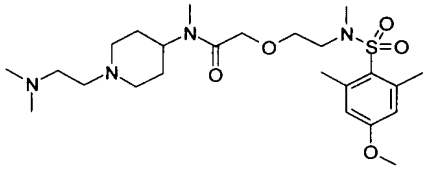
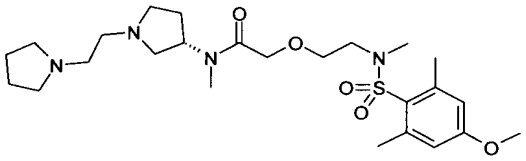
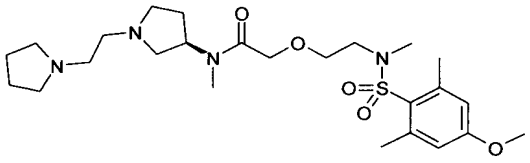
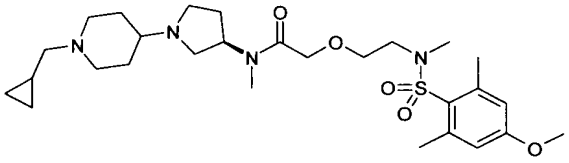
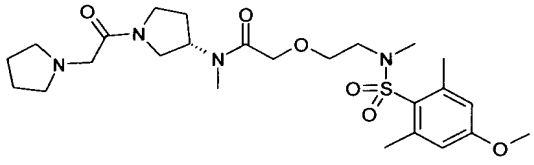
Exemplo	Estrutura
(313)	
(314)	
(315)	Chiral 
(316)	
(317)	
(318)	
(319)	
(320)	Chiral 

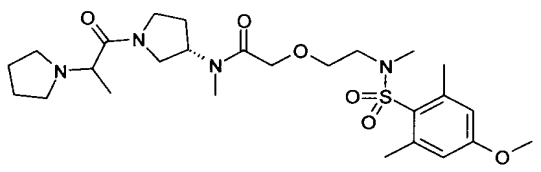
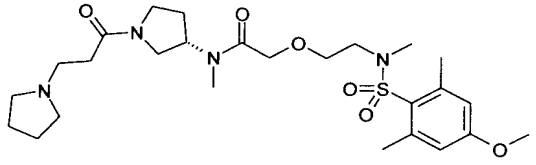
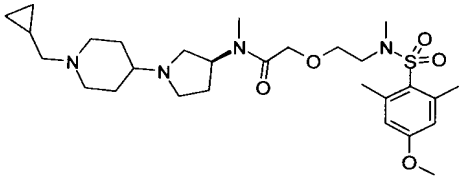
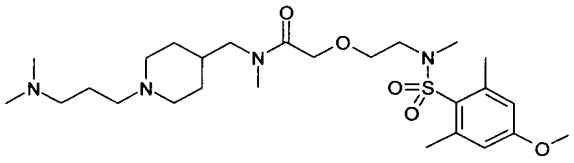
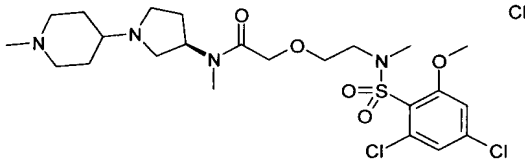
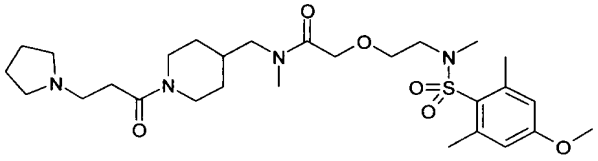
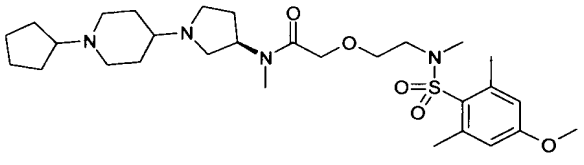
Exemplo	Estrutura
(321)	 Chiral
(322)	
(323)	 Chiral
(324)	 Chiral
(325)	 Chiral
(326)	 Chiral
(327)	
(328)	

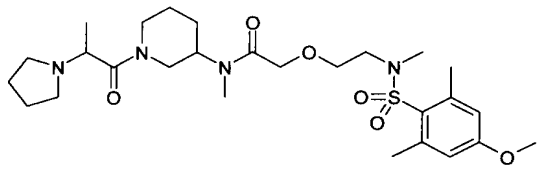
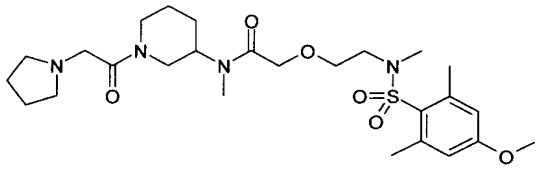
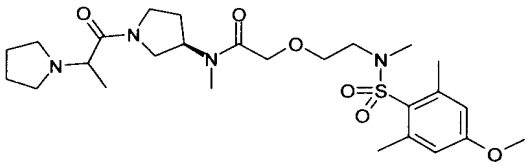
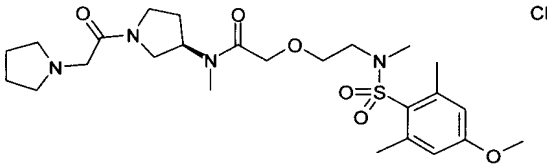
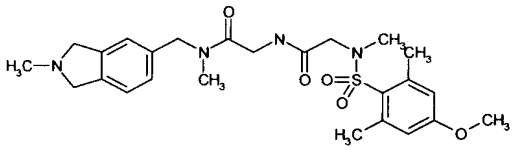
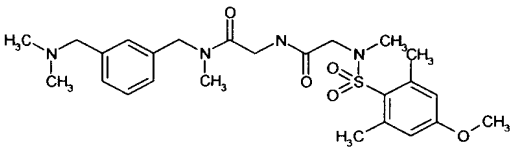
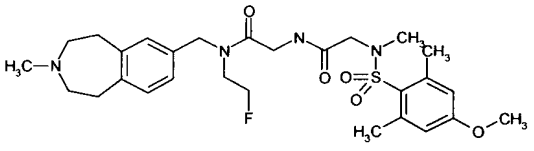
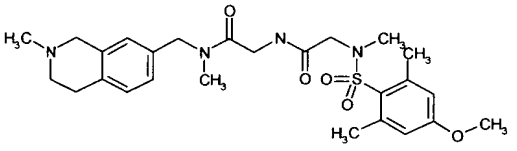
Exemplo	Estrutura
(329)	
(330)	
(331)	
(332)	
(333)	
(334)	
(335)	
(336)	

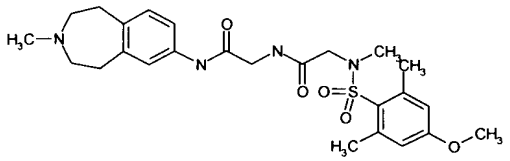
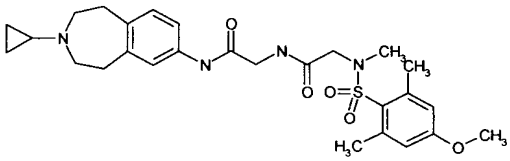
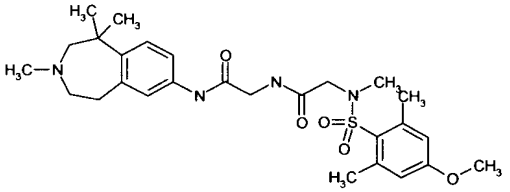
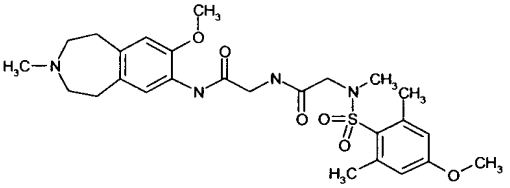
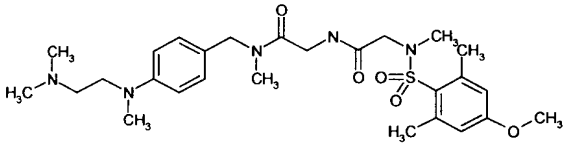
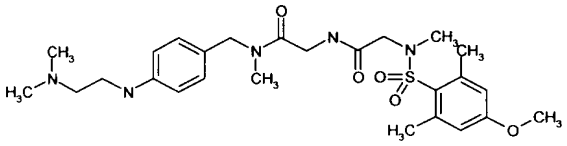
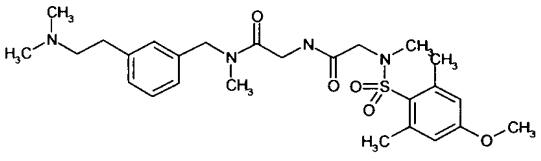
Exemplo	Estrutura
(337)	
(338)	Chiral 
(339)	Chiral 
(340)	Chiral 
(341)	
(342)	Chiral 
(343)	Chiral 
(344)	Chiral 

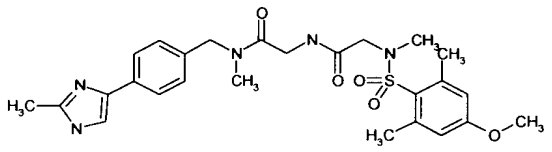
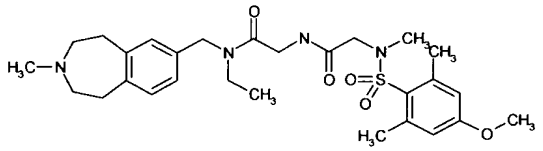
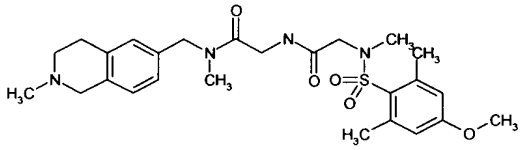
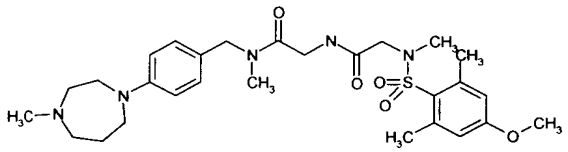
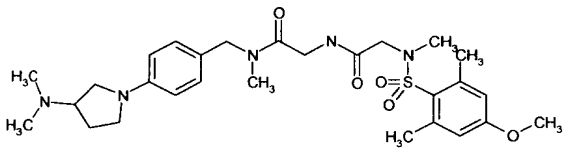
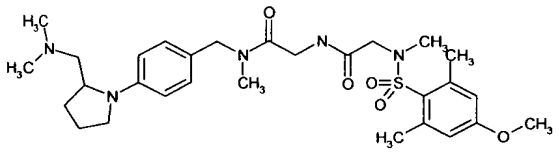
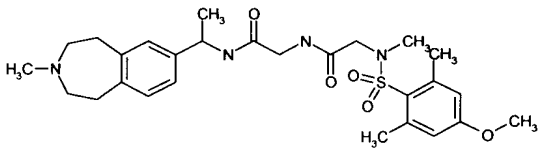
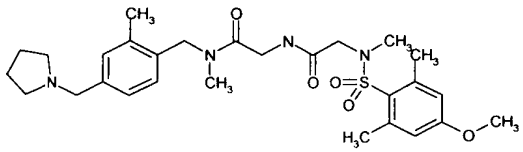
Exemplo	Estrutura
(345)	
(346)	
(347)	 Chiral
(348)	 Chiral
(349)	 Chiral
(350)	 Chiral
(351)	
(352)	

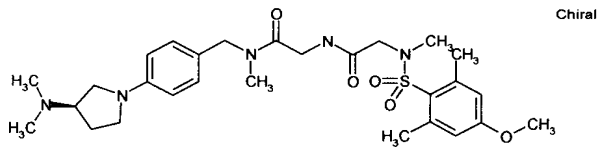
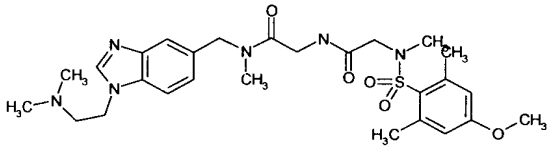
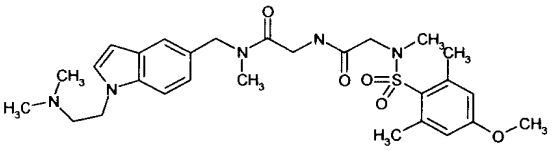
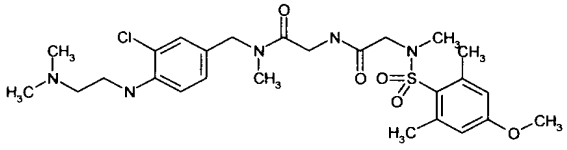
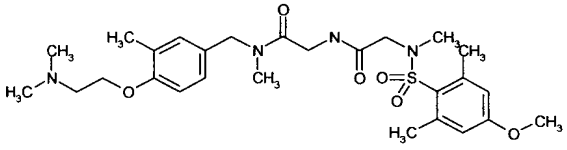
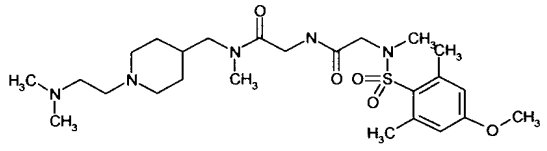
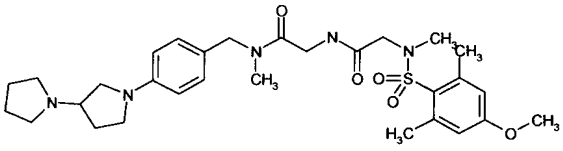
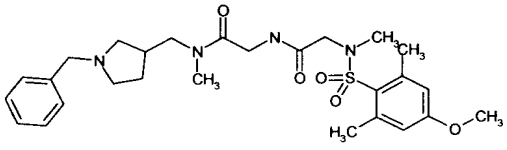
Exemplo	Estrutura
(353)	
(354)	
(355)	
(356)	
(357)	
(358)	Chiral 
(359)	

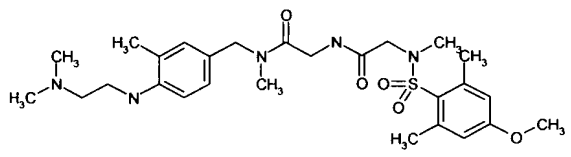
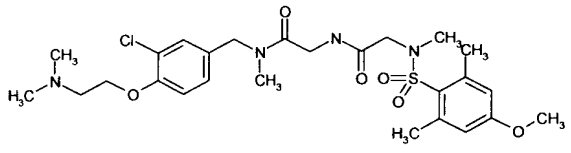
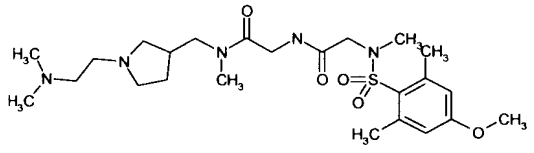
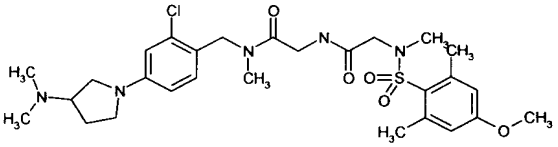
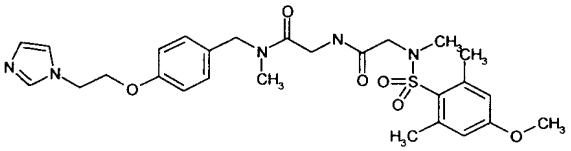
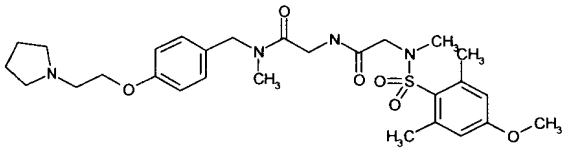
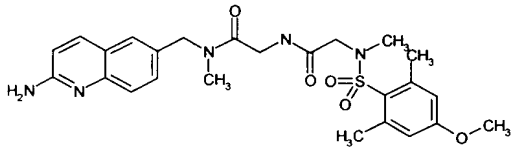
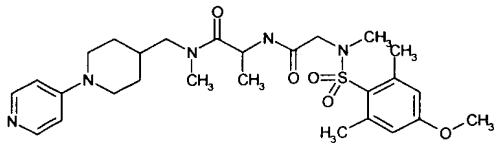
Exemplo	Estrutura
(360)	
(361)	
(362)	
(363)	
(364)	 Chiral
(365)	
(366)	 Chiral

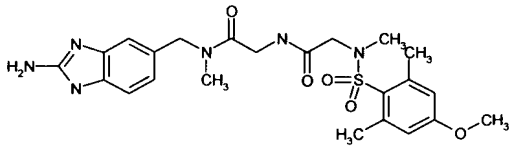
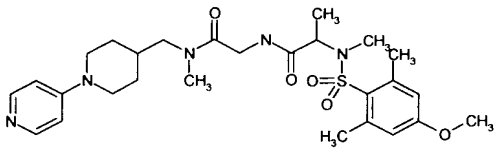
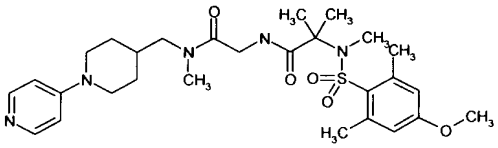
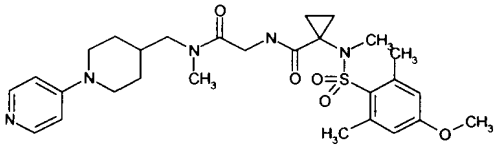
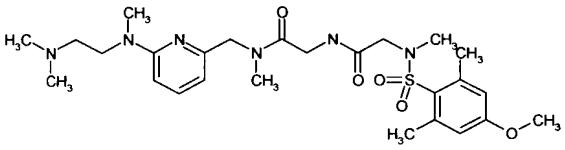
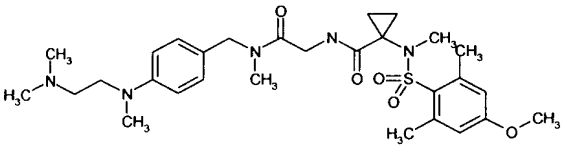
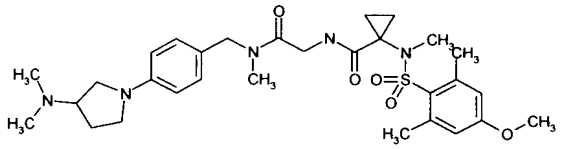
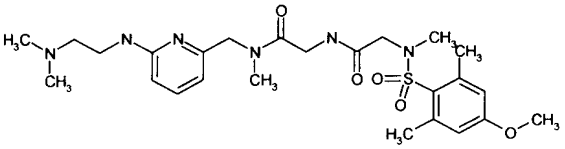
Exemplo	Estrutura
(367)	
(368)	
(369)	Chiral 
(370)	Chiral 
(371)	
(372)	
(373)	
(374)	

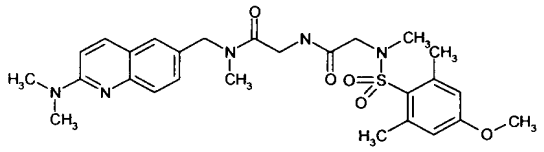
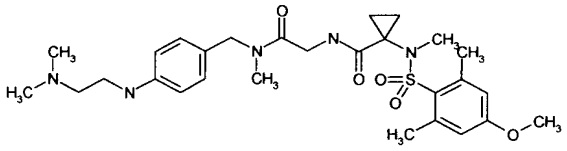
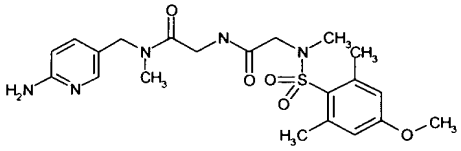
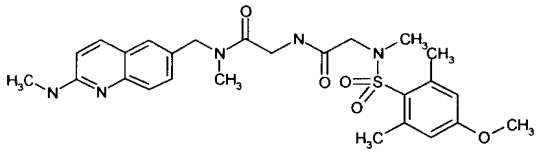
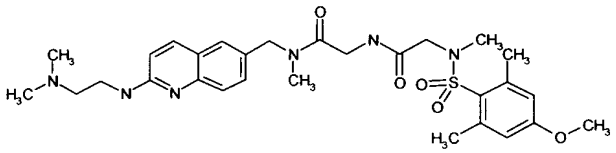
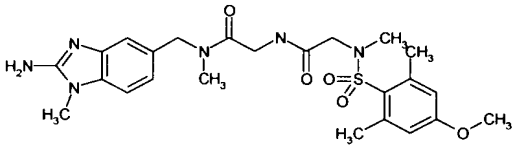
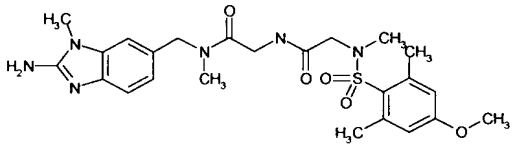
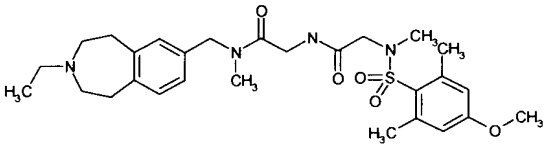
Exemplo	Estrutura
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(376)	
(377)	
(378)	
(379)	
(380)	
(381)	

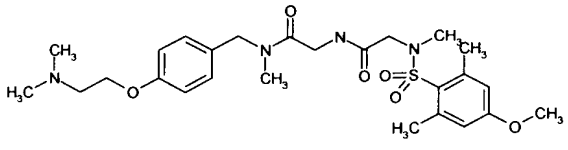
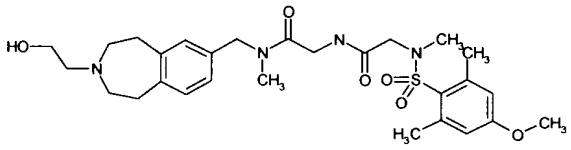
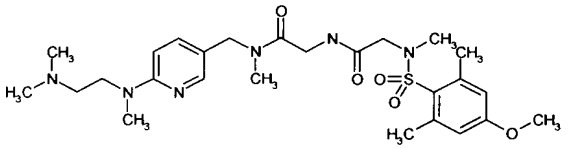
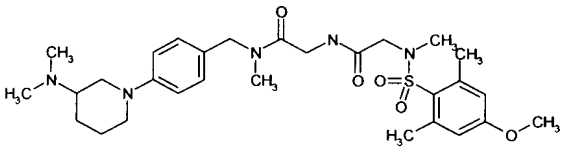
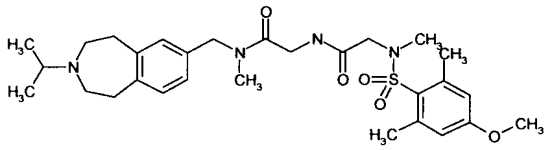
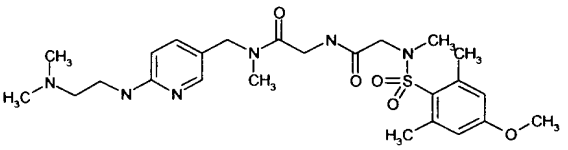
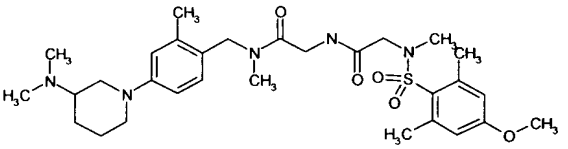
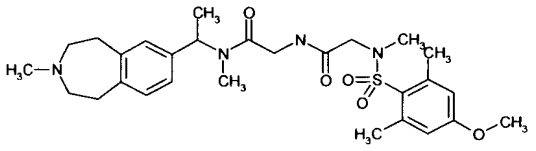
Exemplo	Estrutura
(382)	
(383)	
(384)	
(385)	
(386)	
(387)	
(388)	
(389)	

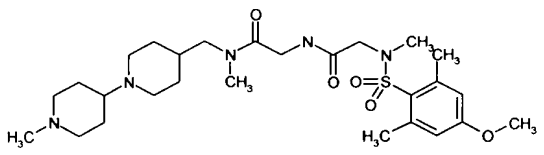
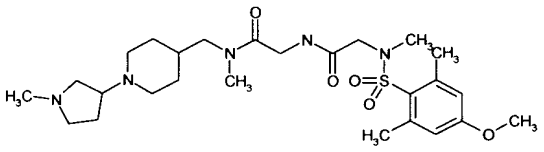
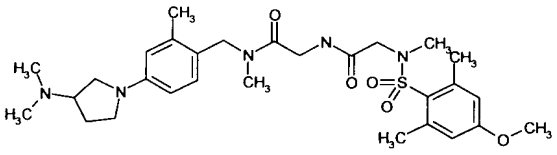
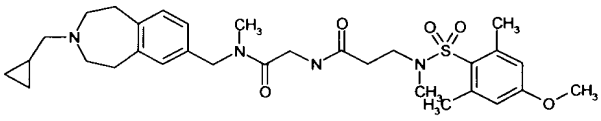
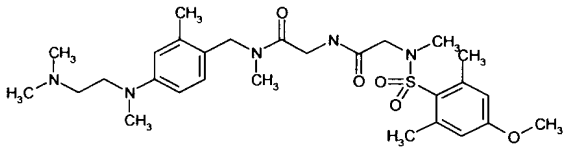
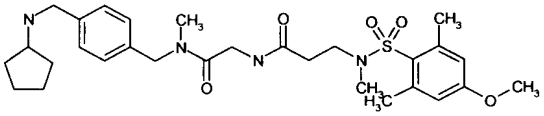
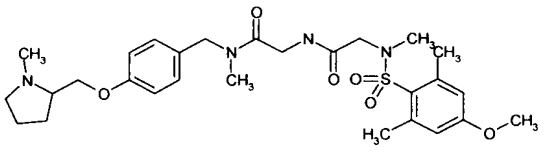
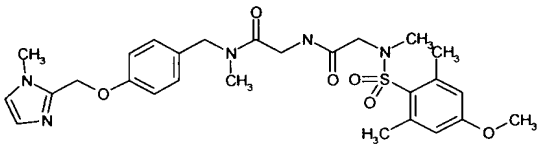
Exemplo	Estrutura
(390)	 Chiral
(391)	
(392)	
(393)	
(394)	
(395)	
(396)	
(397)	

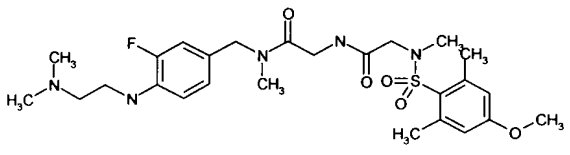
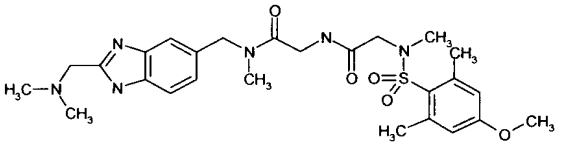
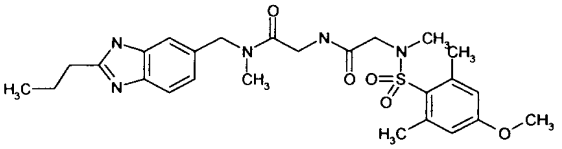
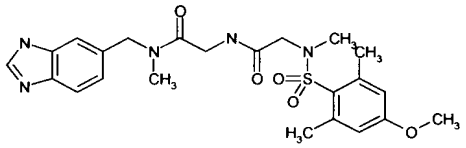
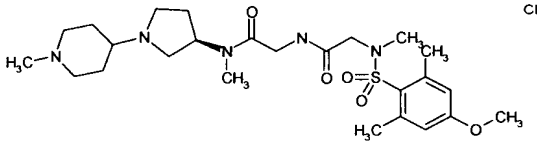
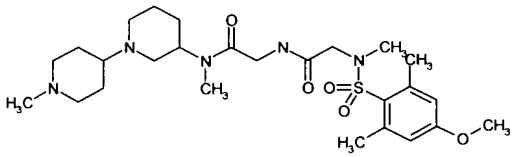
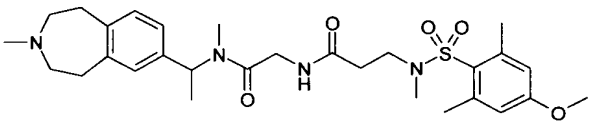
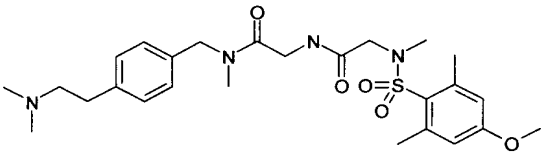
Exemplo	Estrutura
(398)	
(399)	
(400)	
(401)	
(402)	
(403)	
(404)	
(405)	

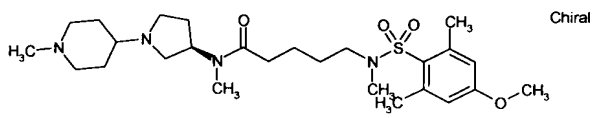
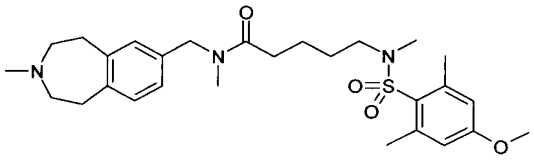
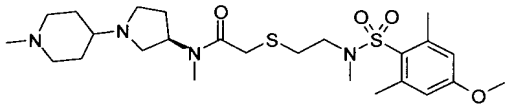
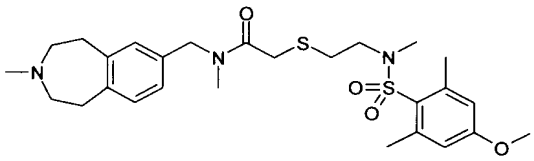
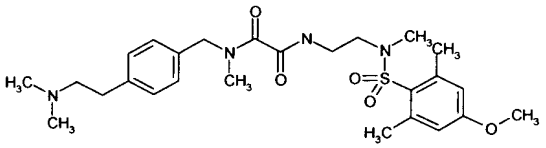
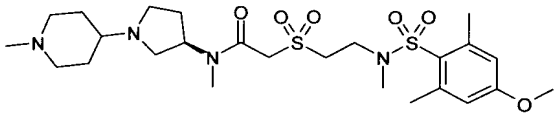
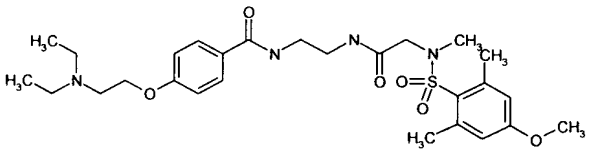
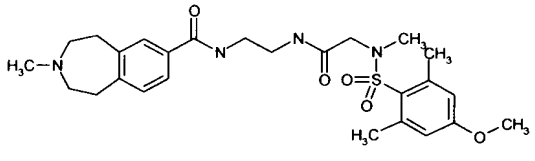
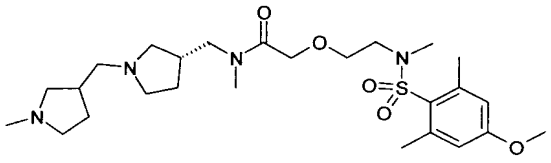
Exemplo	Estrutura
(406)	
(407)	
(408)	
(409)	
(410)	
(411)	
(412)	
(413)	

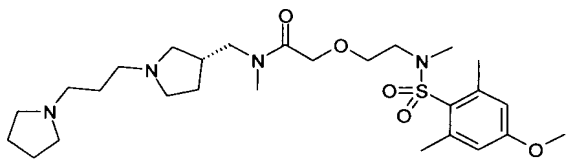
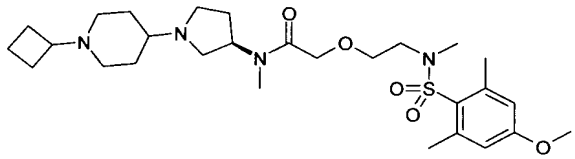
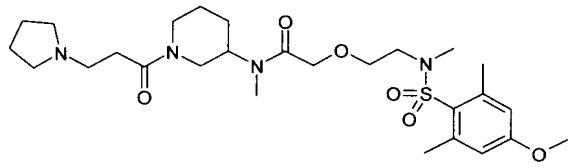
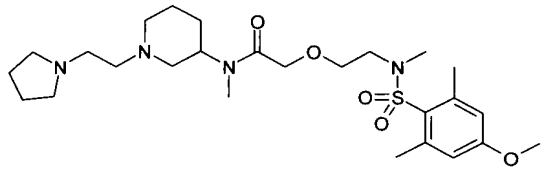
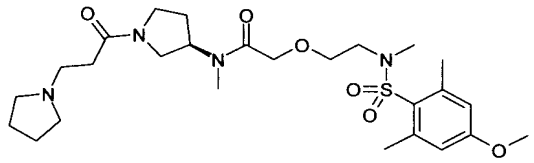
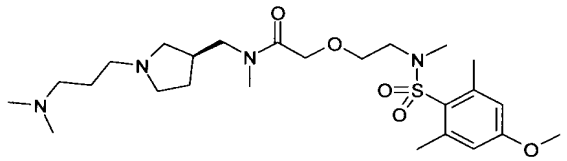
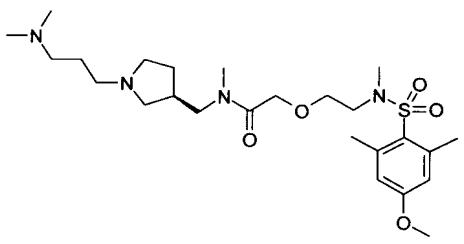
Exemplo	Estrutura
(414)	
(415)	
(416)	
(417)	
(418)	
(419)	
(420)	
(421)	

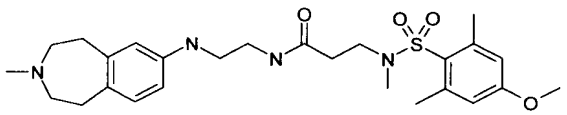
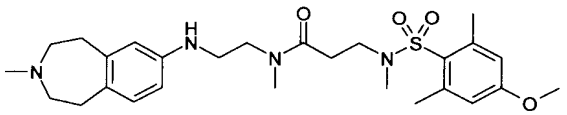
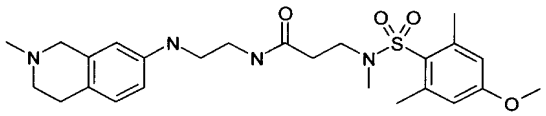
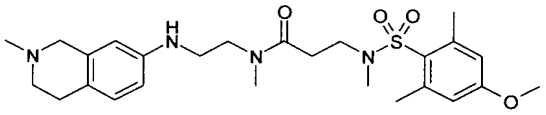
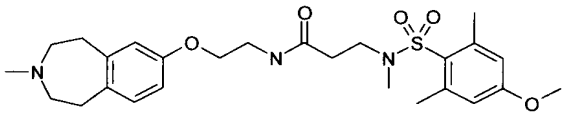
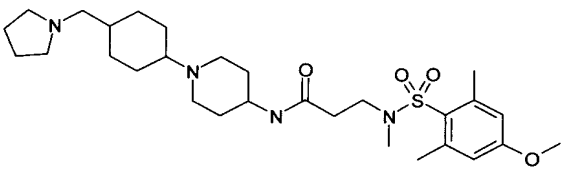
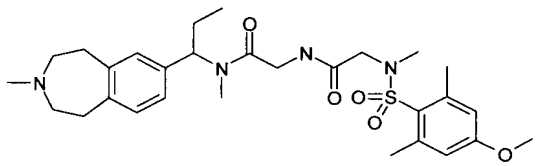
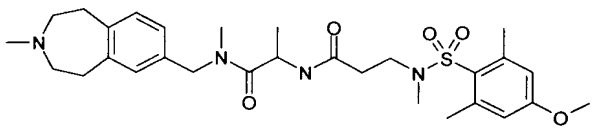
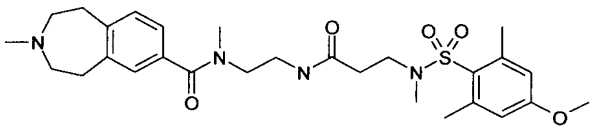
Exemplo	Estrutura
(422)	
(423)	
(424)	
(425)	
(426)	
(427)	
(428)	
(429)	

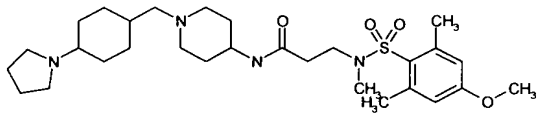
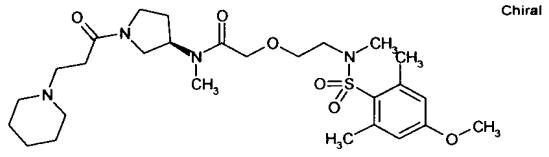
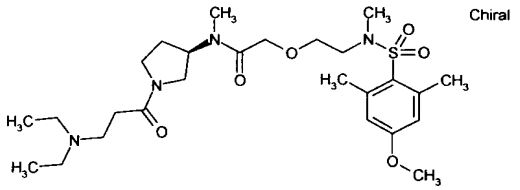
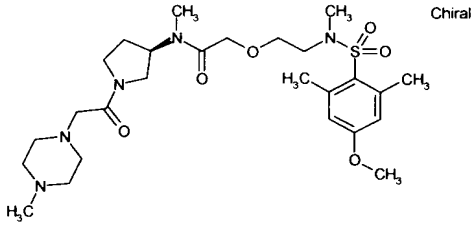
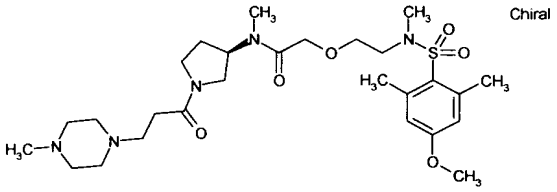
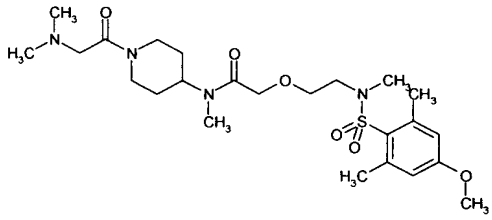
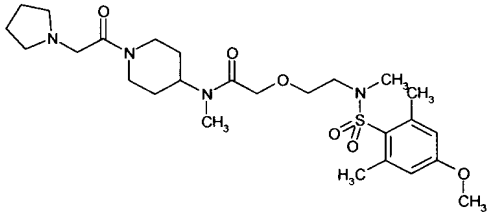
Exemplo	Estrutura
(430)	
(431)	
(432)	
(433)	
(434)	
(435)	
(436)	
(437)	

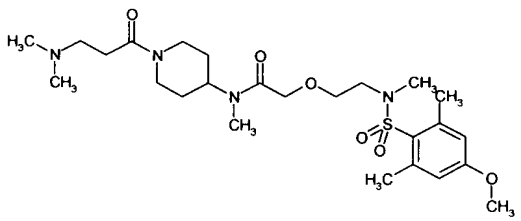
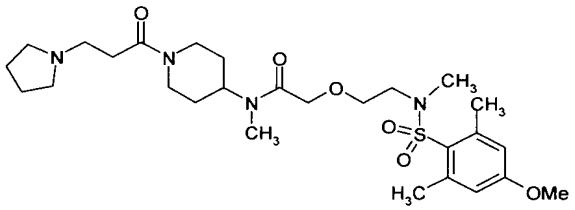
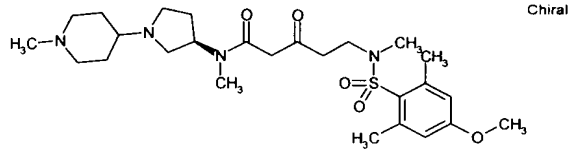
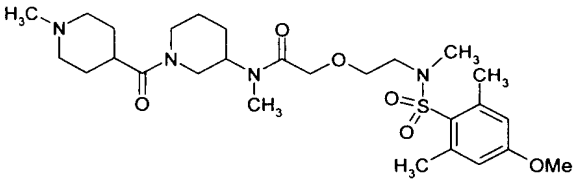
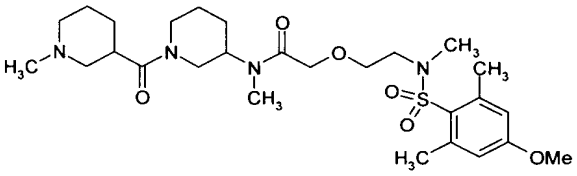
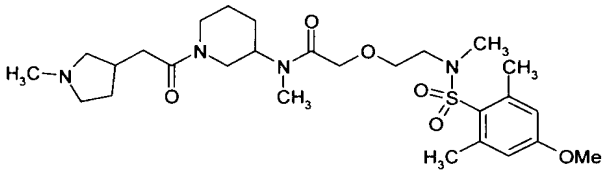
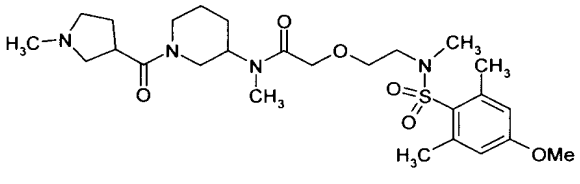
Exemplo	Estrutura
(438)	
(439)	
(440)	
(441)	
(442)	 Chiral
(443)	
(444)	
(445)	

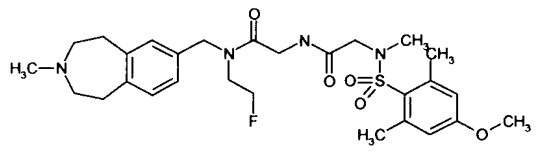
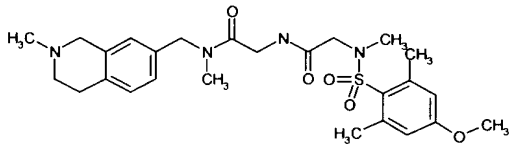
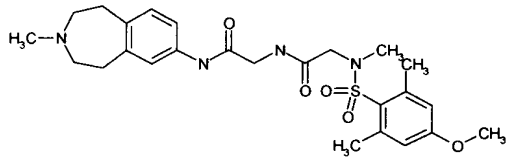
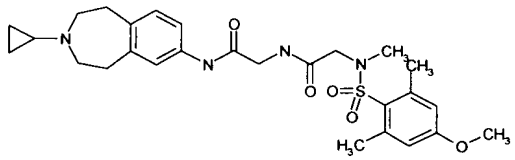
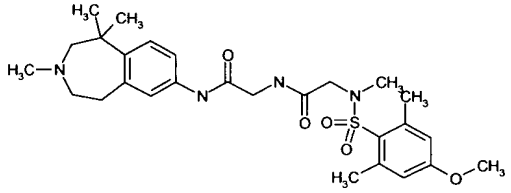
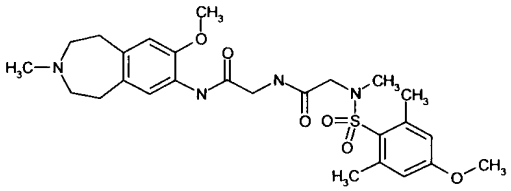
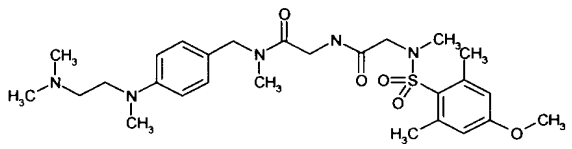
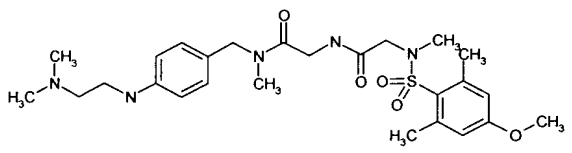
Exemplo	Estrutura
(446)	 Chiral
(447)	
(448)	
(449)	
(450)	
(451)	
(452)	
(453)	
(454)	

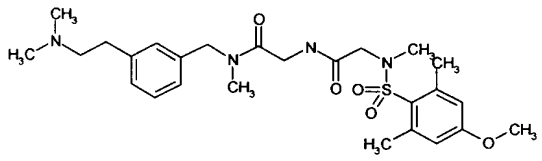
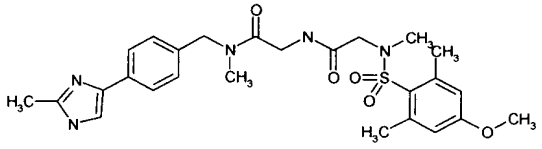
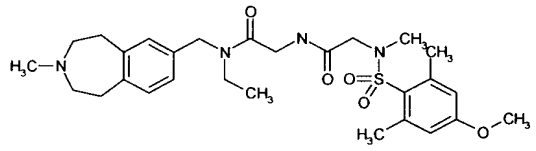
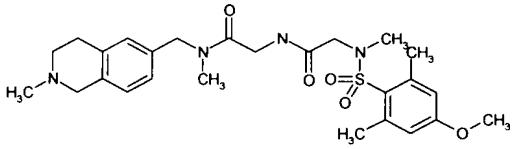
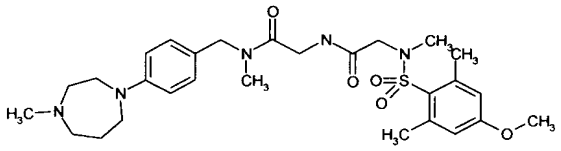
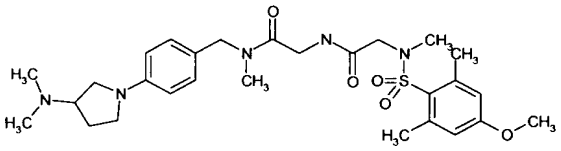
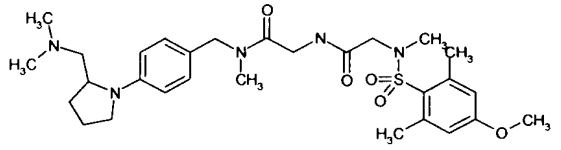
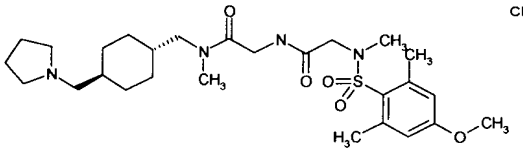
Exemplo	Estrutura
(455)	
(456)	
(457)	
(458)	
(459)	
(460)	
(461)	

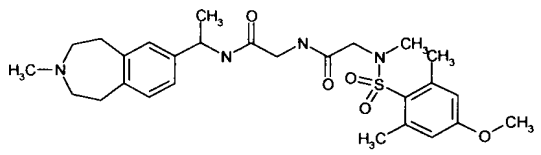
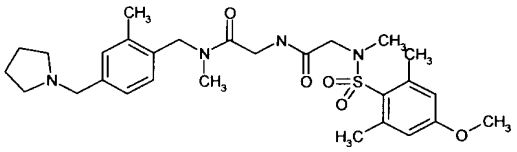
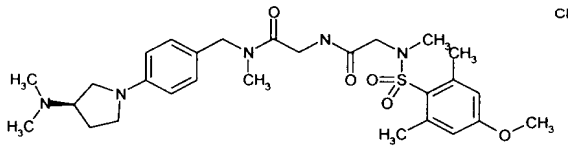
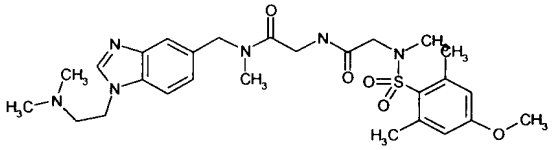
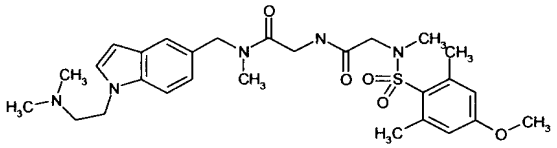
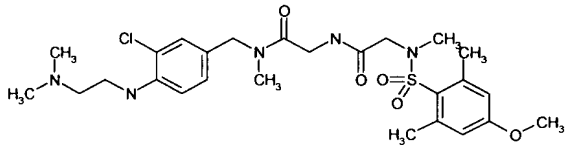
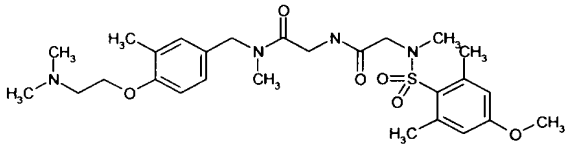
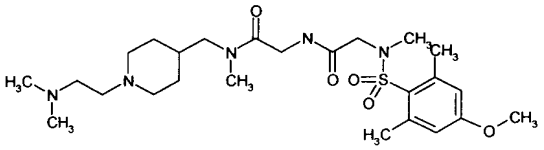
Exemplo	Estrutura
(462)	
(463)	
(464)	
(465)	
(466)	
(467)	
(468)	
(469)	
(470)	

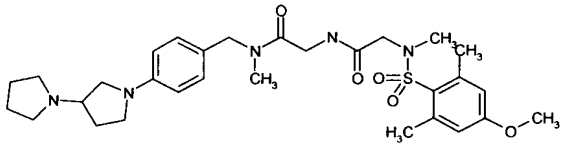
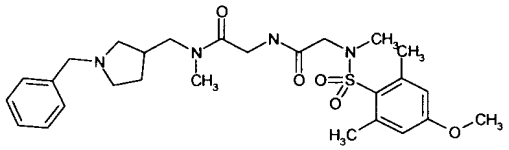
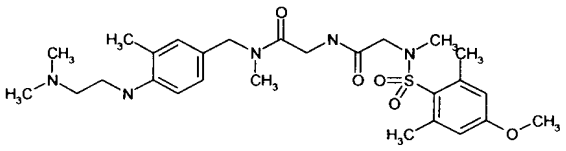
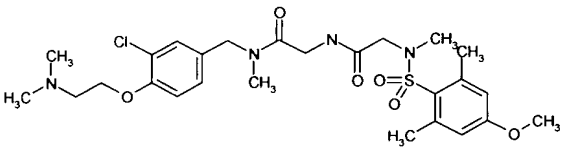
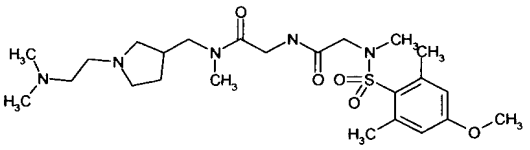
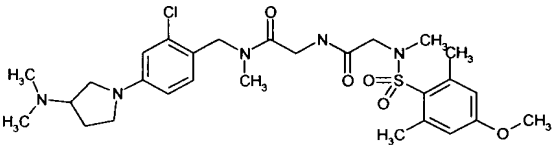
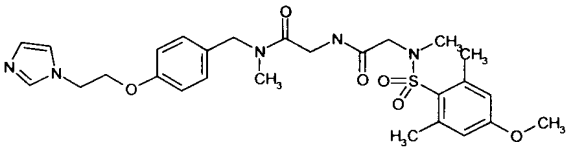
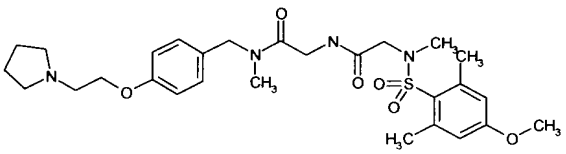
Exemplo	Estrutura
(471)	
(472)	 Chiral
(473)	 Chiral
(474)	 Chiral
(475)	 Chiral
(476)	
(477)	

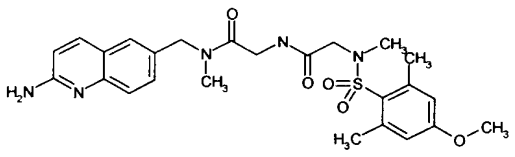
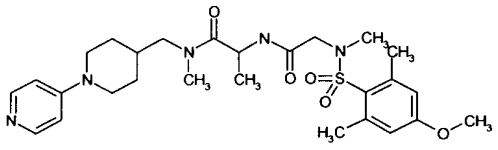
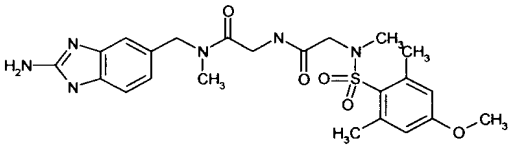
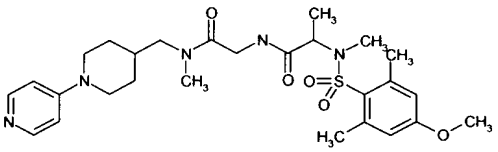
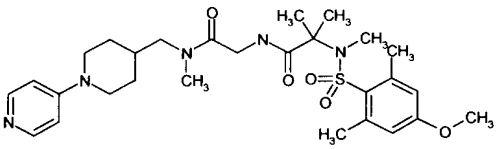
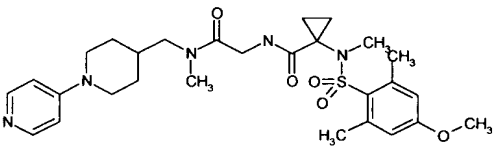
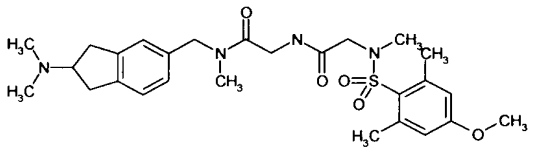
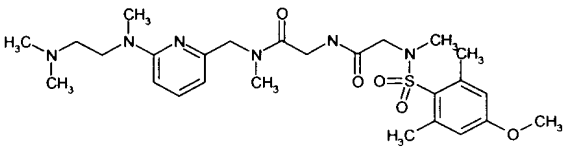
Exemplo	Estrutura
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(479)	
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(482)	
(483)	
(484)	

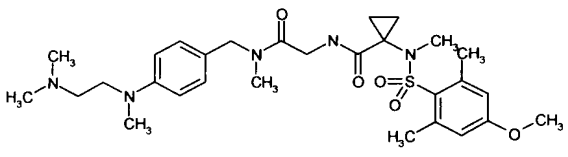
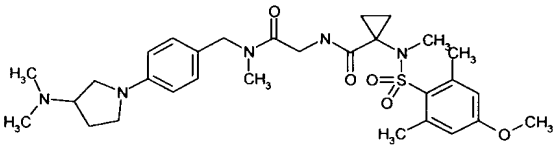
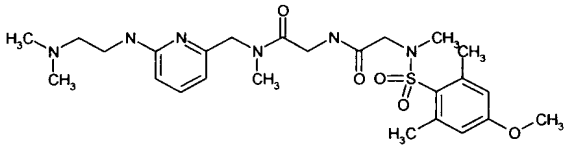
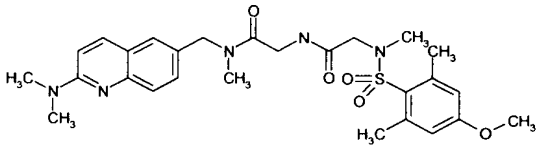
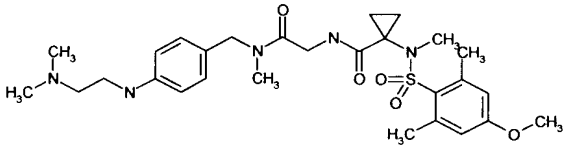
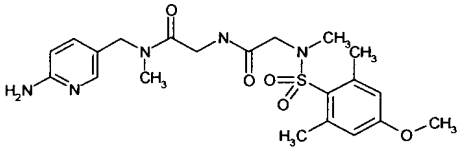
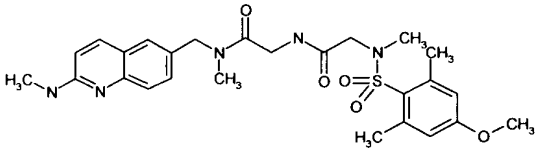
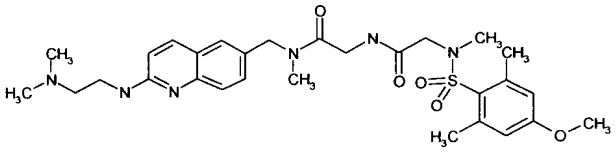
Exemplo	Estrutura
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(487)	
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(491)	
(492)	

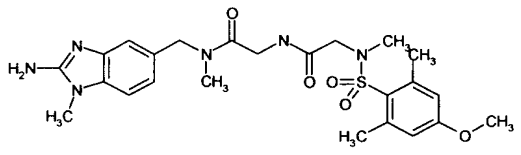
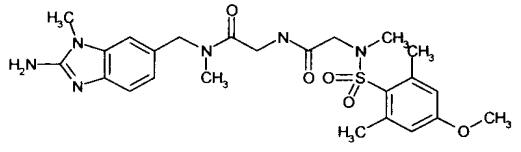
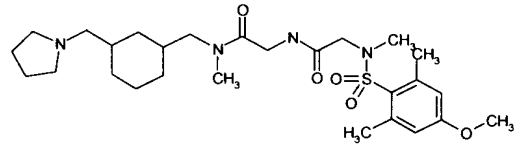
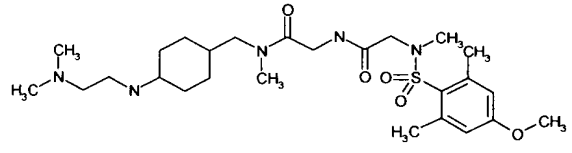
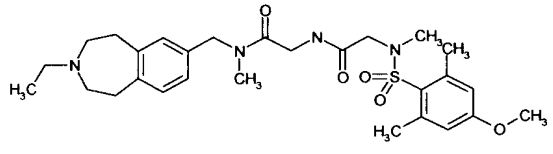
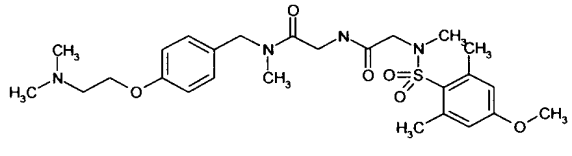
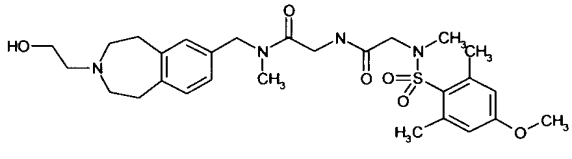
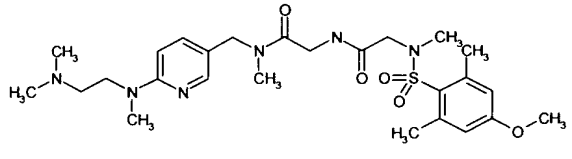
Exemplo	Estrutura
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(494)	
(495)	
(496)	
(497)	
(498)	
(499)	
(500)	 Chiral

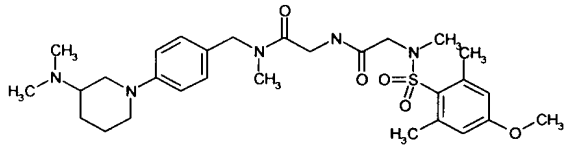
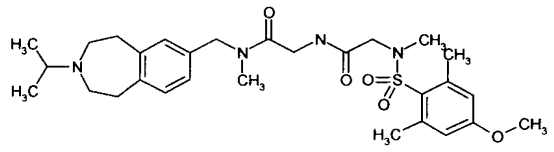
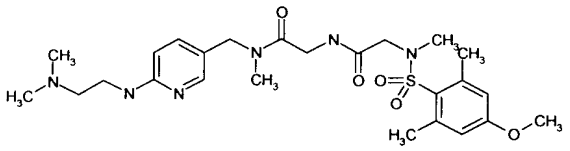
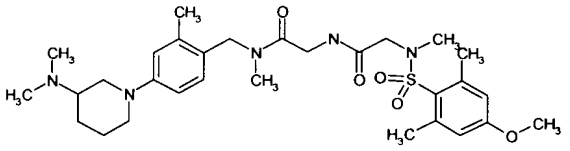
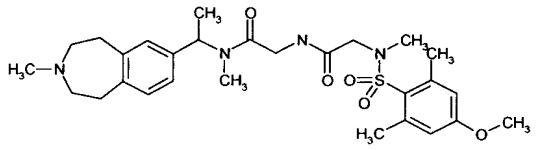
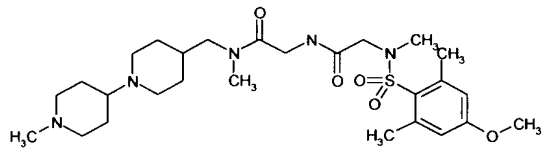
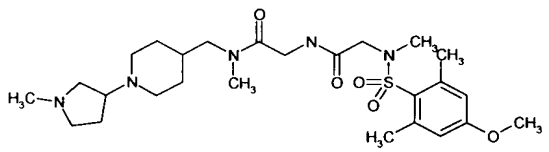
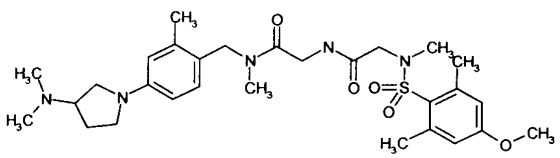
Exemplo	Estrutura
(501)	
(502)	
(503)	Chiral 
(504)	
(505)	
(506)	
(507)	
(508)	

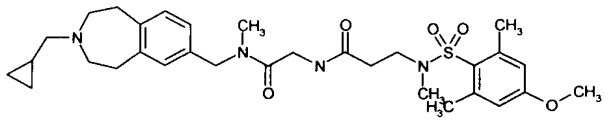
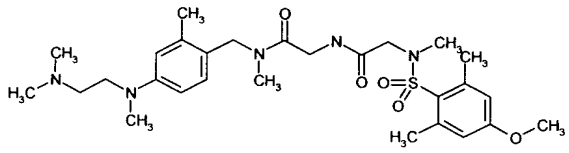
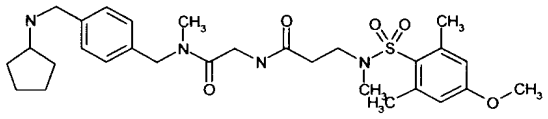
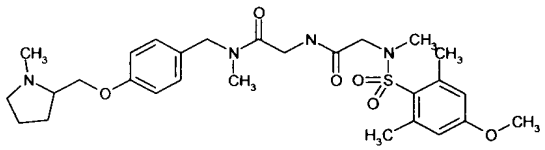
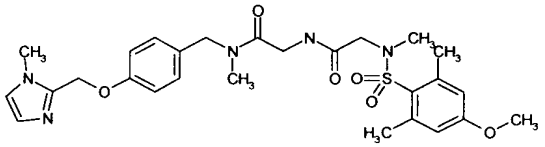
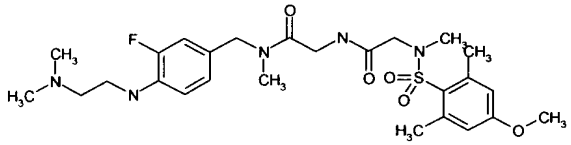
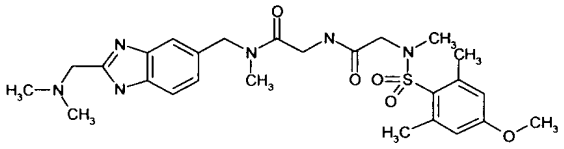
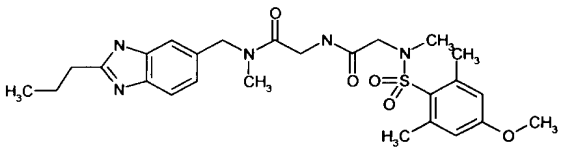
Exemplo	Estrutura
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(511)	
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(513)	
(514)	
(515)	
(516)	

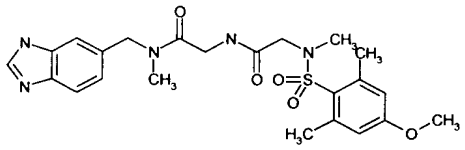
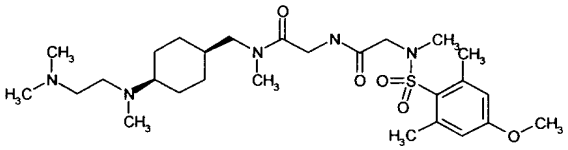
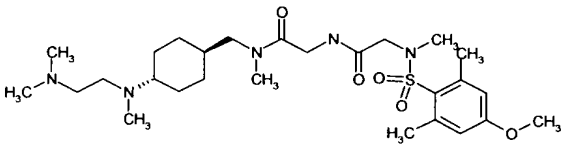
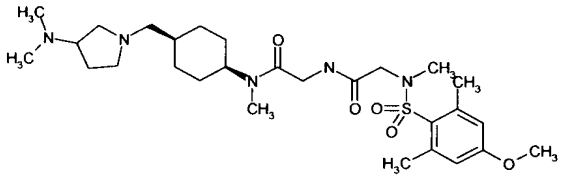
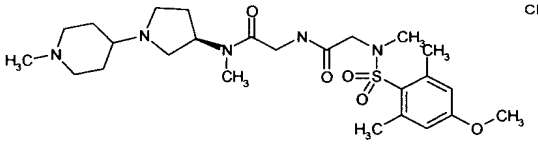
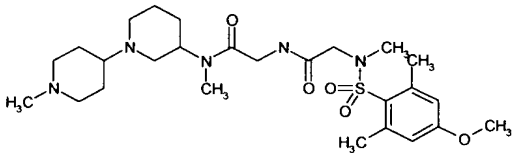
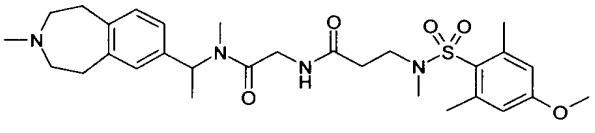
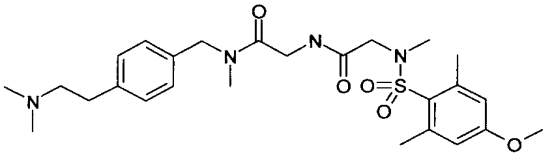
Exemplo	Estrutura
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(519)	
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(522)	
(523)	
(524)	

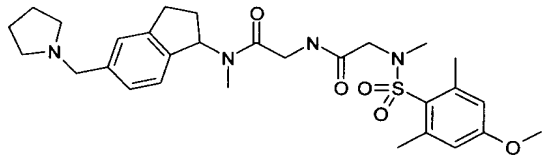
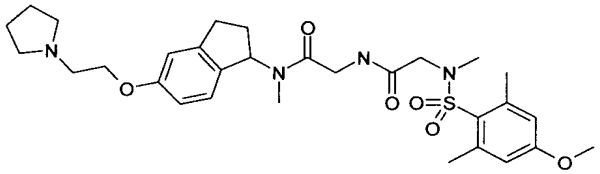
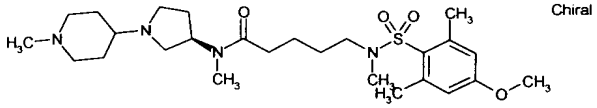
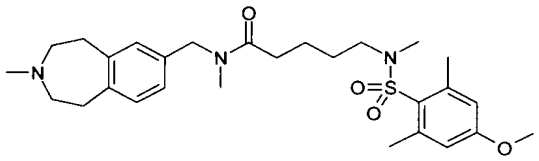
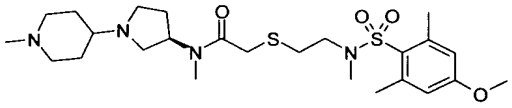
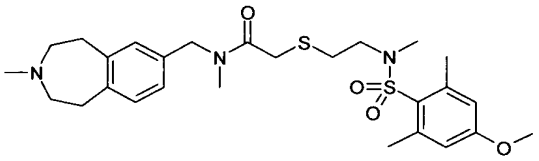
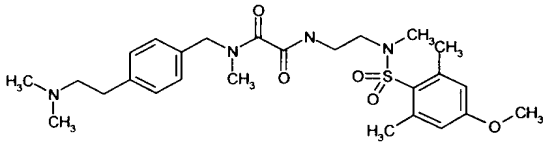
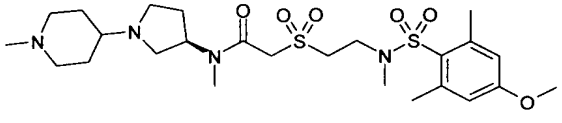
Exemplo	Estrutura
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(526)	
(527)	
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(529)	
(530)	
(531)	
(532)	

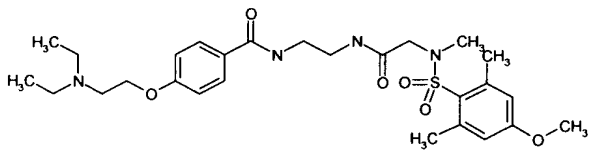
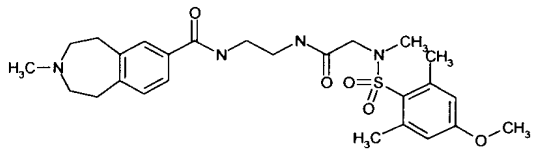
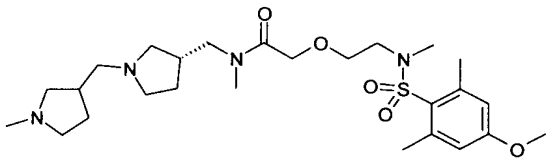
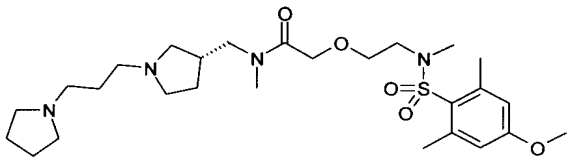
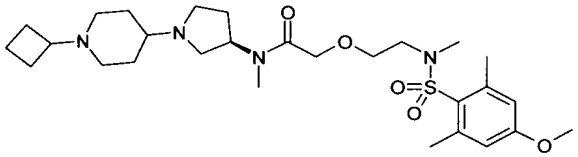
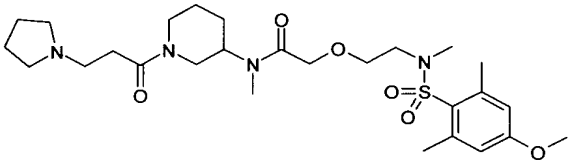
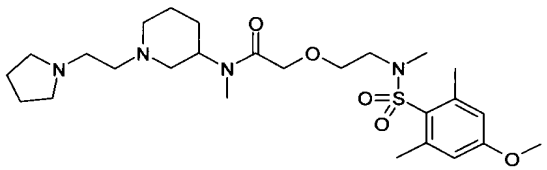
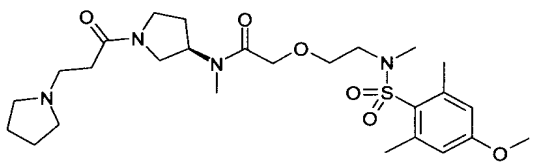
Exemplo	Estrutura
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(534)	
(535)	
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(540)	

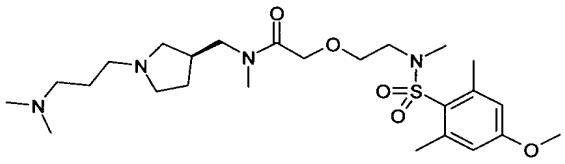
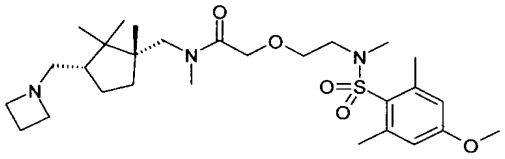
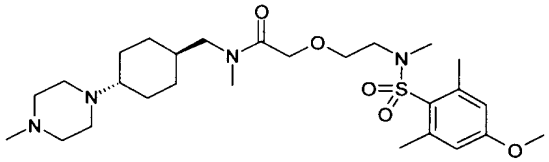
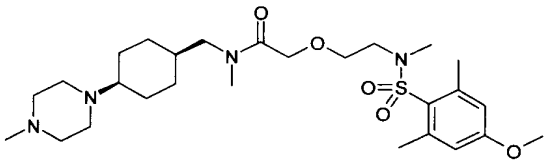
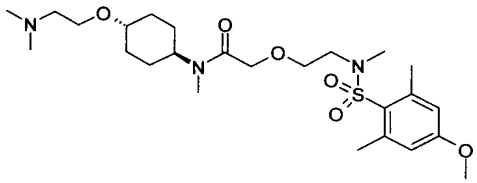
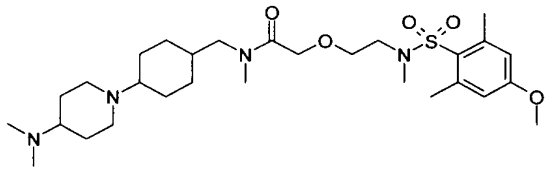
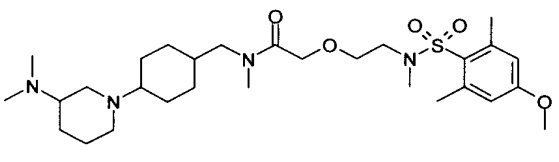
Exemplo	Estrutura
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(542)	
(543)	
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(545)	
(546)	
(547)	
(548)	

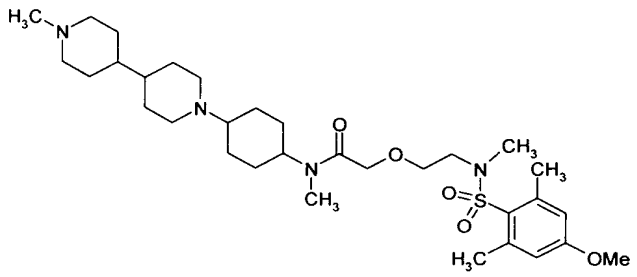
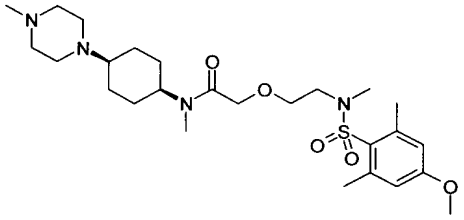
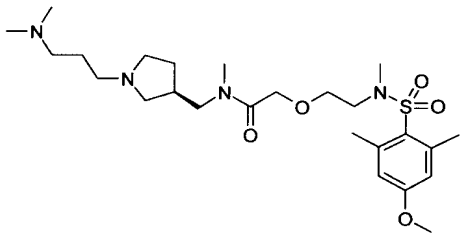
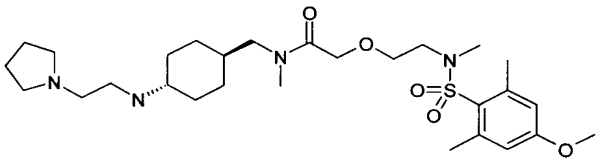
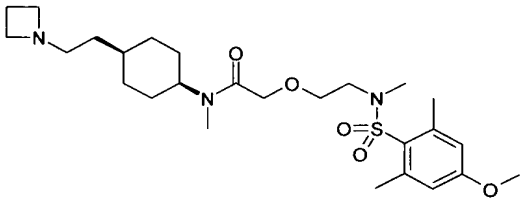
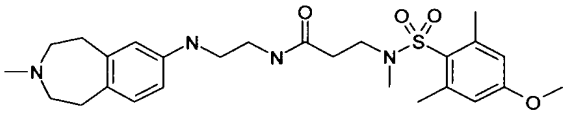
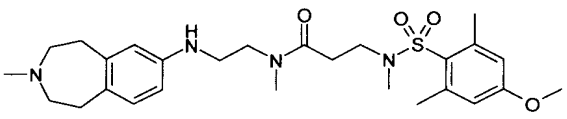
Exemplo	Estrutura
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(550)	
(551)	
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(553)	
(554)	
(555)	
(556)	

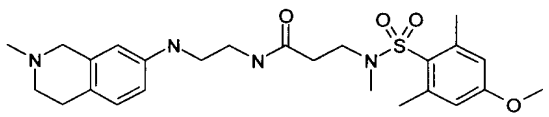
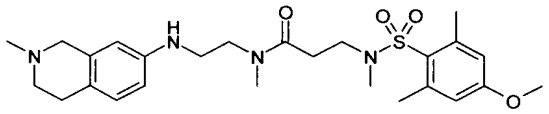
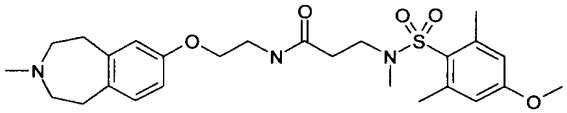
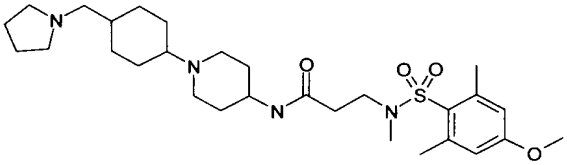
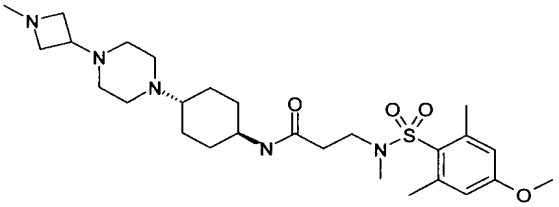
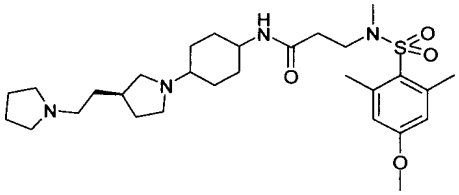
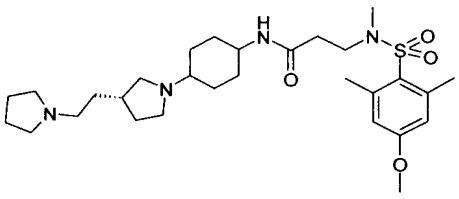
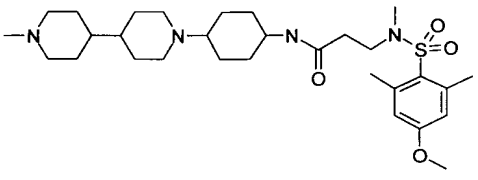
Exemplo	Estrutura
(557)	
(558)	
(559)	
(560)	
(561)	 Chiral
(562)	
(563)	
(564)	

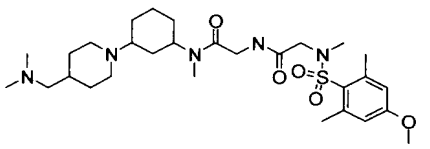
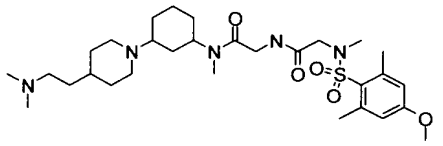
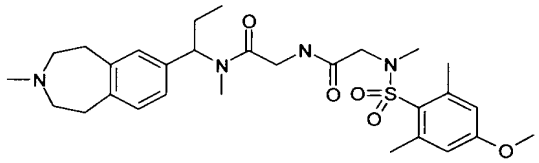
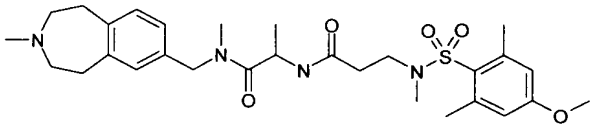
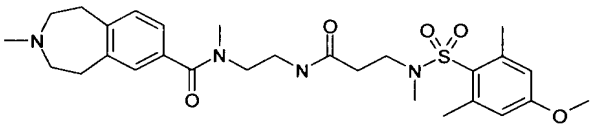
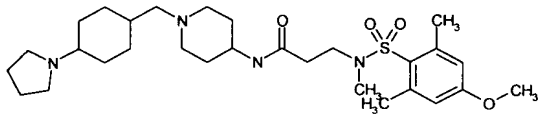
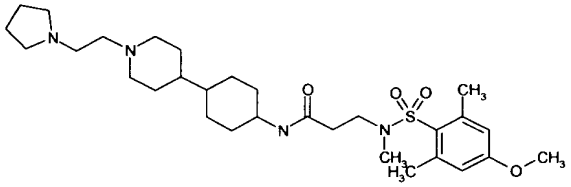
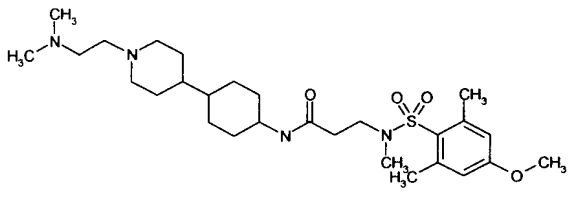
Exemplo	Estrutura
(565)	
(566)	
(567)	 Chiral
(568)	
(569)	
(570)	
(571)	
(572)	

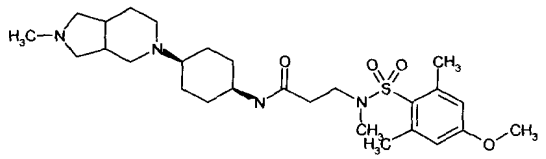
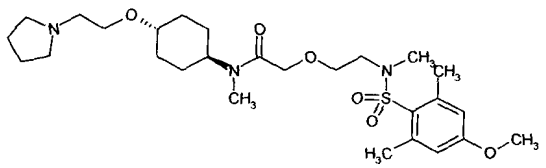
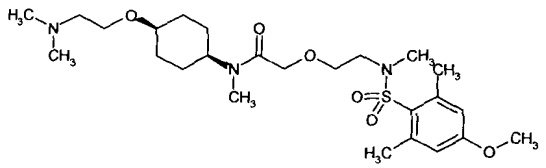
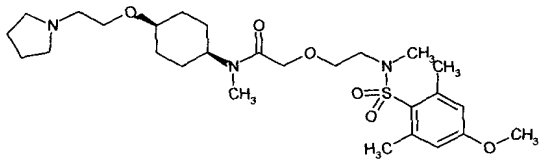
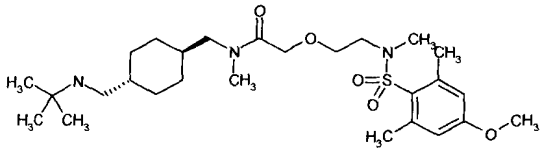
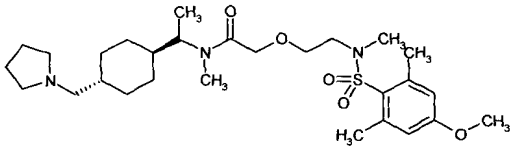
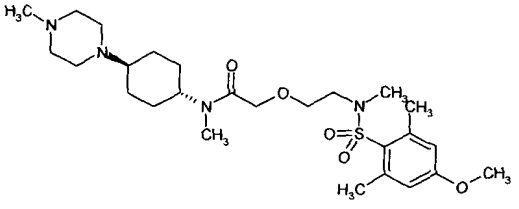
Exemplo	Estrutura
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(574)	
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(577)	
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(579)	
(580)	

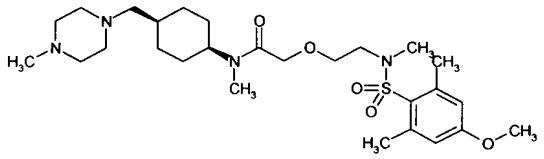
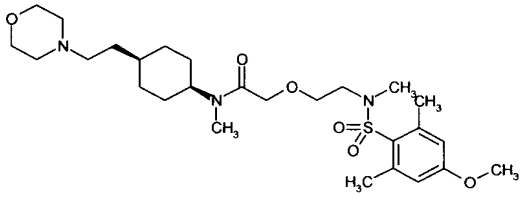
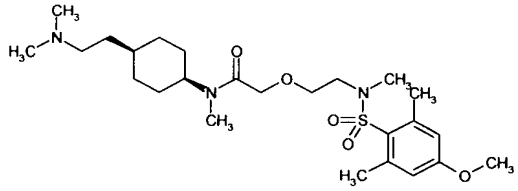
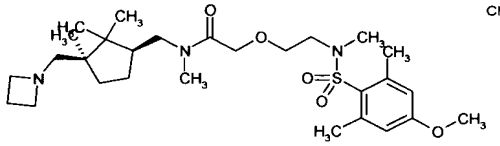
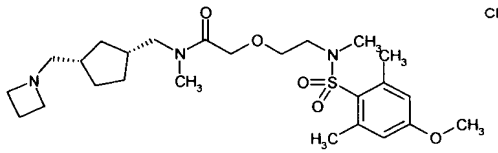
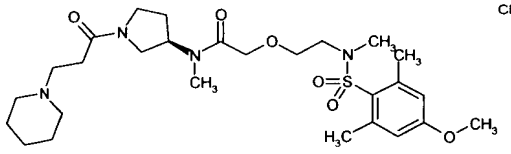
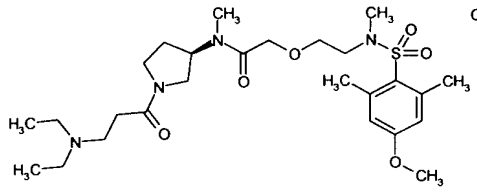
Exemplo	Estrutura
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(582)	
(583)	
(584)	
(585)	
(586)	
(587)	

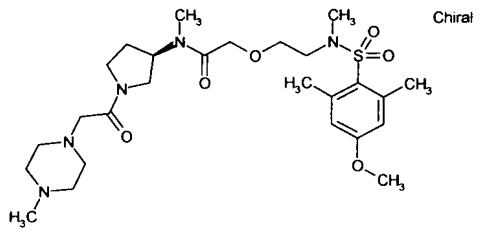
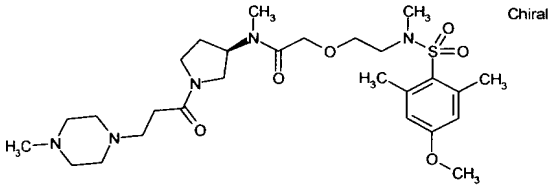
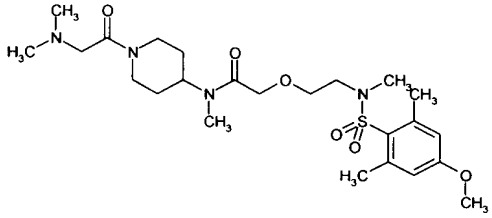
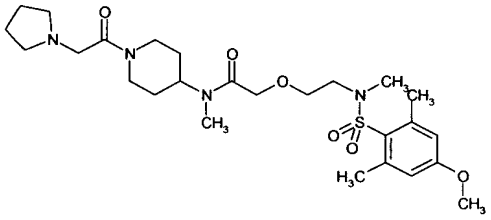
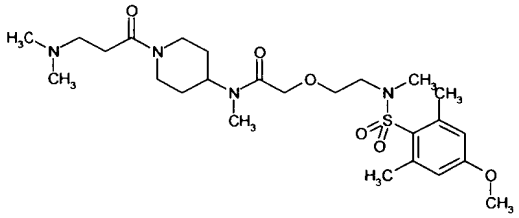
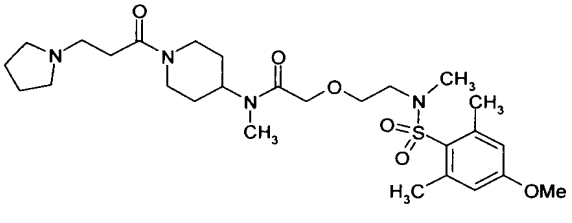
Exemplo	Estrutura
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(593)	
(594)	

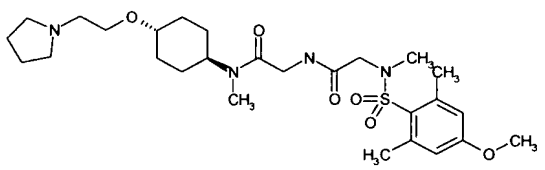
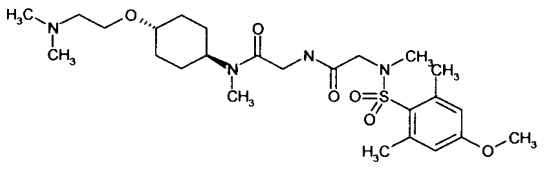
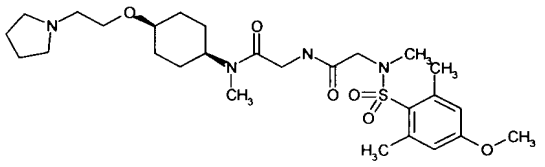
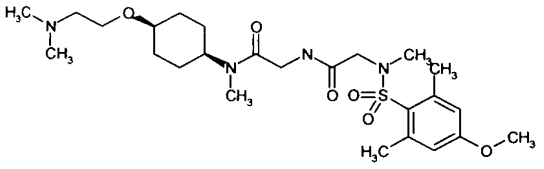
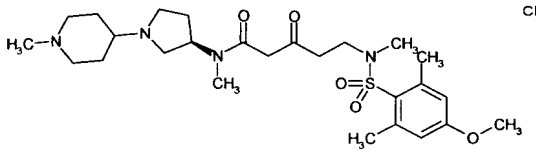
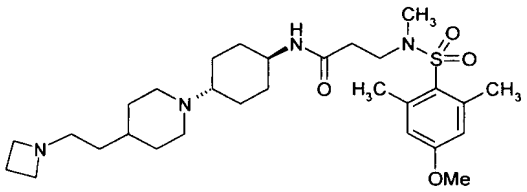
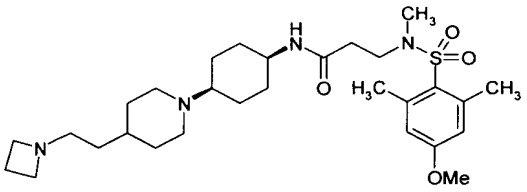
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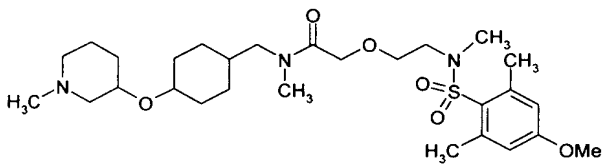
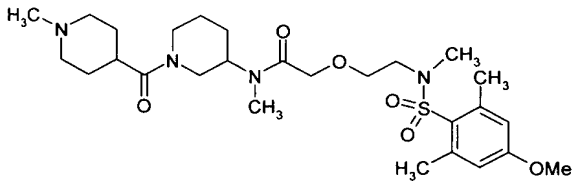
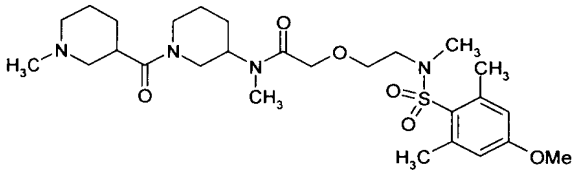
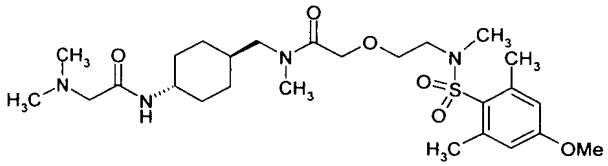
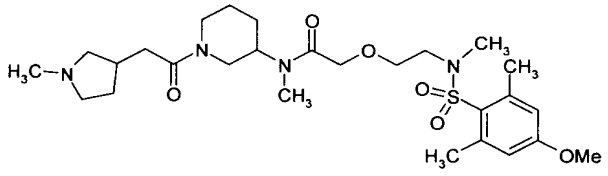
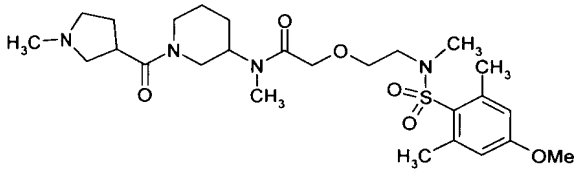
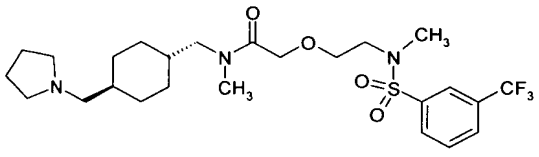
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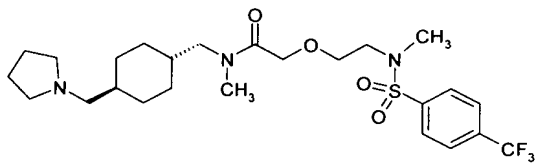
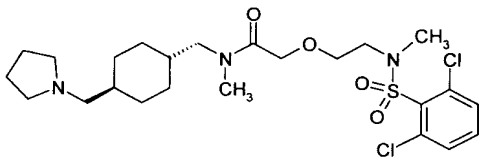
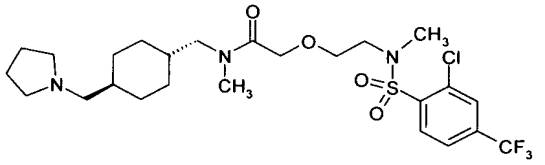
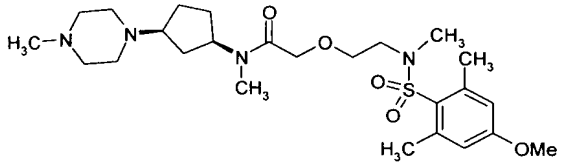
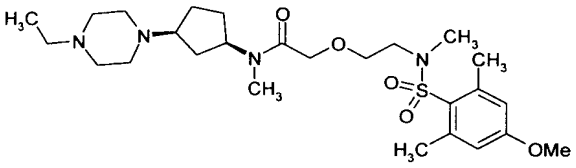
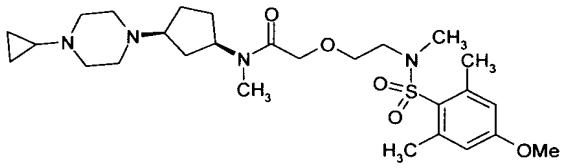
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Exemplo	Estrutura
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Exemplo	Estrutura
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Exemplo	Estrutura
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Exemplo	Estrutura
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Exemplo	Estrutura
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seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos.

Termos e Definições Usados

Desde que não seja indicado de outro modo, todos os substituintes são independentes uns dos outros. Se em um grupo há, por exemplo, vários grupos C_{1-6}-alquila como substituintes, então no caso de três substituintes C_{1-6}-alquila independentes uns dos outros, estes deveriam representar

uma vez metila, uma vez *n*-propila e uma vez *terc*-butila.

No contexto deste pedido, na definição de possíveis substituintes, esses também podem ser representados na forma de uma fórmula estrutural. Com isso, caso exista, uma estrela (*) na fórmula estrutural do substituinte é entendida como o ponto de ligação para o radical da molécula.

Do mesmo modo, o objeto desta invenção compreende os compostos de acordo com a invenção, inclusive seus sais, nos quais um ou mais átomos de hidrogênio, por exemplo, um, dois, três, quatro ou cinco átomos de hidrogênio, são permutados por deutério.

Pelo termo "C_{1-2}-alquila" (também desde que sejam componente de outros radicais) são entendidos grupos alquila com 1 a 2 átomos de carbono, pelo termo "C_{1-3}-alquila", grupos alquila ramificados e não ramificados com 1 a 3 átomos de carbono, pelo termo "C_{1-4}-alquila", grupos alquila ramificados e não ramificados com 1 a 4 átomos de carbono, pelo termo "C_{1-5}-alquila", grupos alquila ramificados e não ramificados com 1 a 5 átomos de carbono, pelo termo "C_{1-6}-alquila", grupos alquila ramificados e não ramificados com 1 a 6 átomos de carbono e pelo termo "C_{1-8}-alquila", grupos alquila ramificados e não ramificados com 1 a 8 átomos de carbono. Destes mencionam-se, por exemplo: metila, etila, *n*-propila, *iso*-propila, *n*-butila, *iso*-butila, *sec*-butila, *terc*-butila, *n*-pentila, *iso*-pentila, *neo*-pentila, hexila, heptila e octila. Eventualmente utilizam-se para os grupos mencionados acima também as abreviações Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu e outros. Desde que não seja descrito de outro modo, as definições propila, butila, pentila, hexila, heptila e octila compreendem todas as formas isômeras concebíveis dos respectivos radicais. Dessa maneira, por exemplo, propila compreende *n*-propila e *iso*-propila, butila compreende *iso*-butila, *sec*-butila e *terc*-butila e assim por diante.

Além disso, os termos mencionados acima também compreendem aqueles radicais, nos quais cada grupo metileno pode ser substituído com até dois e cada grupo metila com até três átomos de flúor.

Pelo termo "C_{1-2}-alquileno" são entendidos grupos alquileno ramificados e não ramificados com 1 a 2 átomos de carbono, pelo termo "C_{1-3}-

alquileno" (também desde que sejam componente de outros radicais) são entendidos grupos alquileno ramificados e não ramificados com 1 a 3 átomos de carbono, pelo termo "C_{1-4}-alquileno", grupos alquileno ramificados e não ramificados com 1 a 4 átomos de carbono, pelo termo "C_{1-6}-alquileno", grupos alquileno ramificados e não ramificados com 1 a 6 átomos de carbono e pelo termo "C_{2-4}-alquileno", grupos alquileno ramificados e não ramificados com 2 a 4 átomos de carbono. Destes mencionam-se, por exemplo: metileno, etileno, etan-1,1-diila, propileno, propan-2,2-diila, 1-metiletileno, butileno, 1-metilpropileno, 1,1-dimetiletileno, 1,2-dimetiletileno. Desde que não seja descrito de outro modo, as definições propileno e butileno compreendem todas as formas isômeras concebíveis com o mesmo número de carbono. Dessa maneira, por exemplo, propileno compreende também 1-metiletileno, 1,1-dimetiletileno, 1,2-dimetiletileno. Além disso, os termos mencionados acima também compreendem aqueles radicais, nos quais cada grupo metileno pode ser substituído com até dois átomos de flúor.

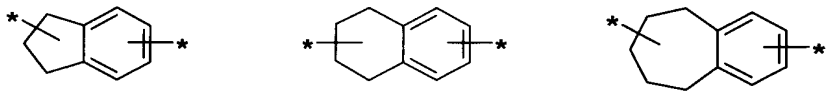
Pelo termo "C_{3-5}-cicloalquila" são entendidos grupos alquila cíclicos com 3 a 5 átomos de carbono, pelo termo "C_{3-6}-cicloalquila" são entendidos grupos alquila cíclicos com 3 a 6 átomos de carbono e pelo termo "C_{3-7}-cicloalquila" (também desde que sejam componente de outros radicais), são entendidos grupos alquila cíclicos com 3 a 7 átomos de carbono. Destes, mencionam-se, por exemplo: ciclopropila, ciclobutila, ciclopentila, ciclohexila ou cicloheptila. Desde que não seja descrito de outro modo, os grupos alquila cíclicos podem ser substituídos com um ou mais radicais selecionados do grupo consistindo em metila, etila, *iso*-propila *terc*-butila, hidróxi, flúor, cloro, bromo e iodo.

Pelo termo "C_{3-6}-cicloalquileno" (também desde que sejam componente de outros radicais), são entendidos grupos alquileno cíclicos com 3 a 6 átomos de carbono, pelo termo "C_{3-7}-cicloalquileno", grupos alquileno cíclicos com 3 a 7 átomos de carbono e pelo termo "C_{4-6}-cicloalquileno", grupos alquileno cíclicos com 4 a 6 átomos de carbono. Destes, mencionam-se, por exemplo: ciclopropileno, ciclobutileno, ciclopentileno, ciclohexileno ou cicloheptileno. Desde que não seja descrito de outro modo, os grupos alqui-

leno cíclicos podem ser substituídos com um ou mais radicais selecionados do grupo consistindo em metila, etila, *iso*-propila, *terc*-butila, hidróxi, flúor, cloro, bromo e iodo.

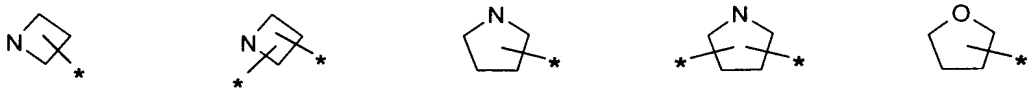
Um grupo C_4- ou um grupo C_5-cicloalquileno pode estar ligado com a molécula restante na posição 1,2 ou na posição 1,3, preferivelmente na posição 1,3. Um grupo C_6- ou um grupo C_7-cicloalquileno pode estar ligado com a molécula restante na posição 1,2, na posição 1,3 ou na posição 1,4, preferivelmente na posição 1,3.

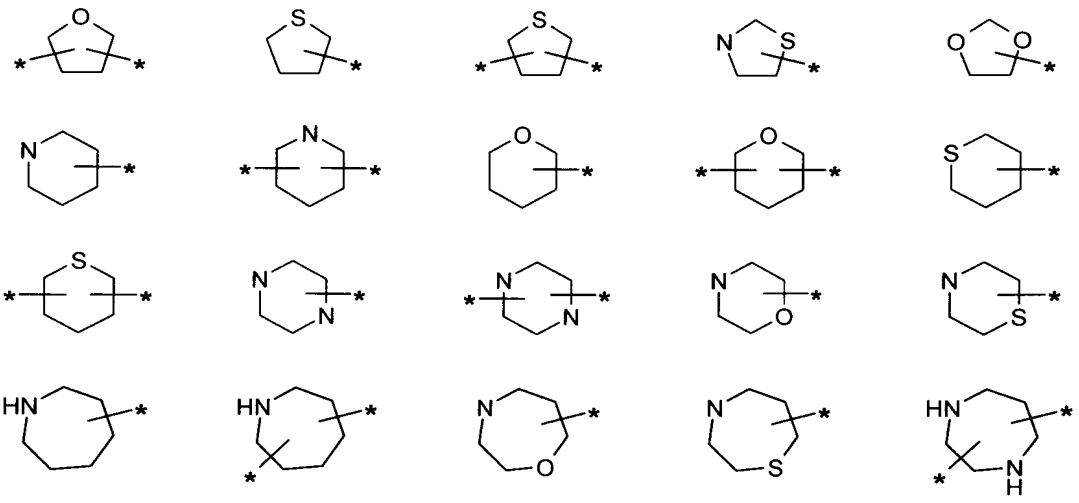
Pelo termo "C_{5-7}-cicloalquenileno" (também desde que sejam componente de outros radicais), são entendidos grupos alquileno cíclicos com 5 a 7 átomos de carbono, que contêm uma ligação insaturada e que são condensados com um anel fenila através dessa ligação insaturada. Destes, mencionam-se, por exemplo: ciclopentenila, ciclohexenila ou cicloheptenila:



Desde que não seja descrito de outro modo, os grupos alquenila cíclicos podem ser substituídos com um ou mais radicais selecionados do grupo consistindo em metila, etila, *iso*-propila, *terc*-butila, hidróxi, flúor, cloro, bromo e iodo.

Pelo termo "anéis heterocíclicos saturados" são entendidos anéis heterocíclicos com quatro, cinco, seis ou sete membros, que podem conter um, dois ou três heteroátomos, selecionados do grupo oxigênio, enxofre e nitrogênio. Nesse caso, o anel pode estar ligado com a molécula através de um átomo de carbono e/ou – caso presente – através de um átomo de nitrogênio ou também através de dois átomos de carbono ou através de dois átomos de nitrogênio. Embora compreendido pelo termo "anéis heterocíclicos", o termo "anéis heterocíclicos, não aromáticos" define anéis saturados com cinco, seis ou sete membros. Como exemplos mencionam-se:

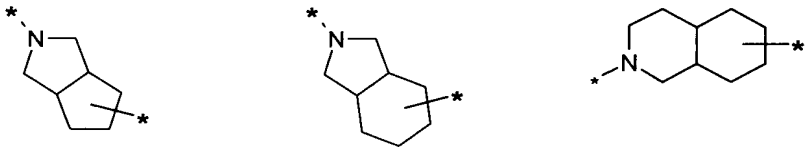




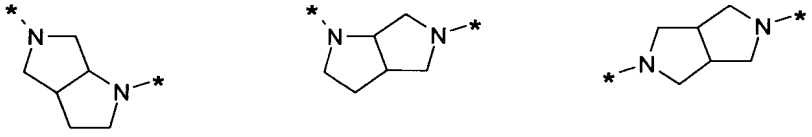
Pelo termo "diaza-heterociclos saturados" são entendidos anéis heterocíclicos com seis ou sete membros, que contêm dois átomos de nitrogênio. Nesse caso, o anel está ligado com a molécula restante através dos dois átomos de nitrogênio. Como exemplos são mencionados:

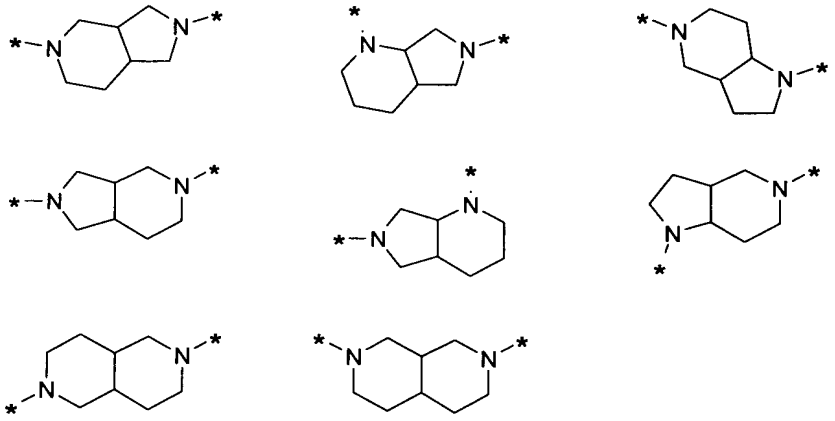


Pelo termo "aza-heterobiciclos" são entendidos anéis heterobicíclicos com oito, nove ou dez membros, que contêm um átomo de nitrogênio. Nesse caso, o anel está ligado com a molécula restante através um átomo de carbono e o átomo de nitrogênio. Como exemplos são mencionados:

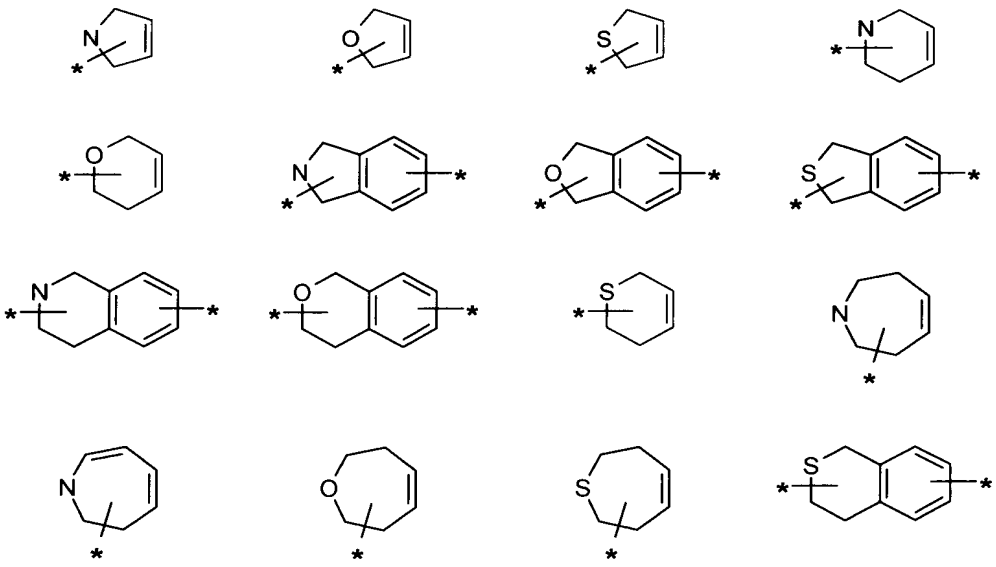


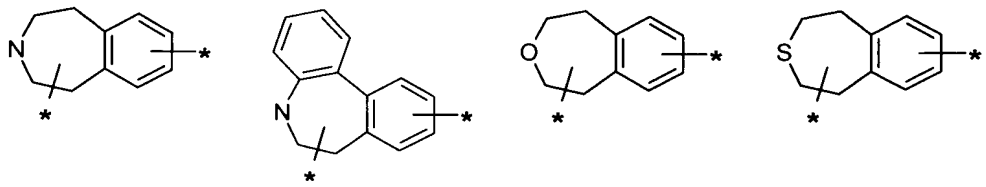
Pelo termo "diaza-heterobiciclos saturados" são entendidos anéis heterobicíclicos com oito, nove ou dez membros, que contêm dois átomos de nitrogênio. Nesse caso, o radical está ligado com a molécula restante através de dois átomos de nitrogênio. Como exemplos são mencionados:



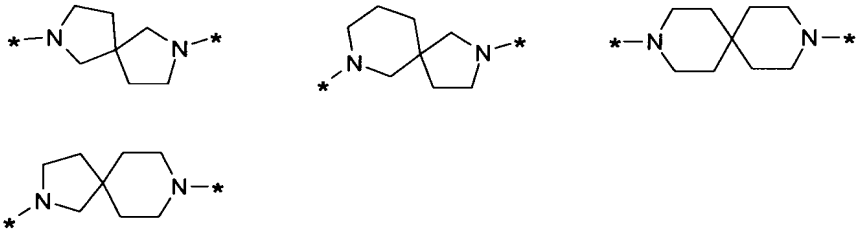


Pelo termo "anéis heterocíclicos insaturados" são entendidos anéis heterocíclicos uma ou duas vezes insaturados, com cinco, seis ou sete membros, que podem conter um, dois ou três heteroátomos, selecionados do grupo oxigênio, enxofre e nitrogênio e que estão condensados com um ou dois anéis fenila através das ligações insaturadas. Nesse caso, o anel heterocíclico pode estar ligado com a molécula através de um átomo de carbono e/ou – caso presente – através de um átomo de nitrogênio ou através de dois átomos de carbono ou através de dois átomos de nitrogênio. Como exemplos são mencionados:



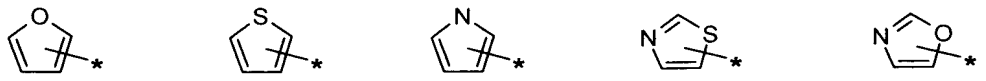


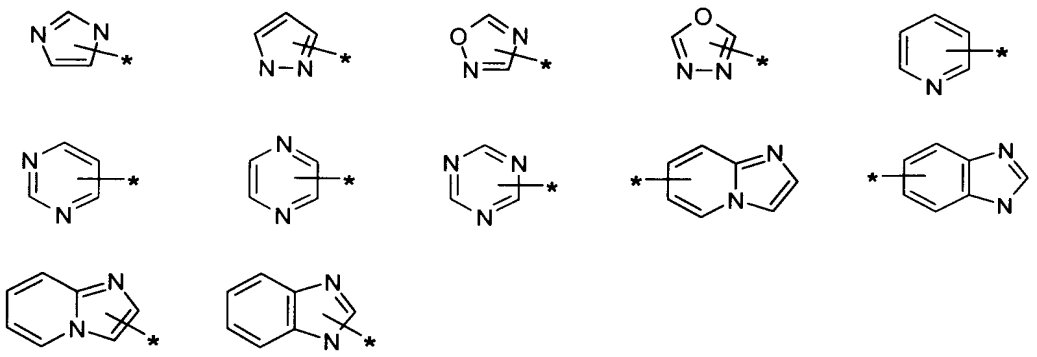
Pelo termo "diaza-spirociclos saturados" são entendidos anéis spirocíclicos com nove, dez ou onze membros, que contêm dois átomos de nitrogênio. Nesse caso, o spirociclo está ligado com a molécula restante através dos dois átomos de nitrogênio. Como exemplos são mencionados:



Pelo termo "arila" (também desde que sejam componente de outros radicais) são entendidos sistemas cíclicos aromáticos com 6 ou 10 átomos de carbono. Destes mencionam-se, por exemplo, fenila, 1-naftila ou 2-naftila; radicais arila preferidos são fenila e 1-naftila; radical arila particularmente preferido é fenila. Desde que não seja descrito de outro modo, os compostos aromáticos podem ser substituídos com um ou mais radicais selecionados do grupo consistindo em metila, etila, *n*-propila, *iso*-propila, *terc*-butila, hidróxi, metóxi, trifluormetóxi, flúor, cloro, bromo e iodo, sendo que os radicais podem ser iguais ou diferentes.

Pelo termo "heteroarila" são entendidos compostos aromáticos heterocíclicos com cinco ou seis membros ou anéis heteroarila bicíclicos com 9-11 membros, que podem conter um, dois ou três heteroátomos, selecionados do grupo oxigênio, enxofre e nitrogênio e adicionalmente contêm tantas ligações duplas conjugadas, que se forma um sistema aromático. Como exemplos de compostos aromáticos heterocíclicos com cinco ou seis membros são mencionados:

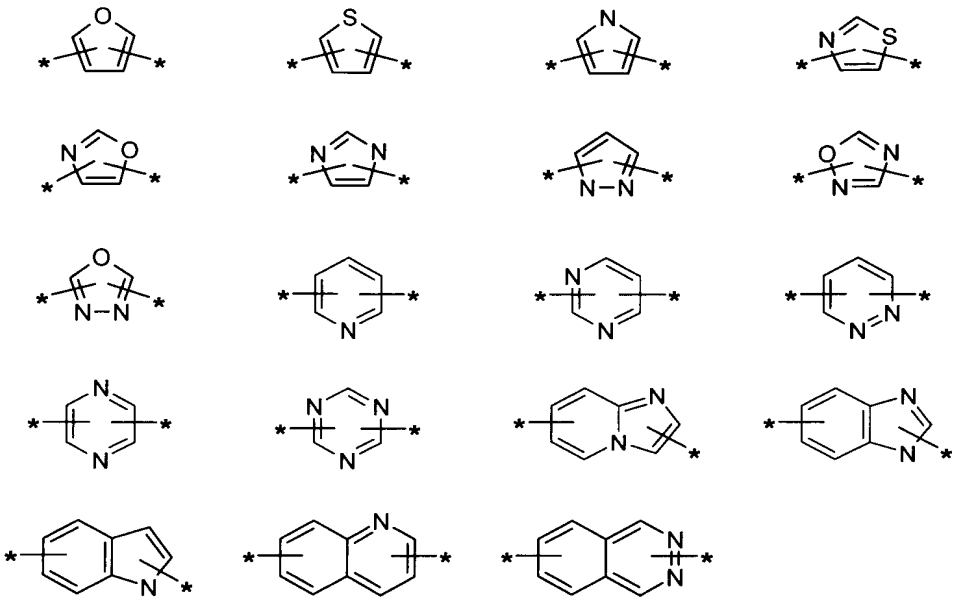




Desde que não seja descrito de outro modo, as heteroarilas mencionadas acima podem ser substituídas com um ou mais radicais selecionados do grupo consistindo em metila, etila, *n*-propila, *iso*-propila, *terc*-butila, hidróxi, metóxi, trifluormetóxi, flúor, cloro, bromo e iodo, em que os radicais podem ser iguais ou diferentes. Nesse caso, os anéis heteroarila bicíclicos podem ser substituídos no radical fenila.

Pelo termo "arileno" (também desde que sejam componente de outros radicais), são entendidos sistemas cíclicos aromáticos com 6 ou 10 átomos de carbono. Destes mencionam-se, por exemplo: fenileno, 1-naftileno ou 2-naftileno, de modo mais preferido o radical arileno é fenileno. Desde que não seja descrito de outro modo, os compostos aromáticos podem ser substituídos com um ou mais radicais selecionados do grupo consistindo em metila, etila, *n*-propila, *iso*-propila, *terc*-butila, hidróxi, metóxi, trifluormetóxi, flúor, cloro, bromo e iodo. Esses sistemas cíclicos aromáticos estão ligados à molécula restante em dois pontos independentes uns dos outros através de respectivamente um átomo de carbono.

Pelo termo "heteroarileno" são entendidos compostos aromáticos heterocíclicos com cinco ou seis membros ou anéis heteroarila bicíclicos com 9-11 membros, que podem conter um, dois ou três heteroátomos, selecionados do grupo oxigênio, enxofre e nitrogênio e adicionalmente contêm tantas ligações duplas conjugadas, que se forma um sistema aromático. Esses compostos aromáticos heterocíclicos estão ligados em dois pontos independentes uns dos outros através de carbono/e ou de nitrogênio. Como exemplos de compostos aromáticos heterocíclicos com cinco ou seis membros, são mencionados:



Desde que não seja descrito de outro modo, os compostos heteroaromáticos podem ser substituídos com um ou mais radicais selecionados do grupo consistindo em metila, etila, *n*-propila, *iso*-propila, *terc*-butila, hidróxi, metóxi, trifluormetóxi, flúor, cloro, bromo e iodo. Preferivelmente, os substituintes nos anéis heteroarila bicíclicos com 5-10 membros mencionados acima, encontram-se no anel fenila.

Compostos da fórmula geral **I**, desde que contenham funções básicas adequadas, por exemplo, grupos amino, podem ser convertidos em seus sais fisiologicamente toleráveis com ácidos inorgânicos ou orgânicos, especialmente para aplicações farmacêuticas. Ácidos inorgânicos interessantes para esse fim são, por exemplo, ácido bromídrico, ácido fosfórico, ácido nítrico, ácido clorídrico, ácido sulfúrico, ácido metanossulfônico, ácido etanossulfônico, ácido benzenossulfônico ou ácido p-toluenossulfônico, ácidos inorgânicos interessantes são, por exemplo, ácido málico, ácido succínico, ácido acético, ácido fumárico, ácido maléico, ácido mandélico, ácido láctico, ácido tartárico ou ácido cítrico. Além disso, os grupos amino terciários eventualmente presentes na molécula podem ser quaternizados. Nesse caso, os halogenetos de alquila são usados para a reação. De acordo com a invenção, o iodeto de metila é preferivelmente usado para a quaternização.

Além disso, os compostos da fórmula geral **I**, desde que conte-

nham funções de ácido carboxílico adequadas, podem ser eventualmente convertidos para seus sais de adição com bases inorgânicas ou orgânicas. Bases inorgânicas importantes para esse fim são, por exemplo, hidróxidos de metais alcalinos ou alcalino-terrosos, por exemplo, hidróxido de sódio ou hidróxido de potássio ou carbonatos, amoníaco, hidróxidos de zinco ou amônio; aminas orgânicas importantes são, por exemplo, dietilamina, trietilamina, etanolamina, dietanolamina, trietanolamina, ciclohexilamina ou diciclohexilamina.

Os compostos de acordo com a invenção, podem estar presentes como racematos, desde que possuam somente um elemento de quiralidade, mas estes também podem ser obtidos como enantiômeros puros, isto é, na forma (R) ou (S).

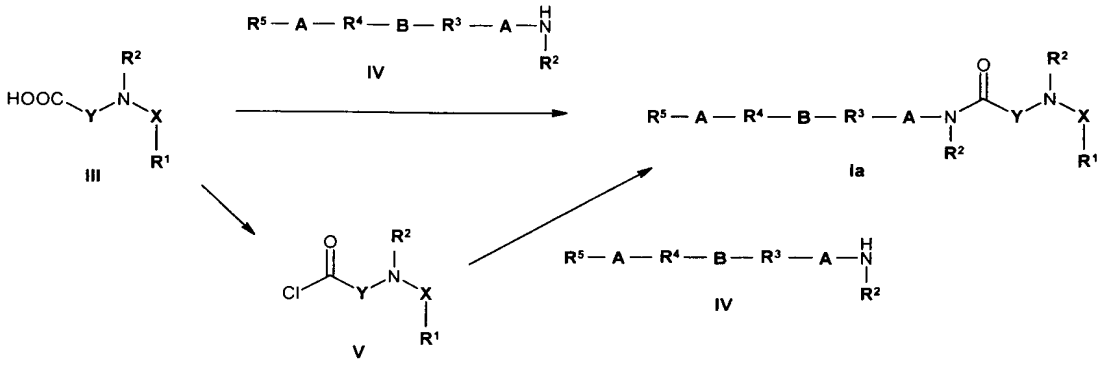
Contudo, o pedido compreende também os pares de antípodas diastereômeros individuais ou suas misturas, que estão presentes, quando há mais do que um elemento de quiralidade nos compostos da fórmula geral **I**, bem como os enantiômeros opticamente ativos, a partir dos quais se compõem os racematos citados.

O objeto da invenção são os respectivos compostos, eventualmente na forma dos isômeros ópticos individuais, misturas dos enantiômeros ou racematos individuais, na forma dos tautômeros bem como na forma das bases livres ou dos sais de adição de ácidos correspondentes com ácidos farmacologicamente inócuos – tais como, por exemplo, sais de adição de ácidos com ácidos halogenídricos – por exemplo, ácido clorídrico ou bromídrico – ou ácidos orgânicos – tais como, por exemplo, ácido oxálico, fumárico, diglicólico ou metanossulfônico.

Processos de Preparação

De acordo com a invenção, obtêm-se os compostos da fórmula geral **I** por processos em si conhecidos, por exemplo, de acordo com os seguintes processos:

Esquema 1



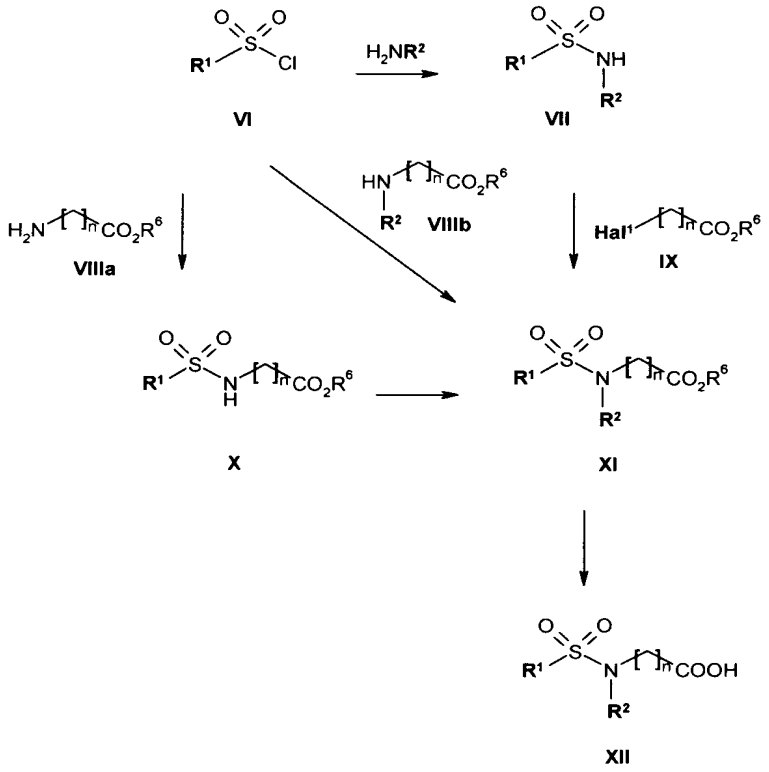
A ligação de ácidos carboxílicos da fórmula geral **III** representada no esquema 1, na qual todos os radicais são definidos tal como mencionado acima, com aminas da fórmula geral **IV**, na qual todos os radicais são definidos tal como citado acima, com formação de amidas de ácido carboxílico da fórmula geral **Ia**, na qual todos os radicais são definidos tal como citado acima, pode ser efetuada com métodos convencionais para a formação da amida.

A copulação é preferivelmente efetuada com o uso de processos conhecidos da química dos peptídeos (vide, por exemplo, Houben-Weyl, Methoden der Organischen Chemie, volume 15/2), em que são usados, por exemplo, carbodiimidas, tais como, por exemplo, diciclohexilcarbodiimida (DCC), diisopropilcarbodiimida (DIC) ou etil-(3-dimetilamino-propil)-carbodiimida, hexafluorfosfato de O-(1H-benzotriazol-1-il)-N,N,N',N'-tetrametilurônio (HBTU) ou tetrafluorborato de O-(1H-benzotriazol-1-il)-N,N,N',N'-tetrametilurônio (TBTU) ou hexafluorfosfato de 1H-benzotriazol-1-il-óxi-tris-(dimetilamino)-fosfônio (BOP). A velocidade da reação pode ser aumentada através da adição de 1-hidroxibenzotriazol (HOBt) ou de 3-hidróxi-4-oxo-3,4-di-hidro-1,2,3-benzotriazina (HOObt). As copulações são normalmente efetuadas com proporções equimolares dos componentes de copulação, bem como do reagente de copulação em solventes, tais como diclorometano, tetrahidrofurano (THF), acetonitrila, dimetilformamida (DMF), dimetilacetamida (DMA), N-metilpirrolidona (NMP) ou misturas destes e a temperaturas entre -30°C e +30°C, preferivelmente -20°C e +25°C. Desde que seja necessário, prefere-se como base auxiliar adicional a diisopropiletilamina (DIPEA) (base de Hünig).

Um método alternativo para a ligação consiste na conversão de um ácido carboxílico da fórmula geral **III**, na qual todos os radicais são definidos tal como citado acima, para um cloreto de ácido carboxílico da fórmula geral **V**, na qual todos os radicais são definidos tal como citado acima e subsequente reação com uma amina da fórmula geral **IV**, na qual todos os radicais são definidos tal como citado acima. A síntese de um cloreto de ácido carboxílico da fórmula geral **V** é efetuada por processos conhecidos da literatura (vide, por exemplo, Houben-Weyl, Methoden der Organischen Chemie, volume E5/1).

Os ácidos carboxílicos da fórmula geral **III** usados como materiais de partida, na qual todos os radicais são definidos tal como citado acima, são obtidos por processos conhecidos da literatura, por exemplo, através dos processos de síntese representados nos esquemas 2 a 7.

Esquema 2



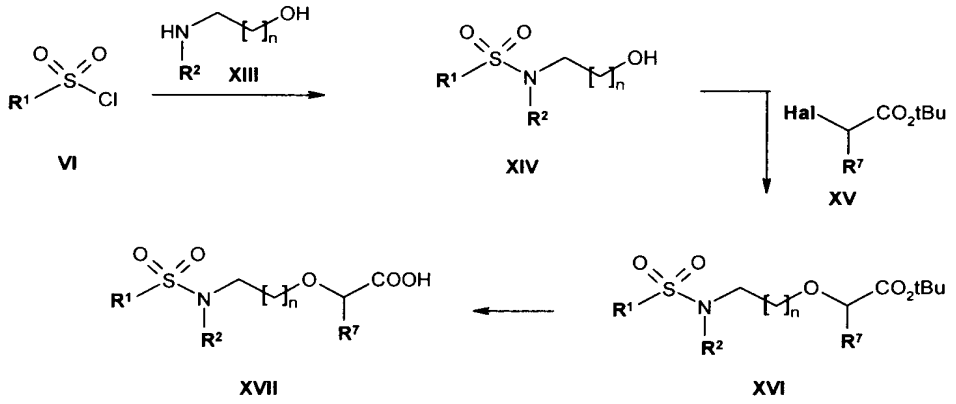
Os cloretos de ácido sulfônico da fórmula geral **VI**, na qual R^1 é definido tal como mencionado acima, são ou conhecidos da literatura ou obteníveis comercialmente. Eles são reagidos de acordo com as condições de

reação padrão com uma amina da fórmula geral H_2N-R^2, **VIIIa** ou **VIIIb** para amidas de ácido sulfônico das fórmulas gerais **VII**, **X** ou **XI**, em que R^1 e R^2 são definidos tal como mencionado acima e **n** representa um número 1, 2, 3 ou 4 e R^6 representa um radical C_{1-6}-alquila. A reação é eventualmente efetuada na presença de uma base, tal como trietilamina, DIPEA ou piridina e de um solvente inerte, tal como diclorometano ou tetrahidrofurano a uma temperatura de 0°C a 100°C com um período de reação típico de uma a 24 horas.

A reação das amidas de ácido sulfônico da fórmula geral **VII** com um halogeneto da fórmula geral **IX**, na qual **Hal**^{1} representa cloro ou bromo, é efetuada por processos conhecidos da literatura, por exemplo, com auxílio de uma base, tal como carbonato de potássio ou de sódio em dimetilformamida ou tetrahidrofurano, a 0°C até 100°C.

A hidrólise dos ésteres de ácido carboxílico da fórmula geral **XI**, na qual R^1 e R^2 são definidos tal como mencionado acima, **n** representa um número 1, 2, 3 ou 4 e R^6 representa um grupo C_{1-3}-alquila, para ácidos carboxílicos da fórmula geral **XII**, na qual R^1 e R^2 são definidos tal como mencionado acima e **n** representa um número 1, 2, 3 ou 4 e R^6 representa um grupo C_{1-3}-alquila, é efetuada em condições conhecidas, por exemplo, com carbonato de lítio ou de sódio e água em metanol e/ou tetrahidrofurano.

Esquema 3



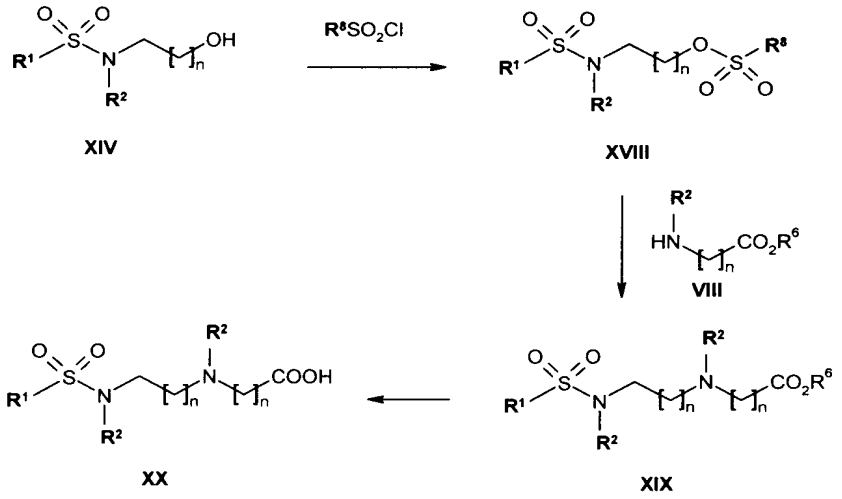
A preparação de amidas de ácido sulfônico da fórmula geral **XIV** é efetuada tal como descrito no esquema 2.

A alquilação da função hidroxila das amidas de ácido sulfônico

da fórmula geral **XIV**, na qual R^1 e R^2 são definidos tal como mencionado acima, com a condição, de que R^2 não represente um átomo de hidrogênio e n representa um número 1, 2, 3 ou 4 e R^6 representa um grupo C_{1-3}-alquila, é efetuada em condições de reação conhecidas da literatura, por exemplo, em condições de duas fases com auxílio de um catalisador de transferência de fases na presença de uma base inorgânica forte, tal como soda cáustica ou lixívia de potassa e em um solvente inerte, tal como tolueno, a 0°C até 100°C.

A dissociação do éster terc-butílico da fórmula geral **XVI**, na qual R^1 e R^2 são definidos tal como mencionado acima, n representa um número 1, 2, 3 ou 4 e R^6 representa um grupo C_{1-3}-alquila e R^7 representa um átomo de hidrogênio ou um grupo C_{1-3}-alquila, é efetuada por processos conhecidos da literatura (vide, por exemplo, Philips, J. Kocienski, Protecting Groups, 3rd Edition, 2005, Georg Thieme Verlag).

Esquema 4



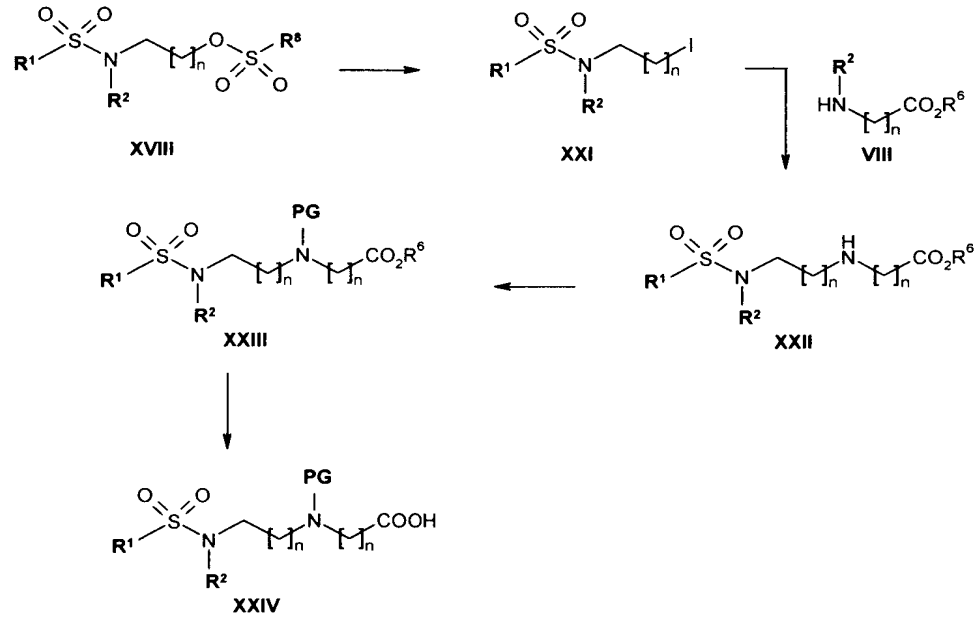
A sulfonação da função hidroxila de um composto da fórmula geral **XIV**, na qual R^1 e R^2 são definidos tal como mencionado acima, com a condição, de que R^2 não representa um átomo de hidrogênio e n representa um número 1, 2, 3 ou 4 e R^6 representa um grupo C_{1-3}-alquila, com um cloreto de ácido sulfônico da fórmula geral R^8SO_2Cl, na qual R^8 representa um grupo C_{1-3}-alquila ou um grupo fenila eventualmente substituído por um grupo C_{1-3}-alquila, para compostos da fórmula geral **XVIII**, na qual todos os ra-

dicais são definidos tal como mencionado acima, é efetuada em condições de reação padrão, tipicamente na presença de uma base, tal como DMAP e/ou piridina e com um solvente inerte, tal como diclorometano ou THF, a -5°C até 35°C. Uma base líquida, tal como piridina, pode ser usada como base e simultaneamente como solvente.

A subsequente alquilação das aminas com a fórmula geral **VII** para compostos da fórmula geral **XIX**, na qual R^1 e R^2 são definidos tal como mencionado acima, n representa um número 1, 2, 3 ou 4 e R^6 representa um grupo C_{1-6}-alquila, é convenientemente efetuada em um solvente, tal como tolueno, clorobenzeno, dimetilformamida, dimetilsulfóxido (DMSO), diclorometano, acetonitrila ou piridina, por exemplo, a temperaturas entre 0°C e 150°C e convenientemente na presença de bases, tais como piridina, trietilamina, DIPEA, carbonato de potássio, terc.-butilato de potássio ou metanolato de sódio, em que o alquilsulfonato serve como grupo de partida.

A hidrólise dos ésteres de ácido carboxílico da fórmula geral **XIX** para ácidos carboxílicos da fórmula geral **XX** é efetuada tal como descrito no esquema 2.

Esquema 5



A reação de Finkelsteinstein de compostos da fórmula geral **XVII**, na qual R^1 e R^2 são definidos tal como mencionado acima, n representa

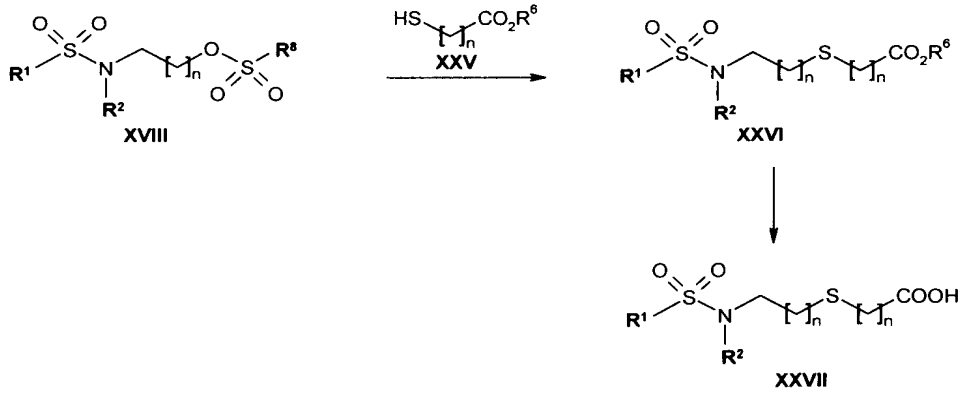
um número 1, 2, 3 ou 4 e R^6 representa um grupo C_{1-3}-alquila e R^8 representa um grupo C_{1-3}-alquila ou um grupo fenila eventualmente substituído por um grupo C_{1-3}-alquila, para halogenetos da fórmula geral **XXI**, na qual R^1 e R^2 são definidos tal como mencionado inicialmente e n representa um número 1, 2, 3 ou 4 e R^6 representa um grupo C_{1-3}-alquila, é efetuada em condições de reação conhecidas (vide, por exemplo, H. Finkelstein, Berichte der Deutschen Chemischen Gesellschaft **43**, 1910, 1528).

A subsequente alquilação do éster glicerínico é efetuada tal como descrito no esquema 4 ($R^2 \neq H$).

A função amino nos compostos da fórmula geral **XXIII** é protegida por um grupo protetor **PG** convencional por processos conhecidos. O grupo protetor selecionado é uma que pode ser dissociada em condições não hidrogenolíticas. Um grupo protetor preferido é o grupo Boc. Uma sinopse sobre a química dos grupos protetores é encontrada em Theodora W. Greene e Peter G. M. Wuts, Protective Groups in Organic Synthesis, Second Edition, 1991, Verlag John Wiley and Sons bem como em Philip J. Kocienski, Protecting Groups, 3rd Edition, 2005, Georg Thieme Verlag.

A dissociação dos ésteres de ácido carboxílico da fórmula geral **XXIII** para ácidos carboxílicos da fórmula geral **XXIV** é efetuada tal como descrito no esquema 2.

Esquema 6

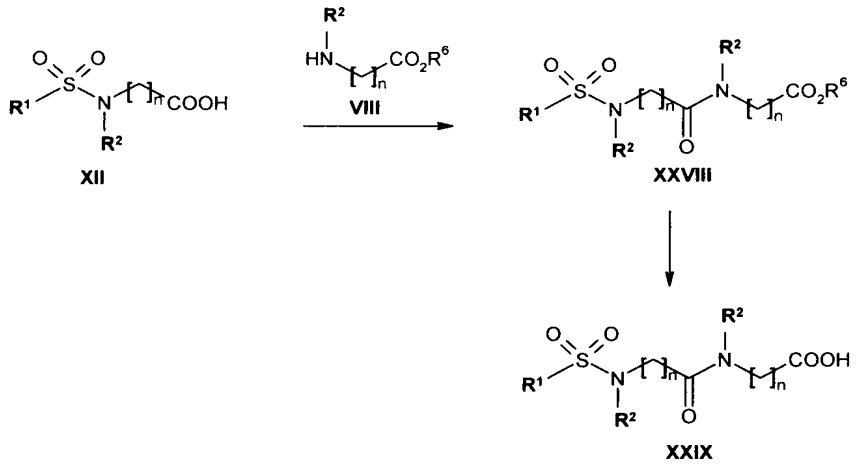


A alquilação de um tiol da fórmula geral **XXV**, na qual n representa um número 1, 2, 3 ou 4 e R^6 representa um grupo C_{1-6}-alquila, para compostos da fórmula geral **XXVI**, na qual R^1 e R^2 são definidos tal como

mencionado acima, n representa um número 1, 2, 3 ou 4 e R^6 representa um grupo C_{1-6}-alquila, é convenientemente efetuada em um solvente, tal como tolueno, clorobenzeno, DMF, DMSO, diclorometano, acetonitrila ou piridina, por exemplo, a temperatura entre 0°C e 150°C e convenientemente na presença de bases, tais como piridina, trietilamina, DIPEA, carbonato de potássio, terc.-butilato de potássio ou metanolato de sódio, em que o alquilsulfonato serve como grupo de partida.

A hidrólise dos ésteres de ácido carboxílico da fórmula geral **XXVI** para ácidos carboxílicos da fórmula geral **XXVII**, na qual todos os radicais são definidos tal como mencionado acima, é efetuada tal como descrito no esquema 2.

Esquema 7



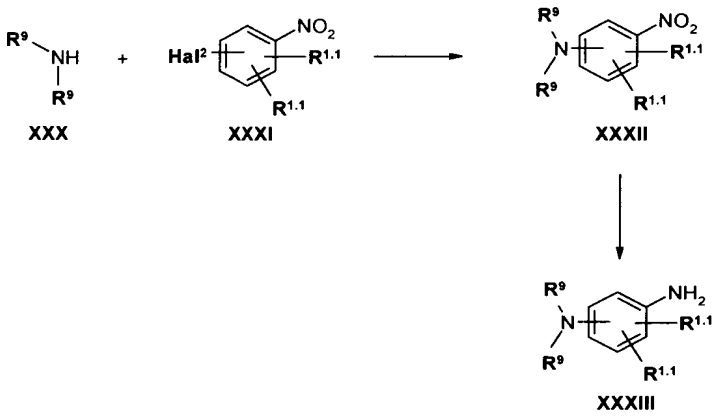
A ligação amida de ácidos carboxílicos da fórmula geral **XII**, na qual R^1 e R^2 são definidos tal como mencionado acima e n representa um número 1, 2, 3 ou 4 e aminoácidos da fórmula geral **VIII**, na qual R^1 e R^2 são definidos tal como mencionado acima, n representa um número 1, 2, 3 ou 4 e R^6 representa um grupo C_{1-6}-alquila, para amidas de ácido carboxílico da fórmula geral **XXVIII**, na qual R^1 e R^2 são definidos tal como mencionado acima e n representa um número 1, 2, 3 ou 4 e R^6 representa um grupo C_{1-6}-alquila, é efetuada tal como descrito no esquema 1.

Tal como mostrado no esquema 2, o éster de ácido carboxílico da fórmula geral **XXVIII** é dissociado para ácido carboxílico da fórmula geral **XXIX**, na qual R^1 e R^2 são definidos tal como mencionado acima e n repre-

senta um número 1, 2, 3 ou 4.

As aminas da fórmula geral **IV** usadas como materiais de partida ou são obteníveis comercialmente ou elas são obtidas por processos conhecidos da literatura, por exemplo, através dos processos de síntese representados no esquema 8 a 12, em que $R^{1.1}$ é definido tal como mencionado acima, Hal^1 representa um átomo de cloro ou bromo e Hal^2 representa um átomo de flúor, cloro ou bromo ou um radical R^9.

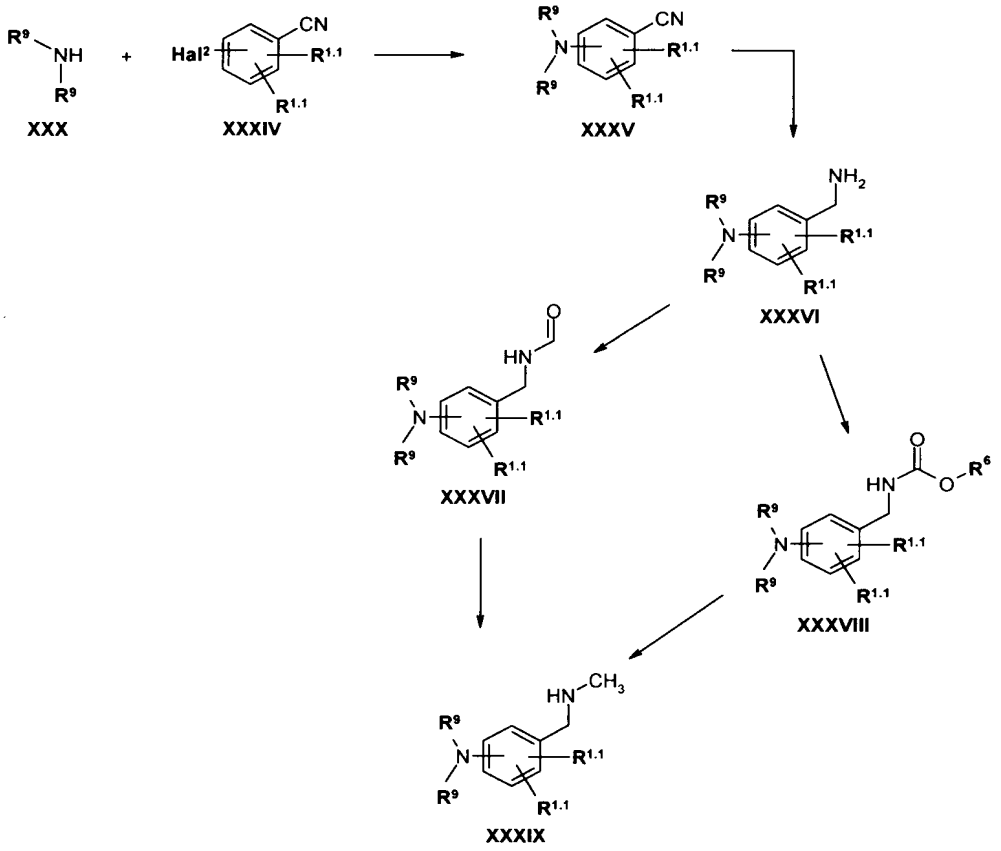
Esquema 8



A reação de uma amina da fórmula geral **XXX**, na qual R^9 representa um grupo C_{1-3}-alquila, com um halogeno-nitrobenzeno da fórmula geral **XXXI**, na qual $R^{1.1}$ é definido tal como mencionado acima e Hal^2 representa um átomo de flúor, cloro ou bromo ou um radical R^9, é efetuada por processos conhecidos, por exemplo, em um solvente, tal como tetrahidrofurano, dimetilformamida ou dimetilsulfóxido e convenientemente na presença de uma base viável, tal como trietilamina ou carbonato de potássio, a uma temperatura de 20°C até 160°C. Se a amina da fórmula geral **XXX** é líquida, a reação também pode ser efetuada sem solvente e base adicional.

A redução do grupo nitro para anilinas da fórmula geral **XXXIII**, na qual $R^{1.1}$ é definido tal como mencionado acima e R^9 representa um grupo C_{1-3}-alquila, é efetuada em condições de reação padrão (vide, por exemplo, Richard C. Larock, Comprehensive Organic Transformations, 1989, V-CH), preferivelmente em condições padrão da hidrogenólise catalítica com um catalisador, tal como paládio sobre carvão ou níquel de Raney, em um solvente tal como metanol ou etanol.

Esquema 9



A reação de compostos das fórmulas gerais **XXX**, na qual R^9 representa um grupo C_{1-3}-alquila, com um composto da fórmula geral **XXXIV**, na qual $R^{1.1}$ é definido tal como mencionado acima e Hal^2 representa um átomo de flúor, cloro ou bromo ou um radical R^9, para compostos com a fórmula geral **XXXV**, na qual $R^{1.1}$ é definido tal como mencionado acima e R^9 representa um grupo C_{1-3}-alquila, é efetuada tal como descrito no esquema 8.

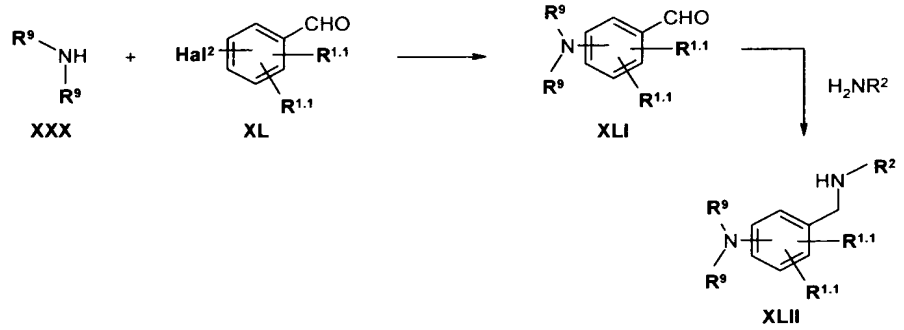
A redução de uma nitrila da fórmula geral **XXXV** para uma amina da fórmula geral **XXXVI**, na qual $R^{1.1}$ é definido tal como mencionado acima e R^9 representa um grupo C_{1-3}-alquila, pode ser efetuada em condições padrão da hidrogenólise catalítica com um catalisador, tal como, por exemplo, níquel de Raney em um solvente, tal como metanol ou etanol amoniacal ou com um agente de redução, tal como hidreto de lítioalumínio ou borohidreto de sódio em um solvente, tal como tetrahidrofurano, eventualmente na presença de cloreto de alumínio.

A formilação de uma amina da fórmula geral **XXXVI** para um composto da fórmula geral **XXXVII**, na qual $R^{1.1}$ é definido tal como mencionado acima e R^9 representa um grupo C_{1-3}-alquila, é convenientemente efetuada em um solvente, tal como diclorometano, por exemplo, a temperaturas de 40°C até 70°C e na presença de anidrido de ácido acético e ácido fórmico.

A formação de carbamato para compostos da fórmula geral **XXXVIII**, na qual $R^{1.1}$ é definido tal como mencionado acima, R^6 representa um grupo C_{1-6}-alquila e R^9 representa um grupo C_{1-3}-alquila, é efetuada por processos conhecidos, por exemplo, com um éster de ácido clorofórmico ou anidrido boc, na presença de uma base, tal como trietilamina ou soda cáustica e de um solvente, tal como THF ou dioxano.

A redução da formila ou do carbamato para compostos da fórmula geral **XXXIX**, na qual $R^{1.1}$ é definido tal como mencionado acima e R^9 representa um grupo C_{1-3}-alquila, é efetuada em condições padrão, preferivelmente com um agente de redução, tal como hidreto de lítioalumínio e em um solvente, tal como tetrahidrofurano, a uma temperatura de 50°C até 100°C.

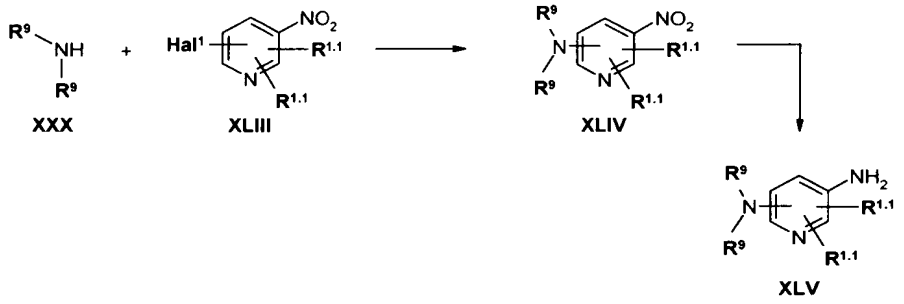
Esquema 10



A permuta de halogênio-nitrogênio em compostos das fórmulas gerais **XXX**, na qual R^9 representa um grupo C_{1-3}-alquila e **XL**, na qual $R^{1.1}$ é definido tal como mencionado acima e Hal^2 representa um átomo de flúor, cloro ou bromo ou um radical R^9, para a preparação de compostos da fórmula geral **XLI**, na qual $R^{1.1}$ é definido tal como mencionado acima e R^9 representa um grupo C_{1-3}-alquila, é efetuada tal como descrito no esquema 8.

A reação de benzaldeídos da fórmula geral **XLI**, na qual $R^{1.1}$ é definido tal como mencionado acima e R^9 representa um grupo C_{1-3}-alquila, com uma amina da fórmula geral H_2NR^2, na qual R^2 é definido tal como mencionado acima, para um composto da fórmula geral **XLII**, na qual $R^{1.1}$ e R^2 são definidos tal como mencionado acima e R^9 representa um grupo C_{1-3}-alquila, é uma aminação redutora. Esta é efetuada por processos conhecidos, por exemplo, com um agente de redução, tal como triacetoxiborohidreto de sódio, borohidreto de sódio ou cianoborohidreto de sódio, convenientemente em um solvente, tal como tetrahidrofurano ou diclorometano, eventualmente com adição de ácido acético.

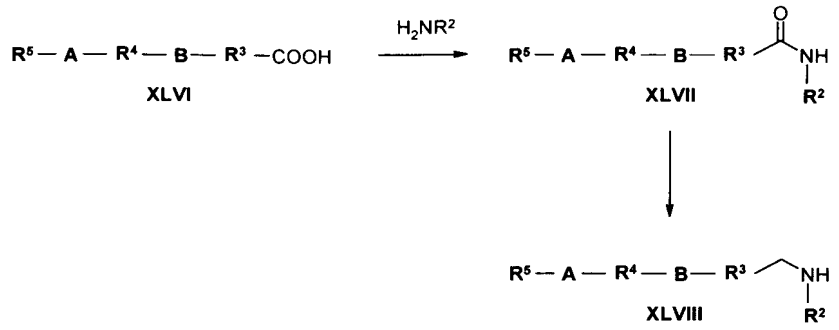
Esquema 11



A reação de uma amina da fórmula geral **XXX**, na qual R^9 representa um grupo C_{1-3}-alquila, com uma halogeno-nitropiridina da fórmula geral **XLIII**, na qual $R^{1.1}$ é definido tal como mencionado acima e Hal^1 representa um átomo de cloro ou bromo, é efetuada por processos conhecidos, por exemplo, em um solvente, tal como tetrahidrofurano, diclorometano, metanol ou DMSO e convenientemente na presença de uma base viável, tal como trietilamina, soda cáustica ou carbonato de potássio e a uma temperatura de 20°C até 100°C.

A subsequente redução do grupo nitro de um composto da fórmula geral **XLIV**, na qual $R^{1.1}$ é definido tal como mencionado acima e R^9 representa um grupo C_{1-3}-alquila, para compostos da fórmula geral **XLV**, na qual $R^{1.1}$ é definido tal como mencionado acima e R^9 representa um grupo C_{1-3}-alquila, é efetuada tal como descrito no esquema 8.

Esquema 12



A ligação amida de ácidos carboxílicos da fórmula geral **XLVI**, na qual todos os radicais são definidos tal como mencionado acima e aminas da fórmula geral H_2NR^2, na qual R^2 é definido tal como mencionado acima, para amidas de ácido carboxílico da fórmula geral **XLVII**, na qual todos os radicais são definidos tal como mencionado acima, é efetuada tal como descrito no esquema 1.

A redução de amidas de ácido carboxílico da fórmula geral **XLVII** para aminas da fórmula geral **XLVIII**, na qual todos os radicais são definidos tal como mencionado acima, é efetuada em condições de reação padrão, preferivelmente na presença de um agente de redução, tal como hidreto de lítioalumínio e de um solvente, tal como tetrahidrofurano a 40°C até 100°C.

Descrição dos métodos para a ligação do receptor hBK1

Células CHO, que exprimem o receptor hBK1, são cultivadas em "Dulbecco's modified medium". O meio é removido de culturas confluentes, as células são lavadas com tampão PBS, raspadas e isoladas através de centrifugação. Em seguida, as células são homogeneizadas em suspensão, o homogeneizado é centrifugado e ressuspenso. Após a determinação do teor de proteína, a preparação da membrana obtida dessa maneira é congelada a -80°C.

Após o descongelamento, 200 µl do homogeneizado (50 a 100 µg de proteína/ensaio) são incubados por 60 minutos à temperatura ambiente com 0,5 a 1,0 nM de calidina (DesArg10,Leu9), [3,4-prolil-3,43H(N)] e crescentes concentrações da substância do teste em um volume total de 250 µl. A incubação é concluída através de rápida filtração através de filtros de fibra de vidro GF/B, que foram previamente tratados com polietilenimina

(0,3%). A radioatividade ligada à proteína foi medida com um TopCountNXT. Como ligação não específica, a radioatividade ligada é definida na presença de 1,0 µM de calidina (DesArg10,Leu9), [3,4-prolil-3,43H(N)]. A análise da curva de ligação de concentração é efetuada com auxílio de um ajuste de curva não linear computadorizada. O valor K_i correspondente é determinado a partir dos dados obtidos dessa maneira para a substância do teste.

Para demonstrar, que os compostos da fórmula geral **I** com diferentes elementos estruturais mostram atividades antagônicas boas até muito boas do receptor bradiquinina-B1, a tabela abaixo indica os valores K_i, que foram obtidos de acordo com o protocolo de ensaio acima. Para isso é observado, que os compostos foram selecionados com respeito aos seus diferentes elementos estruturais e não para destacar compostos específicos:

Exemplo	K_i [nM]
(1)	6,2
(13)	2,1
(22)	7
(53)	2,4
(55)	0,7
(59)	6,3
(61)	3,3
(66)	4,6
(67)	0,4
(72)	2,8
(73)	6,8
(77)	8,7
(78)	5,8
(97)	6,7
(102)	5,0
(109)	6,0
(114)	4,4
(117)	0,99
(130)	5,7

Exemplo	K_i [nM]
(180)	5,2
(181)	7,1
(182)	4,8
(183)	6,6
(184)	1,3
(186)	3,4
(188)	9,4
(216)	4,9
(227)	4,8
(269)	7,8
(303)	6,32
(323)	2,8
(325)	0,94
(326)	6,5
(334)	8,65
(335)	9,37
(338)	1,11
(352)	9,2
(353)	6,1
(356)	8,8
(358)	3,5
(360)	4,4
(361)	7,4
(365)	2,4
(367)	2,7
(368)	1,52
(369)	3,8
(372)	2,39
(381)	8,1
(383)	6,2

Exemplo	K_i [nM]
(384)	9,3
(385)	6,4
(386)	6,3
(389)	3,7
(392)	8,3
(393)	1,6
(394)	1,04
(397)	7,5
(398)	0,74
(399)	3
(400)	0,79
(401)	2,7
(402)	9,3
(404)	2,8
(418)	1,2
(419)	0,65
(420)	9,1
(421)	8,7
(423)	3,4
(424)	1,4
(425)	8,3
(428)	6,3
(435)	1,5
(439)	7,5
(441)	4,6
(444)	6,9
(445)	5,6
(448)	0,82
(451)	9
(458)	4,3

Exemplo	K_i [nM]
(463)	2
(464)	1,5
(465)	3,8
(468)	1
(469)	8
(471)	4,1
(472)	0,68
(473)	1,8
(474)	1,4
(475)	2,4
(476)	2,35
(477)	5,8
(478)	1
(492)	3,2
(576)	0,85
(577)	0,34
(580)	6,2
(582)	9,3
(584)	9,0
(586)	5,1
(587)	9,5
(588)	1,5
(589)	5,1
(591)	1,9
(592)	2,8
(613)	9,7
(614)	2
(616)	3,7
(619)	1,2
(620)	5,9

Exemplo	K_i [nM]
(621)	5,8
(623)	3,4
(624)	8
(630)	5,5

Indicações

Com base em suas propriedades farmacológicas, os novos compostos e seus sais fisiologicamente toleráveis são adequados para o tratamento de doenças e sintomas de doenças, que são pelo menos parcialmente provocados pela estimulação de receptores de bradiquinina-B1.

Com base em seu efeito farmacológico, as substâncias são adequadas para o tratamento

(a) de **dores agudas**, tais como, por exemplo, dor de dente, dores peri- e pós-operatórias, dores traumáticas, dores musculares, dores de queimaduras, dores de insolação, nevralgias do trigêmeo, dores de cólicas, bem como no caso de espasmos do trato gastrintestinal ou do útero;

(b) de **dores abdominais**, tais como, por exemplo, dores crônicas da pelve, dores ginecológicas, dores antes e durante a menstruação, dores no caso da pancreatite, da úlcera péptica, da cistite intersticial, da cólica renal, da angina do peito, dores do cólon irritável, da dispepsia não ulcerosa e da gastrite, dores torácicas não cardíacas e dores da isquemia miocárdica e infarto do coração;

(c) de **dores neuropáticas**, tais como, por exemplo, polineuropatias dolorosas, dores da neuropatia diabética, dores neuropáticas associadas a AIDS, dores do lumbago, na nevralgia não associada ao herpes, nevralgia pós-zoster, de lesões nervosas, trauma crânio-encefálico, dores das danificações nervosas em consequência de toxinas ou quimioterapia, dores fantasmas, dores da esclerose múltipla, da ruptura da raiz nervosa e lesões nervosas individuais dolorosas condicionadas traumaticamente;

(d) de **dores inflamatórias/causadas pelo receptor da dor** em associação com doenças, tais como osteoartrite, artrite reumatóide, febre reumática, tendo-sinovite, inflamações dos tendões, gota, vulvodinia, danos

e doenças dos músculos e fáscias (lesões musculares, fibromialgia), osteoartrite, artrite juvenil, espondilite, artrite por gota, artrite por psoríase, fibromialgia, miosite, cefaléia, doenças dentárias, influenza e outras infecções por virus, tais como resfriados, lupus eritematóide sistêmico,

(e) de **dores tumorais** em associação com doenças de câncer, tais como leucemia linfática ou mielóide, doença de Hodgkin, linfomas não Hodgkin, linfogranulomatose, linfossarcomas, tumores malignos sólidos e metástases expandidas;

(f) de **doenças de dores de cabeça**, tais como, por exemplo, dores de cabeça de diferente origem, dor de cabeça de cluster, cefaléia (com ou sem aura) e dor de cabeça por tensão.

Além disso, os compostos são adequados para o tratamento

(g) de alterações inflamatórias em associação com doenças das vias respiratórias, tais como asma brônquica, inclusive asma alérgica (atópica e não atópica), bem como broncoespasmos no caso de esforços, asma condicionada industrialmente, exacerbação viral ou bacteriana de uma doença asmática existente e outras doenças asmáticas não causadas por alergias;

doença pulmonar obstrutiva crônica (COPD) inclusive enfisema pulmonar, síndrome da angústia respiratória do adulto (ARDS), bronquite, pneumonia, rinite alérgica (sazonal ou anual), rinite vasomotora e pneumoconioses, tais como aluminose, antracose, asbestose, calcose, siderose, silicose, tabacose e bissinose;

(h) de sintomas inflamatórios na insolação e queimaduras, edemas após traumas devido a queimaduras, edemas cerebrais e angioedemas, doenças intestinais inclusive Morbus Crohn e colite ulcerosa, síndrome do intestino irritado, pancreatite, nefrite, cistite (cistite intersticial), uveíte; doenças inflamatórias da pele (tais como, por exemplo, psoríase e eczemas), doenças vasculares do tecido de ligação, lupus, luxações e fraturas;

(i) de diabetes melitus e suas consequências (tais como, por exemplo, vasculopatia, neuropatia diabética, retinopatia diabética) e de sintomas diabéticos na insulite (por exemplo, hiperglicemia, diurese, proteinúria e

excreção aumentada de nitrito e calicreina);

(j) de doenças neurodegenerativas, tais como da doença de Parkinson e da doença de Alzheimer;

(k) de sepse e choque séptico após infecções bacterianas ou após traumas;

(l) de síndromes que provocam prurido e reações alérgicas da pele;

(m) de osteoporose;

(n) de epilepsia;

(o) de feridas e lesões dos tecidos;

(q) de inflamações da gengiva;

(r) de hiperplasia benigna da próstata e bexiga hiperativa;

(s) de prurido;

(t) de vitiligo;

(u) de distúrbios da mortalidade de regiões respiratórias, genitourinárias, gastrintestinais ou vasculares e

(v) de febre pós-operatória.

Além da aptidão como terápico humano, essas substâncias também são úteis na terapia médica-veterinária de animais domésticos, animais exóticos e gado.

Para o tratamento das dores, pode ser vantajoso combinar os compostos de acordo com a invenção, com substâncias estimulantes, tais como cafeína ou outras substâncias ativas diminuidoras da dor. Caso haja substâncias ativas adequadas à disposição para o tratamento da origem das dores, então essas podem ser combinadas com os compostos de acordo com a invenção. Se independentemente do tratamento da dor também são indicados ainda outros tratamentos médicos, por exemplo, contra hipertensão ou diabetes, então as substâncias ativas também necessárias para esse fim, podem ser combinadas com os compostos de acordo com a invenção.

Por exemplo, os seguintes compostos são interessantes para uma terapia de combinação:

antirreumáticos não esteroidais (NSAR): inibidores de COX-2,

tais como derivados de ácido propiônico (alminoprofeno, benoxaprofeno, ácido bucloxínico, carprofeno, fenufeno, fenoprofeno, fiuprofeno, fiulbiprofeno, ibuprofeno, indoprofeno, cetoprofeno, miroprofeno, naproxeno, oxaprozina, pirprofeno, pranoprofeno, suprofeno, ácido tiaprofênico, tioxaprofeno), derivados do ácido acético (indometacina, acemetacina, alcofenaco, isoxepac, oxpinax, sulindac, tiopinac, tolmetina, zidometacina, zemepiraco), derivados do ácido fenamínico (ácido meclofenaminico, ácido mefenamínico, ácido tolfenamínico), derivados do ácido bifenil-carboxílico, oxicame (isoxicam, meloxicam, piroxicam, sudoxicam e tenoxicam), derivados do ácido salicílico (ácido acetilsalicílico, sulfasalazina, por que não também mesalazina, olsalazina e pirazolona (apazona, bezpiperilona, feprazona, mofebutazona, oxifenbutazona, fenilbutazona, por que não também propifenazona e metamizol e coxibe (celecoxib, valecoxib, rofecoxib, etoricoxib).

Agonistas do receptor opiáceo, tais como, por exemplo, morfina, propoxifeno (Darvon), tramadol, buprenorfina.

Agonistas canabinóides, tais como, por exemplo, GW-1000, KDS-2000, SAB-378, SP-104, NVP001-GW-84316, GW-842166X, PRS-211375.

Bloqueadores do canal de sódio, tais como, por exemplo, carbamazepina, mexiletina, lamotrigina, pregabalina, tectina, NW-1029, CGX-1002.

Bloqueadores do canal de cálcio do tipo N, tais como, por exemplo, ziconitida, NMED-160, SP1-860.

Moduladores serotonérgicos e noradrenérgicos, tais como, por exemplo, SR-57746, paroxetina, duloxetina, clonidina, amitriptilina, citalopram.

Corticosteróides, tais como, por exemplo, betametasona, budesonida, cortisona, dexametasona, hidrocortisona, metilprednisolona, prednisolona, prednisona e triamcinolona.

Antagonistas do receptor histamina H1, tais como, por exemplo, bromoftniniramint, clorofeniramina, dexclorofeniramina, triprolidina, clemastina, difenidramina, difenilpiralina, tripelenamina, hidroxizina, metdijazina,

prometazina, trimeprazina, azatadina, ciproheptadina antazolina, feniramina, pirilamina, astemizol, terfenadina, loratadina, cetirizina, desloratadina, fexofenadina, levocetirizina.

Antagonistas do receptor histamina H2, tais como por exemplo, cimetidina, famotidina e ranitidina.

Inibidores da bomba de prótons, tais como, por exemplo, omeprazol, pantoprazol, esomeprazol.

Antagonistas leucotrienos e inibidores da 5-lipoxigenase, tais como, por exemplo, zafirlucast, montelucast, pranlucast e zileuton.

Anestésicos locais, tais como, por exemplo, ambroxol, lidocaína.

Agonistas e antagonistas de VR1, tais como, por exemplo, NGX-4010, WL-1002, ALGRX-4975, WL-10001, AMG-517.

Agonistas do receptor nicotina, tais como, por exemplo, ABT-202, A-366833, ABT-594, BTG-102, A-85380, CGX1204.

Antagonistas do receptor P2X3, tais como, por exemplo, A-317491, ISIS-13920, AZD-9056.

Agonistas e antagonistas de NGF, tais como, por exemplo, RI-724, RI-1024, AMG-819, AMG-403, PPH 207.

Antagonistas de NK1 e NK2, tais como, por exemplo, DA-5018, R-116301, CP-728663, ZD-2249.

Antagonistas de NMDA, tais como, por exemplo, NER-MD-11, CNS-5161, EAA-090, AZ-756, CNP-3381.

Moduladores do canal de potássio, tais como, por exemplo, CL-888, ICA-69673, retigabina.

Moduladores de GABA, tal como, por exemplo, lacosamida.

Moduladores serotonérgicos e noradrenérgicos, tais como, por exemplo, SR-57746, paroxetina, duloxetina, clonidina, amitriptilina, citalopram, flibanserina.

Terápicos contra cefaléia, tais como, por exemplo, sumatriptano, zolmitriptano, naratriptano, eletriptano.

A dosagem necessária para a obtenção de um efeito analgésico na dose intravenosa, importa convenientemente em 0,01 a 3 mg/kg de peso

corporal, preferivelmente 0,1 a 1 mg/kg e na dose oral, em 0,1 a 8 mg/kg de peso corporal, preferivelmente 0,5 a 3 mg/kg, em cada caso 1 a 3 vezes ao doa. Os compostos preparados de acordo com a invenção, podem ser administrados por via intravenosa, subcutânea, intramuscular, intrarretal, intranasal, por inalação, transdérmica ou oral, sendo que para a inalação prestam-se especialmente formulações de aerossol. Elas podem ser eventualmente incorporadas junto com um ou vários veículos e/ou diluentes inertes usuais, por exemplo, com amido de milho, lactose, cana-de-açucar, celulose microcristalina, estearato de magnésio, polivinilpirrolidona, ácido cítrico, ácido tartárico, água, água/etanol, água/glicerina, água/sorbitol, água/polietilenoglicol, propilenoglicol, álcool cetilesteárico, carboximetilcelulose ou substâncias gordurosas, tais como gordura sólida ou suas misturas adequadas, em preparações galênicas usuais, tais como comprimidos, drágeas, cápsulas, pós, suspensões, soluções, aerossóis dosadores ou supositórios.

Parte Experimental

Via de regra, há espectros IR, de RMN-^{1}H e/ou de massa para os compostos preparados. As proporções indicadas nas fases móveis referem-se a unidades de volume dos respectivos solventes. As unidades de volume indicadas no amoníaco, referem-se a uma solução concentrada de amoníaco em água. Desde que não seja anotado de outro modo, as soluções de ácidos, bases e salinas usadas nos processamentos das soluções de reação são sistemas aquosos nas concentrações indicadas.

Para purificações cromatográficas, é usado gel de sílica da empresa Milipore (MATREX®, 35-70 µm) ou Alox (E. Merck, Darmstadt, óxido de alumínio 90 padronizado, 63-200 µm, artigo nº: 1.01097.9050).

Nas descrições dos ensaios são utilizadas as seguintes abreviações:

CDI	1,1'-carbonildiimidazol
DC	cromatograma de camada fina
DIPEA	diisopropiletilamina
DMAP	4-dimetilaminopiridina
DMF	dimetilformamida

DMSO dimetilsulfóxido

HATU hexafluorfosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametilurônio

tert terciário

TBTU tetrafluorborato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametilurônio

THF tetrahidrofurano

Foram utilizados os seguintes métodos analíticos de HPLC:

Método 1: Coluna: XTerra® MS C18, 2,5 µM, 4,6 x 30 mm

Detecção: 210 – 420 nm

Fase móvel A: água/0,1% de ácido fórmico

Fase móvel B: acetonitrila/0,1% de ácido fórmico

Gradiente:

tempo em minutos	% A	% B	taxa da fase móvel em ml/min
0,0	95,0	5,0	1,0
0,1	95,0	5,0	1,0
3,1	2,0	98,0	1,0
4,5	2,0	98,0	1,0
5,0	95,0	5,0	1,0

Método 2: Coluna: Microsorb C18, 3 µM, 4,6 x 50 mm

Detecção: 220 – 320 nm

Fase móvel A: água/0,1% de TFA

Fase móvel B: acetonitrila/0,1% de TFA

Gradiente:

tempo em minutos	% A	% B	taxa de fase móvel em ml/min
0,0	95,0	5,0	1,5
0,5	95,0	5,0	1,5
3,8	2,0	98,0	1,5
4,3	2,0	98,0	1,5
4,35	95,0	5,0	1,5
4,6	95,0	5,0	1,5

Método 3: Coluna: XTerra® MS C18, 3,5 µM, 4,6 x 50 mm

Detecção: 210 – 420 nm

Fase móvel A: água/0,1% de ácido fórmico

Fase móvel B: acetonitrila/0,1% de ácido fórmico

Gradiente:

tempo em minutos	% A	% B	taxa de fase móvel em ml/min
0,0	95,0	5,0	1,0
0,1	95,0	5,0	1,0
7,1	2,0	98,0	1,0
7,9	2,0	98,0	1,0
8,0	95,0	5,0	1,0

Método 4: Coluna: Zorbax Stable Bond C18, 3,5 µM, 4,6 x 75 mm

Detecção: 230 – 360 nm

Fase móvel A: água/0,1% de ácido fórmico

Fase móvel B: acetonitrila/0,1% de ácido fórmico

Gradiente:

tempo em minutos	% A	% B	taxa de fase móvel em ml/min
0,0	95,0	5,0	1,6
0,1	95,0	5,0	1,6
4,5	10,0	90,0	1,6
5,09	10,0	90,0	1,6
5,5	90,0	10,0	1,6

Método 5: Coluna: Interchim Strategy C18, 5 µM, 4,6 x 50 mm

Detecção: 220 -320 nm

Fase móvel A: água/0,1% de TFA

Fase móvel B: acetonitrila

Gradiente:

tempo em minutos	% A	% B	taxa de fase móvel em ml/min
0,0	95,0	5,0	3,0
0,3	95,0	5,0	3,0
2,0	2,0	98,0	3,0
2,4	2,0	98,0	3,0
2,45	95,0	5,0	3,0
2,8	95,0	5,0	3,0

Método 6: Coluna: Merck Cromolith Speed ROD RP18e, 4,6 x 50 mm

Detecção: 190 – 400 nm

Fase móvel A: água/0,1% de ácido fórmico

Fase móvel B: acetonitrila/0,1% de ácido fórmico

Gradiente:

tempo em minutos	% A	% B	taxa de fase móvel em ml/min
0,0	90,0	10,0	1,5
4,5	10,0	90,0	1,5
5,0	10,0	90,0	1,5
5,5	90,0	10,0	1,5

Método 7: Coluna: Waters SunFire C18, 3,5 µM, 4,6 x 50 mm

Detecção: 210 – 500 nm

Fase móvel A: água/0,1% de TFA

Fase móvel B: acetonitrila/0,1% de TFA

Gradiente:

tempo em minutos	% A	% B	taxa de fase móvel em ml/min
0,0	95,0	5,0	1,5
2,0	2,0	98,0	1,5
3,0	2,0	98,0	1,5
3,4	95,0	5,0	1,5

Método 8: Coluna: Waters XBridge C18, 3,5 µM, 4,6 x 50 mm

Detecção: 210 – 500 nm

Fase móvel A: água/0,1% de TFA

Fase móvel B: acetonitrila/0,1% de TFA

Gradiente:

tempo em minutos	% A	% B	taxa de fase móvel em ml/min
0,0	95,0	5,0	1,0
0,1	95,0	5,0	1,0
5,1	2,0	98,0	1,0
6,5	2,0	98,0	1,0
7,0	95,0	5,0	1,0

Método 9: Coluna: Merck Chromolith® Flash RP 18e, 4,6 x 25 mm

Detecção: 190 – 400 nm

Fase móvel A: água/0,1% de ácido fórmico

Fase móvel B: acetonitrila/0,1% de ácido fórmico

Gradiente:

tempo em minutos	% A	% B	taxa de fase móvel em ml/min
0,0	90,0	10,0	1,6
2,7	10,0	90,0	1,6
3,0	10,0	90,0	1,6
3,3	90,0	10,0	1,6

Método 10: Coluna: Merck Chromolith® Flash RP 18e, 4,6 x 25 mm

Detecção: 210 – 400 nm

Fase móvel A: água/0,1% de TFA

Fase móvel B: água/0,1% de TFA

Gradiente:

tempo em minutos	% A	% B	taxa de fase móvel em ml/min
0,0	95,0	5,0	2,5
0,2	95,0	5,0	2,5
1,5	2,0	98,0	2,5
1,7	2,0	98,0	,5
1,9	95,0	5,0	2,5
2,2	95,0	5,0	2,5

Método 11: Coluna: Waters XBridge C18, 3,5 µM, 4,6 x 50 mm

Detecção: 210 – 500 nm

Fase móvel A: água/0,1% de TFA

Fase móvel B: água/0,1% de TFA

Gradiente:

tempo em minutos	% A	% B	taxa de fase móvel em ml/min
0,0	95,0	5,0	1,5
2,0	00	100,0	1,5
3,0	0,0	100,0	1,5
3,4	95,0	5,0	1,5

Método 12: Coluna: YMC-Pack ODS-AQ, 3,0 µM, 4,6 x 75 mm

Detecção: 230 – 360 nm

Fase móvel A: água/0,1% de ácido fórmico

Fase móvel B: acetonitrila/0,1% de ácido fórmico

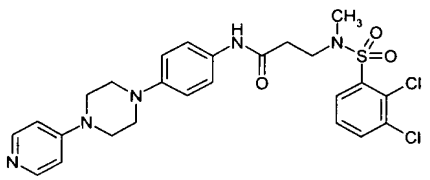
Gradiente:

tempo em minutos	% A	% B	taxa de fase móvel em ml/min
0,0	95,0	5,0	1,6
4,5	10,0	90,0	1,6
5,0	10,0	90,0	1,6
5,5	90,0	10,0	1,6

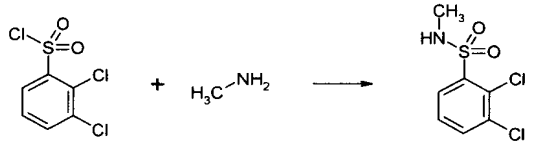
Foi utilizado o seguinte aparelho de micro-ondas: Biotage Emrys Optimizer®.

Preparação dos compostos finais

Exemplo 1



1a)



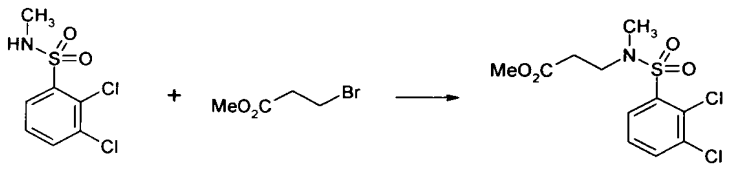
Uma mistura de 1,0 g (4,07 mmols) de cloreto de ácido 2,3-diclorobenzenossulfônico, 0,33 g (4,89 mmols) de cloridrato de metilamina, 2,73 ml (19,55 mmols) de trietilamina e 20 ml de diclorometano é agitada à temperatura ambiente durante a noite. Em seguida, a mistura de reação é lavada uma vez com HCl 1N, solução saturada de bicarbonato de sódio, água e solução saturada de cloreto de sódio, seca sobre sulfato de sódio e depois concentrada à secura.

$C_7H_7Cl_2NO_2S$ (240,00)

$[M+H]^+$ = 240/242/244

DC: gel de sílica, éter de petróleo/acetato de etila 2:1, valor Rf = 0,50.

1b)



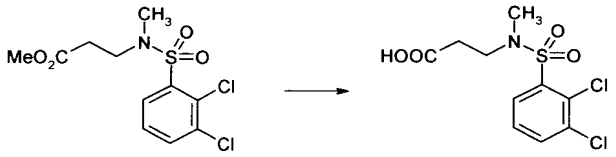
Uma mistura de 0,9 g (3,75 mmols) do produto de 1a e 20 ml de DMF é previamente introduzida e adicionada a 1,55 g (11,24 mmols) de carbonato de potássio e 0,49 ml (4,50 mmols) de éster etílico de ácido 3-bromopropiônico. A mistura de reação é agitada à temperatura ambiente durante a noite e depois adicionada à água. Extrai-se duas vezes com acetato de etila. Os extratos orgânicos são lavados três vezes com água e uma vez com solução saturada de cloreto de sódio, secos sobre sulfato de sódio e concentrados à secura.

$C_{11}H_{13}Cl_2NO_4S$ (326,20)

$[M+H]^+$ = 326/328/330

DC: gel de sílica, éter de petróleo/acetato de etila 2:1, valor Rf = 0,45.

1c)



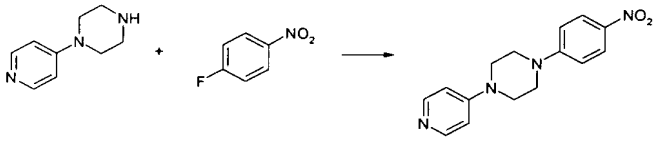
Uma mistura de 1,15 g (3,53 mmols) do produto de 1b, 0,74 g (17,63 mmols) de hidróxido de lítio monohidrato, 15 ml de tetrahidrofurano e 15 ml de água é agitada à temperatura ambiente por uma hora. Depois, o tetrahidrofurano é removido no vácuo e o resíduo acidificado com HCl concentrado. A seguir, a mistura de reação é extraída três vezes com acetato de etila. Os extratos orgânicos são lavados com solução saturada de cloreto de sódio, secos sobre sulfato de sódio e concentrados à secura. O produto bruto é triturado com éter dietílico e aspirado.

$C_{10}H_{11}Cl_2NO_4S$ (312,17)

[M+H]+ = 310/312/314

DC: gel de sílica, éter de petróleo/acetato de etila 2:1, valor Rf = 0,03.

1d)



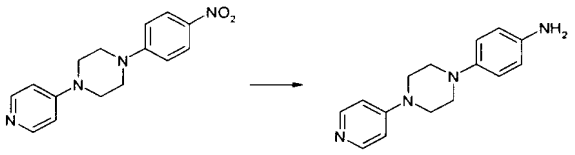
Uma mistura de 5,0 g (30,63 mmols) de 1-piridin-4-il-piperazina, 4,32 g (30,63 mmols) de 1-flúor-4-nitrobenzeno (Aldrich), 10,62 ml (76,59 mmols) de trietilamina e 100 ml de dimetilformamida é aquecida sob refluxo por 50 minutos e em seguida, concentrada à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/etanol/amoníaco 12:1:0,1 a 10:1:0,1).

$C_{15}H_{16}N_4O_2$ (284,31)

[M+H]+ = 285

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,52.

1e)

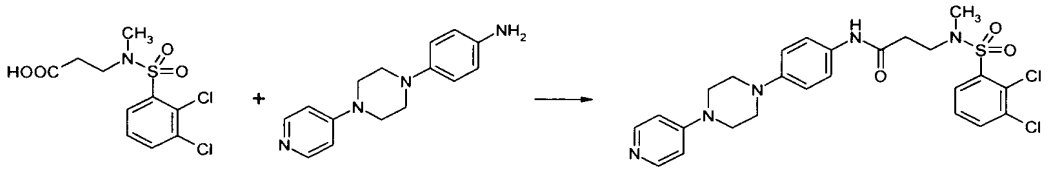


Uma mistura de 4,95 g (17,41 mmols) do produto de 1d, 0,6 g de paládio sobre carvão (10%), 120 ml de diclorometano e 20 ml de metanol é hidrogenada no autoclave à temperatura ambiente por cinco horas. Em seguida, é aspirada e o bolo do filtro ainda é fervido seis vezes com diclorometano/metanol 1:1 e novamente aspirado. Os filtrados purificados são concentrados no vácuo até a secura.

$C_{15}H_{18}N_4$ (254,33)

[M+H]+ = 255.

1f)



Uma mistura de 1,25 g (4,00 mmols) do produto de 1c, 2,0 ml

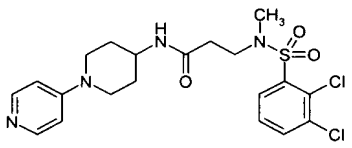
(14,34 mmols) de trietilamina, 1,28 g (4,00 mmols) de TBTU e 7 ml de dimetilformamida é agitada à temperatura ambiente por 45 minutos. Depois, acrescenta-se 1,0 g (3,93 mmols) do produto de 1e e continua-se a agitar à temperatura ambiente durante a noite. Em seguida, a mistura de reação é vertida em água e extraída com diclorometano. Os extratos orgânicos são lavados com água, secos sobre Na_2SO_4 e concentrados à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano com 5-20% de metanol).

$C_{25}H_{27}Cl_2N_5O_3S$ (548,49)

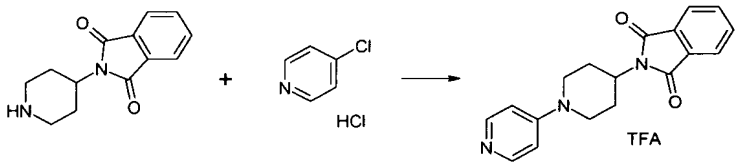
[M+H]+ = 548/550/552

DC: gel de sílica, diclorometano/metanol 4:1, valor Rf = 0,65

Exemplo 2



2a)



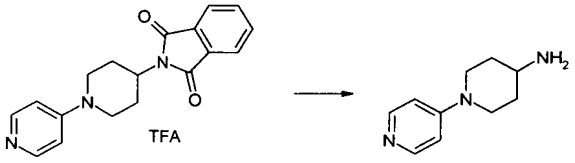
Uma mistura de 0,5 g (2,17 mmols) de *N*-(1-benzilpiperidin-4-il)-ftalimida (Bioorg. Med. Chem. Lett. 11, 2001, 2325-2330), 0,33 g (2,17 mmols) de cloridrato de 4-cloropiridina, 1,2 ml (8,69 mmols) de trietilamina e 2,4 ml de etanol absoluto é aquecida no micro-ondas a 150°C por uma hora. A seguir, a mistura de reação é diluída com etanol, o precipitado formado é filtrado. O filtrado é concentrado até a secura e o produto bruto purificado por meio de HPLC preparatória.

$C_{18}H_{17}N_3O_2 \times C_2HF_3O_2$ (421,37)

[M+H]+ = 308

HPLC (método 1): tempo de retenção = 2,07 min

2b)

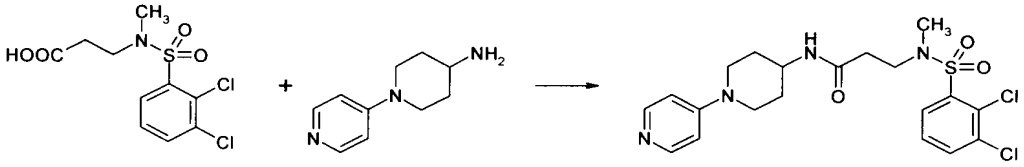


Uma mistura de 0,3 g (0,71 mmol) do produto de 2a, 0,09 g (1,42 mmol) de hidrato de hidrazina a 80% e 6 ml de etanol absoluto é aquecida sob refluxo por quatro horas. A seguir, a mistura de reação é resfriada a 0°C, o precipitado formado é filtrado. O filtrado é concentrado até a secura.

$C_{10}H_{15}N_3$ (177,25)

[M+H]+ = 178

2c)



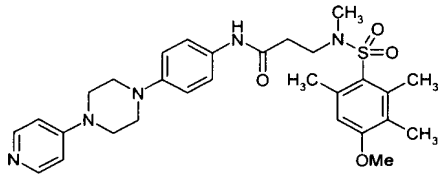
O exemplo 2 é preparado de maneira análoga a 1f a partir de 0,22 g (0,71 mmol) do produto de 1c, 0,24 g (1,35 mmol) do produto de 2b, 0,3 ml (2,13 mmol) de trietilamina e 0,23 g (0,71 mmol) de TBTU em 5,5 ml de dimetilformamida.

$C_{20}H_{24}Cl_2N_4O_3S$ (471,40)

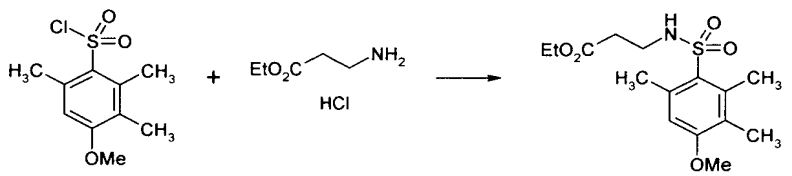
[M+H]+ = 471/473/475

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,2

Exemplo 3



3a)



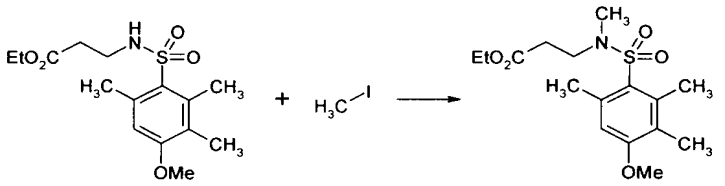
Uma mistura de 0,99 g (4,00 mmols) de cloreto de 4-metóxi-2,3,6-trimetil-benzenossulfonila, 0,69 g (4,51 mmols) de cloridrato de éster β-alaninetílico, 2,23 ml (15,98 mmols) de trietilamina e 20 ml de diclorometano é agitada à temperatura ambiente durante a noite. A seguir, a mistura de reação é lavada com HCl 0,5 M, solução saturada de bicarbonato de sódio, água e solução saturada de cloreto de sódio, seca sobre sulfato de sódio e concentrada no vácuo à secura.

$C_{15}H_{23}NO_5S$ (329,41)

[M+H]+ = 330.

DC: gel de sílica, éter de petróleo/acetato de etila 2:1, valor Rf = 0,43

3b)



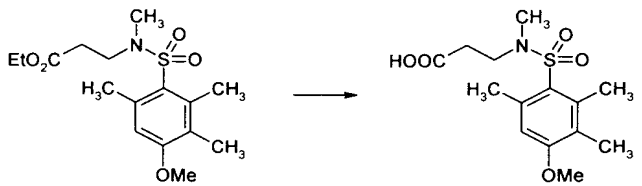
Uma mistura de 1,24 g (3,76 mmols) do produto de 3a, 0,84 ml (13,55 mmols) de iodeto de metila, 1,04 g (7,53 mmols) de carbonato de potássio anidro e 10 ml de dimetilformamida é agitada à temperatura ambiente por cinco horas. A seguir, a mistura de reação é concentrada no vácuo até a secura, o resíduo é retomado em acetato de etila. Lava-se com água, solução saturada de bicarbonato de sódio e solução saturada de cloreto de sódio, seca-se sobre sulfato de sódio e concentra-se no vácuo até a secura.

$C_{16}H_{25}NO_5S$ (343,44)

[M+H]+ = 344

DC: gel de sílica, éter de petróleo/acetato de etila 2:1, valor Rf = 0,52

3c)



O ácido é preparado de maneira análoga a 1c a partir de 1,29 g (3,76 mmols) do produto de 3b, 0,79 g (18,80 mmols) de hidróxido de lítio

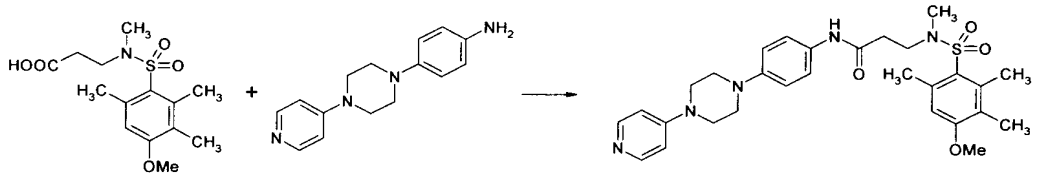
monohidrato, 15 ml de tetrahidrofurano e 15 ml de água.

$C_{14}H_{21}NO_5S$ (315,39)

[M+H]+ = 316

DC: gel de sílica, éter de petróleo/acetato de etila 2:1, valor Rf = 0,07

3d)



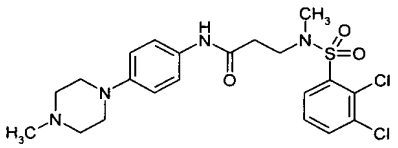
O exemplo 3 é preparado de maneira análoga a 1f a partir de 0,15 g (0,47 mol) do produto de 3c, 0,12 g (0,47 mmol) do produto de 1e, 0,2 ml (1,43 mmol) de trietilamina e 0,15 g (0,48 mmol) de TBTU em 8 ml de dimetilformamida.

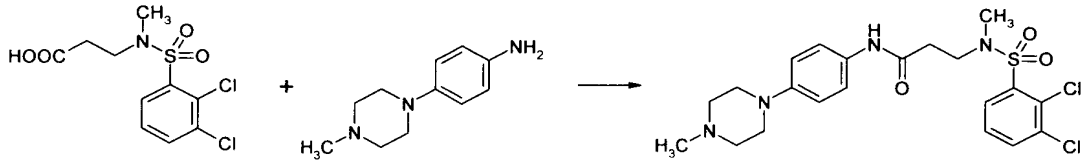
$C_{29}H_{37}N_5O_4S$ (551.70)

[M+H]+ = 552

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,38

Exemplo 4





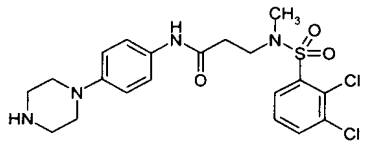
O exemplo 4 é preparado de maneira análoga a 1f a partir de 0,39 g (1,26 mmol) do produto de 1c, 0,24 g (1,26 mmol) de 4-(4-metilpiperazin-1-il)-anilina (J. Med. Chem. SIR 48, 7, 2005, 2371-2387), 0,35 ml (2,51 mmols) de trietilamina e 0,50 g (1,32 mmol) de HATU em 5 ml de dimetilformamida.

$C_{21}H_{26}CL_2N_4O_3S$ (485,43)

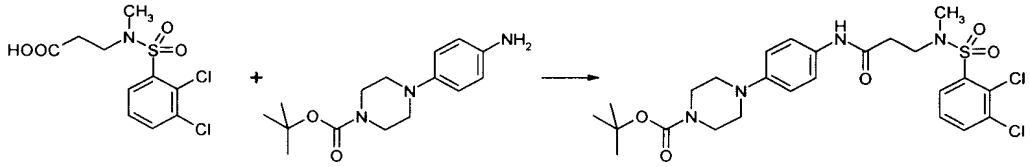
[M+H]+ = 485/487/489

HPLC (método 2): tempo de retenção = 2,64 min.

Exemplo 5



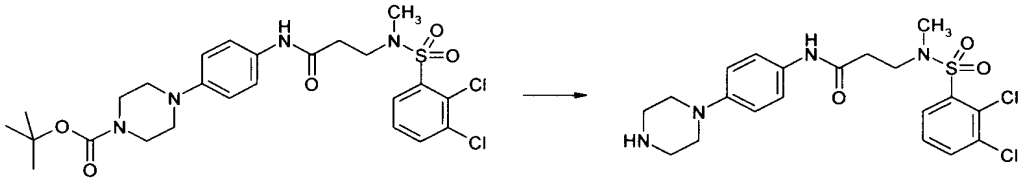
5a)



5a é preparado de maneira análoga a 1f a partir de 0,39 g (1,26 mmol) do produto de 1c, 0,24 g (1,26 mmol) de 4-(4-metilpiperazin-1-il)-anilina (J. Med. Chem. SIR 48, 7, 2005, 2371-2387), 0,35 ml (2,51 mmols) de trietilamina e 0,5 g (1,32 mmol) de HATU em 5 ml de dimetilformamida.

$C_{25}H_{32}CL_2N_4O_5S$ (571.52)

5b)



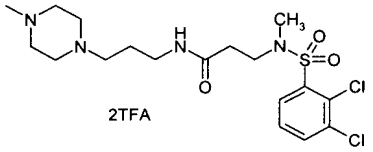
Uma mistura de 0,60 g (1,05 mmol) do produto de 5a, 3 ml de TFA e 3 ml de diclorometano é agitada à temperatura ambiente por duas horas. A mistura de reação é concentrada até a secura e o produto bruto purificado por meio de HPLC preparatória.

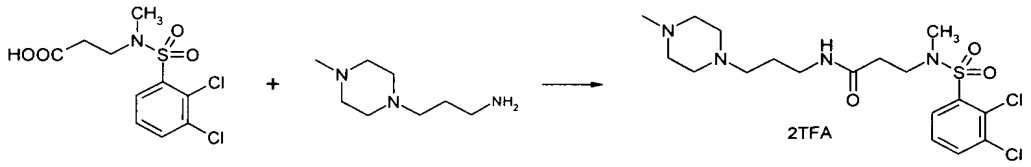
$C_{20}H_{24}Cl_2N_4O_3S$ (471,40)

[M+H]+ = 471/473/475

HPLC (método 2): tempo de retenção = 2,58 min.

Exemplo 6





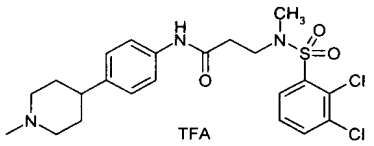
O exemplo 6 é preparado de maneira análoga a 1f a partir de 0,22 g (0,71 mmol) do produto de 1c, 0,12 g (0,78 mmol) de 3-(4-metilpiperazin-1-il)-propilamina (Bioorg. Med. Chem. Lett. 13, 2003, 2131-2136), 0,30 ml (2,13 mmols) de trietilamina e 0,23 g (0,71 mmol) de TBTU em 5,5 ml de tetrahidrofurano.

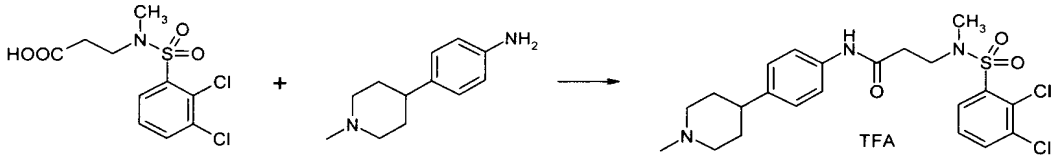
$C_{18}H_{28}Cl_2N_4O_3S \times 2C_2HF_3O_2$ (679,46)

[M+H]+ = 451/453/455

HPLC (método 5): tempo de retenção = 1,27 min

Exemplo 7





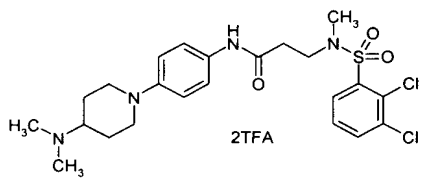
O exemplo 7 é preparado de maneira análoga a 1f a partir de 0,22 g (0,71 mmol) do produto de 1c, 0,14 (0,71 mmol) de 4-(1-metilpiperidin-4-il)-anilina (JW Pharmlab), 0,30 ml (2,13 mmols) de trietilamina e 0,23 g (0,71 mmol) de TBTU em 5,5 ml de tetrahidrofurano.

$C_{22}H_{27}Cl_2N_3O_3S \times C_2HF_3O_2$ (598,46)

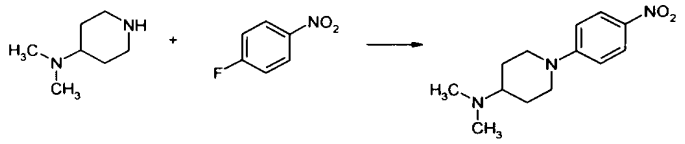
[M+H]+ = 484/486/488

HPLC (método 5): tempo de retenção = 1,57 min.

Exemplo 8



8a)

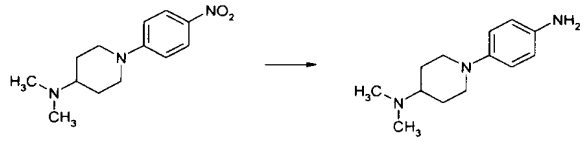


8a é preparado de maneira análoga a 1d a partir de 0,5 g (3,90 mmols) de 4-dimetilamino-piperidina (Alfa Aesar), 0,44 g (4,18 mmols) de 1-flúor-4-nitrobenzeno (Aldrich) e 1,33 ml (76,59 mmols) de trietilamina em 12 ml de dimetilformamida.

$C_{13}H_{19}N_3O_2$ (249,31)

[M+H]+ = 250

8b)



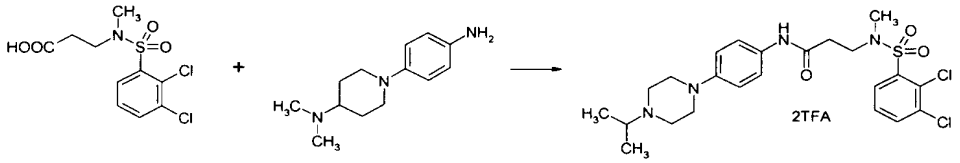
Uma mistura de 1,66 g (6,67 mmols) do produto de 8a, 0,17 g de paládio sobre carvão (5%) e 132 ml de etanol é hidrogenada no autoclave à temperatura ambiente. Em seguida, o catalisador é aspirado e o filtrado concentrado no vácuo até a secura.

$C_{13}H_{21}N_3$ (219,33)

[M+H]+ = 220

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,1

8c)



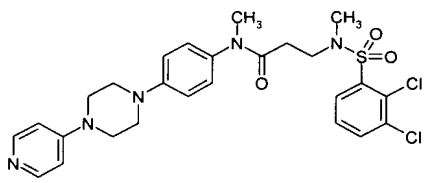
O exemplo 8 é preparado de maneira análoga a 1f a partir de 0,22 g (0,71 mmol) do produto de 1c, 0,16 g (0,71 mmol) do produto de 8b, 0,30 ml (2,13 mmols) de trietilamina e 0,23 g (0,71 mmol) de TBTU em 5,5 ml de tetrahidrofurano.

$C_{23}H_{30}Cl_2N_4O_3S \times 2C_2HF_3O_2$ (741,53)

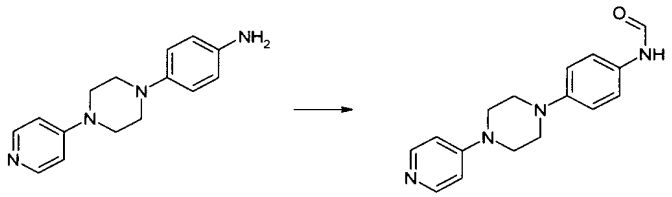
[M+H]+ = 513/515/517

HPLC (método 5): tempo de retenção = 1,46 min.

Exemplo 9



9a)

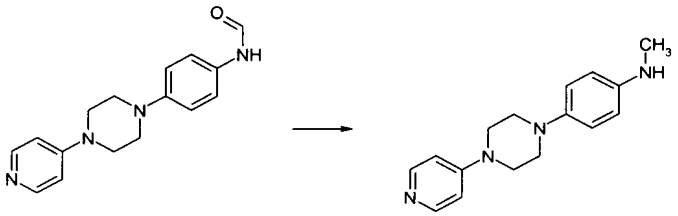


13 ml de anidrido de ácido acético são previamente introduzidos e lentamente adicionados a 8 ml de ácido fórmico. A mistura de reação é aquecida a 50°C por 1,5 horas e depois adicionada a 80 ml de diclorometano. Sob resfriamento com banho de gelo acrescentam-se, em seguida, 5,0 g (19,66 mmols). Agita-se por uma hora à temperatura ambiente e depois, concentra-se até a secura. O resíduo é adicionado à solução semi-saturada de bicarbonato de sódio e extraído duas vezes com diclorometano. Os extratos orgânicos são lavados com solução saturada de cloreto de sódio, secos sobre sulfato de sódio e concentrados à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/metanol/amoníaco 9:1:0,1).

$C_{16}H_{18}N_4O$ (282.34)

$[M+H]^+ = 283$

9b)

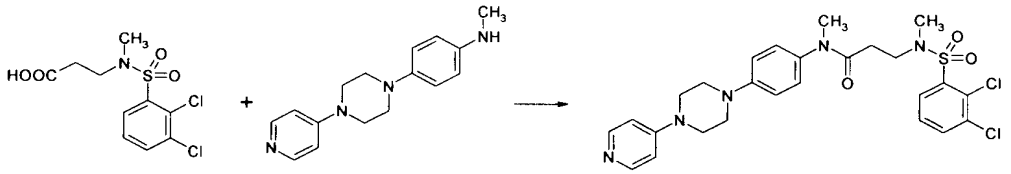


A 60°C, uma mistura de 10,63 ml de hidreto de lítioalumínio 2 M em tetrahidrofurano (21,25 mmols) e 50 ml de tetrahidrofurano é lentamente adicionada a 3,0 g (10,63 mmols) do produto de 9a. A mistura de reação é

agitada por oito horas a 60°C e por quatro horas à temperatura ambiente. Sob resfriamento em banho de gelo acrescentam-se, em seguida, 20 ml de água. Filtra-se sobre celite e lava-se posteriormente com tetrahidrofurano e diclorometano. O filtrado é concentrado à secura. O resíduo é adicionado a diclorometano, lavado com água e soda cáustica 1 N, seco sobre solução de sulfato de sódio e concentrado à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/metanol/amoníaco 9:1:0,1).

$C_{16}H_{20}N_4$ (268,36)

9c)



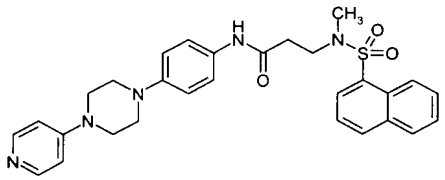
O exemplo 9 é preparado de maneira análoga a 1f a partir de 0,15 g (0,48 mmol) do produto de 1c, 0,14 g (0,51 mmol) do produto de 9b, 0,13 ml (0,96 mmol) de trietilamina e 0,19 g (0,51 mmol) de HATU em 5 ml de dimetilformamida.

$C_{26}H_{29}Cl_2N_5O_3S$ (562,51)

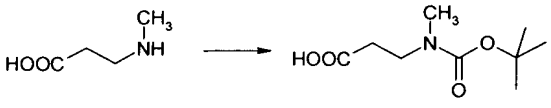
[M+H]+ = 562/564/566

HPLC (método 2): tempo de retenção = 2,86 min.

Exemplo 10



10a)



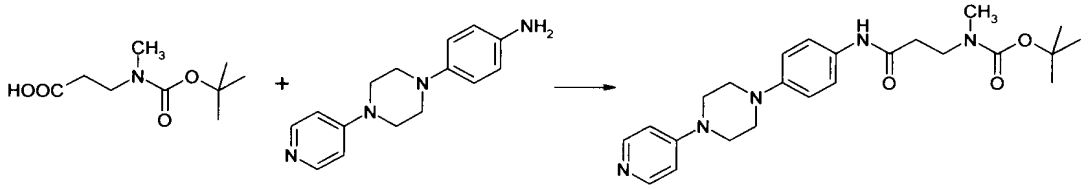
Uma mistura de 1,0 g (9,70 mmols) de N-metil-β-alanina (Convertex), 24 ml de dioxano, 12 ml de água e 2,68 g (19,38 mmols) de carbonato de potássio anidro é adicionada, sob resfriamento em banho de gelo, a

2,33 g (10,66 mmols) de anidrido boc. A mistura de reação é agitada à temperatura ambiente por 3 dias. Depois, o dioxano é removido no vácuo. O resíduo aquoso é extraído com acetato de etila (rejeitar as fases de acetato de etila), em seguida, é levemente acidificado com ácido clorídrico 1 M e depois extraído com diclorometano. Os extratos de diclorometano orgânicos são lavados com solução saturada de cloreto de sódio, secos sobre sulfato de sódio e concentrados à secura.

$C_9H_{17}NO_4$ (203,24)

[M+H]+ = 204

10b)



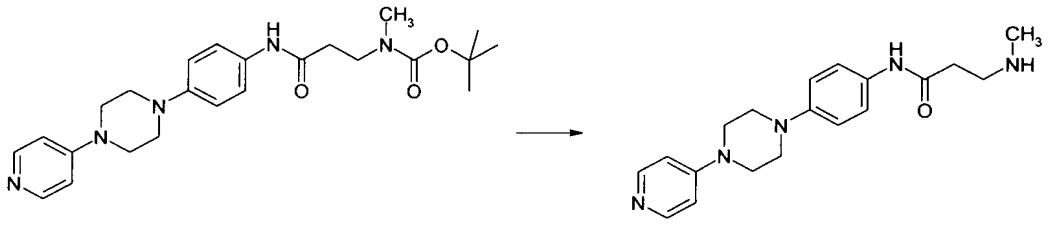
10b é preparado de maneira análoga a 1f a partir de 1,85 g (9,10 mmols) do produto de 10a, 2,32 g (9,10 mmols) do produto de 1e, 3,81 ml (27,31 mmols) de trietilamina e 2,92 g (9,10 mmols) de TBTU em 80 de dimetilformamida.

$C_{24}H_{33}N_5O_3$ (439.55)

[M+H]+ = 440

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,49.

10c)



Uma mistura de 3,20 g (7,28 mmols) do produto de 10b, 20 ml de TFA e 60 ml de diclorometano é agitada à temperatura ambiente por 30 minutos. Em seguida, a mistura de reação é concentrada no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometa-

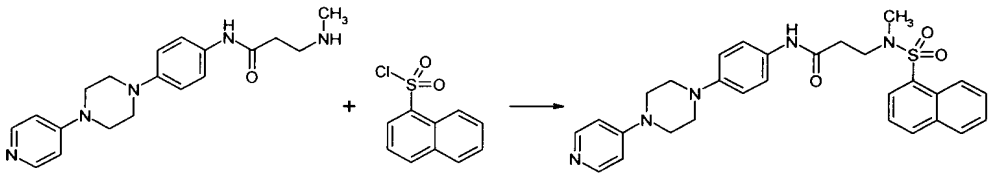
no/etanol/amoníaco 9:1:0,1 a 4:1:0,1).

$C_{19}H_{25}N_5O$ (339.43)

[M+H]+ = 340

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1 , valor Rf = 0,25.

10d)



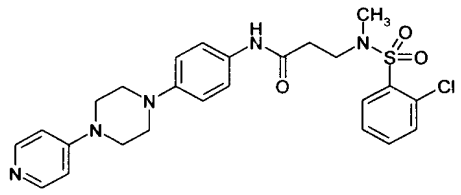
Uma mistura de 0,1 g (0,30 mmol) do produto de 10c, 0,056 g (0,25 mmol) de cloreto de ácido 1-naftil-sulfônico, 0,137 ml (0,98 mmol) de trietilamina e 5 ml de diclorometano é agitada à temperatura ambiente durante a noite. Em seguida, a mistura de reação é concentrada no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/etanol/amoníaco 12:1:0,1).

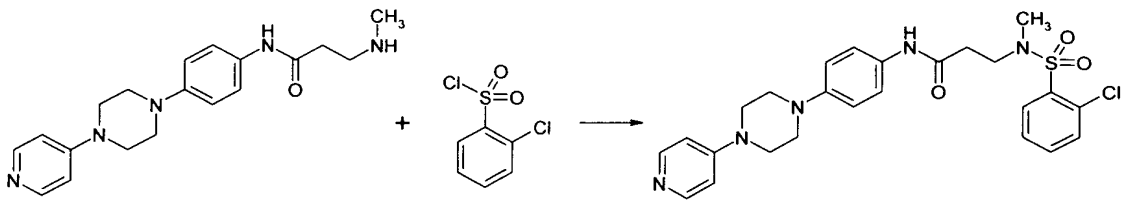
$C_{29}H_{31}N_5O_3S$ (529,65)

[M+H]+ = 530

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1 , valor Rf = 0,44.

Exemplo 11





O exemplo 11 é preparado de maneira análoga a 10d a partir de 0,10 g (0,30 mmol) do produto de 10c, 0,052 g (0,25 mmol) de cloreto de ácido 2-clorobenzenossulfônico, 0,14 ml (98 mmols) de trietilamina em 5 ml

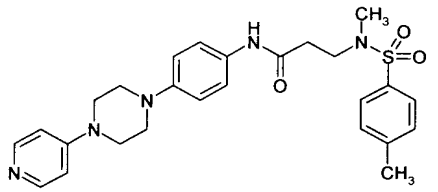
de diclorometano.

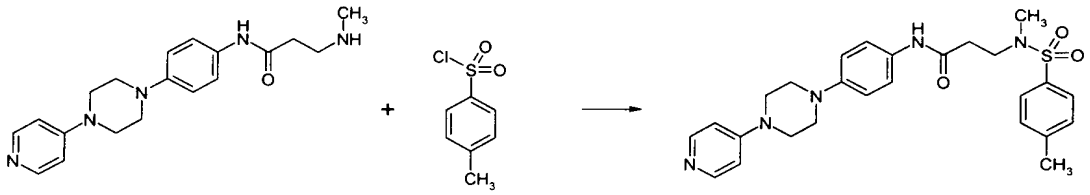
$C_{25}H_{28}ClN_5O_3S$ (514,04)

[M+H]+ = 514/516

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,47.

Exemplo 12





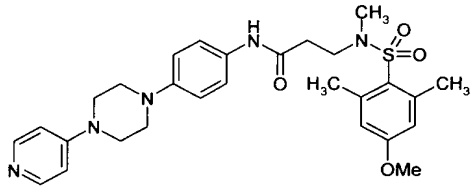
O exemplo 12 é preparado de maneira análoga a 10d a partir de 0,10 g (0,30 mmol) do produto de 10c, 0,047 g (0,25 mmol) de cloreto de ácido p-toluenossulfônico, 0,14 ml (98 mmols) de trietilamina em 5 ml de diclorometano.

$C_{26}H_{31}N_5O_3S$ (493,62)

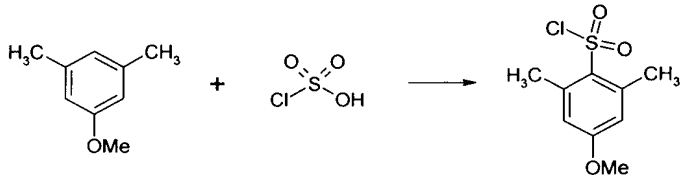
[M+H]+ = 494

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1 , valor Rf = 0,43.

Exemplo 13



13a)



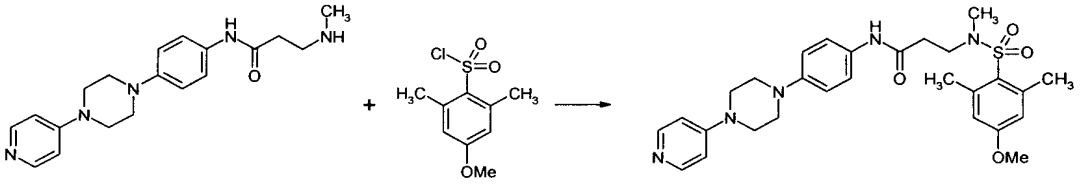
Uma mistura de 2,0 g (14,69 mmols) de 3,5-dimetilanisol e 20 ml de diclorometano é adicionada a 5,85 ml (88,0 mmols) de ácido clorossulfônico sob resfriamento com gelo. Em seguida, a mistura de reação é agitada por 20 minutos à temperatura ambiente e em seguida, vertida sobre 50 ml de água gelada. Extrai-se com 100 ml de diclorometano. Os extratos orgânicos são lavados com solução de bicarbonato de sódio a 5%, secos sobre sulfato de sódio e concentrados à secura.

$C_9H_{11}ClO_3S$ (234,70)

[M+H]+ = 234/236

DC: gel de sílica, éter de petróleo/acetato de etila 9:1, valor Rf = 0,46

13b)



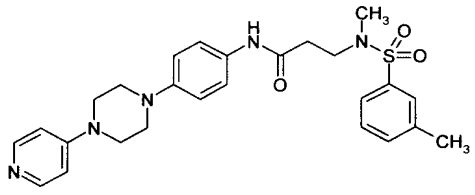
O exemplo 13 é preparado de maneira análoga a 10d a partir de 0,10 g (0,30 mmol) do produto de 10c, 0,058 g (0,25 mmol) do produto de 13a, 0,14 ml (98 mmols) de trietilamina em 5 ml de diclorometano.

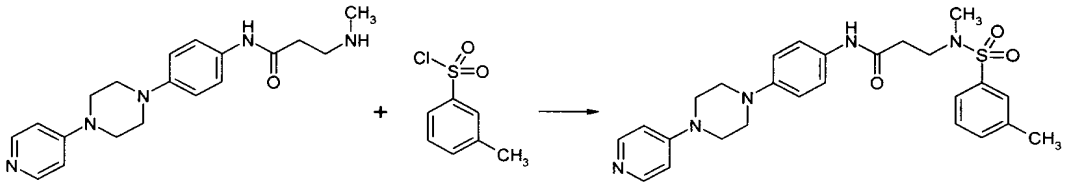
$C_{28}H_{35}N_5O_4S$ (537.67)

[M+H]+ = 538

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1 , valor Rf = 0,62.

Exemplo 14





O exemplo 14 é preparado de maneira análoga a 10d a partir de 0,10 g (0,30

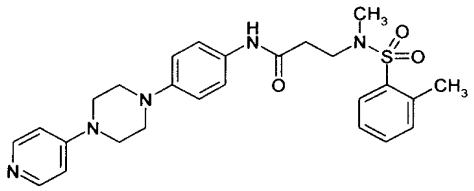
mmol) do produto de 10c, 0,047 g (0,25 mmol) de cloreto de ácido m-toluenossulfônico, 0,14 ml (98 mmols) de trietilamina em 5 ml de diclorometano.

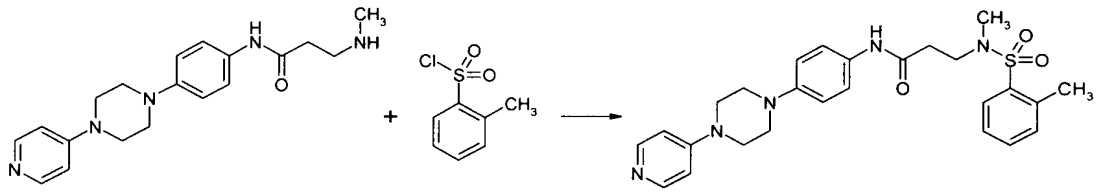
$C_{26}H_{31}N_5O_3S$ (493.62)

[M+H]+ = 494

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1 , valor Rf = 0,47.

Exemplo 15





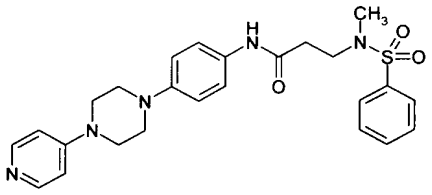
O exemplo 15 é preparado de maneira análoga a 10d a partir de 0,10 g (0,30 mmol) do produto de 10c, 0,047 g (0,25 mmol) de cloreto de ácido o-toluenossulfônico, 0,14 ml (98 mmols) de trietilamina em 5 ml de diclorometano.

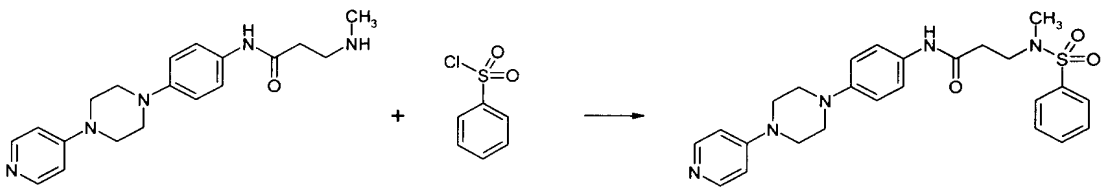
$C_{26}H_{31}N_5O_3S$ (493,62)

[M+H]+ = 494

HPLC (método 1): tempo de retenção = 2,37 min.

Exemplo 16





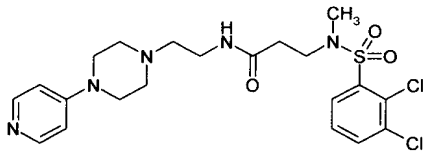
O exemplo 16 é preparado de maneira análoga a 10d a partir de 0,10 g (0,30 mmol) do produto de 10c, 0,043 (0,25 mmol) de cloreto de ácido benzenossulfônico, 0,14 ml (98 mmols) de trietilamina em 5 ml de diclorometano.

$C_{25}H_{29}N_5O_3S$ (479,60)

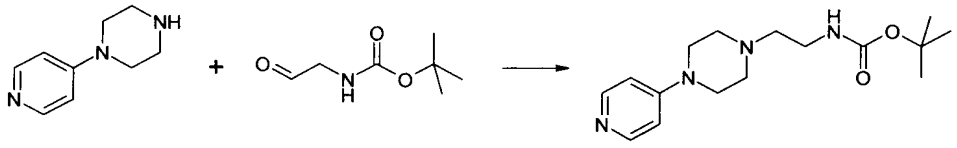
[M+H]+ = 480

HPLC (método 1): tempo de retenção = 2,40 min.

Exemplo 17



17a)

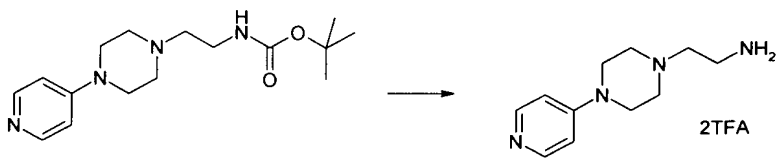


Uma mistura de 1,03 g (6,28 mmols) de 1-(4-piridil)-piperazina (Girindus) e 50 ml de diclorometano é adicionada a 1,0 g (6,28 mmols) de *terc*-butil-N-(2-oxoetil)-carbamato (Aldrich). A seguir, a mistura de reação é agitada à temperatura ambiente por 30 minutos, em seguida, adicionada a 2,66 g (12,56 mmols) de triacetoxiborohidreto de sódio sob resfriamento com gelo e depois, agitada à temperatura ambiente durante a noite. São acrescentados mais 60 l de diclorometano e a mistura de reação é lavada com solução saturada de bicarbonato de sódio e solução saturada de cloreto de sódio. A fase orgânica é seca sobre sulfato de sódio e concentrada à secura. O produto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/etanol/amoníaco 14:1:0,1 a 10:1:0,1).

$C_{16}H_{26}N_4O_2$ (306.40)

[M+H]+ = 307.

17b)



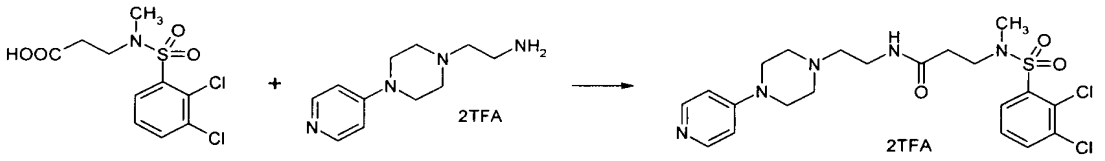
Uma mistura de 0,36 g (1,19 mmol) do produto de 17a, 1,19 ml (15,50 mmols) de TFA e 2 ml de diclorometano é agitada à temperatura ambiente por duas horas. A seguir, a mistura de reação é concentrada no vácuo à secura.

$C_{11}H_{18}N_4 \times 2C_2HF_3O_2$ (434.33)

[M+H]+ = 207

HPLC (método 2): tempo de retenção = 0,98 min.

17c)



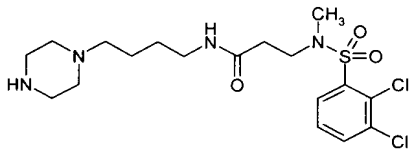
O exemplo 17 é preparado de maneira análoga a 1f a partir de 0,22 g (0,71 mmol) do produto de 1c, 0,34 g (0,78 mmol) do produto de 17b, 0,50 ml (3,56 mmols) de trietilamina e 0,23 g (0,71 mmol) de TBTU em 5,5 ml de tetrahidrofurano.

$C_{21}H_{27}Cl_2N_5O_3S \times 2C_2HF_3O_2$ (728.49)

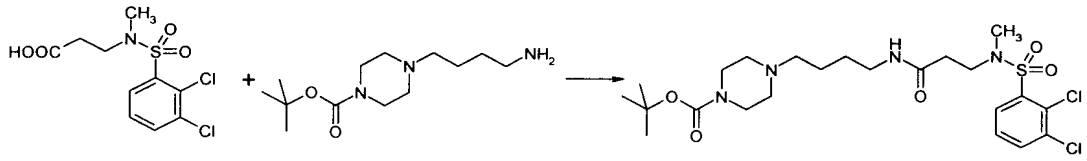
[M+H]+ = 500/502/504

HPLC (método 2): tempo de retenção = 3,14 min.

Exemplo 18



18a)



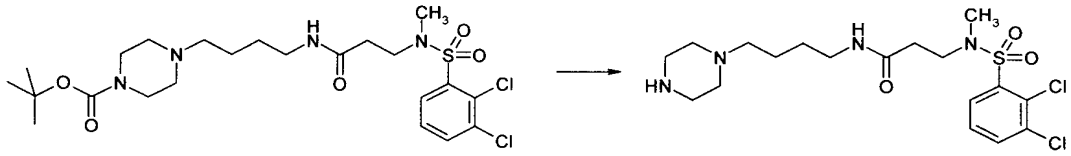
18a é preparado de maneira análoga a 1f a partir de 0,20 g (0,64 mmol) do produto de 1c, 0,17 g (0,64 mmol) de éster terc-butílico de ácido 4-(4-aminobutil)-piperazin-1-carboxílico (J. Med. Chem. 47, 2004, 4300-4315), 0,27 ml (1,92 mmol) de trietilamina e 0,21 g (0,64 mmol) de TBTU em 5 ml de tetrahidrofurano.

$C_{23}H_{36}CL_2N_4O_5S$ (551,53)

[M+H]+ = 551/553/555

DC: gel de sílica, diclorometano/metanol 30:1, valor Rf = 0,1

18b)



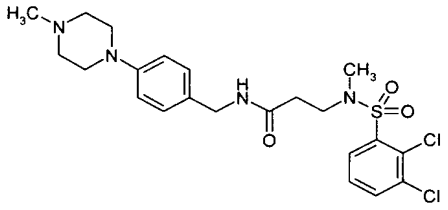
Uma mistura de 0,29 g (0,53 mmol) do produto de 18a, 0,53 ml de TFA e 1 ml de diclorometano é agitada à temperatura ambiente por duas horas. A mistura de reação é lavada com solução saturada de bicarbonato de sódio. Após a separação de fases, a fase aquosa ainda é extraída três vezes com diclorometano. Os extratos orgânicos são secos sobre sulfato de sódio e concentrados no vácuo à secura.

$C_{18}H_{28}Cl_2N_4O_3S$ (451.41)

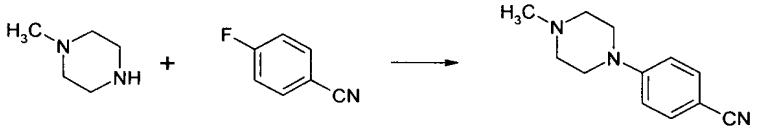
[M+H]+ = 451/453/455

HPLC (método 2): tempo de retenção = 2,22 min.

<u>Exemplo 19</u>



19a)



Uma mistura de 5,0 ml (45,13 mmols) de *N*-metilpiperazina e 0,73 g (6,00 mmols) de 4-fluorbenzonitrila (Aldrich) é aquecida a 80°C por 12

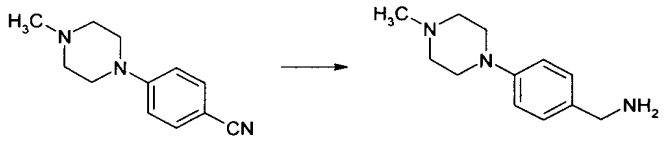
horas. A seguir, esta é concentrada até a secura e o resíduo é adicionado à água. Extrai-se três vezes com acetato de etila. Os extratos orgânicos são secos sobre sulfato de sódio e concentrados no vácuo à secura.

$C_{12}H_{15}N_3$ (201.27)

M+H]+ = 202

DC: gel de sílica, diclorometano/etanol 95:5, valor Rf = 0,31.

19b)

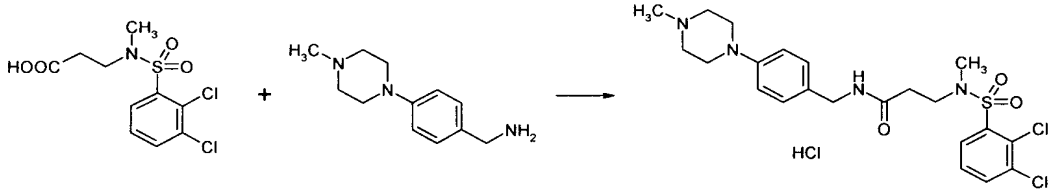


Uma mistura de 1,17 g (5,81 mmols) do produto de 19a, 0,3 g de níquel de Raney e 50 ml de solução metanólica de amoníaco é hidrogenada no autoclave a 50°C. A seguir, o catalisador é filtrado e o filtrado é concentrado no vácuo à secura.

$C_{12}H_{19}N_3$ (205,30)

[M+H]+ = 206.

19c)



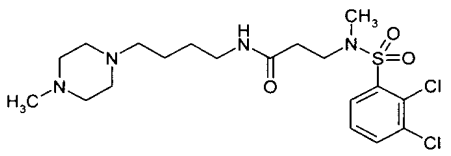
O exemplo 19 é preparado de maneira análoga a 1f a partir de 0,16 g (0,50 mmol) do produto de 1c, 0,10 g (0,50 mmol) do produto de 19b, 0,14 ml (1,00 mmol) de trietilamina e 0,16 g (0,50 mmol) de TBTU em 3 ml de dimetilformamida.

$C_{22}H_{28}Cl_2N_4O_3S$ x HCl (535.91)

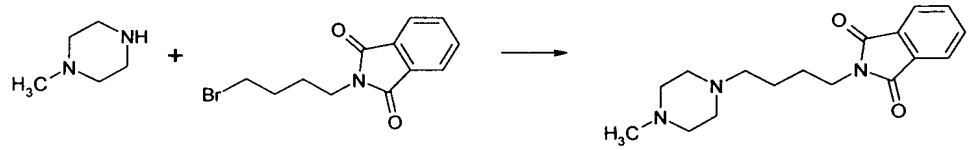
[M+H]+ = 499/501/503

HPLC (método 3): tempo de retenção = 3,49 min.

Exemplo 20



20a)

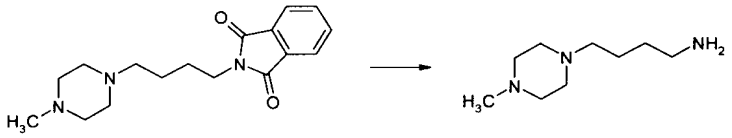


Uma mistura de 0,5 g (4,99 mmols) de *N*-metilpiperazina (Aldrich), 1,41 g (4,99 mmols) de N-(4-bromobutil-ftalimida (Fluka), 0,86 ml (4,99 mmols) de DIPEA e 9,3 ml de acetonitrila é aquecida no micro-ondas a 120°C por 45 minutos. A seguir, concentra-se à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/metanol 98:2).

$C_{17}H_{23}N_3O_2$ (301.38)

[M+H]+ = 302.

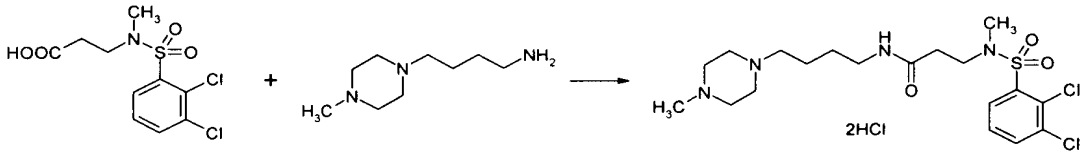
20b)



Uma mistura de 1,94 g (6,44 mmols) do produto de 20a, 1,61 g (25,75 mmols) de hidrato de hidrazina hidrato e 15 ml de etanol absoluto é aquecida no autoclave a 120°C por 5,5 horas. O precipitado formado é filtrado. A seguir, concentra-se o filtrado à secura.

$C_9H_{21}N_3$ (171,28)

20c)



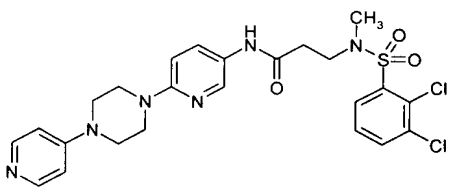
O exemplo 20 é preparado de maneira análoga a 1f a partir de 0,50 g (1,61 mmol) do produto de 1c, 0,55 g (3,22 mmols) do produto de 20b, 0,67 ml (4,83 mmols) de trietilamina e 0,52 g (1,61 mmol) de TBTU em 30 ml de dimetilformamida.

$C_{19}H_{30}Cl_2N_4O_3S$ x 2HCl (538.36)

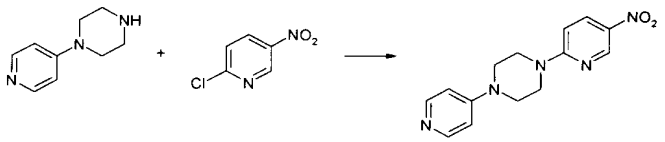
[M+H]+ = 465/467/469

HPLC (método 1): tempo de retenção = 2,15 min.

Exemplo 21



21a)



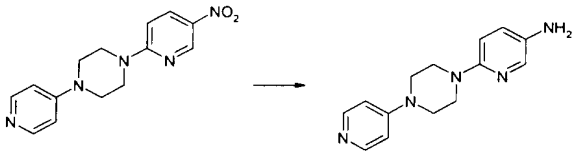
Uma mistura de 2,06 g (12,62 mmols) de 1-piridin-4-il-piperazina (Girindus), 2,00 g (12,62 mmols) de 2-cloro-5-nitropiridina (Fluka) e 50 ml de diclorometano é agitada à temperatura ambiente por 15 minutos e em seguida, adicionada a 6,31 ml (12,62 mmols) de soda cáustica 2 M. A mistura de reação é agitada à temperatura ambiente por 20 horas e depois, adicionada a 300 ml de diclorometano e 100 ml de solução de bicarbonato de sódio a 5%. Após a separação de fases, a fase orgânica é seca sobre sulfato de sódio e concentrada no vácuo à secura. O produto bruto é misturado com 100 ml de éter dietílico/etanol 2:1, filtrado e seco.

$C_{14}H_{15}N_5O_2$ (285.30)

$[M+H]^+ = 286$

DC: gel de sílica, diclorometano/etanol 9:1, valor Rf = 0,10

21b)



Uma mistura de 1,75 g (6,13 mmols) do produto de 21a, 0,4 g de paládio sobre carvão (10%), 100 ml de diclorometano e 50 ml de metanol é hidrogenada no autoclave à temperatura ambiente por cinco horas. Em seguida, o catalisador é aspirado e o filtrado é concentrado no vácuo à secura. O resíduo é misturado com 100 ml de éter dietílico/etanol 2:1 e aspirado. O produto bruto obtido dessa maneira é purificado por meio de cromatografia

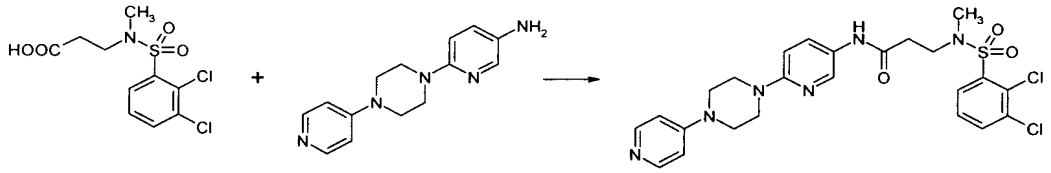
de coluna sobre gel de sílica (agente de eluição: diclorometano/metanol/amoníaco 95:5:0,5).

$C_{14}H_{17}N_5$ (255,32)

[M+H]+ = 256

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,37

21c)



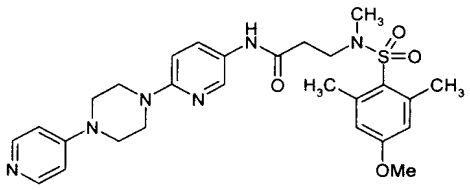
O exemplo 21 é preparado de maneira análoga a 1f a partir de 0,11 g (0,35 mmol) do produto de 1c, 0,089 g (0,35 mmol) do produto de 21b, 0,098 ml (0,70 mmol) de trietilamina e 0,13 g (0,42 mmol) de TBTU em 15 ml de tetrahidrofurano.

$C_{24}H_{26}Cl_2N_6O_3S$ (549.47)

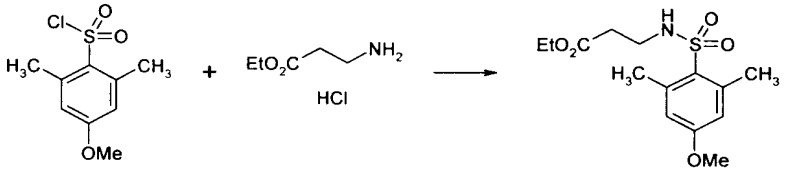
[M+H]+ = 549/551/553

HPLC (método 4): tempo de retenção = 2,7 min.

Exemplo 22



22a)



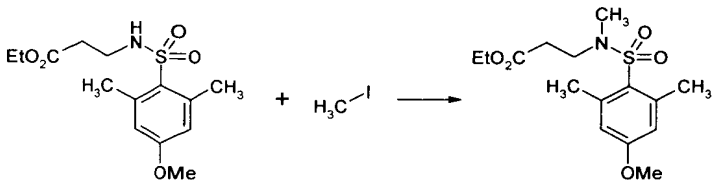
22a é preparado de maneira análoga a 3a a partir de 3,00 g (12,78 mmols) do produto de 13a, 2,16 g (14,06 mmols) de cloridrato de éster β-alanínico, 7,13 ml (51,13 mmols) de trietilamina em 70 ml de diclorometano.

$C_{14}H_{21}NO_5S$ (315.39)

[M+H]+ = 316

DC: gel de sílica, éter de petróleo/acetato de etila 2:1, valor Rf = 0,23.

22b)



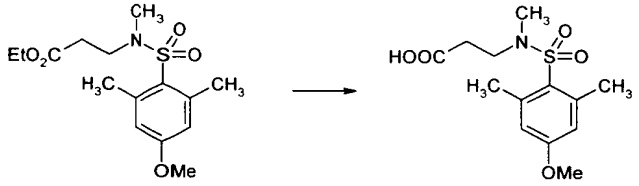
22 b é preparado de maneira análoga a 3b a partir de 4,06 g (12,87 mmols) do produto de 22a, 2,40 ml (38,62 mmols) de iodeto de metila, 3,56 g (25,75 mmols) de carbonato de potássio anidro em 40 ml de dimetilformamida.

$C_{15}H_{23}NO_5S$ (329.41)

[M+H]+ = 330

DC: gel de sílica, éter de petróleo/acetato de etila 2:1, valor Rf = 0,36.

22c)



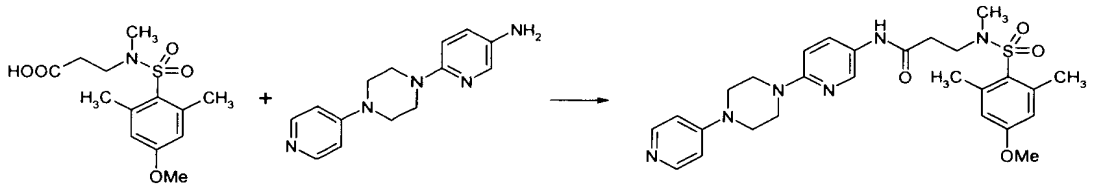
O ácido é preparado de maneira análoga a 1c a partir de 3,83 g (11,63 mmols) do produto de 22b, 2,44 g (58,13 mmols) de monohidrato de hidróxido de lítio em 30 ml de tetrahidrofurano e 30 ml de água.

$C_{13}H_{19}NO_5S$ (301.36)

[M+H]+ = 302

gel de sílica, éter de petróleo/acetato de etila 1:1, valor Rf = 0,12.

22d)



O exemplo 22 é preparado de maneira análoga a 1f a partir de 0,13 g (0,42 mmol) do produto de 22c, 0,089 g (0,35 mmol) do produto de

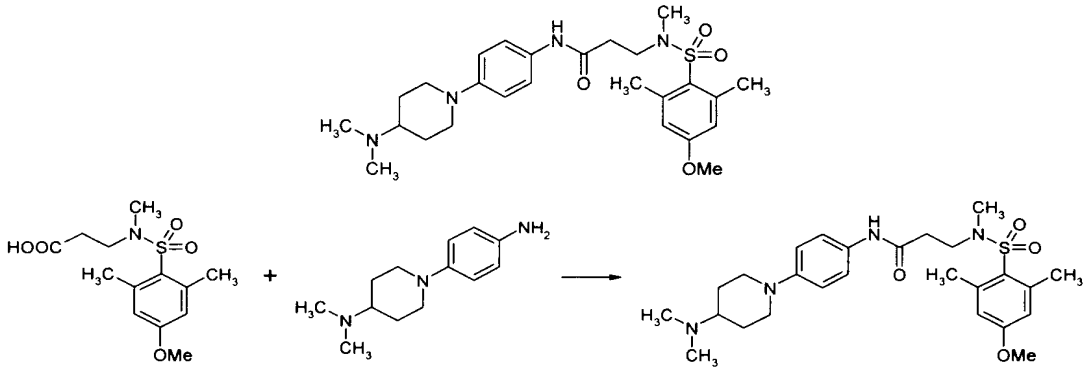
21b, 0,098 ml (0,70 mmol) de trietilamina e 0,13 g (0,42 mmol) de TBTU em 15 ml de tetrahidrofurano.

$C_{27}H_{34}N_6O_4S$ (538.66)

[M+H]+ = 539

HPLC (método 4): tempo de retenção = 2,6 min.

Exemplo 23



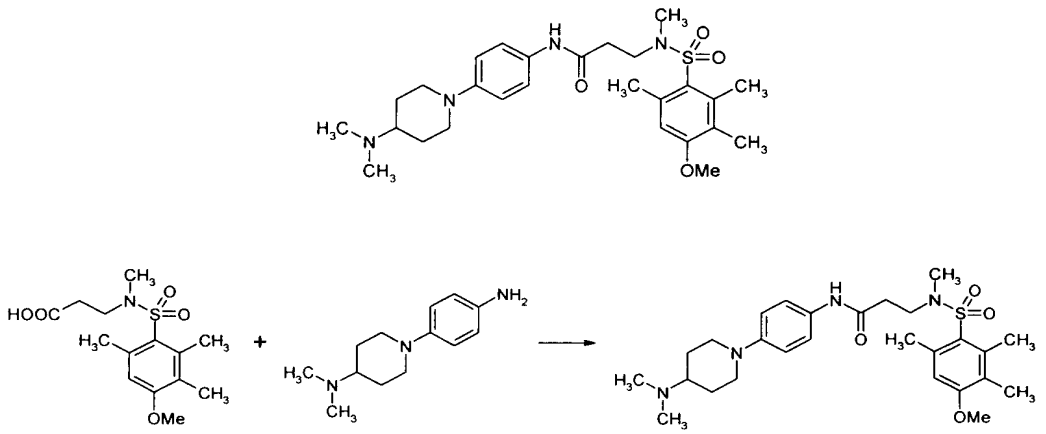
O exemplo 23 é preparado de maneira análoga a 1f a partir de 0,30 g (1,00 mmol) do produto de 22c, 0,22 g (1,00 mmol) do produto de 8b, 0,42 ml (2,99 mmols) de trietilamina e 0,32 g (1,00 mmol) de TBTU em 15 ml de dimetilformamida.

$C_{26}H_{38}N_4O_4S$ (502.67)

[M+H]+ = 503

HPLC (método 1): tempo de retenção = 2,47 min.

Exemplo 24



O exemplo 24 é preparado de maneira análoga a 1f a partir de 0,25 g (0,80 mmol) do produto de 3c, 0,18 g (0,80 mmol) do produto de 8b,

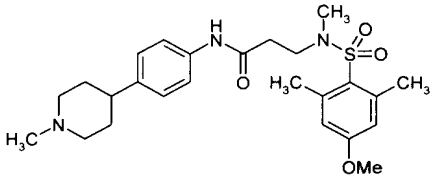
0,33 ml (2,39 mmols) de trietilamina e 0,26 g (0,80 mmol) de TBTU em 10 ml de dimetilformamida.

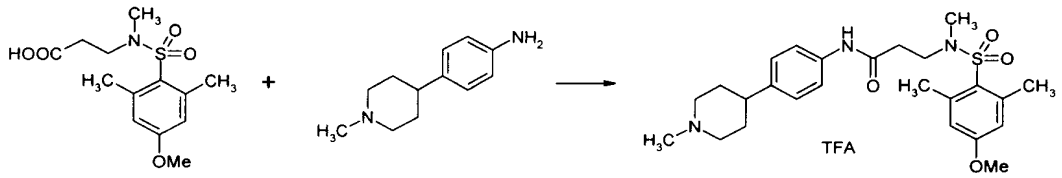
$C_{27}H_{40}N_4O_4S$ (516.70)

[M+H]+ = 517

HPLC (método 1): tempo de retenção = 2,50 min.

Exemplo 25





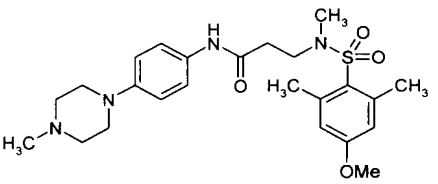
O exemplo 25 é preparado de maneira análoga a 1f a partir de 0,20 g (0,66 mmol) do produto de 22c, 0,14 g (0,73 mmol) de 4-(1-metilpiperidin-4-il)-anilina (JW Pharmlab), 0,28 ml (1,99 mmol) de trietilamina e 0,21 g (0,66 mmol) de TBTU em 50 ml de tetrahidrofurano.

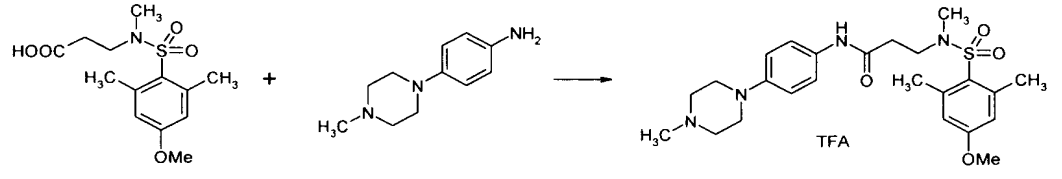
$C_{27}H_{40}N_4O_4S \times C_2HF_3O_2$ (587.65)

[M+H]+ = 474

HPLC (método 2): tempo de retenção = 3,03 min.

Exemplo 26





O exemplo 26 é preparado de maneira análoga a 1f a partir de

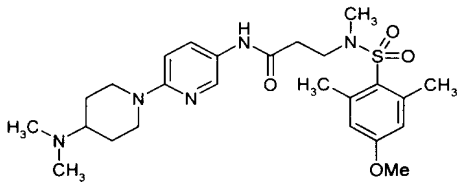
0,20 g (0,66 mmol) do produto de 22c, 0,14 g (0,73 mmol) de 4-(1-metilpiperidin-4-il)-anilina (J. Med. Chem. SIR 48, 7, 2005, 2371-2387), 0,28 ml (1,99 mmol) de trietilamina e 0,21 g (0,66 mmol) de TBTU em 5 ml de tetrahidrofurano.

$C_{24}H_{34}N_4O_4S \times C_2HF_3O_2$ (588.65)

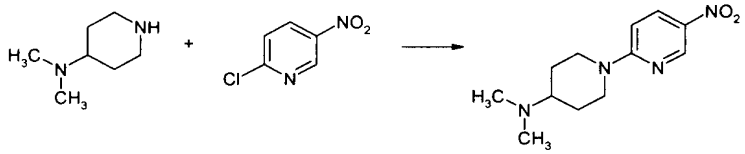
$[M+H]^+ = 475$

HPLC (método 5): tempo de retenção = 1,50 min.

Exemplo 27



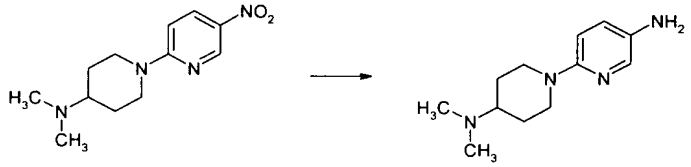
27a)



Uma mistura de 1,00 g (6,31 mmols) de 2-cloro-5-nitropiridina (Fluka), 1,32 ml (9,46 mmols) de trietilamina e 2 ml de metanol é previamente introduzida e lentamente adicionada a 1,13 g (8,83 mmols) de 4-dimetilamino-piperidina (Alfa Aesar). Em seguida, a solução de reação é bruscamente resfriada com cloreto de sódio semi-saturado, o precipitado formado é aspirado e seco.

$C_{12}H_{18}N_4O_2$ (250,30).

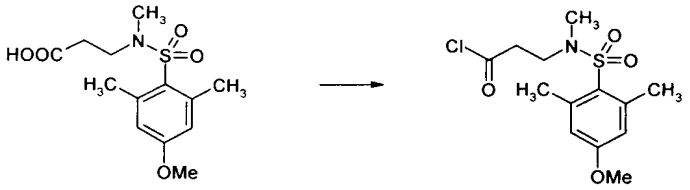
27b)



27b é preparado de maneira análoga a 8b a partir de 1,50 g (5,99 mmols) do produto de 27a, 0,20 g de paládio sobre carvão (10%) e 15 ml de metanol

$C_{12}H_{20}N_4$ (220,31).

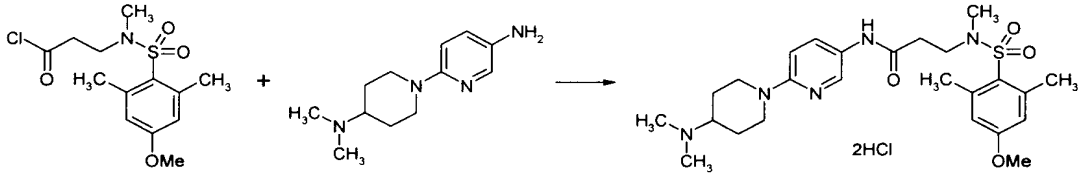
27c)



Uma mistura de 0,11 g (0,35 mmol) do produto de 22c e 2,0 ml de cloreto de tionila é agitada à temperatura ambiente por duas horas. A seguir, a mistura de reação é concentrada no vácuo à secura.

$C_{13}H_{18}ClNO_4S$ (319,81)

27d)



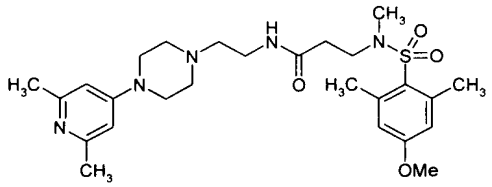
Uma mistura de 0,11 g (0,34 mmol) do produto de 27c, 0,091 g (0,41 mmol) do produto de 27b, 0,18 ml (1,03 mmol) de DIPEA e 45 ml de tetrahidrofurano é agitada à temperatura ambiente por duas horas. Em seguida, a mistura de reação é concentrada no vácuo à secura. O produto bruto é purificado por meio de HPLC preparatória. A seguir, o cloridrato é preparado com auxílio de HCl 4 M em dioxano.

$C_{25}H_{37}N_5O_4S$ x 2HCl (576.58)

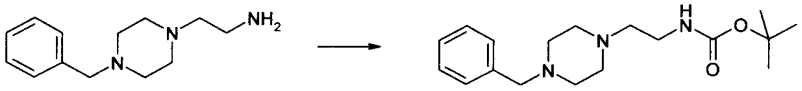
[M+H]+ = 504

HPLC (método 2): tempo de retenção = 2,73 min.

<u>Exemplo 28</u>



28a)



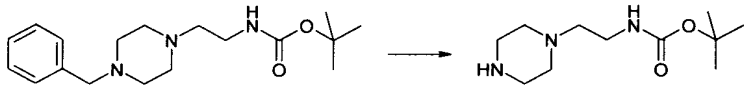
Uma mistura de 1,50 g (6,84 mmols) de 1-(2-aminoetil)-4-

benzilpiperazina (Maybridge), 1,64 g (7,52 mmols) de anidrido boc e 30 ml de diclorometano é agitada à temperatura ambiente por uma hora. Em seguida, a solução de reação é diluída com 100 ml de diclorometano e lavada com soda cáustica 1 M e água. A fase orgânica é seca sobre sulfato de sódio e concentrada no vácuo à secura.

$C_{18}H_{29}N_3O_2$ (319.44)

HPLC (método 4): tempo de retenção = 2,6 min.

28b)



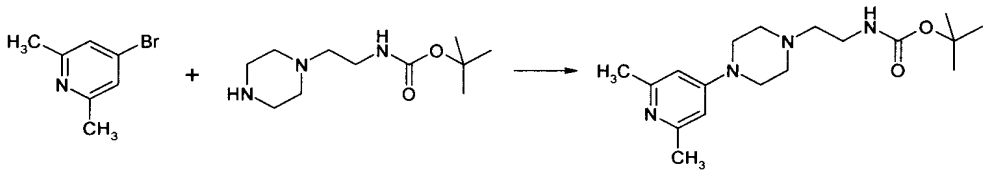
Uma mistura de 2,10 g (6,57 mmols) do produto de 28a, 0,25 g de paládio sobre carvão (10%) e 30 ml de metanol é hidrogenada no autoclave à temperatura ambiente por 15 horas. Em seguida, o catalisador é aspirado e o filtrado é concentrado no vácuo à secura.

$C_{11}H_{23}N_3O_4$ (229.32)

$[M+H]^+ = 230$

DC: gel de sílica, diclorometano/etanol 9:1, valor Rf = 0,08.

28c)



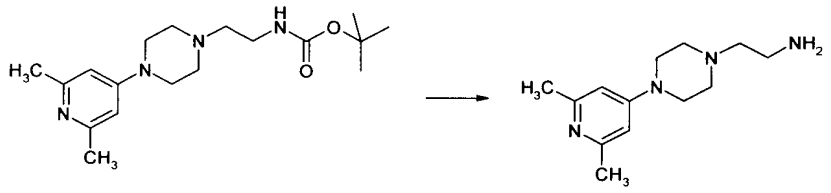
Uma mistura de 1,18 g (6,32 mmols) de 4-bromo-2,6-dimetilpiridina (Acta Chem. Scand. Ser. B 42, 1988, 373-377), 1,45 g (6,32 mmols) do produto de 28b e 2,2 ml de DIPEA é aquecida a 130°C no micro-ondas por 50 minutos. A mistura de reação é adicionada ao acetato de etila e solução semi-saturada de carbonato de potássio e em seguida, as fases são separadas. A fase orgânica é seca sobre sulfato de sódio e concentrada no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição): diclorometano/metanol/amoníaco 95:5:0,5).

$C_{18}H_{30}N_4O_2S$ (334.46)

[M+H]+ = 335

DC: diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,37.

28d)



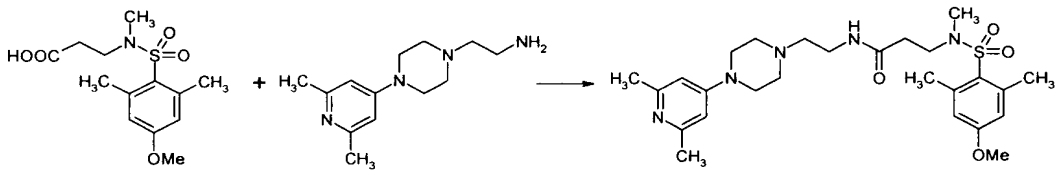
Uma mistura de 1,61 g (4,81 mmols) do produto de 28c, 3,70 ml de TFA e 30 ml de diclorometano é agitada à temperatura ambiente por seis horas. Em seguida, a mistura de reação é diluída com diclorometano e lavada com solução de bicarbonato de sódio a 5%. A fase aquosa ainda é extraída por duas vezes com acetato de etila. As fases orgânicas combinadas são secas sobre sulfato de sódio e concentradas no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/metanol/amoníaco 90:10:1).

$C_{13}H_{22}N_4$ (234.34)

[M+H]+ = 235

DC: gel de sílica, diclorometano /metanol/amoníaco 9:1:0,1, valor Rf = 0,10.

28e)



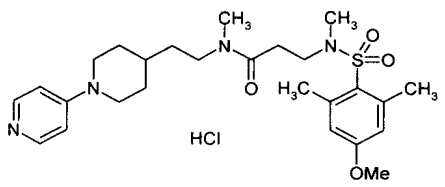
O exemplo 28 é preparado de maneira análoga a 1f a partir de 0,11 g (0,35 mmol) do produto de 22c, 0,082 g (0,35 mmol) do produto de 28d, 0,098 ml (0,70 mmol) de trietilamina e 0,13 g (0,42 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{26}H_{39}N_5O_4S$ (517.69)

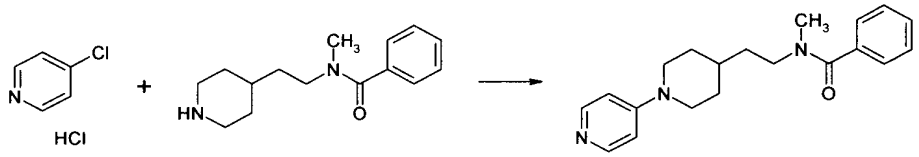
[M+H]+ = 518

HPLC (método 4): tempo de retenção = 2,4 min.

Exemplo 29



29a)

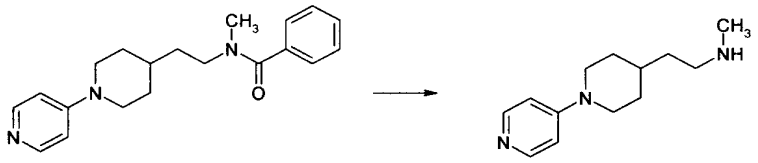


29a é preparado de maneira análoga a 28c a partir de 0,12 g (0,80 mmol) de cloridrato de 4-cloropiridina (Aldrich), 0,20 g (0,80 mmol) de N-metil-N-(2-piperidin-4-il-etil)-benzamida (J. Med. Chem. 33, 1990, 1880-1887), 0,23 ml (1,68 mmol) de trietilamina e 5 ml de etanol.

$C_{20}H_{25}N_3O$ (323.43)

[M+H]+ = 324

29b)



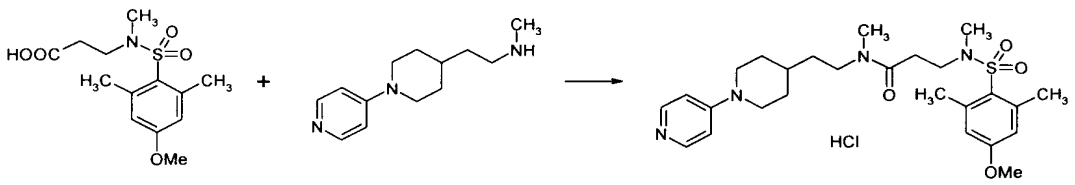
Uma mistura de 0,52 g (1,61 mmol) do produto de 29a, 10 ml de lixívia de potassa 2 M e 10 ml de etanol é aquecida sob refluxo por 30 horas. A mistura de reação é concentrada no vácuo até a metade e depois é extraída com diclorometano. Os extratos orgânicos são secos sobre sulfato de sódio e concentrados no vácuo à secura.

$C_{13}H_{21}N_3$ (219.33)

[M+H]+ = 220

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,01, valor Rf = 0,46.

29c)



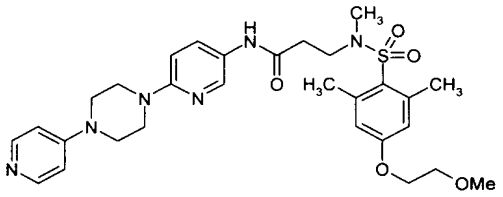
O exemplo 29 é preparado de maneira análoga a 1f a partir de 0,14 g (0,46 mmol) do produto de 22c, 0,10 g (0,46 mmol) do produto de 29b, 0,15 ml (1,09 mmol) de trietilamina e 0,16 g (0,50 mmol) de TBTU em 30 ml de tetrahidrofurano e 5 ml de dimetilformamida.

$C_{26}H_{38}N_4O_4S$ x HCl (539.13)

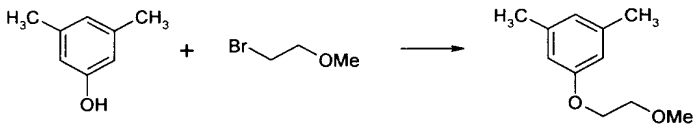
[M+H]+ = 503

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,01, valor Rf = 0,41.

Exemplo 30



30a)



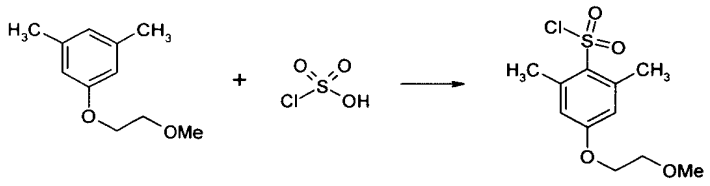
Uma mistura de 3,25 g (26,60 mmols) de 3,5-dimetilfenol (Aldrich), 3,20 g (28,52 mmols) de *terc*-butilato de potássio e 40 ml de dimetilsulfóxido é agitada à temperatura ambiente por uma hora. A seguir, gotejam-se 3,80 g (27,34 mmols) de éter bromoetilmetílico (Aldrich) e agita-se à temperatura ambiente por mais duas horas. A mistura de reação é vertida sobre água e extraída com éter dietílico. Os extratos orgânicos são lavados com água e solução saturada de cloreto de sódio, secos sobre sulfato de sódio e concentrados no vácuo à secura.

$C_{11}H_{16}O_2$ (180.24)

[M+H]+ = 181

DC: gel de sílica, éter de petróleo/acetato de etila 9:1, valor Rf = 0,31.

30b)

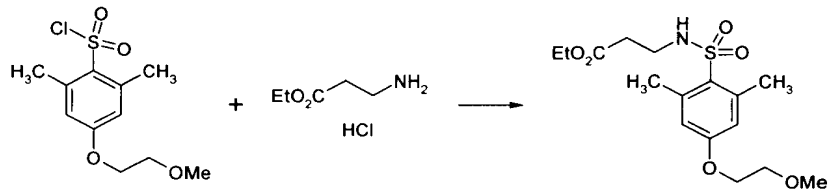


30b é preparado de maneira análoga a 13a a partir de 4,30 g (23,86 mmols) do produto de 30a e 5,60 g (48,06 mmols) de ácido clorossulfônico em 100 ml de diclorometano.

$C_{11}H_{15}ClO_4S$ (278.75)

DC: gel de sílica, éter de petróleo/acetato de etila 9:1, valor Rf = 0,06.

30c)



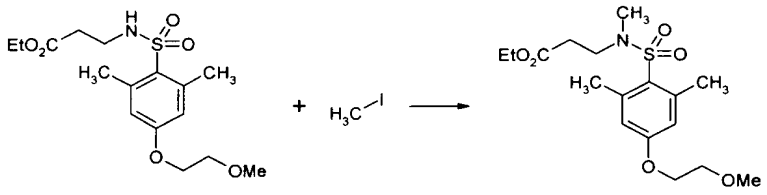
30a é preparado de maneira análoga a 3a a partir de 1,70 g (6,10 mmols) do produto de 30b, 1,20 g (7,81 mmols) de cloridrato de éster β-alanínico, 2,60 ml (18,65 mmols) de trietilamina em 30 ml de diclorometano.

$C_{16}H_{25}NO_6S$ (359.44)

[M+H]+ = 360

DC: gel de sílica, diclorometano/metanol 19:1, valor Rf = 0,51.

30d)

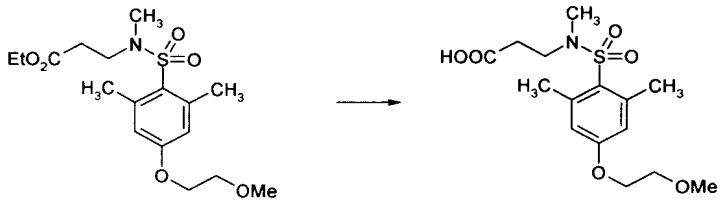


30d é preparado de maneira análoga a 3b a partir de 1,90 g (5,29 mmols) do produto de 30c, 1,10 g (7,75 mmols) de iodeto de metila, 1,50 g (10,85 mmols) de carbonato de potássio anidro em 30 ml de dimetilformamida.

$C_{17}H_{27}NO_6S$ (373.47)

[M+H]+ = 374.

30e)

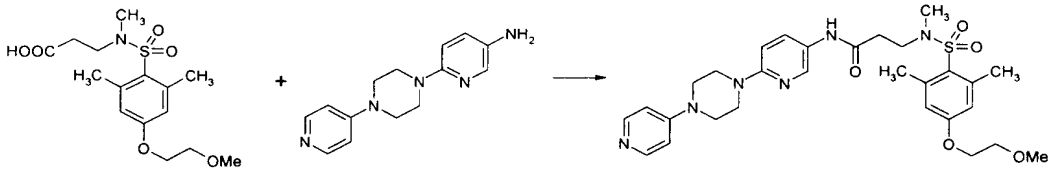


O ácido é preparado de maneira análoga a 1c a partir de 1,70 g (4,55 mmols) do produto de 30d, 0,80 g (20,00 mmols) de hidróxido de sódio em 30 ml de etanol e 10 ml de água.

$C_{15}H_{23}NO_6S$ (345.41)

[M+H]+ = 346

30f)



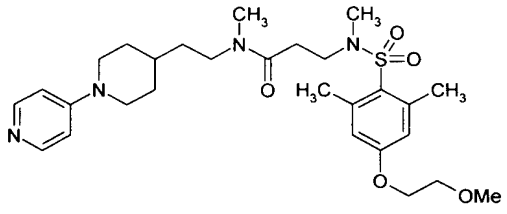
O exemplo 30 é preparado de maneira análoga a 1f a partir de 0,14 g (0,39 mmol) do produto de 30e, 0,10 g (0,39 mmol) do produto de 21b, 0,10 ml (0,99 mmol) de trietilamina e 0,14 g (0,44 mmol) de TBTU em 30 ml de tetrahidrofurano e 5 ml de dimetilformamida.

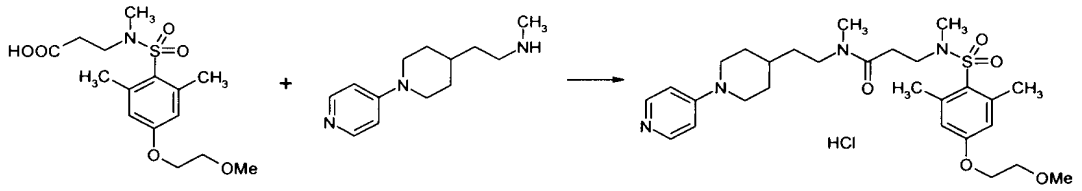
$C_{29}H_{38}N_6O_5S$ (582.72)

[M+H]+ = 583

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,01, valor Rf = 0,44.

Exemplo 31





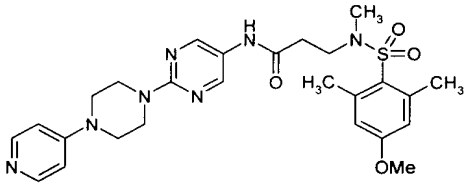
O exemplo 31 é preparado de maneira análoga a 1f a partir de 0,16 g (0,46 mmol) do produto de 30e, 0,10 g (0,46 mmol) do produto de 29b, 0,11 ml (1,09 mmol) de trietilamina e 0,16 g (0,50 mmol) de TBTU em 30 ml de tetrahidrofurano e 5 ml de dimetilformamida.

$C_{28}H_{42}N_4O_5S$ x HCl (583.18)

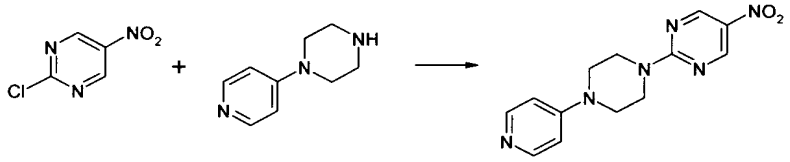
[M+H]+ = 547

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,01, valor Rf = 0,52.

Exemplo 32



32a)



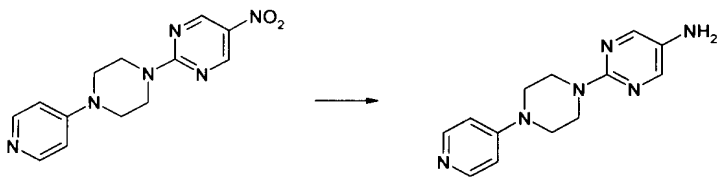
Uma mistura de 3,00 g (18,81 mmols) de 2-cloro-5-nitropirimidina (Apin), 3,07 g (18,81 mmols) de 1-(4-piridil)-piperazina (Girindus), 9,40 ml (18,81 mmols) de soda cáustica 2 M em 80 l de diclorometano é agitada à temperatura ambiente por 2,5 horas. A seguir, a mistura de reação é diluída com 100 ml de diclorometano e lavada com solução de bicarbonato de sódio a 5%. A fase orgânica é seca sobre sulfato de sódio e concentrada no vácuo à secura. O produto bruto é triturado com uma mistura de 50 ml de água e 30 ml de acetato de etila, filtrado e seco.

$C_{13}H_{14}N_6O_2$ (286.29)

[M+H]+ = 287

HPLC (método 4): tempo de retenção = 2,6 min.

32b)



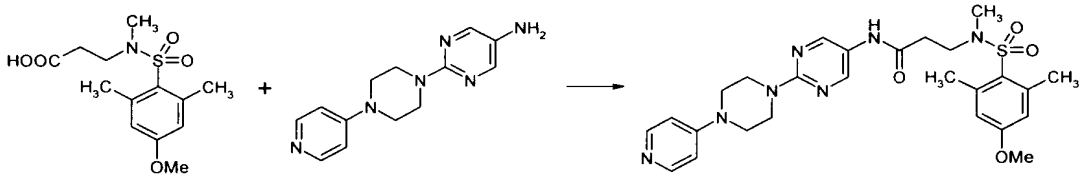
32 b é preparado de maneira análoga a 21b a partir de 1,93 g (6,74 mmols) do produto de 32a e 0,3 g de paládio sobre carvão (10%) em 60 ml de diclorometano e 30 ml de metanol.

$C_{13}H_{16}N_6$ (256.31)

[M+H]+ = 257

DC: gel de sílica, diclorometano/metanol 8:2, valor Rf = 0,11.

32c)



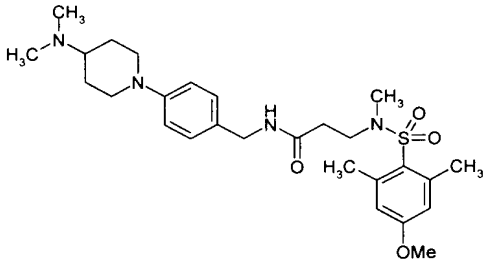
O exemplo 32 é preparado de maneira análoga a 1f a partir de 0,11 g (0,35 mmol) do produto de 22c, 0,090 g (0,35 mmol) do produto de 32b, 0,098 ml (0,70 mmol) de trietilamina e 0,13 g (0,42 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{26}H_{33}N_7O_4S$ (539.65)

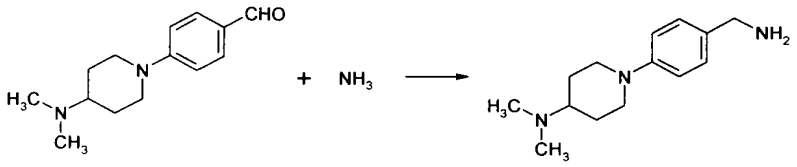
[M+H]+ = 540

HPLC (método 4): tempo de retenção = 2,9 min.

Exemplo 33



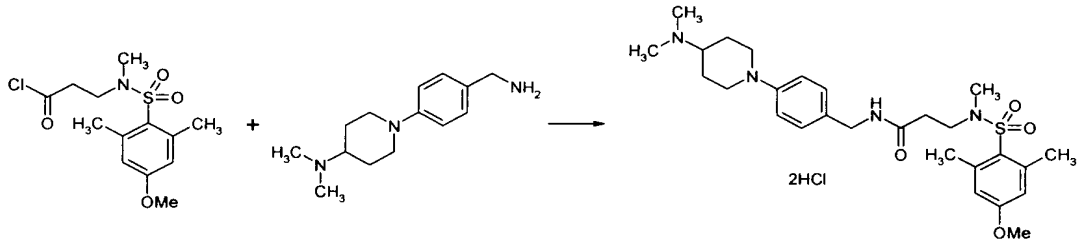
33a)



Uma mistura de 0,68 g (2,91 mmols) de 4-(4-dimetilamino-piperidin-1-il)-benzaldeído (Tetrahedron 57, 2001, 4781-4785), 15 ml de amoníaco 2 M em etanol e 0,10 g de níquel de Raney é hidrogenada no autoclave à temperatura ambiente. A seguir, o catalisador é filtrado e o filtrado concentrado no vácuo à secura.

$C_{14}H_{23}N_3$ (233,35).

33b)



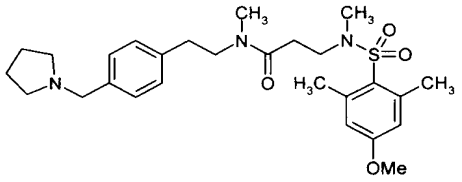
O exemplo 33 é preparado de maneira análoga a 27d a partir de 0,27 g (0,84 mmol) do produto de 27c, 0,63 g (2,68 mmols) do produto de 33a, 0,22 ml (1,26 mmol) de DIPEA em 3 ml de diclorometano.

$C_{27}H_{40}N_4O_4S$ x 2HCl (589.62)

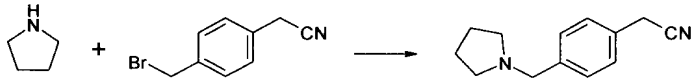
[M+H]+ = 517

HPLC (método 5): tempo de retenção = 1,46 min.

Exemplo 34



34a)



Uma mistura de 4,97 ml (59,50 mmols) de pirrolidina e 100 ml de

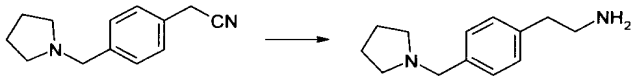
diclorometano é lentamente adicionada a 5,00 g (23,80 mmols) de (4-bromometil-fenil)-acetonitrila sob resfriamento com banho de gelo (Tetrahedron 47, 1991, 3969-3980). A seguir, a mistura de reação é aquecida à temperatura ambiente, lavada com água, seca sobre sulfato de magnésio e concentrada no vácuo à secura.

$C_{13}H_{16}N_2$ (200.28)

[M+H]+ = 201

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,58

34b)

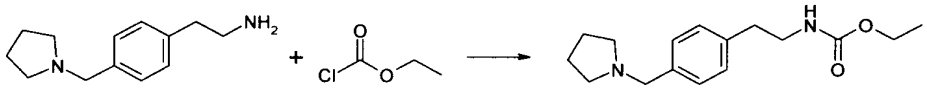


Uma mistura de 4,70 g (23,47 mmols) do produto de 34a, 0,5 g de níquel de Raney e 50 ml de solução metanólica de amoníaco é hidrogenada no autoclave a 50°C. Em seguida, o catalisador é filtrado e o filtrado é concentrado no vácuo à secura.

$C_{13}H_{20}N_2$ (204.31)

[M+H]+ = 205

34c)

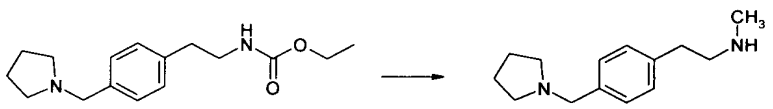


Uma mistura de 4,09 g (20,00 mmols) do produto de 34b, 5,62 ml (40,00 mmols) de trietilamina e 100 ml de diclorometano é lentamente adicionada a 2,17 ml (22,00 mmols) de éster etílico de ácido clorofórmico sob resfriamento com gelo (Aldrich). A seguir, agita-se à temperatura ambiente por cinco horas. Em seguida, a mistura de reação é bruscamente resfriada com água e extraída com éter MTB. Os extratos orgânicos são lavados duas vezes com água, secos sobre sulfato de magnésio e concentrados no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/metanol/amoníaco 9:1:0,1).

$C_{16}H_{24}N_2O_2$ (276.37)

[M+H]+ = 277

34d)

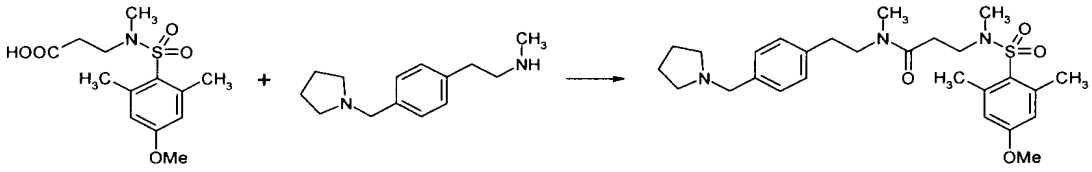


Uma mistura de 3,60 g (13,03 mmols) do produto de 34c e 25 ml de tetrahidrofurano é lentamente adicionada a 51,05 ml (51,05 mmols) de hidreto de lítioalumínio 1 M em tetrahidrofurano (Aldrich). A seguir, agita-se à temperatura ambiente por duas horas e a 70°C por duas horas. Em seguida, a mistura de reação é bruscamente resfriada com água e soda cáustica 15% e agitada por mais uma hora à temperatura ambiente. O precipitado formado é filtrado e o filtrado é concentrado no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/metanol/amoníaco 9:1:0,1).

$C_{14}H_{22}N_2$ (218.34)

[M+H]+ = 219

34e)



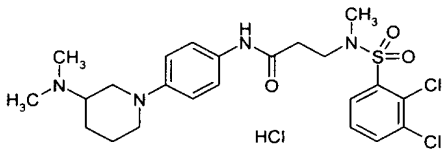
O exemplo 34 é preparado de maneira análoga a 1f a partir de 0,11 g (0,35 mmol) do produto de 22c, 0,076 g (0,35 mmol) do produto de 34d, 0,098 ml (0,70 mmol) de trietilamina e 0,13 g (0,42 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{27}H_{39}N_3O_4S$ (501.68)

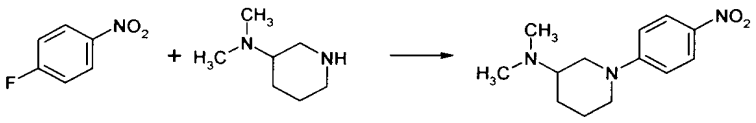
[M+H]+ = 502

HPLC (método 4): tempo de retenção = 3,1 min.

<u>Exemplo 35</u>



35a)



Uma mistura de 0,33 g (2,34 mmols) de 1-flúor-4-nitrobenzeno (Aldrich), 0,30 g (2,34 mmols) de 3-dimetilamino-piperidina (Chess), 0,46 ml (3,27 mmols) de trietilamina e 4 ml de dimetilformamida é agitada à temperatura ambiente por seis horas. A seguir, a mistura de reação é bruscamente resfriada com água e extraída com diclorometano. Os extratos orgânicos são lavados com solução saturada de cloreto de sódio, secos sobre sulfato de sódio e concentrados no vácuo à secura.

$C_{13}H_{19}N_3O_2$ (249.31)

[M+H]+ = 250

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,56.

35b)

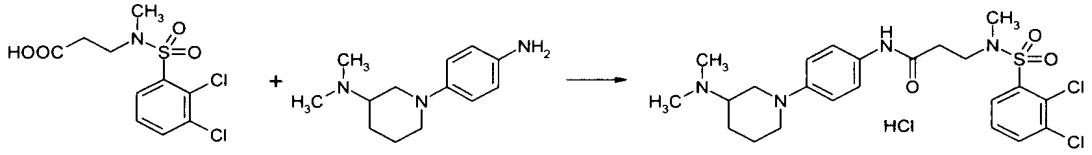


Uma mistura de 0,25 g (1,00 mmol) do produto de 35a, 30 mg de níquel de Raney e 10 ml de acetato de etila é hidrogenada no autoclave à temperatura ambiente. O catalisador é filtrado e o filtrado é concentrado no vácuo à secura.

$C_{13}H_{21}N_{13}$ (219,33)

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,25.

35c)



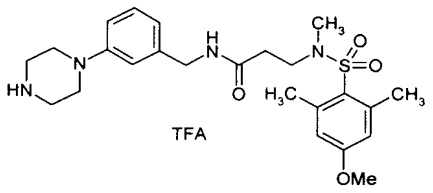
O exemplo 35 é preparado de maneira análoga a 1f a partir de 0,16 g (0,50 mmol) do produto de 1c, 0,11 g (0,50 mmol) do produto de 35b, 0,14 ml (1,00 mmol) de trietilamina e 0,16 g (0,50 mmol) de TBTU em 3 ml de dimetilformamida.

$C_{23}H_{30}Cl_2N_4O_3S$ x HCl (539.14)

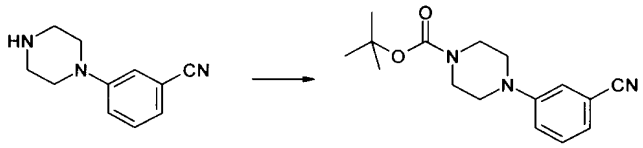
[M+H]+ = 513/515/517

HPLC (método 1): tempo de retenção = 2,43 min.

Exemplo 36



36a)

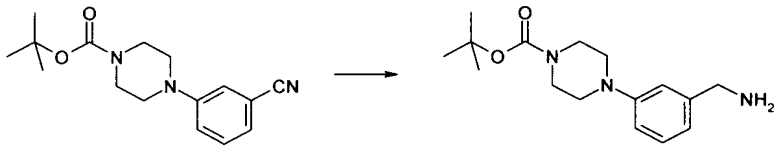


Uma mistura de 2,50 (13,35 mmols) de 3-piperazin-1-il-benzonitrila (Tetrahedron 55, 1999, 13285-13300), 3,00 g (13,75 mmols) de anidrido boc, 2,40 ml (13,78 mmols) de DIPEA e 50 ml de tetrahidrofurano é agitada à temperatura ambiente por quatro horas e depois concentrada no vácuo à secura. O resíduo é retomado em água e extraído com éter dietílico. Os extratos orgânicos são secos sobre sulfato de sódio e concentrados no vácuo à secura.

$C_{16}H_{21}N_3O_2$ (287,36)

[M+H]+ = 310

36b)

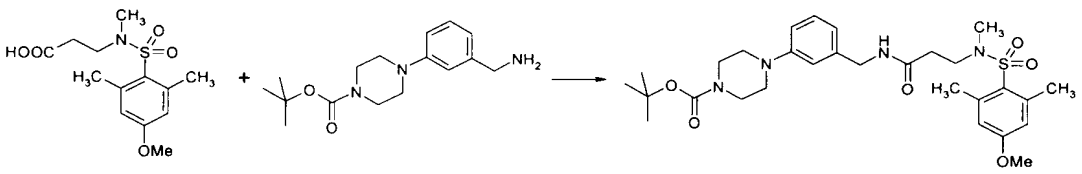


36 b é preparado de maneira análoga a 34b a partir de 4,40 g (15,31 mmols) do produto de 36a, 0,7 g de níquel de Raney e 45 ml de solução metanólica de amoníaco.

$C_{16}H_{25}N_3O_2$ (291.39)

[M+H]+ = 292

36c)



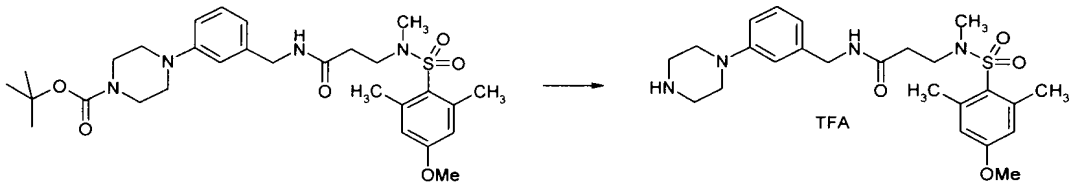
36 c é preparado de maneira análoga a 1f a partir de 0,40 g (1,3 mmol) do produto de 22c, 0,43 g (1,46 mmol) do produto de 36b, 0,56 ml (3,98 mmols) de trietilamina e 0,43 g (1,33 mmol) de TBTU em 10 ml de tetrahidrofurano.

$C_{29}H_{42}N_4O_6S$ (574.73)

[M+H]+ = 575

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,53.

36d)



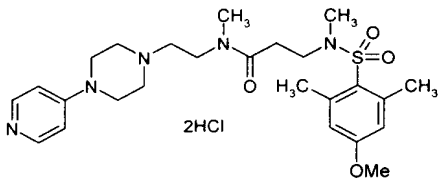
O exemplo 36 é preparado de maneira análoga a 18b a partir de 0,50 g (0,57 mmol) do produto de 36c, 0,44 ml de TFA em 5 ml de diclorometano.

$C_{18}H_{28}Cl_2N_4O_3S \times C_2HF_3O_2$ (588.64)

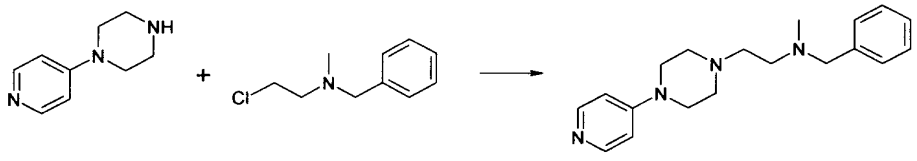
[M+H]+ = 475

HPLC (método 2): tempo de retenção = 2,95 min.

<u>Exemplo 37</u>



37a)



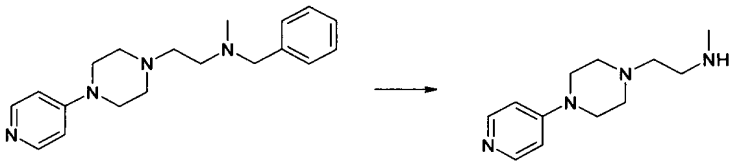
Uma mistura de 2,00 g (12,25 mmols) de 1-(4-piridil)-piperazina (Girindus), 1,65 g (14,70 mmols) de terc.-butilato de potássio e 50 ml de dimetilsulfóxido é agitada à temperatura ambiente por 30 minutos e a seguir, adicionada a 2,25 g (12,25 mmols) de 1-benzilmetilamino-2-cloretano (Chem. Pharm. Bull. 45, 1997, 996-1007). A mistura de reação é agitada à temperatura ambiente durante a noite e em seguida, vertida sobre água gelada. Extrai-se quatro vezes com diclorometano. Os extratos orgânicos são secos sobre sulfato de sódio e concentrados no vácuo à secura. O produto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/metanol/amoníaco 9:1:0,1).

$C_{19}H_{26}N_4$ (310.44)

[M+H]+ = 311

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,22.

37b)



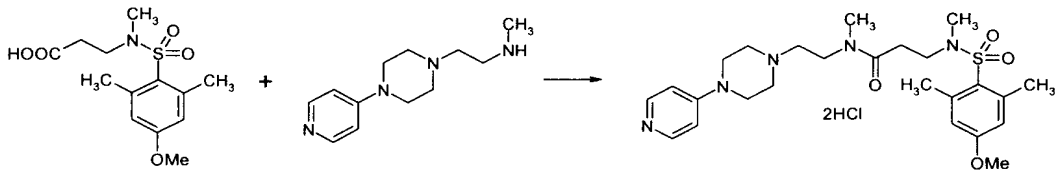
Uma mistura de 1,78 g (5,73 mmols) do produto de 37a, 0,40 g de hidróxido de paládio e 50 ml de metanol é hidrogenada no autoclave a 40°C. O catalisador é filtrado e o filtrado é concentrado no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/metanol/amoníaco 9:1:0,1).

$C_{12}H_{20}N_4$ (220.31)

[M+H]+ = 221

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,13.

37c)



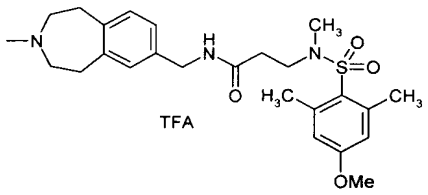
O exemplo 37 é preparado de maneira análoga a 1f a partir de 0,11 g (0,35 mmol) do produto de 22c, 0,072 g (0,35 mmol) do produto de 37b, 0,098 ml (0,70 mmol) de trietilamina e 0,13 g (0,42 mmol) de TBTU em 7 ml de tetrahidrofurano.

$C_{25}H_{37}N_5O_4S$ x 2HCl (576.58)

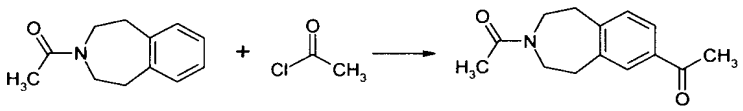
[M+H]+ = 504

HPLC (método 4): tempo de retenção = 2,5 min.

Exemplo 38



38a)

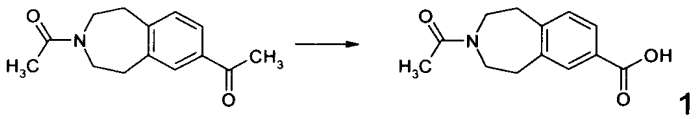


Uma mistura de 4,44 g (33,29 mmols) de cloreto de alumínio (Merck) e 16 ml de diclorometano é previamente introduzida e lentamente adicionada a 1,24 ml (17,44 mmols) de cloreto de acetila sob resfriamento com gelo (Aldrich). Deixa-se agitar à temperatura ambiente por 30 minutos. Em seguida, acrescentam-se lentamente 3,00 g (15,85 mmols) de 1-(1,2,4,5-tetrahidrobenzo[d]azepin-3-il)-etanona (J. Med. Chem. 46, 2003, 4952-4964) à mistura de reação em 7 ml de diclorometano. Após agitar por duas horas à temperatura ambiente, a mistura de reação é vertida em uma mistura de HCl 6 M e gelo. Após a separação de fases, a fase aquosa ainda é extraída três vezes com diclorometano. As fases orgânicas combinadas são lavadas com água, secas sobre sulfato de sódio e concentradas no vácuo à secura. O produto bruto obtido dessa maneira é triturado com éter dietílico, filtrado e seco.

$C_{14}H_{17}NO_2$ (231,29)

[M+H]+ = 232

38b)



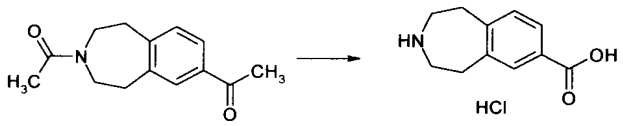
1

Uma mistura de 2,86 g (12,37 mmols) do produto de 38a e 79 ml de soda cáustica 2,5 M é lentamente adicionada a 2,48 ml (48,23 mmols) de bromo à temperatura ambiente. A seguir, a mistura de reação é agitada à temperatura ambiente por uma hora. O precipitado formado é filtrado e o filtrado é extraído com éter MTB. A seguir, a fase aquosa é adicionada, sob resfriamento com gelo, a HCl concentrado e pouca solução de dissulfeto de sódio. O precipitado formado é filtrado e seco na estufa de ar circulante a 30°C.

$C_{13}H_{15}NO_3$ (233,26)

[M+H]+ = 234.

38c)

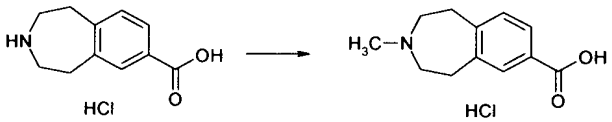


Uma mistura de 2,12 g (9,09 mmols) do produto de 38b e 20 ml de HCl 6 M é aquecida a 100°C por 3,5 dias. A seguir, a mistura de reação é resfriada com uma mistura de gelo e etanol. O precipitado formado é filtrado, lavado com pouca acetona resfriada e éter dietílico e seco no dessecador.

$C_{11}H_{13}NO_2$ x HCl (227.69)

[M+H]+ = 192

38d)



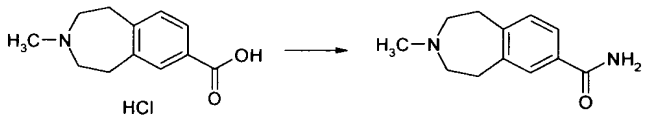
Uma mistura de 2,03 g (8,92 mmols) do produto de 38c e 3,36 ml (89,16 mmols) de ácido fórmico é inicialmente lentamente adicionada a 0,94 ml (17,83 mmols) de soda cáustica a 50%, depois a 2,66 ml (35,66 mmols) de solução de formalina a 37%. A mistura de reação é aquecida a 70°C por duas horas e depois é concentrada no vácuo à secura. O resíduo é

adicionado à água e HCl concentrado e novamente concentrado à secura. O produto bruto é triturado com um pouco de água gelada, filtrado e seco a 60°C na estufa de secagem de ar circulante.

$C_{12}H_{15}NO_2$ x HCl (241.71

[M+H]+ = 206

38e)



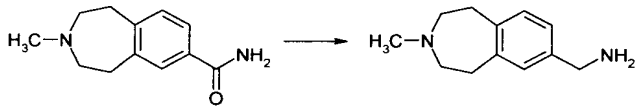
38e é preparado de maneira análoga a 1f a partir de 2,00 g (8,27 mmols) do produto de 38d, 18,20 ml (9,10 mmols) de amoníaco 0,5 M em dioxano (Aldrich), 3,46 ml (24,82 mmols) de trietilamina e 3,19 g (9,93 mmols) de TBTU em 30 ml de tetrahidrofurano.

$C_{12}H_{16}N_2O$ (204.27)

[M+H]+ = 205

HPLC (método 2): tempo de retenção = 1,54 min.

38f)



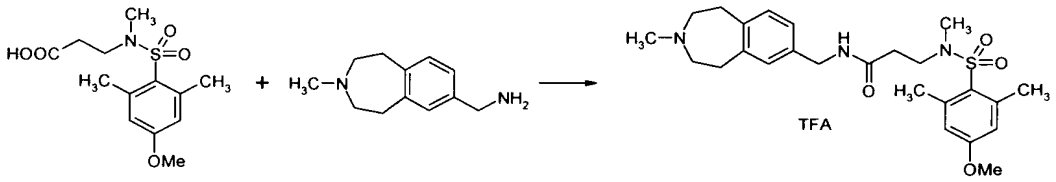
Uma mistura de 5,20 ml (5,20 mmols) de hidreto de lítioalumínio 1 M em tetrahidrofurano (Aldrich) e 18 ml de tetrahidrofurano é aquecida a 50°C e lentamente adicionada a 0,84 g (2,64 mmols) do produto de 38e. A seguir, a mistura de reação é agitada a 50°C por 30 minutos. Em seguida, resfria-se a -20°C e resfria-se a mistura de reação bruscamente inicialmente com uma mistura de água e tetrahidrofurano, depois com soda cáustica 2 M. Agita-se à temperatura ambiente por uma hora. O precipitado formado é filtrado, o filtrado é concentrado no vácuo à secura. O resíduo é retomado em diclorometano e lavado com solução saturada de bicarbonato de sódio. A fase orgânica é seca sobre sulfato de sódio e concentrada no vácuo à secura.

$C_{12}H_{18}N_2$ (190.28)

[M+H]+ = 191

HPLC (método 2): tempo de retenção = 2,21 min.

38g)



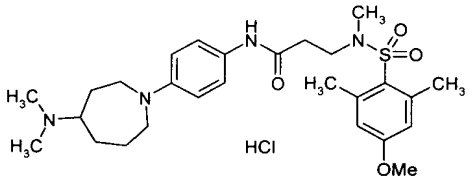
O exemplo 38 é preparado de maneira análoga a 1f a partir de 0,19 g (0,63 mmol) do produto de 22c, 0,12 g (0,63 mmol) do produto de 38f, 0,26 ml (1,89 mmol) de trietilamina e 0,20 g (0,63 mmol) de TBTU em 5 ml de tetrahidrofurano.

$C_{25}H_{35}N_3O_4S \times C_2HF_3O_2$ (587.65)

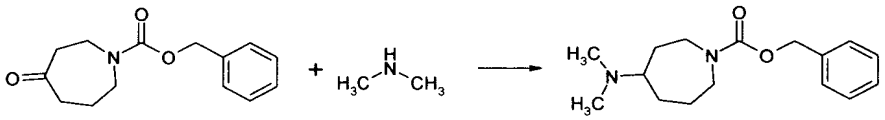
[M+H]+ = 474

HPLC (método 4): tempo de retenção = 2,98 min.

Exemplo 39



39a)



Uma mistura de 1,50 g (6,07 mmols) de éster benzílico de ácido 4-oxo-azepan-1-carboxílico (Tyger), 20 ml (40,00 mmols) de dimetilamina 2 M em tetrahidrofurano (Aldrich) e 0,34 ml (6,07 mmols) de ácido acético é agitada à temperatura ambiente por 20 minutos e a seguir, adicionada a 3,82 g (18,00 mmols) de triacetoxiborohidreto de sódio (Aldrich). Deixa-se agitar à temperatura ambiente durante a noite. Em seguida, a mistura de reação é adicionada à solução saturada de bicarbonato de sódio e extraída com acetato de etila. Os extratos orgânicos são lavados com solução saturada de cloreto de sódio, secos sobre sulfato de sódio e concentrados no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cro-

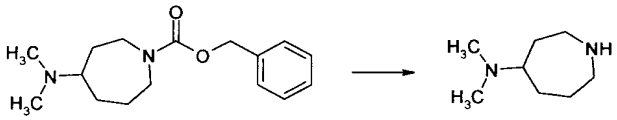
matografia de coluna sobre gel de sílica (agente de eluição: diclorometano/4-12 % (metanol + 10% de amoníaco).

$C_{16}H_{24}N_2O_2$ (276,37)

[M+H]+ = 277

HPLC (método 1): tempo de retenção = 2,12 min.

39b)



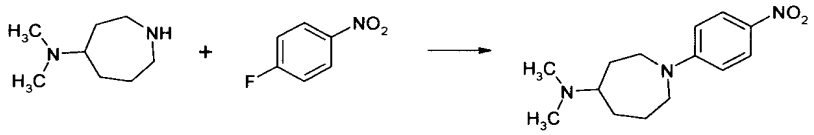
Uma mistura de 1,00 g (3,62 mmols) do produto de 39a, 0,10 g de paládio sobre carvão (10%) e 30 ml de metanol é hidrogenada no autoclave à temperatura ambiente. A seguir, o catalisador é filtrado, o filtrado é concentrado no vácuo à secura.

$C_8H_{18}N_2$ (142,24)

[M+H]+ = 143

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,12.

39c)



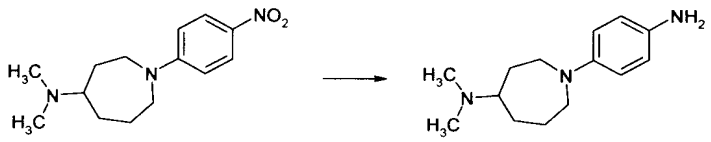
39c é preparado de maneira análoga a 1d a partir de 0,56 g (4,37 mmols) do produto de 39b, 0,64 g (4,50 mmols) de 4-flúor-nitrobenzeno (Aldrich), 0,65 ml (4,60 mmols) de trietilamina em 5 ml de dimetilformamida.

$C_{14}H_{21}N_2O_2$ (263,34)

[M+H]+ = 264

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,60.

39d)



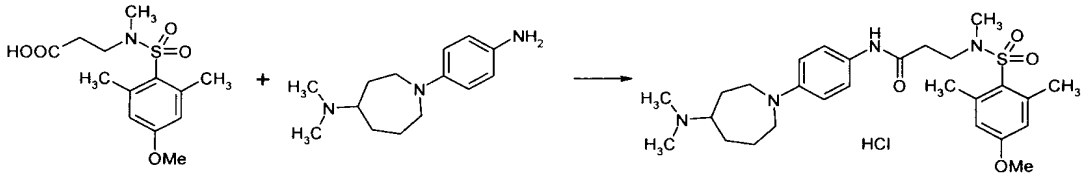
39d é preparado de maneira análoga a 8b a partir de 0,94 (3,55

mmols) do produto de 39c e 0,10 g de paládio sobre carvão (10%) em 30 ml de metanol.

$C_{14}H_{23}N_3O_2$ (233,35)

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,15.

39e)



O exemplo 39 é preparado de maneira análoga a 1f a partir de 0,30 g (1,00 mmol) do produto de 22c, 0,23 g (1,00 mmol) do produto de 39d, 0,42 ml (3,00 mmols) de trietilamina e 0,32 g (1,00 mmol) de TBTU em 15 ml de dimetilformamida.

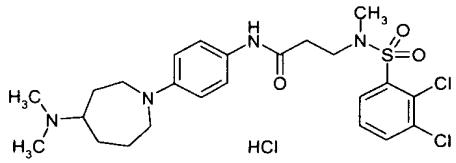
$C_{27}H_{40}N_4O_4S$ x HCl (553.16)

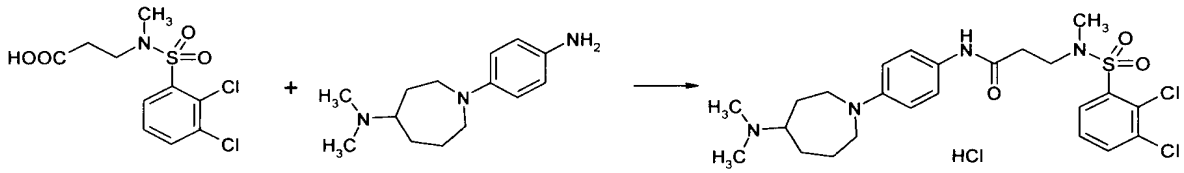
[M+H]+ = 517

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,42

HPLC (método 5): tempo de retenção = 1,50 min.

Exemplo 40





O exemplo é preparado de maneira análoga a 1f a partir de 0,16 g (0,50 mmol) do produto de 1c, 0,12 g (0,50 mmol) do produto de 39d, 0,21 ml (1,50 mmol) de trietilamina e 0,16 g (0,50 mmol) de TBTU em 5 ml de dimetilformamida.

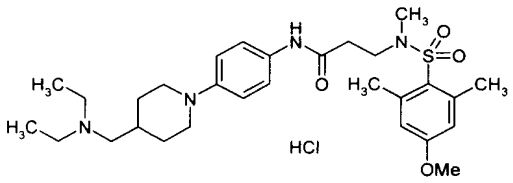
$C_{24}H_{32}Cl_2N_4O_3S$ x HCl (563,97)

[M+H]+ = 527/529/531

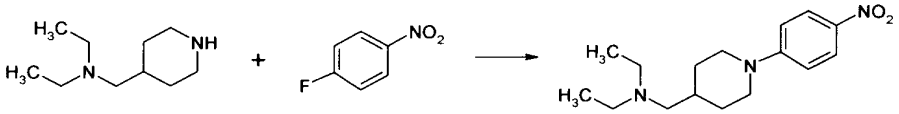
DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,48

HPLC (método 5): tempo de retenção = 1,53 min.

Exemplo 41



41a)



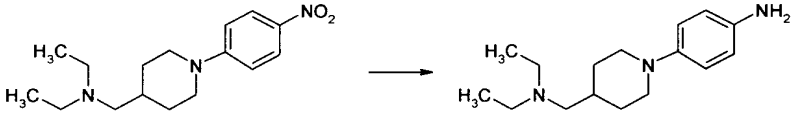
41a é preparado de maneira análoga a 1d a partir de 1,00 g (5,87 mmols) de dietil-piperidin-4-ilmetil-amina (Chem. Pharm. Bull. 42, 1994, 74-84), 0,83 g (5,87 mmols) de 4-flúor-nitrobenzeno (Aldrich), 1,14 ml (8,20 mmols) de trietilamina em 12 ml de dimetilformamida.

$C_{16}H_{25}N_3O_2$ (291.39)

[M+H]+ = 292

DC: gel de sílica, diclorometano/etanol 9:1:0,1, valor Rf = 0,5

41b)

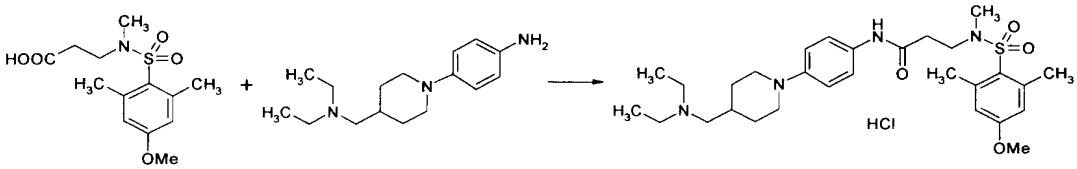


Uma mistura de 0,40 g (1,37 mmol) do produto de 41a, 0,10 g de paládio sobre carvão (10%) e 30 ml de metanol é hidrogenada no autoclave à temperatura ambiente. Em seguida, o catalisador é filtrado, o filtrado é concentrado no vácuo à secura.

$C_{16}H_{27}N_3$ (261.41)

DC: gel de sílica, diclorometano/etanol 9:1, valor Rf = 0,1

41c)



O exemplo 41 é preparado de maneira análoga a 1f a partir de

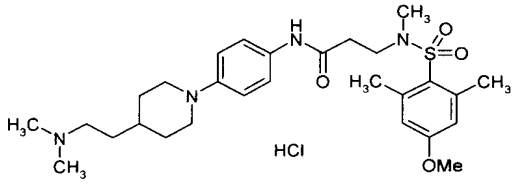
0,40 g (1,34 mmol) do produto de 22c, 0,35 g (1,34 mmol) do produto de 41b, 0,47 ml (3,35 mmols) de trietilamina e 0,43 g (1,34 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{29}H_{44}N_4O_4S$ x HCl (581.21)

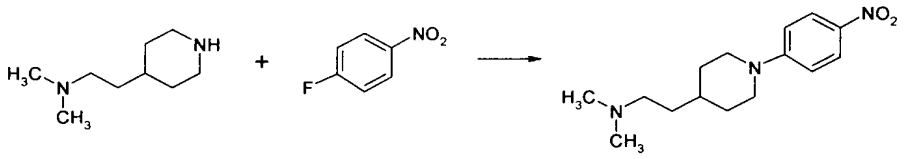
[M+H]+ = 545

HPLC (método 5): tempo de retenção = 1,42 min.

Exemplo 42



42a)



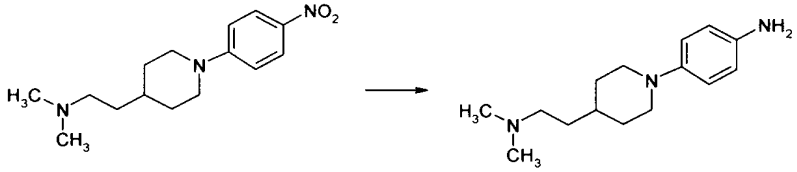
42a é preparado de maneira análoga a 1d a partir de 1,88 g (12,00 mmols) de dimetil-(2-piperidin-4-il-etil)-amina (J. Med. Chem. 36, 1993, 162-165), 1,69 g (12,00 mmols) de 4-flúor-nitrobenzeno (Aldrich), 2,37 ml (17,00 mmols) de trietilamina em 15 ml de dimetilformamida.

$C_{15}H_{23}N_3O_2$ (277.36)

[M+H]+ = 278

DC: gel de sílica, diclorometano/etanol 9:1, valor Rf = 0,2.

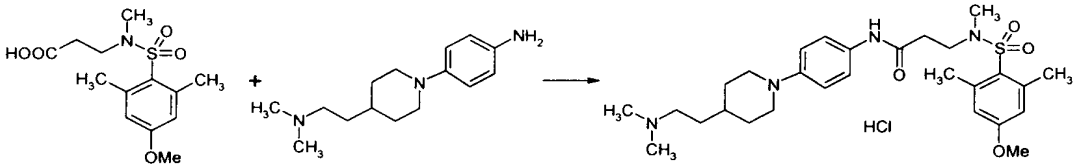
42b)



Uma mistura de 0,30 g (1,08 mmol) do produto de 42a, 0,10 g de paládio sobre carvão (10%) e 30 ml de metanol é hidrogenada no autoclave à temperatura ambiente. A seguir, o catalisador é filtrado, o filtrado é concentrado no vácuo à secura.

$C_{15}H_{25}N_3$ (247,38).

42c)



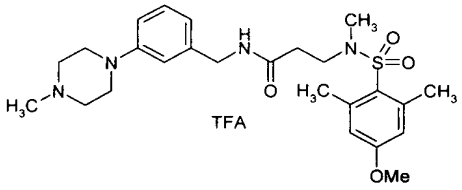
O exemplo 42 é preparado de maneira análoga a 1f a partir de 0,33 g (1,08 mmol) do produto de 22c, 0,27 g (1,08 mmol) do produto de 42b, 0,38 ml (2,70 mmols) de trietilamina e 0,35 g (1,08 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

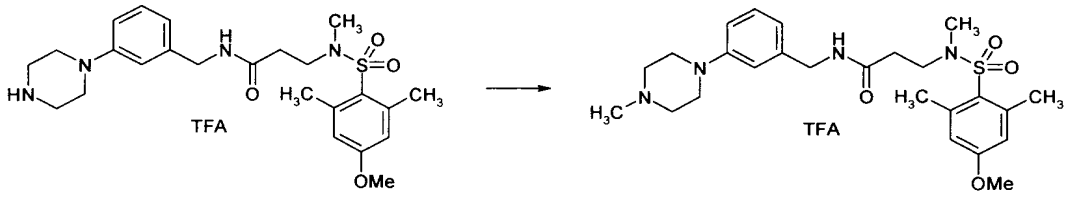
$C_{28}H_{42}N_4O_4S$ (530.72)

[M+H]+ = 531

HPLC (método 5): tempo de retenção = 1,41 min.

Exemplo 43





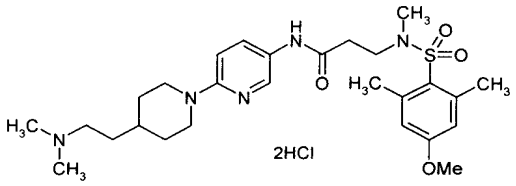
Uma mistura de 0,15 g (0,25 mmol) do produto de 36d, 0,025 ml (0,40 mmol) de iodeto de metila (Aldrich), 0,10 ml (0,75 mmol) de carbonato de potássio e 5 ml de acetonitrila é agitada à temperatura ambiente durante a noite. A seguir, a mistura de reação é adicionada a TFA a 10%, o produto é separado por meio de HPLC preparatória.

$C_{25}H_{36}N_4O_4S \times C_2HF_3O_2$ (602.67

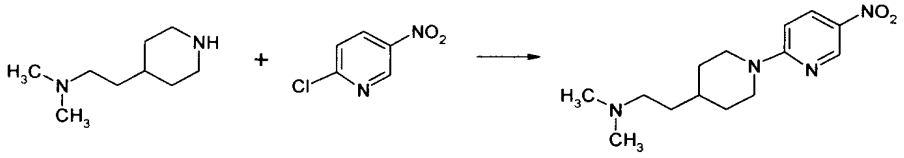
[M+H]+ = 489

HPLC (método 2): tempo de retenção = 2,99 min.

Exemplo 44



44a)

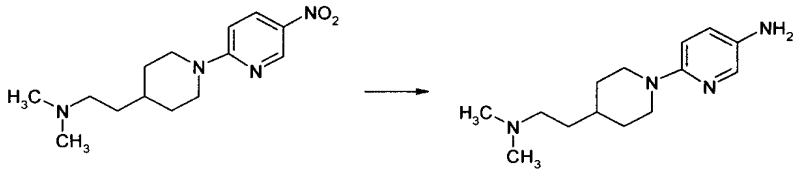


Uma mistura de 0,72 g (4,61 mmols) de dimetil-(2-piperidin-4-il-etil)-amina (J. Med. Chem. 36, 1993, 162-165), 0,73 g (4,61 mmols) de 2-cloro-5-nitropiridina (Fluka), 1,30 g (9,41 mmols) de carbonato de potássio e 100 ml de tetrahidrofurano é agitada à temperatura ambiente durante o final de semana. O precipitado é filtrado, o filtrado é concentrado no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/metanol 19:1 a 4:1).

$C_{14}H_{22}N_4O_2$ (278,35)

[M+H]+ = 279.

44b)

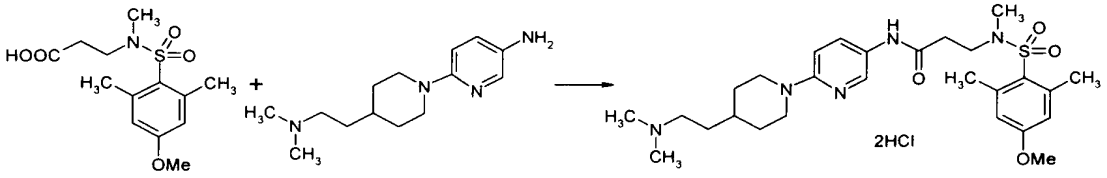


Uma mistura de 0,26 g (0,93 mmol) do produto de 44a, 0,05 g de paládio sobre carvão (10%) e 30 ml de metanol é hidrogenada no autoclave à temperatura ambiente. A seguir, o catalisador é filtrado, o filtrado é concentrado no vácuo à secura.

$C_{14}H_{24}N_4$ (248.37)

[M+H]+ = 249

44c)



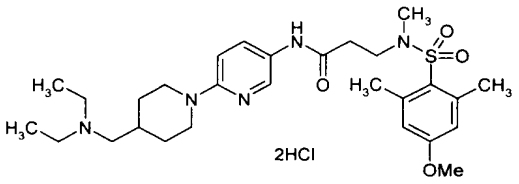
O exemplo 44 é preparado de maneira análoga a 1f a partir de 0,12 g (0,40 mmol) do produto de 22c, 0,10 g (0,40 mmol) do produto de 44b, 0,069 ml (0,50 mmol) de trietilamina e 0,14 g (0,44 mmol) de TBTU em 40 ml de tetrahidrofurano e 5 ml de dimetilformamida.

$C_{27}H_{41}N_5O_4S$ x 2HCl (604.63)

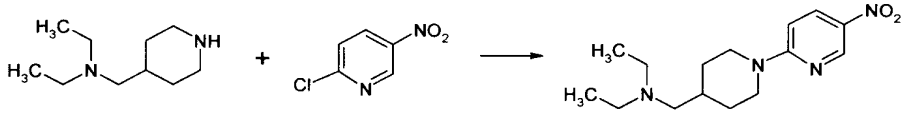
[M+H]+ = 532

HPLC (método 5): tempo de retenção = 1,40 min.

Exemplo 45



45a)

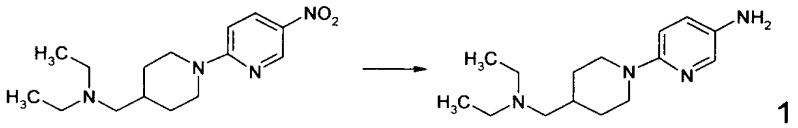


45a é preparado de maneira análoga a 44a a partir de 1,00 g (5,87 mmols) de dietil-piperidin-4-ilmetil-amina (Chem. Pharm. Bull. 42, 1994, 74-84), 0,93 g (5,87 mmols) de 2-cloro-5-nitropiridina (Fluka) e 1,70 g (12,30 mmols) de carbonato de potássio em 100 ml de tetrahidrofurano.

$C_{15}H_{24}N_4O_2$ (292.38)

[M+H]+ = 293.

45b)



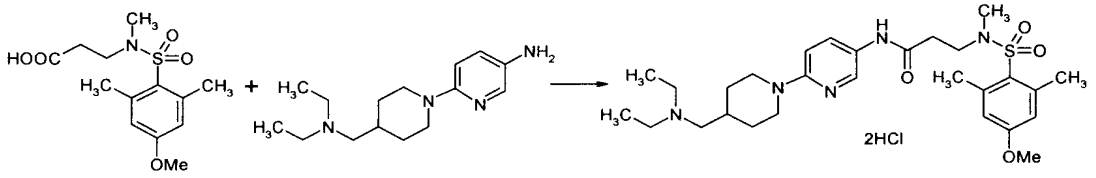
Uma mistura de 0,20 g (0,68 mmol) do produto de 45a, 0,03 g de

paládio sobre carvão (10%) e 30 ml de metanol é hidrogenada no autoclave à temperatura ambiente. A seguir, o catalisador é filtrado, o filtrado é concentrado no vácuo à secura.

$C_{15}H_{26}N_4$ (262.39)

[M+H]+ = 263.

45c)



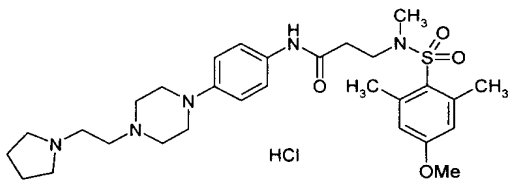
O exemplo 45 é preparado de maneira análoga a 1f a partir de 0,16 g (0,53 mmol) do produto de 22c, 0,14 g (0,53 mmol) do produto de 45b, 0,096 ml (0,69 mmol) de trietilamina e 0,19 g (0,58 mmol) de TBTU em 40 ml de tetrahidrofurano e 5 ml de dimetilformamida.

$C_{28}H_{43}N_5O_4S$ x 2HCl (618,66)

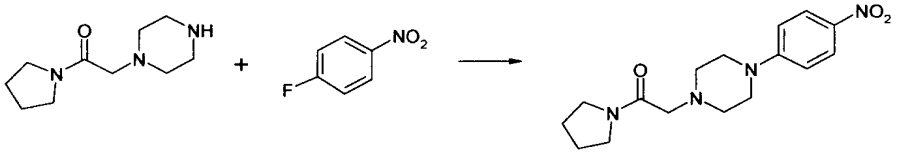
[M+H]+ = 546

HPLC (método 5): tempo de retenção = 1,40 min.

Exemplo 46



46a)



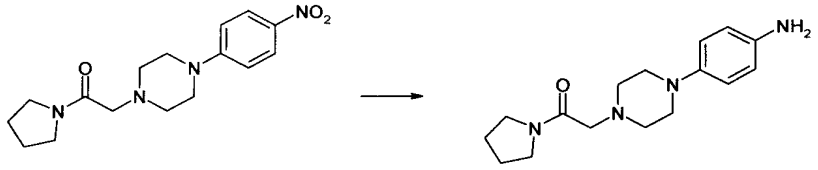
46a é preparado de maneira análoga a 1d a partir de 3,00 g (15,21 mmols) de 2-piperazin-1-il-1-pirrolidin-1-il-etanona (Chess), 2,15 g (15,21 mmols) de 1-flúor-4-nitrobenzeno (Aldrich) e 3,07 ml (22,00 mmols) de trietilamina em 25 ml de dimetilformamida.

$C_{16}H_{22}N_4O_3$ (318.37)

[M+H]+ = 319

DC: gel de sílica, diclorometano/etanol 9:1, valor Rf = 0,4.

46b)

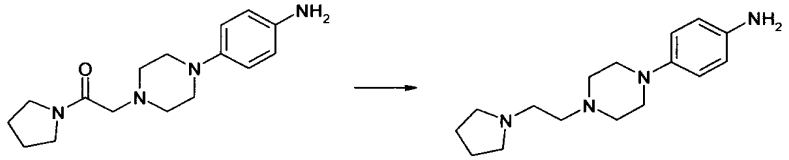


Uma mistura de 3,00 g (9,42 mmols) do produto de 46a, 0,30 g de paládio sobre carvão (10%) e 200 ml de metanol é hidrogenada no autoclave à temperatura ambiente. A seguir, o catalisador é filtrado, o filtrado concentrado no vácuo à secura.

$C_{16}H_{24}N_4O$ (288.39)

DC: gel de sílica, diclorometano/etanol 9:1, valor Rf = 0,42.

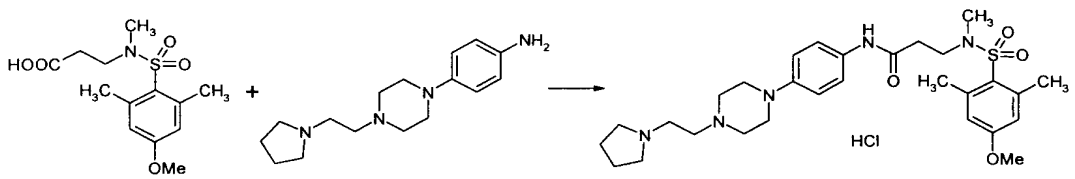
46c)



30,00 ml (30,00 mmols) de hidreto de lítioalumínio 1 M em tetrahidrofurano (Aldrich) são previamente introduzidos em 50 ml de tetrahidrofurano e à temperatura ambiente, adicionados a uma mistura de 2,70 g (9,36 mmols) do produto de 46b e 20 ml de tetrahidrofurano. A seguir, a mistura de reação é agitada à temperatura ambiente por três horas e em seguida, adicionada a soda cáustica a 20% sob resfriamento com banho de gelo. O precipitado formado é filtrado, o filtrado concentrado no vácuo à secura.

$C_{16}H_{26}N_4$ (274.40).

46d)



O exemplo 46 é preparado de maneira análoga a 1f a partir de 0,30 g (1,00 mmol) do produto de 22c, 0,27 g (1,00 mmol) do produto de 46c, 0,35 ml (2,50 mmols) de trietilamina e 0,32 g (1,00 mmol) de TBTU em

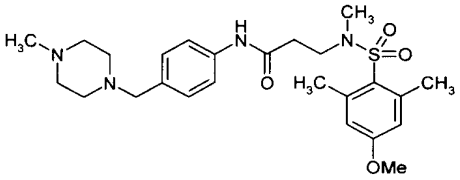
7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

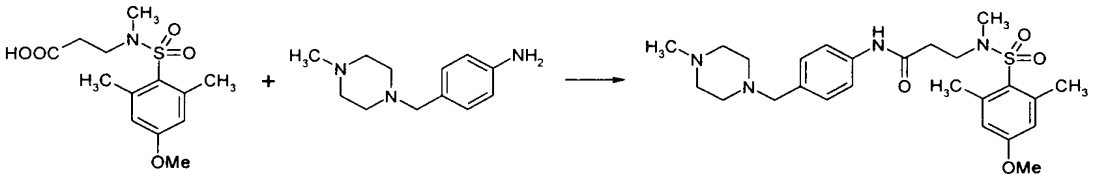
$C_{29}H_{43}N_5O_4S$ x HCl (594.21)

[M+H]+ = 558

HPLC (método 5): tempo de retenção = 1,43 min.

Exemplo 47





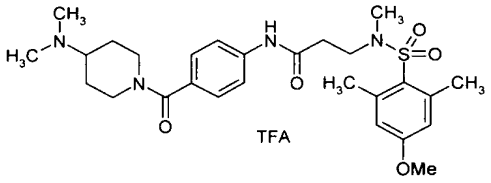
O exemplo 47 é preparado de maneira análoga a 1f a partir de 0,20 g (0,66 mmol) do produto de 22c, 0,14 g (0,66 mmol) de 4-(4-metil-piperazin-1-ilmetil)-fenilamina (Med. Chem. Res. 9, 1999, 149-161), 0,28 ml (1,99 mmol) de trietilamina e 0,21 g (0,66 mmol) de TBTU em 5 ml de tetra-hidrofurano.

$C_{25}H_{36}N_4O_4S$ (488.64)

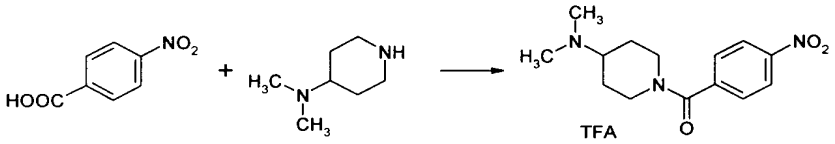
[M+H]+ = 489

HPLC (método 5): tempo de retenção = 1,42 min.

Exemplo 48



48a)



48a é preparado de maneira análoga a 1f a partir de 0,24 g (1,45

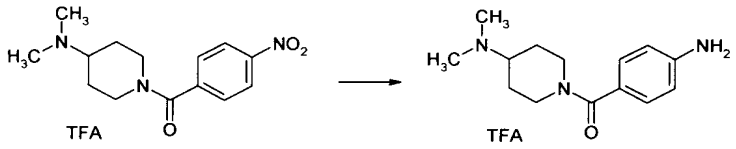
mmol) de ácido 4-nitrobenzóico (Aldrich), 0,19 g (1,45 mmol) de 4-dimetilamino-piperidina (Alfa Aesar), 0,21 ml (1,52 mmol) de trietilamina e 0,49 g (1,52 mmol) de TBTU em 8 ml de dimetilformamida.

$C_{14}H_{19}N_3O_3 \times C_2HF_3O_2$ (391.34)

[M+H]+ = 278

HPLC (método 2): tempo de retenção = 2,29 min.

48b)



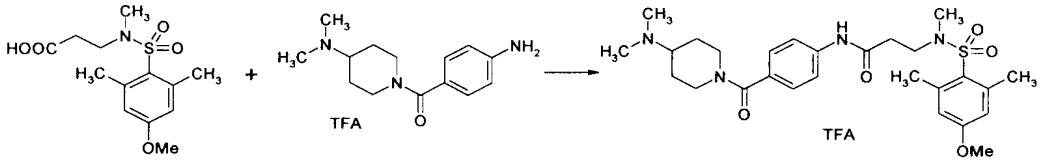
Uma mistura de 0,36 g (0,92 mmol) do produto de 48a, 0,092 g de paládio sobre carvão (10%) e 5 ml de metanol é hidrogenada no autoclave à temperatura ambiente. A seguir, o catalisador é filtrado, o filtrado é concentrado no vácuo à secura.

$C_{14}H_{21}N_3O \times C_2HF_3O_2$ (361.36)

[M+H]+ = 248

HPLC (método 2): tempo de retenção = 0,66 min.

48c)



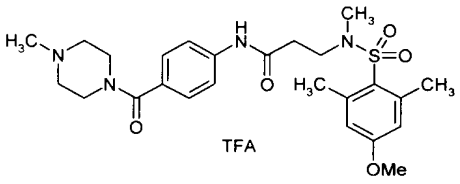
O exemplo 48 é preparado de maneira análoga a 1f a partir de 0,15 g (0,50 mmol) do produto de 22c, 0,18 g (0,50 mmol) do produto de 48b, 0,21 ml (1,49 mmol) de trietilamina e 0,16 g (0,50 mmol) de TBTU em 3 ml de tetrahidrofurano.

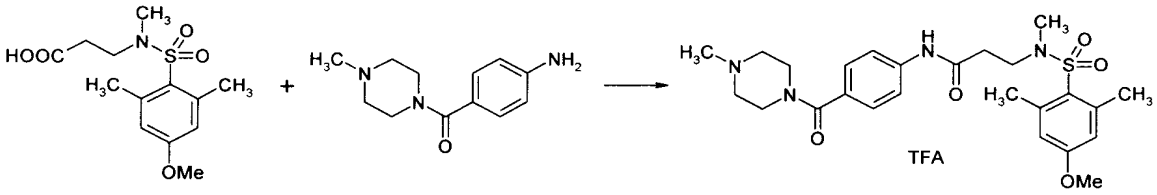
$C_{27}H_{38}N_4O_5S \times C_2HF_3O_2$ (644.70)

[M+H]+ = 531

HPLC (método 5): tempo de retenção = 1,48 min.

Exemplo 49





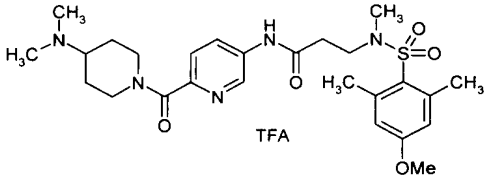
O exemplo 48 é preparado de maneira análoga a 1f a partir de 0,15 g (0,50 mmol) do produto de 22c, 0,11 g (0,50 mmol) de (4-aminofenil)-(4-metilpiperazin-1-il)-metanona (J. Org. Chem. 24, 1959, 459-463), 0,21 ml (1,49 mmol) de trietilamina e 0,16 g (0,50 mmol) de TBTU em 3 ml de tetra-hidrofurano.

$C_{25}H_{34}N_4O_5S \times C_2HF_3O_2$ (616.65)

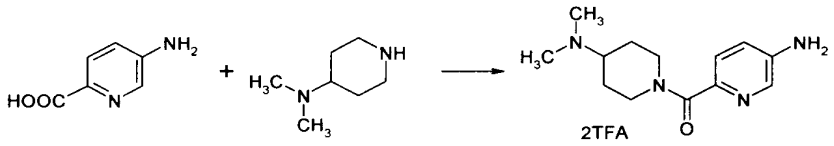
[M+H]+ = 503

HPLC (método 5): tempo de retenção = 1,47 min.

Exemplo 50



50a)



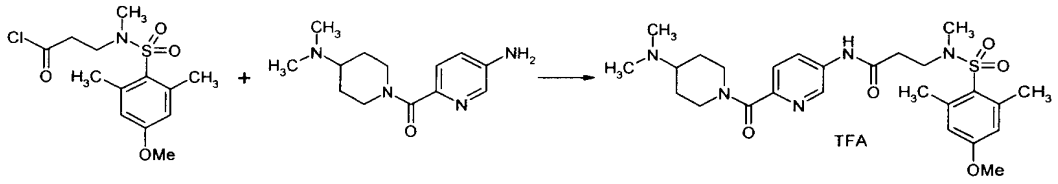
50a é preparado de maneira análoga a 1f a partir de 0,60 g (4,34 mmols) de ácido 5-amino-piridin-2-carboxílico (Pharm. Acta Helv. 44, 1969, 637-643), 0,56 g (4,34 mmols) de 4-dimetilamino-piperidina (Alfa Aesar), 0,64 ml (4,56 mmols) de trietilamina e 1,46 g (4,56 mmols) de TBTU em 24

ml de dimetilformamida.

$C_{13}H_{20}N_4O \times 2C_2HF_3O_2$ (476.37)

HPLC (método 2): tempo de retenção = 0,65 min.

50b)



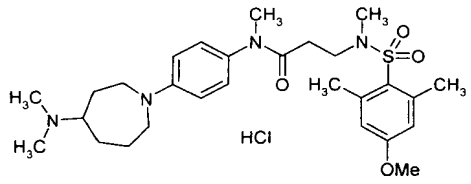
Uma mistura de 0,64 g (1,99 mmol) do produto de 27c, 1,90 g (2,39 mmols) do produto de 50a, 0,08 g (0,33 mmol) de DMAP e 16 ml de clorobenzeno é aquecida a 15°C por 39 horas. A seguir, a mistura de reação é concentrada no vácuo à secura. O produto é obtido por meio de HPLC preparatória.

$C_{26}H_{37}N_5O_5S \times C_2HF_3O_2$ (645.69)

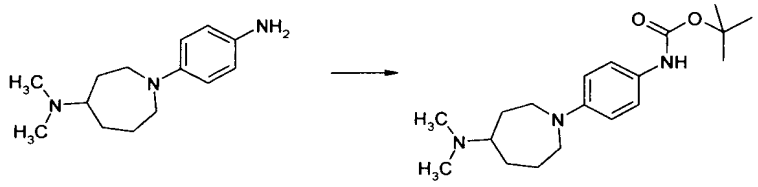
[M+H]+ = 532

HPLC (método 5): tempo de retenção = 1,44 min.

Exemplo 51



51a)



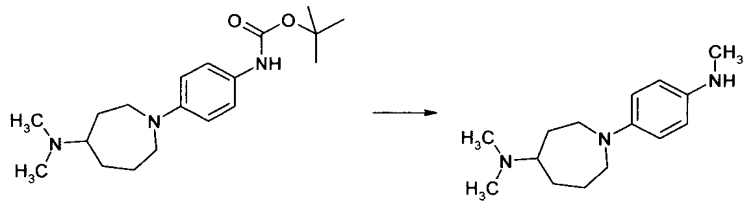
Uma mistura de 0,26 g (1,11 mmol) do produto de 39d, 0,27 g (1,22 mmol) de anidrido boc, 0,17 ml (1,22 mmol) de trietilamina e 15 ml de diclorometano é agitada à temperatura ambiente durante a noite. A seguir, a mistura de reação é diluída com diclorometano, lavada com solução saturada de bicarbonato de sódio e solução saturada de cloreto de sódio, seca sobre sulfato de sódio e concentrada no vácuo à secura.

$C_{19}H_{31}N_3O_2$ (333.47)

[M+H]+ = 334

HPLC (método 1): tempo de retenção = 2.40 min.

51b)

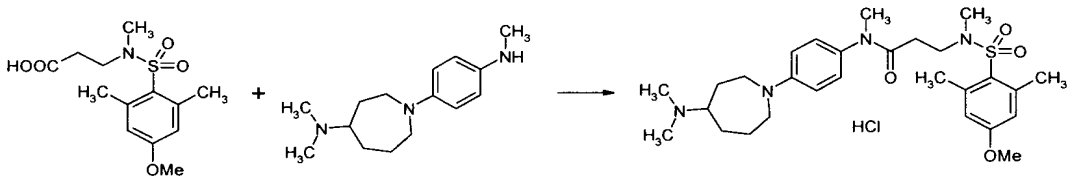


0,13 g (3,40 mmols) de hidreto de lítioalumínio são previamente introduzidos em 5 ml de tetrahidrofurano, aquecidos a 60°C e adicionados a 0,38 g (1,14 mmol) do produto de 51a em 5 ml de tetrahidrofurano. A seguir, a mistura de reação é aquecida sob refluxo por quatro horas e agitada à temperatura ambiente durante a noite. Em seguida, a mistura de reação é bruscamente resfriada com água e soda cáustica 1 M. O precipitado formado é filtrado sobre celite, o filtrado é concentrado no vácuo à secura.

$C_{15}H_{25}N_3$ (247.38)

DC: gel de sílica, diclorometano/metanol/amoníaco 4:1:0,2, valor RF = 0,68.

51c)



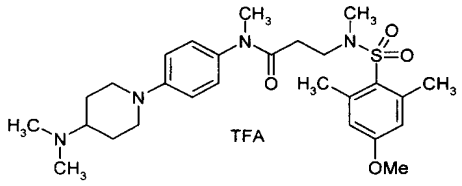
O exemplo 51 é preparado de maneira análoga a 1f a partir de 0,15 g (0,50 mmol) do produto de 22c, 0,12 g (0,50 mmol) do produto de 51b, 0,21 ml (1,50 mmol) de trietilamina e 0,18 g (0,55 mmol) de TBTU em 8 ml de dimetilformamida.

$C_{28}H_{42}N_4O_4S$ x HCl (567.18)

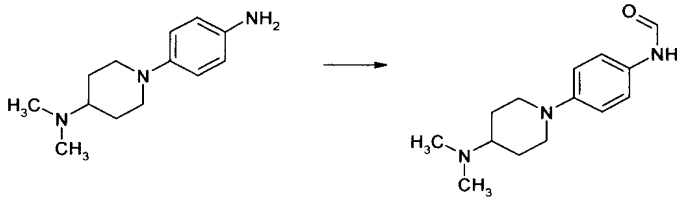
[M+H]+ = 531

HPLC (método 1): tempo de retenção = 2.5 min.

Exemplo 52



52a)



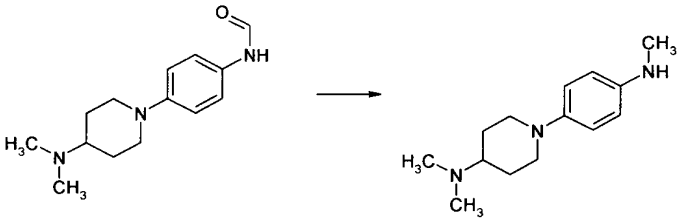
0,70 ml (7,36 mmols) de anidrido de ácido acético são previamente introduzidos sob atmosfera de nitrogênio e sob resfriamento com gelo, são adicionados a 0,42 ml (9,06 mmols) de ácido fórmico. A mistura de reação é aquecida a 50-60°C por duas horas e em seguida, sob resfriamento com gelo, adicionada a 0,50 g (2,28 mmols) do produto de 8b em 7 ml de diclorometano. Após agitar por 20 minutos à temperatura ambiente, a mistura de reação é concentrada no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/metanol/amoníaco 9:1:0,1).

$C_{14}H_{21}N_3O$ (247.34)

[M+H]+ = 248

HPLC (método 5): tempo de retenção = 0.50 min.

52b)

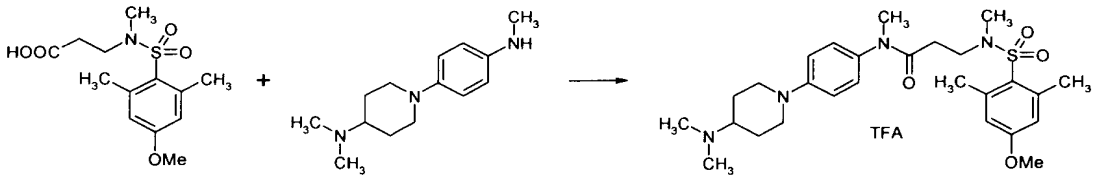


52b é preparado de maneira análoga a 51b a partir de 0,17 g (4,51 mmols) de hidreto de lítioalumínio e 0,58 g (2,34 mmols) do produto de 52a em 10 ml de tetrahidrofurano.

$C_{14}H_{23}N_3$ (233,35)

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,5.

52c)



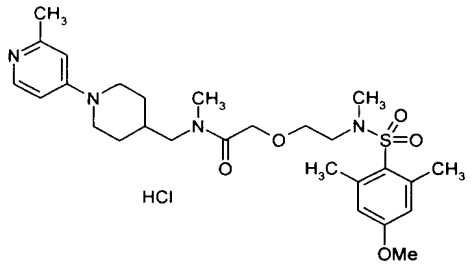
O exemplo 52 é preparado de maneira análoga a 1f a partir de 0,21 g (0,68 mmol) do produto de 22c, 0,24 g (0,68 mmol) do produto de 52b, 0,28 ml (2,04 mmols) de trietilamina e 0,22 g (0,68 mmol) de TBTU em 4 ml de tetrahidrofurano.

$C_{27}H_{40}N_4O_4S \times C_2HF_3O_2$ (630.72)

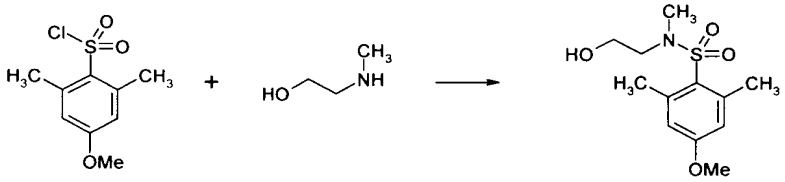
[M+H]+ = 517

HPLC (método 5): tempo de retenção = 1.50 min.

Exemplo 53



53a)



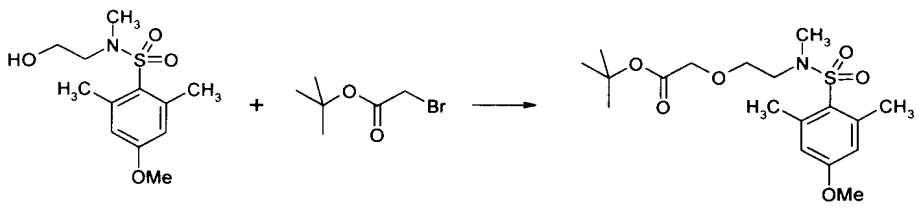
53a é preparado de maneira análoga a 3a a partir de 4,50 g (19,17 mmols) do produto de 13a, 1,69 g (21,10 mmols) de N-metilaminoetanol (BASF), 6,68 ml (47,90 mmols) de trietilamina em 150 ml de diclorometano.

$C_{12}H_{19}NO_4S$ (273.35)

[M+H]+ = 274

DC: gel de sílica, diclorometano/etanol 19:1, valor Rf = 0,43.

53b)



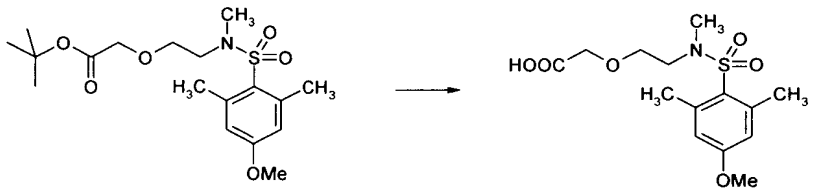
Uma mistura de 5,15 g (18,84 mmols) do produto de 53a, 1,75 g (6,60 mmols) de cloreto de tetrabutilamônio (Fluka) e 80 ml de tolueno é adicionada, a 0°C, inicialmente a 100 ml de soda cáustica a 35%, depois a 4,18 ml (28,26 mmols) de éster terc-butílico de ácido bromacético em 20 ml de tolueno. Em seguida, a mistura de reação é agitada à temperatura ambiente por 1,5 horas, depois diluída com éter dietílico. Após a separação de fases, a fase orgânica é lavada até a neutralidade com água, seca sobre sulfato de sódio e concentrada no vácuo à secura. O produto obtido dessa maneira, é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: éter de petróleo/acetato de etila 4:1).

$C_{18}H_{29}NO_6S$ (387.49)

[M+H]+ = 388

DC: gel de sílica, éter de petróleo/acetato de etila 7:3, valor Rf = 0,59.

53c)



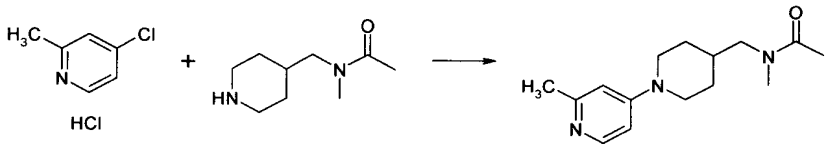
Uma mistura de 6,80 g (17,55 mmols) do produto de 53b, 8 ml de TFA e 100 ml de diclorometano é agitada à temperatura ambiente por 2,5 horas. A seguir, a mistura de reação é concentrada no vácuo à secura. O resíduo é adicionado à soda cáustica 1 M e extraído duas vezes com acetato de etila (rejeitar os extratos orgânicos). A fase aquosa é acidificada com HCl 2 M, depois novamente extraída com acetato de etila. Os extratos orgânicos são lavados com água, secos sobre sulfato de sódio e concentrados no vácuo à secura.

$C_{14}H_{21}NO_6S$ (331.29)

[M+H]+ = 332

HPLC (método 4): tempo de retenção = 3.4 min.

53d)



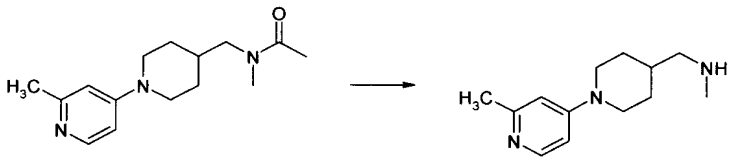
53d é preparado de maneira análoga a 28c a partir de 1,00 g (6,10 mmols) de cloridrato de 4-cloro-2-metilpiridina (Alfa Aesar) e 2,08 g (12,20 mmols) de N-metil-N-piperidin-4-ilmetil-acetamida (DE 1100635, Rhône-Poulenc, 1961).

$C_{15}H_{23}N_3O$ (261.36)

[M+H]+ = 262

HPLC (método 4): tempo de retenção = 1.9 min.

53e)



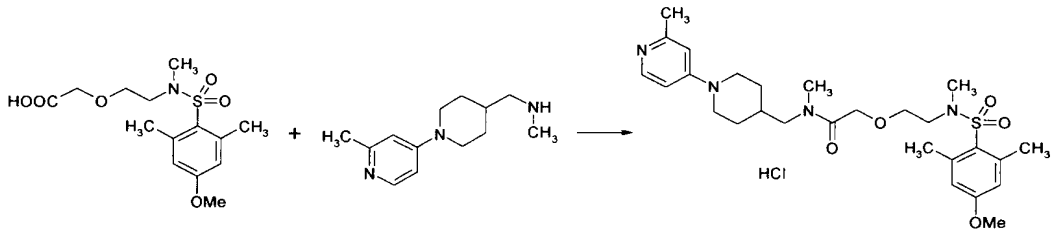
Uma mistura de 1,37 g (5,24 mmols) do produto de 53d e 15 ml de HCl semiconcentrado é aquecida sob refluxo por quatro dias. A mistura de reação é alcalinizada com soda cáustica a 20% e extraída com diclorometano. Os extratos orgânicos são secos sobre sulfato de sódio e concentrados no vácuo à secura.

$C_{13}H_{21}N_3$ (219.33)

[M+H]+ = 220

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,2, valor Rf = 0,48.

53f)



O exemplo 53 é preparado de maneira análoga a 1f a partir de

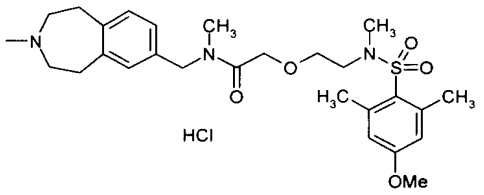
0,099 g (0,30 mmol) do produto de 53c, 0,066 g (0,30 mmol) do produto de 53e, 0,10 ml (0,75 mmol) de trietilamina e 0,12 g (0,36 mmol) de TBTU em 8 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{27}H_{40}N_4O_5S$ x HCl (569.16)

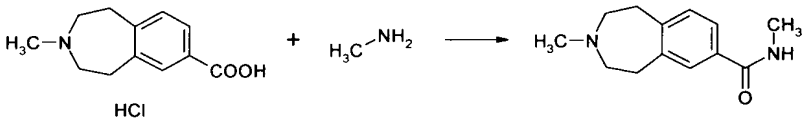
[M+H]+ = 533

HPLC (método 4): tempo de retenção = 3.1 min.

Exemplo 54



54a)



54a é preparado de maneira análoga a 1f a partir de 2,00 g (8,27 mmols) do produto de 38d, 8,28 ml (16,55 mmols) sde metilamina 2 M em tetrahidrofurano (Aldrich), 3,46 ml (24,82 mmols) de trietilamina e 3,19 g (9,93 mmols) de TBTU em 30 ml de tetrahidrofurano.

$C_{13}H_{18}N_2O$ (218.29)

[M+H]+ = 219

DC: gel de sílica, diclorometano/metanol 8:2, valor Rf = 0,14.

54b)



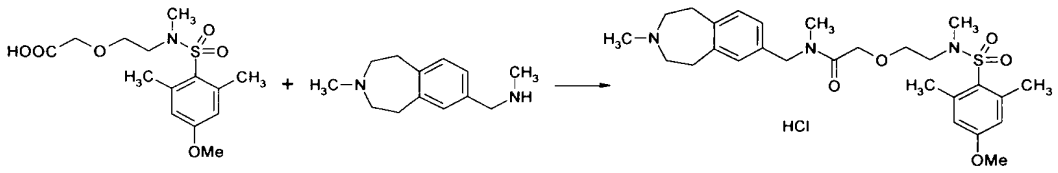
54b é preparado de maneira análoga a 38f a partir de 1,00 g (4,58 mmols) do produto de 54a e 9,00 ml (9,00 mmols) de hidreto de lítioalumínio 1 M em tetrahidrofurano (Aldrich) em 30 ml de tetrahidrofurano.

$C_{13}H_{20}N_2$ (204,31)

[M+H]+ = 205

DC: gel de sílica, diclorometano/metanol 8:2, valor Rf = 0,07.

54c)



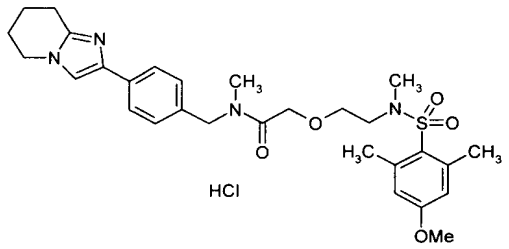
O exemplo 54 é preparado de maneira análoga a 1f a partir de 0,099 g (0,30 mmol) do produto de 53c, 0,088 g (0,30 mmol) do produto de 54b, 0,10 ml (0,75 mmol) de trietilamina e 0,12 g (0,36 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{27}H_{39}N_3O_5S$ x HCl (554.14)

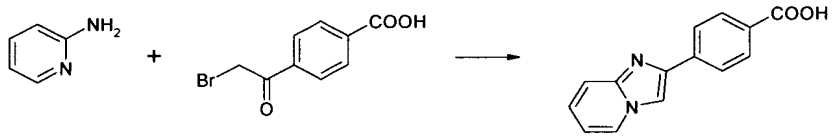
M+H]+ = 518

HPLC (método 4): tempo de retenção = 3.1 min.

Exemplo 55



55a)

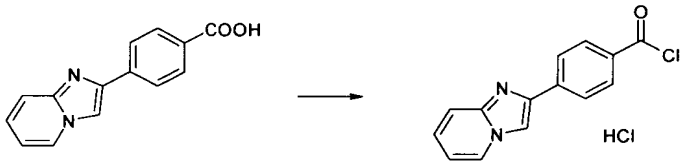


Uma mistura de 3,20 g (34,00 mmols) de 2-aminopiridina (Aldrich), 2,75 g (11,31 mmols) de ácido 4-bromacetilbenzóico (Fluorochem) e 100 ml de etanol é aquecida sob refluxo por seis horas e agitada à temperatura ambiente durante a noite. O precipitado formado é filtrado e seco.

$C_{14}H_{10}N_2O_2$ (238.24)

[M+H]+ = 239

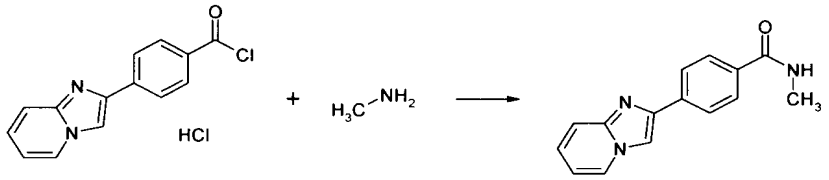
55b)



55b é preparado de maneira análoga a 27c a partir de 1,7 g (7,14 mmols) do produto de 55a e 30 ml de cloreto de tionila.

$C_{14}H_9ClN_2O$ x HCl (293.15)

55c)

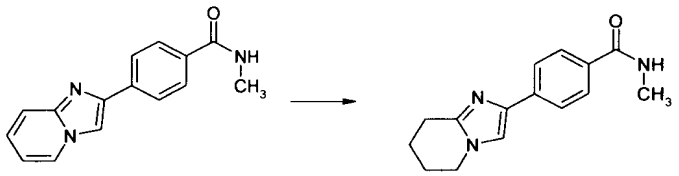


2,10 g (7,14 mmols) do produto de 55b em 100 ml de diclorometano são adicionados a 25 ml (50,00 mmols) de metilamina 2 M em tetrahidrofurano (Aldrich) sob resfriamento com gelo. A seguir, a mistura de reação é agitada à temperatura ambiente por duas horas e em seguida, concentrada no vácuo à secura. O resíduo é triturado com água, filtrado e seco. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/metanol 97:3).

$C_{15}H_{13}N_3O$ (251.28)

[M+H]+ = 252.

55d)

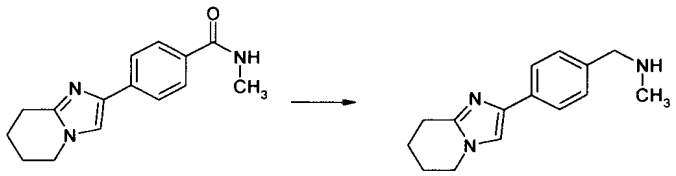


Uma mistura de 0,70 g (2,79 mmols) do produto de 55c, 0,15 g de paládio sobre carvão (20%), 100 ml de metanol e 30 ml de diclorometano é hidrogenada no autoclave à temperatura ambiente. O catalisador é filtrado, o filtrado concentrado no vácuo à secura.

$C_{15}H_{17}N_3O$ (255.32)

[M+H]+ = 256.

55e)

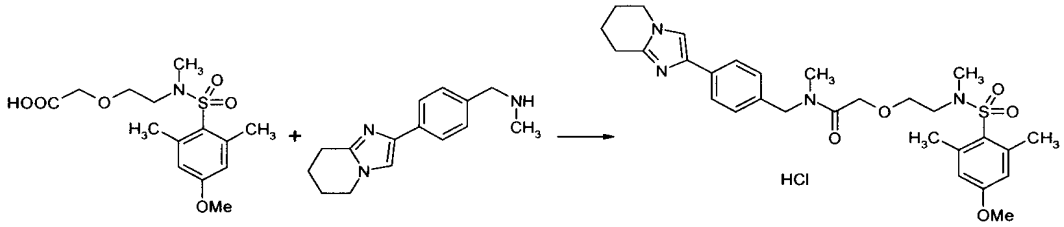


55e é preparado de maneira análoga a 38f a partir de 0,80 g (3,13 mmols) do produto de 55d e 20,00 ml (20,00 mmols) de hidreto de lítioalumínio 1 M em tetrahidrofurano (Aldrich) em 50 ml de piridina.

$C_{15}H_{19}N_3$ (241.33)

[M+H]+ = 242.

55f)



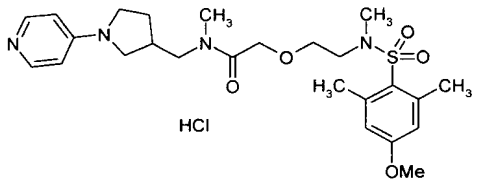
O exemplo 55 é preparado de maneira análoga a 1f a partir de 0,14 g (0,42 mmol) de 53c, 0,10 g (0,41 mmol) do produto de 55e, 0,14 ml (0,99 mmol) de trietilamina e 0,15 g (0,46 mmol) de TBTU em 30 ml de tetrahidrofurano e 5 ml de dimetilformamida.

$C_{29}H_{38}N_4O_5S$ x HCl (591.16)

[M+H]+ = 555

DC: gel de sílica, diclorometano/metanol 9:1 valor Rf = 0,26.

Exemplo 56



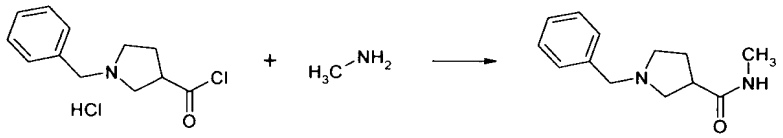
56a)



56b é preparado de maneira análoga a 55c a partir de 1,45 g (5,57 mmols) do produto de 56a, 10 ml (50,0 mmols) de metilamina 2 M em tetrahidrofurano (Aldrich) em 50 ml de tetrahidrofurano.

$C_{12}H_{14}ClNO$ x HCl (260.16).

56b)

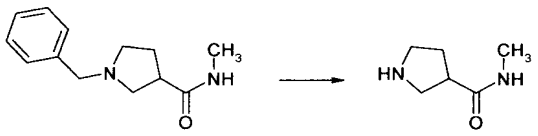


56b é preparado de maneira análoga a 55c a partir de 1,45 g (5,57 mmols) do produto de 56a, 10 ml (50,00 mmols) de metilamina 2 M em tetrahidrofurano (Aldrich) em 50 ml de tetrahidrofurano.

$C_{13}H_{18}N_2O$ (218,29)

[M+H]+ = 219.

56c)

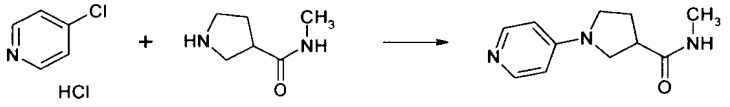


Uma mistura de 1,10 g (5,04 mmols) do produto de 56b, 0,20 g de hidróxido de paládio e 40 ml de metanol é hidrogenada no autoclave a 50°C. O catalisador é filtrado, o filtrado concentrado no vácuo à secura.

$C_6H_{12}N_2O$ (128,17)

[M+H]+ = 129

56d)



56d é preparado de maneira análoga a 28c a partir de 0,76 g (5,08 mmols) de cloridrato de 4-cloropiridina (Aldrich), 0,65 g (5,07 mmols) do produto de 56c e 1,52 ml (10,88 mmols) de trietilamina em 10 ml de eta-

nol.

$C_6H_{12}N_2O$ (128.17)

[M+H]+ = 206

56e)

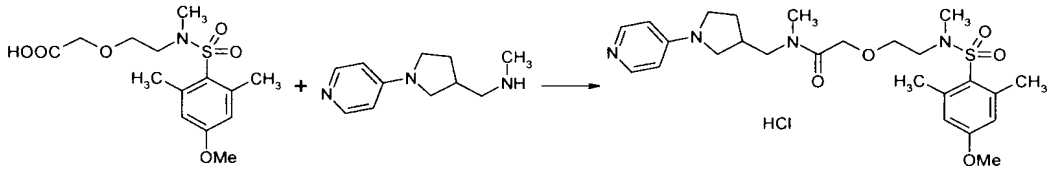


56e é preparado de maneira análoga a 38f a partir de 0,45 g (2,19 mmols) do produto de 56d e 7,00 ml (7,00 mmols) de hidróxido de lítioalumínio 1 M em tetrahidrofurano (Aldrich) em 30 ml de tetrahidrofurano.

$C_{11}H_{15}N_3O$ (205.26)

[M+H]+ = 192

56f)



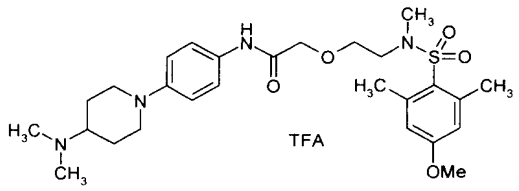
O exemplo 56 é preparado de maneira análoga a 1f a partir de 0,14 g (0,42 mmol) do produto de 53c, 0,10 g (0,42 mmol) do produto de 56e, 0,18 ml (1,29 mmol) de trietilamina e 0,18 g (0,56 mmol) de TBTU em 30 de tetrahidrofurano e 5 ml de dimetilformamida.

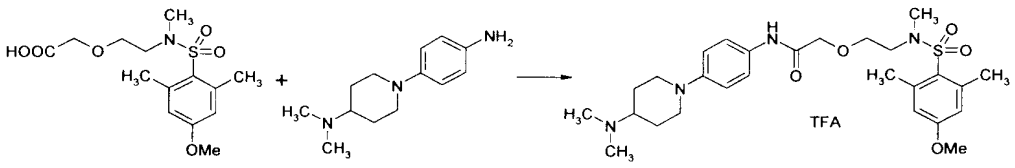
$C_{25}H_{36}N_4O_5S$ x HCl (541.10)

[M+H]+ = 505

HPLC (método 5): tempo de retenção = 1.51 min.

Exemplo 57





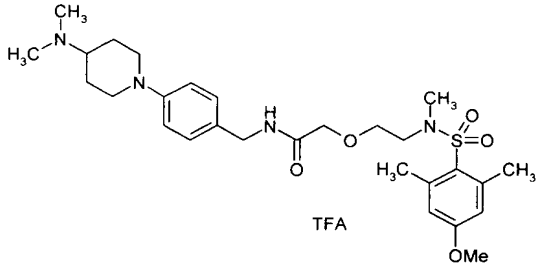
O exemplo 57 é preparado de maneira análoga a 1f a partir de 0,10 g (0,30 mmol) do produto de 53c, 0,066 g (0,30 mmol) do produto de 8b, 0,13 ml (0,91 mmol) de trietilamina e 0,097 g (0,30 mmol) de TBTU em 5 ml de dimetilformamida.

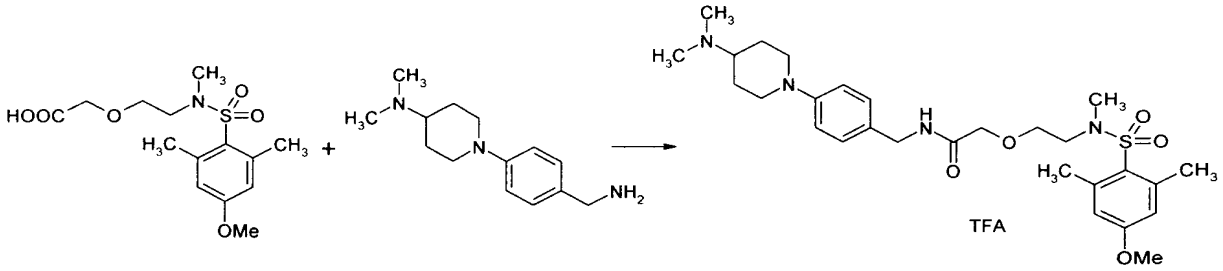
$C_{27}H_{40}N_4O_5S \times C_2HF_3O_2$ (646.72)

[M+H]+ = 533

HPLC (método 5): tempo de retenção = 1.51 min.

Exemplo 58





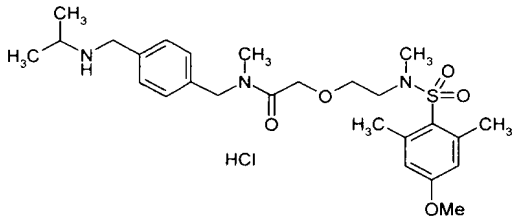
O exemplo 58 é preparado de maneira análoga a 1f a partir de 0,10 g (0,30 mmol) do produto de 53c, 0,07 g (0,30 mmol) do produto de 33a, 0,13 ml (0,91 mmol) de trietilamina e 0,097 g (0,30 mmol) de TBTU em 5 ml de dimetilformamida.

$C_{28}H_{42}N_4O_5S \times C_2HF_3O_2$ (660.75)

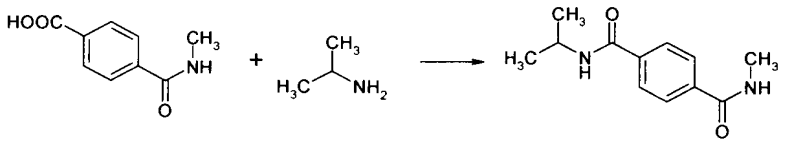
[M+H]+ = 547

HPLC (método 5): tempo de retenção = 1.48 min.

Exemplo 59



59a)



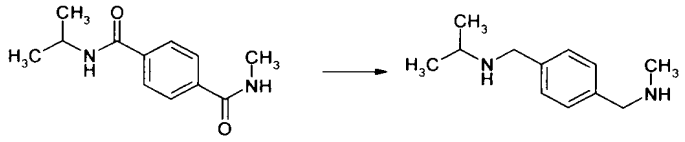
59a é preparado de maneira análoga a 1f a partir de 2,00 g (11,16 mmols) de monometilamida de ácido tereftálico (EMKA), 1,90 ml (22,32 mmols) de isopropilamina (Aldrich), 3,11 ml (22,32 mmols) de trietilamina e 4,30 g (13,40 mmol) de TBTU em 60 ml de tetrahidrofurano.

$C_{12}H_{16}N_2O_2$ (220.27)

[M+H]+ = 221

HPLC (método 4): tempo de retenção = 2.3 min.

59b)



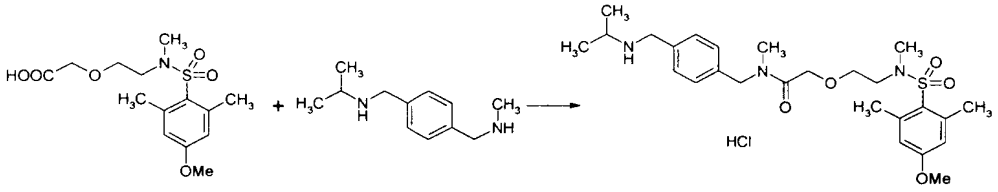
59b é preparado de maneira análoga a 38f a partir de 1,34 g (6,08 mmols) do produto de 59a e 25,00 ml (25,00 mmols) de hidreto de lítioalumínio 1 M em tetrahidrofurano (Aldrich) em 150 ml de tetrahidrofurano.

$C_{12}H_{20}N_2$ (192,30)

[M+H]+ = 193

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 017.

59c)



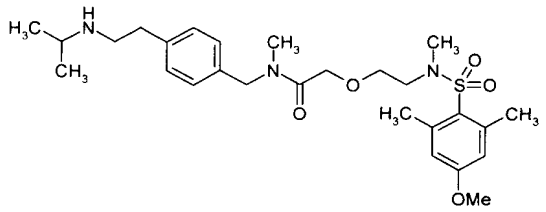
O exemplo 59 é preparado de maneira análoga a 1f a partir de 0,099 g (0,30 mmol) do produto de 53c, 0,058 g (0,30 mmol) do produto de 59b, 0,10 ml (0,75 mmol) de trietilamina e 0,12 g (0,36 mmol) de TBTU em 8 ml de tetrahidrofurano.

$C_{26}H_{39}N_3O_5S$ x HCl (542.13)

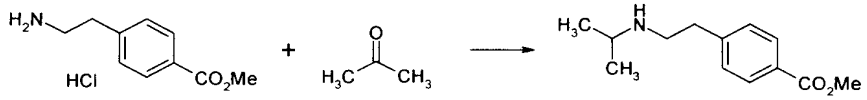
[M+H]+ = 506

HPLC (método 4): tempo de retenção = 3.1 min.

Exemplo 60



60a)



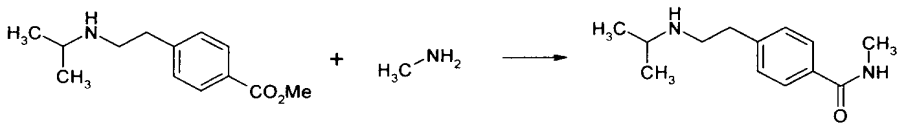
Uma mistura de 3,00 g (13,91 mmols) de éster metílico de ácido 4-aminoetilbenzóico (EMKA), 1,94 ml (13,91 mmols) de trietilamina e 50 ml de tetrahidrofurano é agitada à temperatura ambiente por 10 minutos e depois adicionada a 1,13 ml (15,30 mmols) de acetona. A mistura de reação é agitada à temperatura ambiente por mais 30 minutos, depois são acrescentados 3,24 g (15,30 mmols) de triacetoxiborohidreto de sódio e 1,19 ml (20,86 mmols) de ácido acético. Deixa-se agitar à temperatura ambiente por 16 horas. A mistura de reação é concentrada no vácuo à secura, o resíduo é retomado com HCl 1 M e extraído com acetato de etila (rejeitar a fase orgânica). A fase aquosa é alcalinizada com solução saturada de carbonato de potássio e extraída com acetato de etila. Os extratos orgânicos são secos sobre sulfato de sódio e concentrados no vácuo à secura.

$C_{13}H_{19}NO_2$ (221.30)

[M+H]+ = 222

HPLC (método 4): tempo de retenção = 2.2 min.

60b)



Uma mistura de 2,52 g (11,39 mmols) do produto de 60a, 11,40 ml (22,80 mmols) de metilamina 2 M em tetrahidrofurano (Aldrich), 0,54 g (5,70 mmols) de cloreto de magnésio (Aldrich) e 100 ml de tetrahidrofurano é

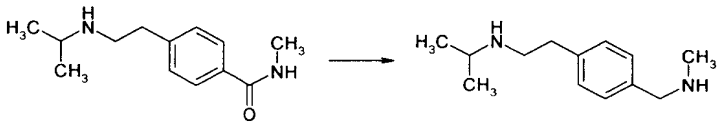
agitada no autoclave a 120°C por 17 horas. A mistura de reação é filtrada, o filtrado concentrado no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/metanol/amoníaco 9:1:0,1).

$C_{13}H_{20}N_2O$ (220.31)

[M+H]+ = 221

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,21.

60c)



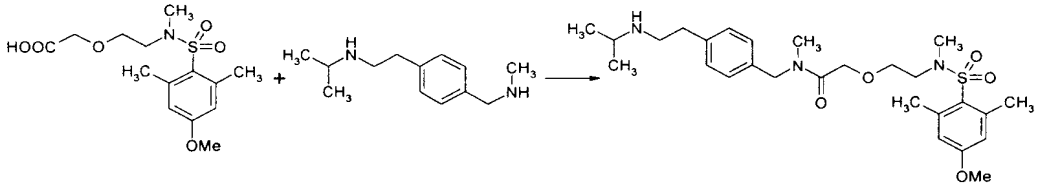
60c é preparado de maneira análoga a 38f a partir de 1,49 g (6,76 mmols) do produto de 60b e 10,00 ml (10,00 mmols) de hidreto de lítioalumínio 1 M em tetrahidrofurano (Aldrich) em 60 ml de tetrahidrofurano.

$C_{13}H_{22}N_2$ (206.33)

[M+H]+ = 207

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,10.

60d)



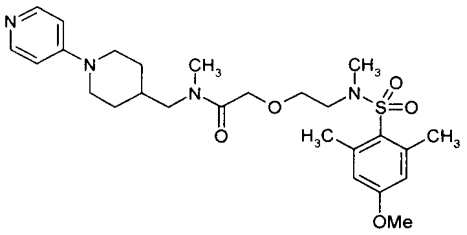
O exemplo 60 é preparado de maneira análoga a 1f a partir de 0,099 g (0,30 mmol) do produto de 53c, 0,062 g (0,30 mmol) do produto de 60c, 0,083 ml (0,60 mmol) de trietilamina e 0,12 g (0,36 mmol) de TBTU em 8 ml de tetrahidrofurano.

$C_{27}H_{41}N_3O_5S$ (519.70)

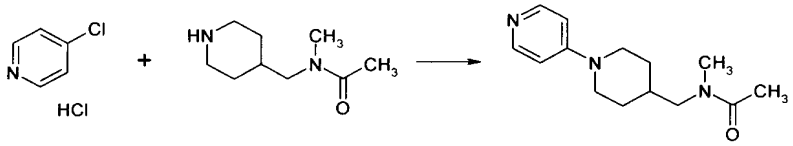
[M+H]+ = 520

HPLC (método 4): tempo de retenção = 3.2 min.

Exemplo 61



61a)

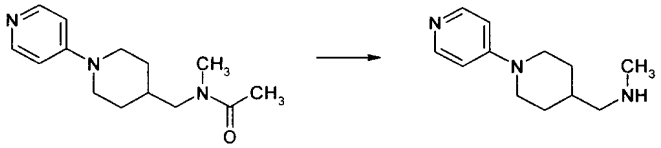


61 é preparado de maneira análoga a 28c a partir de 1,00 g (6,67 mmols) de cloridrato de 4-cloropiridina (Aldrich) e 2,55 g (15,00 mmols) de N-metil-N-piperidin-4-ilmetil-acetamida (DE 110635, Rhône-Poulenc, 1961) em 1 ml de água.

$C_{14}H_{21}N_3O$ (247.34)

[M+H]+ = 248

61b)

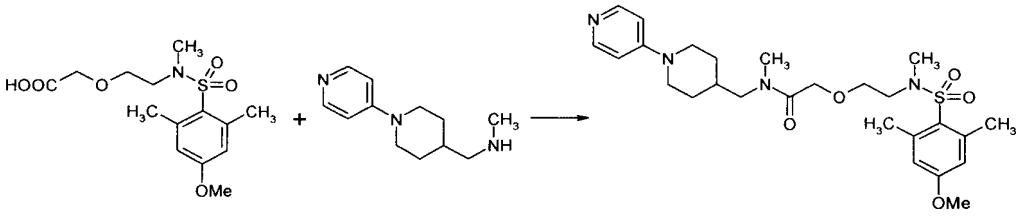


Uma mistura de 1,00 g (4,04 mmols) do produto de 61a e 10 ml de HCl semiconcentrado é aquecida sob refluxo por três dias. A seguir, a mistura de reação é diluída com água, alcalinizada com soda cáustica a 20% e extraída com acetato de etila. Os extratos orgânicos são secos sobre sulfato de sódio e concentrados no vácuo à secura.

$C_{12}H_{19}N_3$ (205.30)

DC: gel de sílica, diclorometano/etanol 9:1, valor Rf = 0,2.

61c)



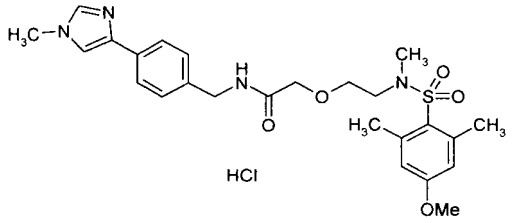
O exemplo 61 é preparado de maneira análoga a 1f a partir de 0,099 g (0,30 mmol) do produto de 53c, 0,062 g (0,30 mmol) do produto de 61b, 0,083 ml (0,60 mmol) de trietilamina e 0,12 g (0,36 mmol) de TBTU em 8 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{26}H_{38}N_4O_5S$ (518.67)

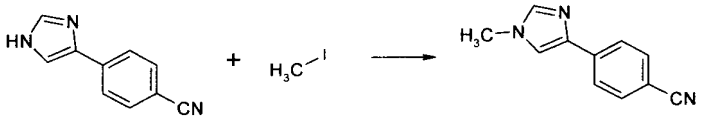
[M+H]+ = 519

HPLC (método 4): tempo de retenção = 3.2 min.

Exemplo 62



62a)



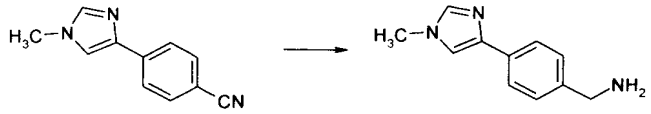
Uma mistura de 1,69 g (10,00 mmols) de 4-(1H-imidazol-4-il)-benzonitrila (J. Am. Chem. Soc. 93, 1971, 4256-4263), 1,12 g (10,00 mmols) de terc-butilato de potássio e 25 ml de dimetilsulfóxido é inicialmente agitada à temperatura ambiente por 30 minutos, depois lentamente adicionada a 0,62 ml (10,00 mmols) de iodeto de metila e em seguida, agitada por mais 2,5 horas à temperatura ambiente. A seguir, a mistura de reação é colocada em água, o precipitado formado é filtrado e seco no vácuo. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/etanol 19:1).

$C_{11}H_9N_3$ (183.21)

[M+H]+ = 184

HPLC (método 4): tempo de retenção = 1.9 min.

62b)

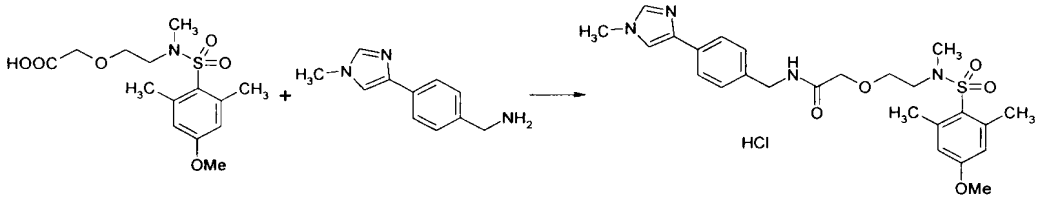


62b é preparado de maneira análoga a 34b a partir de 1,02 g (5,57 mmols) do produto de 62a, 0,20 g de níquel de Raney e 30 ml de solução metanólica de amoníaco.

$C_{11}H_{13}N_3$ (187.24)

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,27.

62c)



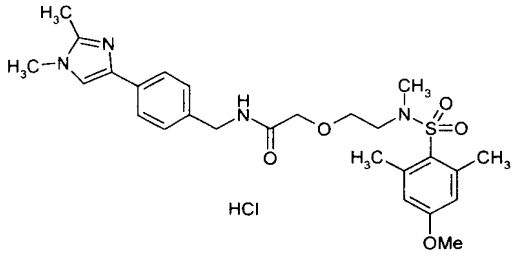
O exemplo 62 é preparado de maneira análoga a 1f a partir de 0,099 g (0,30 mmol) do produto de 53c, 0,056 g (0,30 mmol) do produto de 62b, 0,083 ml (0,60 mmol) de trietilamina e 0,12 g (0,36 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{25}H_{32}N_4O_5S$ x HCl (537.07)

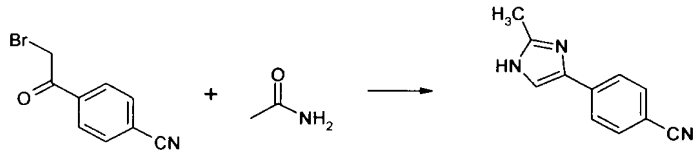
[M+H]+ = 501

HPLC (método 4): tempo de retenção = 3.2 min.

Exemplo 63



63a)



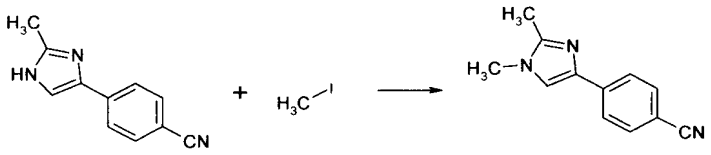
5,00 g (22,32 mmols) de 2-bromo-4'-ciano-acetofenona (Aldrich) e 10,00 g (169,29 mmols) de acetamida (Merck) são aquecidos juntos a 210°C sob agitação por duas horas. Após o resfriamento, a mistura de reação é misturada à água e acidificada com HCl 2 M. O precipitado é filtrado e rejeitado. O filtrado é alcalinizado com solução de amoníaco concentrada, o precipitado é filtrado e seco no vácuo. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/etanol 19:1).

$C_{11}H_9N_3$ (183.21)

[M-H]- = 182

HPLC (método 4): tempo de retenção = 1.9 min.

63b)



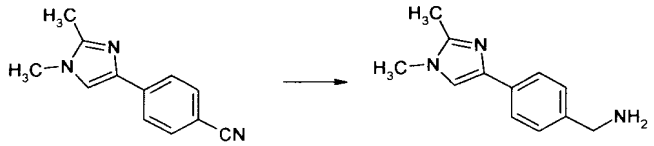
63b é preparado de maneira análoga a 62a a partir de 2,39 g (13,05 mmols) do produto de 63a, 1,46 g (13,05 mmols) de terc-butilato de potássio e 0,81 ml (13,05 mmols) de iodeto de metila em 50 ml de dimetilsulfóxido.

$C_{12}H_{11}N_3$ (197.24)

[M+H]+ = 198

HPLC (método 4): tempo de retenção = 1.9 min.

63c)



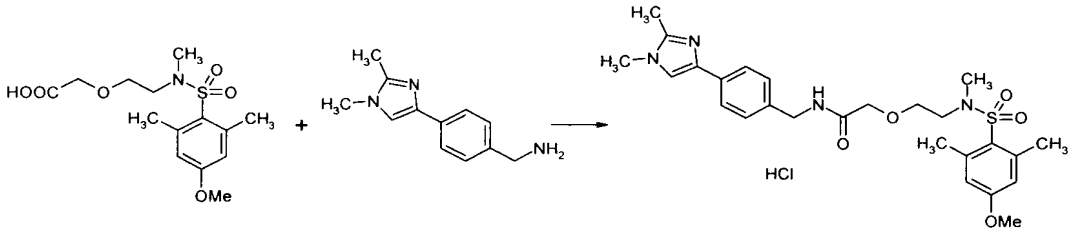
63c é preparado de maneira análoga a 34b a partir de 2,04 g (10,34 mmols) do produto de 63b, 0,40 g de níquel de Raney e 50 ml de so-

lução metanólica de amoníaco.

$C_{12}H_{15}N_3$ (201.27)

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,19.

63d)



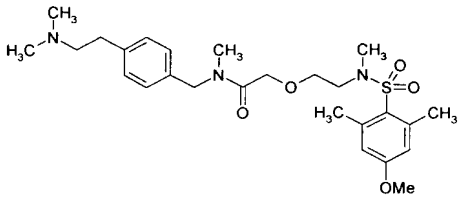
O exemplo 63 é preparado de maneira análoga a 1f a partir de 0,099 g (0,30 mmol) do produto de 53c, 0,060 g (0,30 mmol) do produto de 63c, 0,083 ml (0,60 mmol) de trietilamina e 0,12 g (0,36 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{26}H_{34}N_4O_5S$ x HCl (551.10)

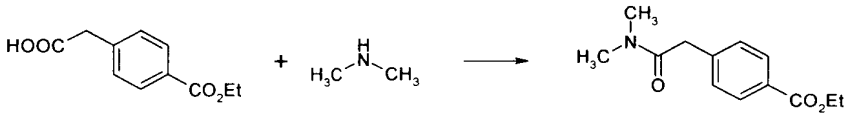
[M+H]+ = 515

HPLC (método 4): tempo de retenção = 3.2 min.

Exemplo 64



64a)



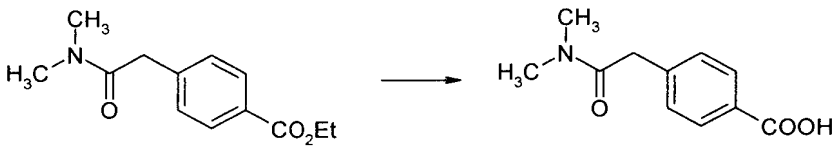
64a é preparado de maneira análoga a 1f a partir de 4,00 g (19,21 mmols) de éster etílico de ácido 4-carboximetil-benzóico (J. Med. Chem. 41, 1998, 5219-5246), 19,21 ml (38,42 mmols) de dimetilamina 2 M em tetrahidrofurano (Aldrich), 5,36 ml (38,42 mmols) de trietilamina e 7,39 g (23,00 mmol) de TBTU em 100 ml de tetrahidrofurano.

$C_{13}H_{17}NO_3$ (235,28)

[M+H]+ = 236

HPLC (método 4): tempo de retenção = 3,3 min.

64b)



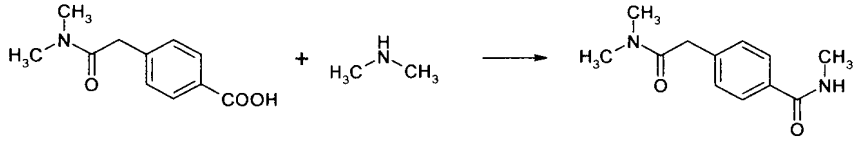
Uma mistura de 3,07 g (13,05 mmols) do produto de 64a, 9,75 ml (39,00 mmols) de soda cáustica 4 M, 9,75 ml de água e 50 ml de etanol é agitada à temperatura ambiente durante a noite. A seguir, o etanol é removido no vácuo. O resíduo aquoso é acidificado com HCl 4 M e extraído com acetato de etila. Os extratos orgânicos são secos sobre sulfato de sódio e concentrados no vácuo à secura. O produto obtido dessa maneira é triturado com éter dietílico e seco.

$C_{11}H_{13}NO_3$ (207.23)

[M+H]+ = 208

HPLC (método 4): tempo de retenção = 2.3 min.

64c)



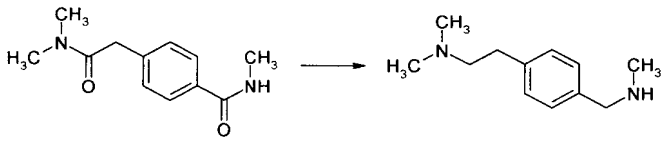
64c é preparado de maneira análoga a 1f a partir de 2,30 g (11,10 mmols) do produto de 64b, 11,10 ml (22,20 mmols) de dimetilamina 2 M em tetrahidrofurano (Aldrich), 3,09 ml (22,20 mmols) de trietilamina e 4,28 g (13,32 mmols) de TBTU em 70 ml de tetrahidrofurano.

$C_{12}H_{16}N_2O_2$ (220.27)

[M+H]+ = 221

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,44.

64d)



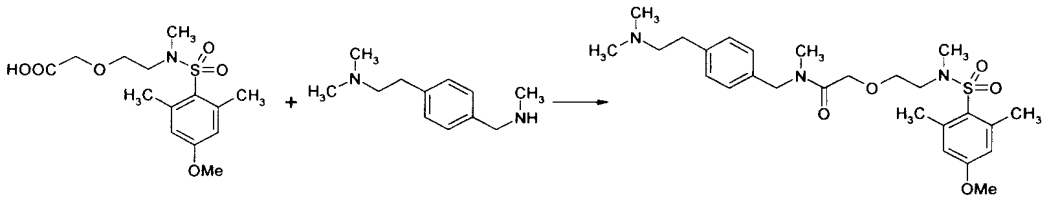
64d é preparado de maneira análoga a 38f a partir de 1,92 g (8,72 mmols) do produto de 64c e 40,00 ml (40,00 mmols) de hidreto de lítioalumínio 1 M em tetrahidrofurano (Aldrich) em 150 ml de tetrahidrofurano.

$C_{12}H_{20}N_2$ (192.30)

[M+H]+ = 193

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,10.

64e)



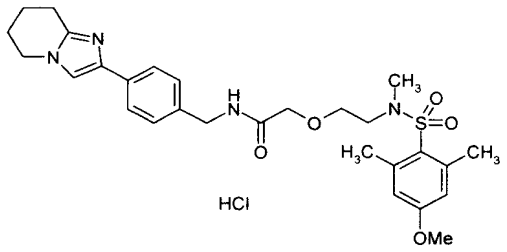
O exemplo 64 é preparado de maneira análoga a 1f a partir de 0,099 g (0,30 mmol) do produto de 53c, 0,058 g (0,30 mmol) do produto de 64d, 0,083 ml (0,60 mmol) de trietilamina e 0,12 g (0,36 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{26}H_{39}N_3O_5S$ (505.67)

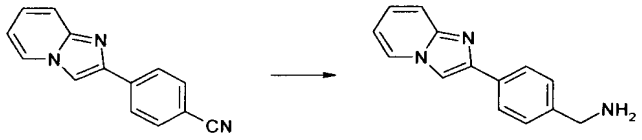
[M+H]+ = 508

HPLC (método 4): tempo de retenção = 3.0 min.

Exemplo 65



65a)



65a é preparado de maneira análoga a 34b a partir de 0,40 g (1,82 mmol) de 4-imidazo[1,2-a]piridin-2-il-benzonitrila (J. Med. Chem. 41, 1998, 4317-4328), 0,10 g de níquel de Raney e 40 ml de solução metanólica de amoníaco.

$C_{14}H_{13}N_3$ (223.27)

[M+H]+ = 224

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,06.

65b)

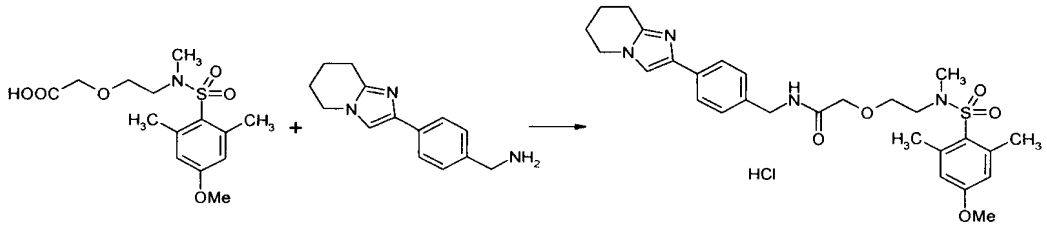


Uma mistura de 0,40 g (1,79 mmol) do produto de 65a, 0,05 g de óxido de platina e 40 ml de metanol é hidrogenada no autoclave a 50°C. O catalisador é filtrado, o filtrado é concentrado no vácuo à secura.

$C_{14}H_{17}N_3$ (227.30)

[M+H]+ = 228

65c)



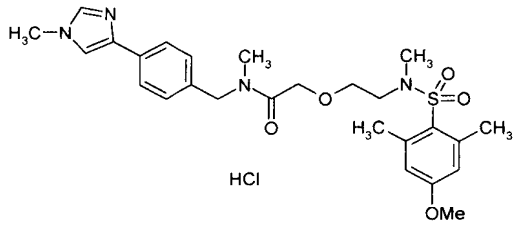
O exemplo 65 é preparado de maneira análoga a 1f a partir de 0,15 g (0,44 mmol) do produto de 53c, 0,10 g (0,44 mmol) do produto de 65b, 0,15 ml (1,09 mmol) de trietilamina e 0,16 g (0,48 mmol) de TBTU em 30 ml de tetrahidrofurano e 10 ml de dimetilformamida.

$C_{28}H_{36}N_4O_5S$ x HCl (577.14)

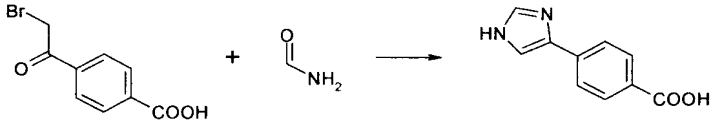
[M+H]+ = 541

HPLC (método 5): tempo de retenção = 1.57 min.

Exemplo 66



66a)

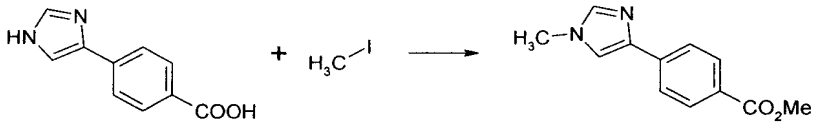


Uma mistura de 0,50 g (2,06 mmols) de ácido 4-bromoacetilbenzóico (Fluorochem) e 5 ml de formamida é agitada no micro-ondas por uma hora a 150°C. Depois de resfriar, o produto precipitado é filtrado, lavado com éter dietílico e seco.

$C_{10}H_8N_2O_2$ (188.18)

[M+H]+ = 189

66b)

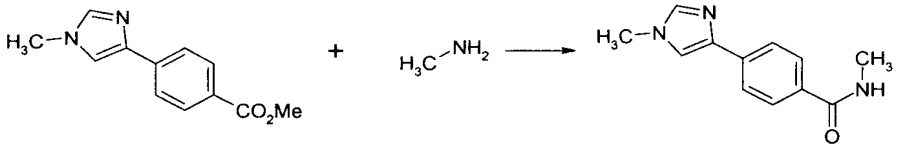


Uma mistura de 1,60 g (8,50 mmols) do produto de 66a, 5,40 g (38,04 mmols) de iodeto de metila, 7,00 g (25,33 mmols) de carbonato de potássio e 30 ml de dimetilformamida é agitada à temperatura ambiente durante a noite. A mistura de reação é filtrada, o filtrado concentrado no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/metanol 100:1 a 75:1).

$C_{12}H_{12}N_2O_2$ (216.24)

[M+H]+ = 217.

66c)

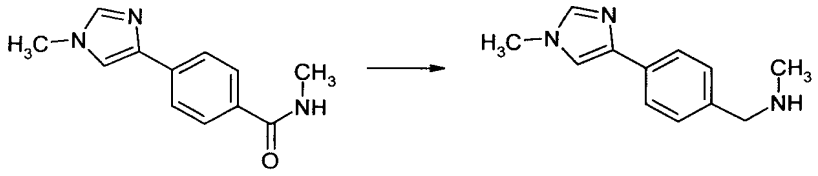


Uma mistura de 0,75 g (3,47 mmols) do produto de 66b e 20 ml de metilamina a 33% em etanol (Fluka) é aquecida no autoclave a 160°C durante a noite. A mistura de reação é concentrada no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/metanol 50:1 a 25:1).

$C_{12}H_{13}N_3O$ (215.25)

[M+H]+ = 216.

66d)



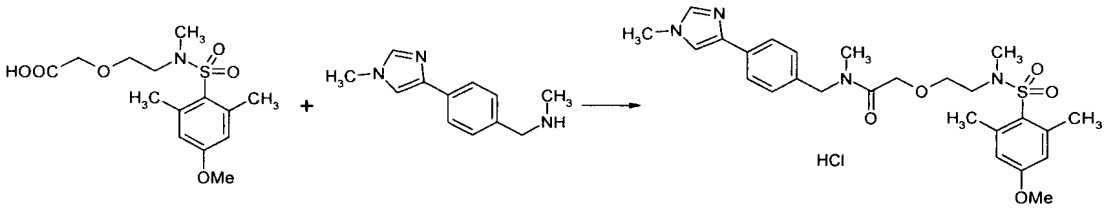
66d é preparado de maneira análoga a 38f a partir de 0,41 g (1,91 mmol) do produto de 66c e 3,00 ml (3,00 mmols) de hidreto de lítioa-lumínio 1 M em tetrahidrofurano (Aldrich) em 70 ml de tetrahidrofurano.

$C_{12}H_{15}N_3$ (201.27)

[M+H]+ = 202

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,1, valor Rf = 0,16.

66e)



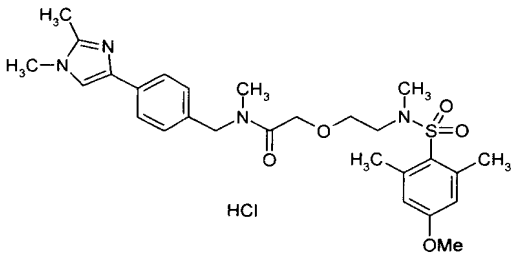
O exemplo 66 é preparado de maneira análoga a 1f a partir de 0,15 g (0,45 mmol) do produto de 53c, 0,09 g (0,45 mmol) do produto de 66d, 0,11 ml (1,09 mmol) de trietilamina e 0,16 g (0,50 mmol) de TBTU em 30 ml de tetrahidrofurano e 5 ml de dimetilformamida.

$C_{26}H_{34}N_4O_5S$ x HCl (551.10)

[M+H]+ = 515

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,52.

Exemplo 67



67a)



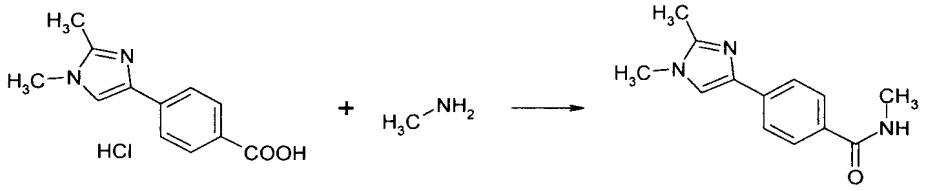
Uma mistura de 1,21 g (6,14 mmols) do produto de 63b, 20 ml de soda cáustica a 20% e 40 ml de etanol é agitada sob refluxo durante a noite. O etanol é removido no vácuo. O resíduo é diluído com água e acidificado com HCl 4 M. O produto precipitado é filtrado e seco na estufa de secagem de ar circulante a 50°C.

$C_{12}H_{12}N_2O_2$ (252,70)

[M+H]+ = 217

HPLC (método 4): tempo de retenção = 1,7 min.

67b)



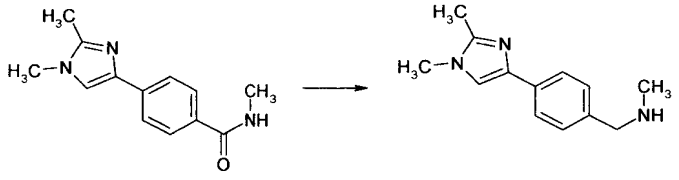
67b é preparado de maneira análoga a 1f a partir de 1,55 g (6,13 mmols) do produto de 67a, 4,60 ml (9,20 mmols) de metilamina 2 M em tetrahidrofurano (Aldrich), 1,71 ml (12,30 mmols) de trietilamina e 2,38 g (7,40 mmols) de TBTU em 50 ml de tetrahidrofurano.

$C_{13}H_{15}N_3O$ (229.28)

[M+H]+ = 230

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,47.

67c)



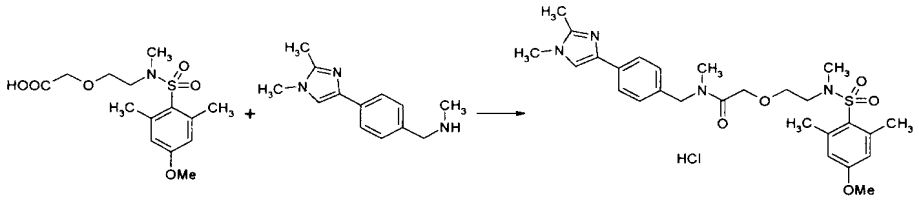
67c é preparado de maneira análoga a 38f a partir de 1,33 g (5,80 mmols) do produto de 67b e 15,00 ml (15,00 mmols) de hidreto de lítioalumínio 1 M em tetrahidrofurano (Aldrich) em 80 ml de tetrahidrofurano.

$C_{13}H_{17}N_3$ (215.29)

[M+H]+ = 216

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,29.

67d)



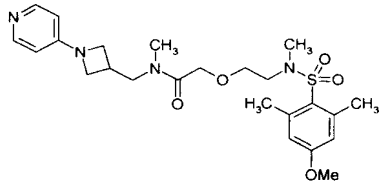
O exemplo 67 é preparado de maneira análoga a 1f a partir de 0,099 g (0,30 mmol) do produto de 53c, 0,065 g (0,30 mmol) do produto de 67c, 0,083 ml (0,60 mmol) de trietilamina e 0,12 g (0,36 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{27}H_{36}N_4O_5S$ x HCl (565.13)

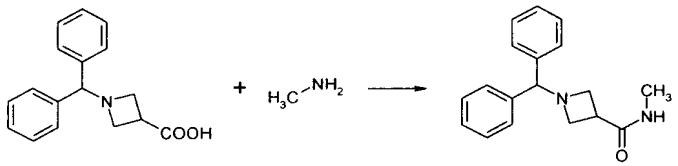
[M+H]+ = 529

HPLC (método 4): tempo de retenção = 3.1 min.

Exemplo 68



68a)

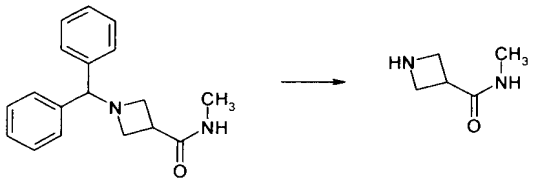


68a é preparado de maneira análoga a 1f a partir de 5,39 g (20,16 mmols) de ácido 1-benzidril-azetidina-3-carboxílico (Acros), 15 ml (30,00 mmols) de metilamina 2 M em tetrahidrofurano (Aldrich), 5,58 ml (40,00 mmols) de trietilamina e 7,71 g (24,00 mmols) de TBTU em 150 ml de tetrahidrofurano.

$C_{18}H_{20}N_2O$ (280.36)

HPLC (método 4): tempo de retenção = 2.5 min.

68b)

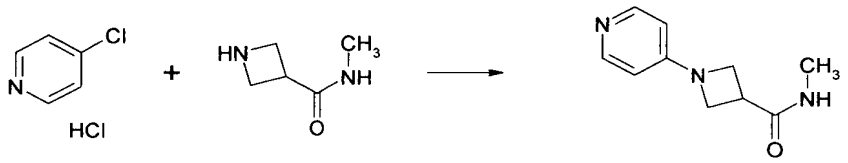


Uma mistura de 5,32 g (18,98 mmols) do produto de 68a, 0,50 g de paládio sobre carvão (10%) e 100 ml de metanol é hidrogenada no autoclave à temperatura ambiente por 24 horas. O catalisador é filtrado, o filtrado é concentrado no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/metanol /amoníaco 70:30:3).

$C_5H_{10}N_2O$ (114.15)

DC: gel de sílica, diclorometano/metanol/amoníaco 7:3:0,3 valor Rf = 0,17.

68c)



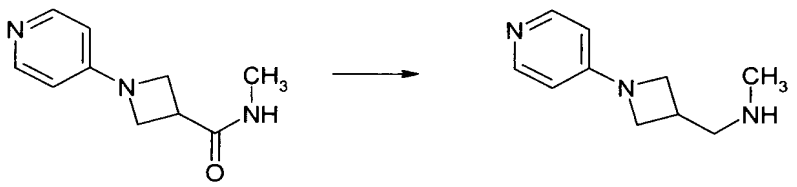
68c é preparado de maneira análoga a 28c a partir de 1,31 g (8,76 mmols) de cloridrato de 4-cloropiridina (Aldrich), 1,00 g (8,76 mmols) do produto de 68b e 2,40 ml (17,22 mmols) de trietilamina em 5 ml de etanol.

$C_{10}H_{13}N_3O$ (191.23)

[M+H]+ = 192

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,25.

68d)



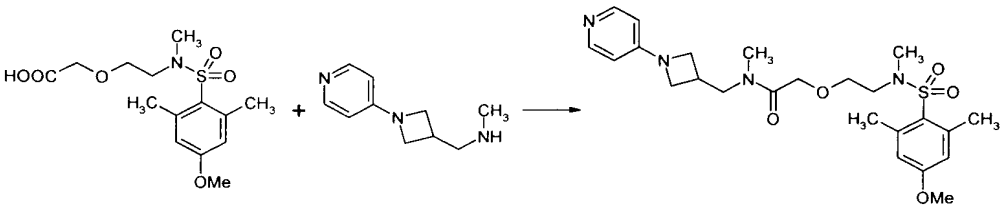
68d é preparado de maneira análoga a 38f a partir de 0,46 g (2,41 mmols do produto de 68c e 5,00 ml (5,00 mmols) de hidreto de lítioalumínio 1 M em tetrahidrofurano (Aldrich) em 20 ml de tetrahidrofurano.

$C_{10}H_{15}N_3$ (177.25)

[M+H]+ = 178

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,2, valor Rf = 0,40.

68e)



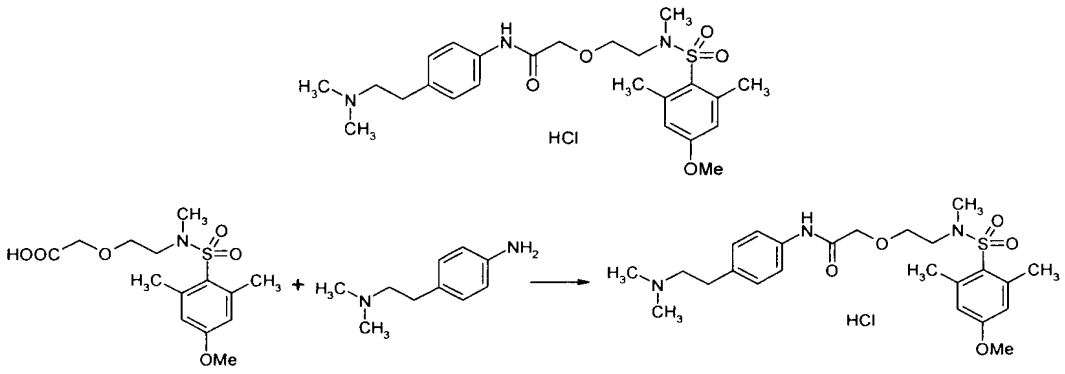
O exemplo 68 é preparado de maneira análoga a 1f a partir de 0,083 g (0,25 mmol) do produto de 53c, 0,044 g (0,25 mmol) do produto de 68d, 0,070 ml (0,50 mmol) de trietilamina e 0,096 g (0,30 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{24}H_{34}N_4O_5S$ (490.62)

[M+H]+ = 491

HPLC (método 4): tempo de retenção = 2.9 min.

Exemplo 69



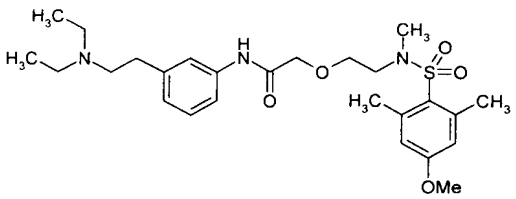
O exemplo 69 é preparado de maneira análoga a 1f a partir de 0,083 g (0,25 mmol) do produto de 53c, 0,041 g (0,25 mmol) de 4-(2-dimetilamino-etil)-fenilamina (JW Pharmlab), 0,070 ml (0,50 mmol) de trietilamina e 0,096 g (0,30 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

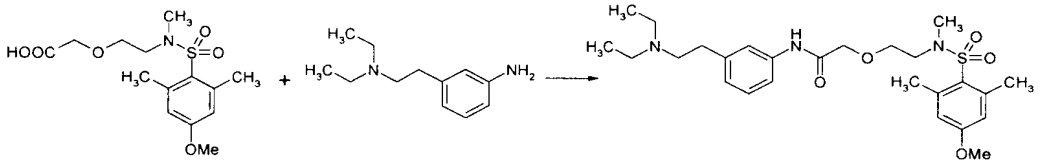
$C_{24}H_{35}N_3O_5S$ x HCl (514.08)

[M+H]+ = 478

HPLC (método 4): tempo de retenção = 3.1 min.

Exemplo 70





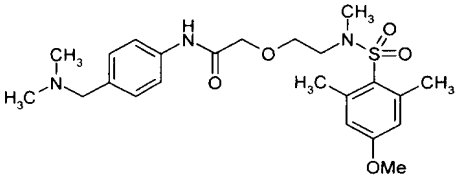
O exemplo 70 é preparado de maneira análoga a 1f a partir de 0,083 g (0,25 mmol) do produto de 53c, 0,048 g (0,25 mmol) de 3-(2-dietilamino-etil)-fenilamina (de maneira análoga a J. Med. Chem. 28, 1985, 1533-1536), 0,070 ml (0,50 mmol) de trietilamina e 0,096 g (0,30 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

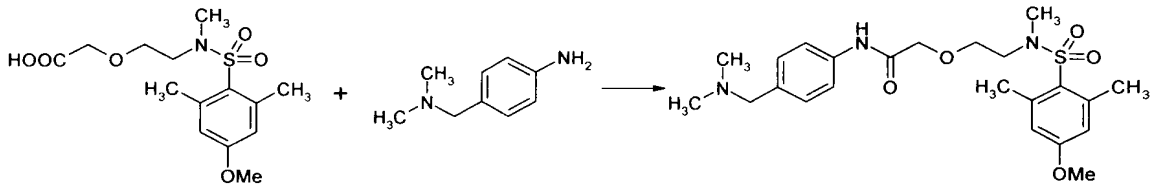
$C_{26}H_{39}N_3O_5S$ (505.67)

[M+H]+ = 509

HPLC (método 4): tempo de retenção = 3.4 min.

Exemplo 71





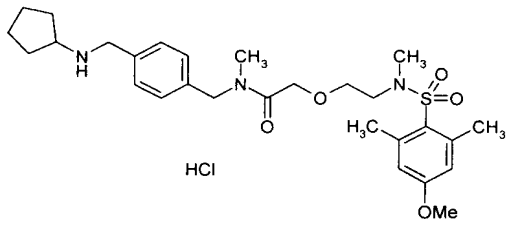
O exemplo 71 é preparado de maneira análoga a 1f a partir 0,083 g (0,25 mmol) do produto de 53c, 0,038 g (0,25 mmol) de 4-dimetilaminometil-fenilamina (J. Chem. Soc. 1935, 871), 0,070 ml (0,50 mmol) de trietilamina e 0,096 g (0,30 mmol) de TBTU em 7 ml de tetrahidro-furano e 1 ml de dimetilformamida.

$C_{23}H_{33}N_3O_5S$ (463.59)

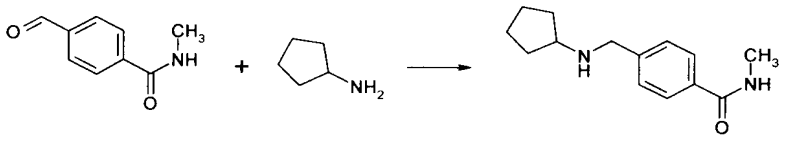
[M+H]+ = 464

HPLC (método 4): tempo de retenção = 3.1 min.

Exemplo 72



72a)

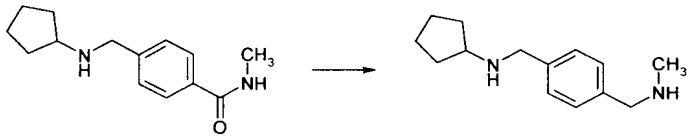


72a é preparado de maneira análoga a 60a a partir de 0,82 g (5,00 mmols) de metilamida de ácido 4-formil-benzóico (EMKA), 0,50 ml (5,00 mmols) de ciclopentilamina (Aldrich), 0,37 ml (6,50 mmols) de ácido acético e 1,59 g (7,50 mmol) de triacetoxiborohidreto de sódio em 30 ml de tetrahidrofurano.

$C_{14}H_{20}N_2O$ (232.32)

DC: gel de sílica, diclorometano/etanol 9:1, valor Rf = 0,15.

72b)



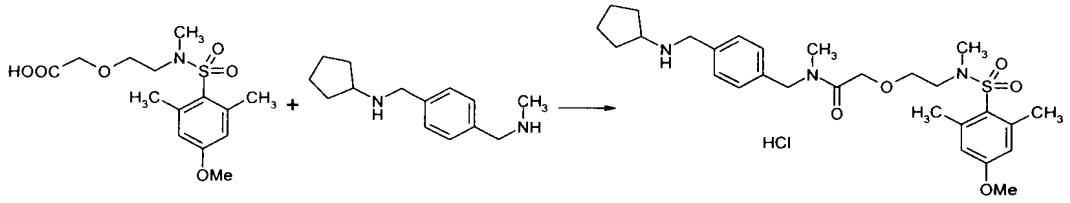
72b é preparado de maneira análoga a 38f a partir de 1,00 g (4,30 mmols) do produto de 72a e 9,00 ml (9,00 mmols) de hidreto de litioalumínio 1 M em tetrahidrofurano (Aldrich) em 40 ml de tetrahidrofurano.

$C_{14}H_{22}N_2$ (218.34)

[M+H]+ = 219

DC: gel de sílica, diclorometano/etanol 9:1, valor Rf = 0,2.

72c)



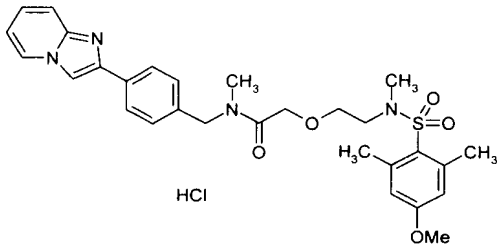
Exemplo 72 é preparado de maneira análoga a 1f a partir de 0,20 g (0,60 mmol) do produto de 53c, 0,13 g (0,60 mmol) do produto de 72b, 0,21 ml (1,50 mmol) de trietilamina e 0,23 g (0,72 mmol) de TBTU em 10 ml de tetrahidrofurano.

$C_{28}H_{41}N_3O_5S$ x HCl (568.17)

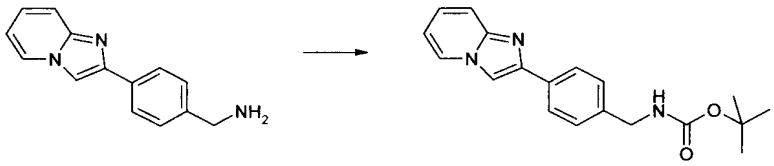
[M+H]+ = 532

HPLC (método 5): tempo de retenção = 1.60 min.

Exemplo 73



73a)



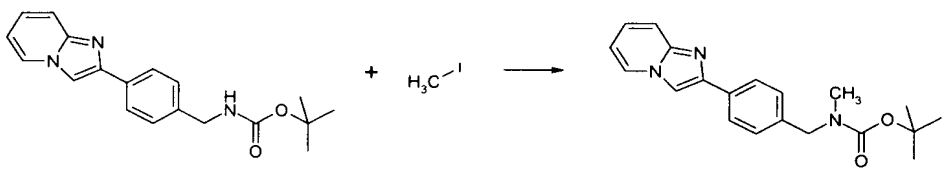
Uma mistura de 2,60 g (11,65 mmols) do produto de 65a, 2,55 g (11,68 mmols) de anidrido boc e 100 ml de dimetilformamida é agitada à temperatura ambiente por duas horas. Em seguida, acrescentam-se lentamente 100 ml de água. O produto precipitado é filtrado, lavado com água e éter de petróleo e seco.

$C_{19}H_{21}N_3O_2$ (323.39)

[M+H]+ = 324

DC: gel de sílica, diclorometano/metanol 9:1: valor Rf = 0,78.

73b)

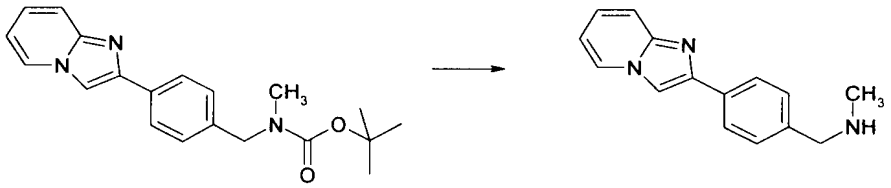


73b é preparado de maneira análoga a 62a a partir de 1,00 g (3,09 mmols) do produto de 73a, 0,70 g (6,24 mmols) de terc-butilato de potássio e 0,98 ml (6,90 mmols) de iodeto de metila em 30 ml de dimetilsulfóxido.

$C_{17}H_{17}N_3O_2$ (295.34)

[M+H]+ = 296

73c)

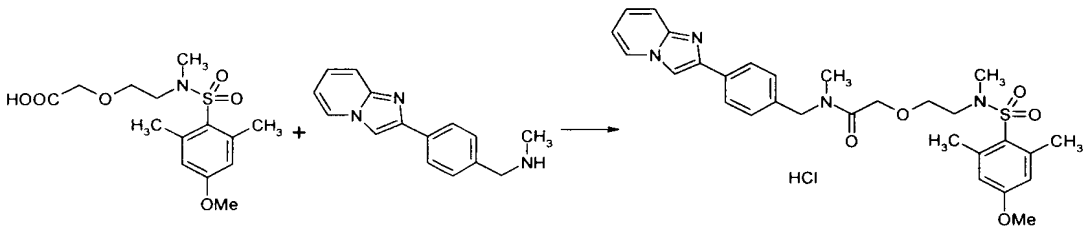


Uma mistura de 0,59 g (1,75 mmol) do produto de 73b, 2 ml de TFA e 30 ml de diclorometano é agitada à temperatura ambiente por três horas. A seguir, a mistura de reação é lavada com água, seca sobre sulfato de sódio e concentrada no vácuo à secura.

$C_{15}H_{15}N_3$ (237.30)

[M+H]+ = 238

73d)



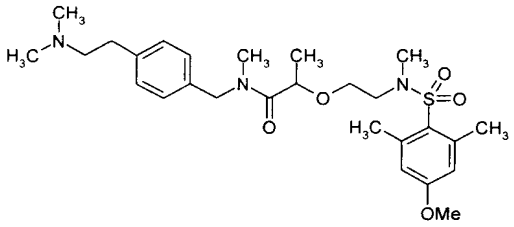
O exemplo 73 é preparado de maneira análoga a 1f a partir de 0,14 g (0,42 mmol) do produto de 53c, 0,10 g (0,42 mmol) do produto de 73c, 0,10 ml (0,99 mmol) de trietilamina e 0,15 g (0,46 mmol) de TBTU em 30 ml de tetrahidrofurano e 5 ml de dimetilformamida.

$C_{29}H_{34}N_4O_5S$ x HCl (587.13)

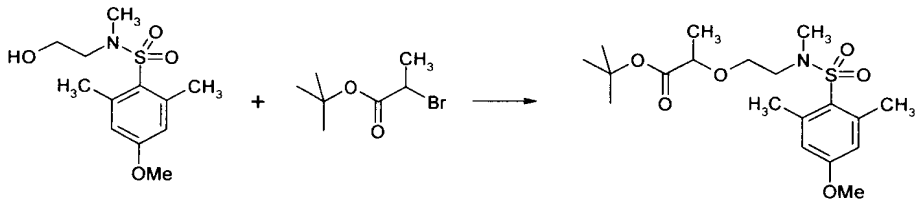
[M+H]+ = 551

HPLC (método 5): tempo de retenção = 1.58 min

Exemplo 74



74a)



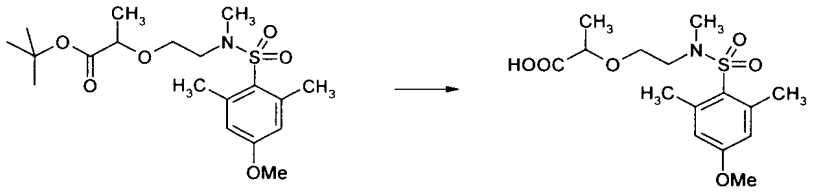
74a é preparado de maneira análoga a 53b a partir de 4,08 g (14,93 mmols) do produto de 53a, 4,68 g (22,39 mmols) de éster terc-butílico de ácido 2-bromopropiônico (TCI), 1,38 g (4,98 mmols) de cloreto de tetrabutilamônio (Fluka) e 70 ml de soda cáustica a 35% em 70 ml de tolueno

$C_{19}H_{31}NO_6S$ (401.52)

[M+H]+ = 402

DC; gel de sílica, éter de petróleo/acetato de etila 7:3, valor Rf = 0,69.

74b)



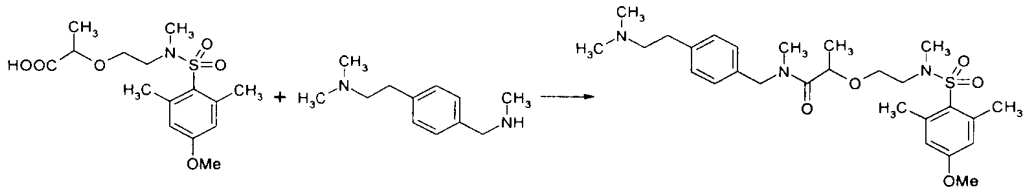
74b é preparado de maneira análoga a 53c a partir de 5,12 g (12,75 mmols) do produto de 74a e 5,89 ml de TFA em 80 ml de diclorometano.

$C_{15}H_{23}NO_6S$ (345.41)

[M+H]+ = 346

DC: gel de sílica, diclorometano/etanol 19:1, valor Rf = 0.25.

74c)



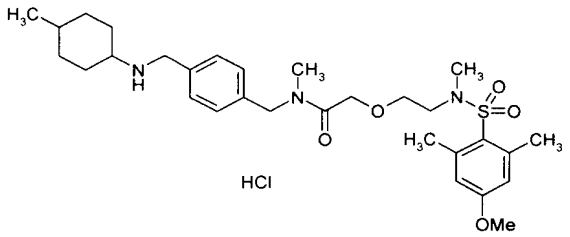
O exemplo 74 é preparado de maneira análoga a 1f a partir de 0,10 g (0,30 mmol) do produto de 74b, 0,058 g (0,30 mmol) do produto de 64d, 0,084 ml (0,60 mmol) de trietilamina e 0,12 g (0,36 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{27}H_{41}N_3O_5S$ (519.70)

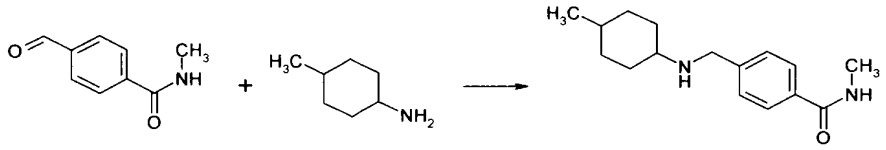
[M+H]+ = 520

HPLC (método 4): tempo de retenção = 3.1 min.

Exemplo 75



75a)

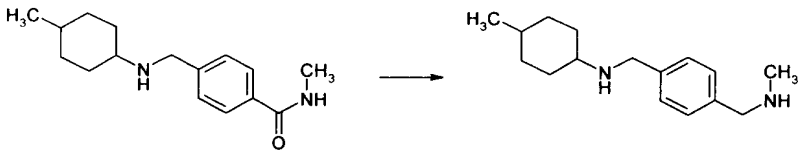


75a é preparado de maneira análoga a 60a a partir de 0,82 g (5,00 mmols) de metilamida de ácido 4-formil-benzóico (EMKA), 0,67 ml (5,00 mmols) de 4-metilciclohexilamina mistura cis/trans (Acros), 0,37 ml (6,50 mmols) de ácido acético e 1,59 g (7,50 mmols) de triacetoxiborohidreto de sódio em 30 ml de tetrahidrofurano.

$C_{16}H_{24}N_2O$ (260.37)

DC: gel de sílica, diclorometano/etanol 9:1: valor Rf = 0,25.

75b)

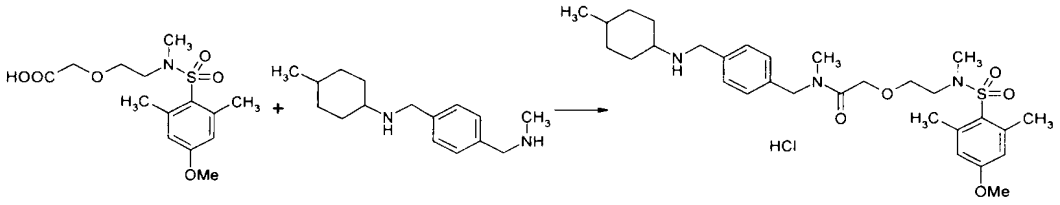


75b é preparado de maneira análoga a 38f a partir de 1,30 g (4,99 mmols) do produto de 75a e 10,00 ml (10,00 mmols) de hidreto de lítioalumínio 1 M em tetrahidrofurano (Aldrich) em 50 ml de tetrahidrofurano.

$C_{16}H_{26}N_2$ (246.39)

DC: gel de sílica, diclorometano/etanol 9:1: valor Rf = 0,2.

75c)



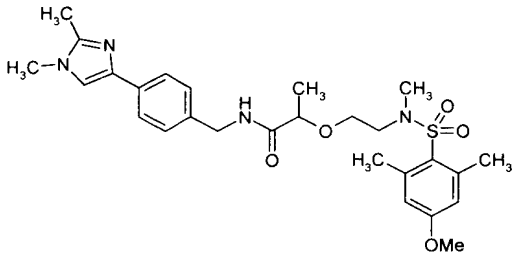
O exemplo 75 é preparado de maneira análoga a 1f a partir de 0,20 g (0,60 mmol) do produto de 53c, 0,15 g (0,60 mmol) do produto de 75b, 0,21 ml (1,50 mmol) de trietilamina e 0,23 g (0,72 mmol) de TBTU em 10 ml de tetrahidrofurano.

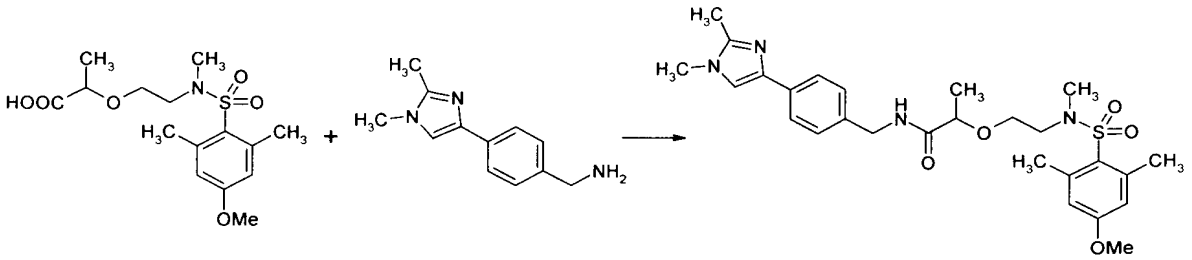
$C_{30}H_{45}N_3O_5S$ x HCl (596.22)

[M+H]+ = 560

HPLC (método 5): tempo de retenção = 1.65 min.

Exemplo 76





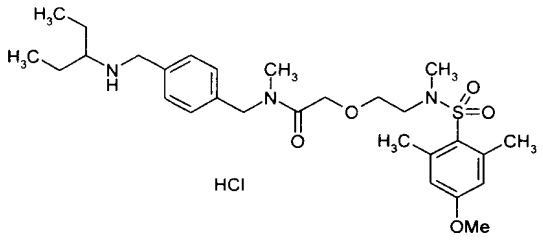
O exemplo 76 é preparado de maneira análoga a 1f a partir de 0,10 g (0,30 mmol) do produto de 74b, 0,060 g (0,30 mmol) do produto de 63c, 0,084 ml (0,60 mmol) de trietilamina e 0,12 g (0,36 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{27}H_{36}N_4O_5S$ (528.66)

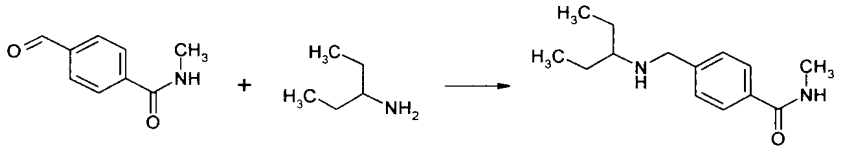
[M+H]+ = 529

HPLC (método 4): tempo de retenção = 3.2 min.

Exemplo 77



77a)



77a é preparado de maneira análoga a 60a a partir de 0,82 g (5,00 mmols) de metilamida de ácido 4-formil-benzóico (EMKA), 0,58 ml (5,00 mmols) de 3-pentilamina (Aldrich), 0,37 ml (6,50 mmols) de ácido acético e 1,59 g (7,50 mmols) de triacetoxiborohidreto de sódio em 30 ml de tetrahidrofurano.

$C_{14}H_{22}N_2O$ (234.34)

[M+H]+ = 235

DC: gel de sílica, diclorometano/etanol 9:1: valor Rf = 0,4.

77b)

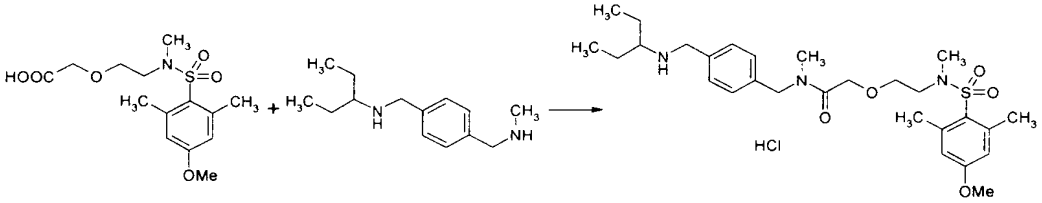


77b é preparado de maneira análoga a 38f a partir de 1,10 g (4,69 mmols) do produto de 77a e 9,40 ml (9,40 mmol) de hidreto de lítioa-lumínio 1 M em tetrahidrofurano (Aldrich) em 40 ml de tetrahidrofurano.

$C_{14}H_{24}N_2$ (220.35)

DC: gel de sílica, diclorometano/etanol 9:1: valor Rf = 0,1.

77c)



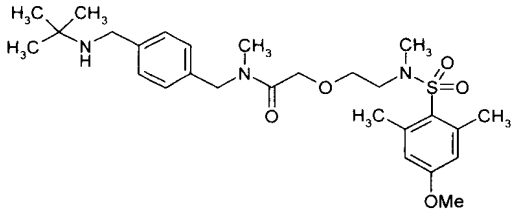
O exemplo 77 é preparado de maneira análoga a 1f a partir de 0,20 g (0,60 mmol) do produto de 53c, 0,13 g (0,60 mmol) do produto de 77b, 0,21 ml (1,50 mmol) de trietilamina e 0,23 g (0,72 mmol) de TBTU em 10 ml de tetrahidrofurano.

$C_{28}H_{43}N_3O_5S$ x HCl (570.18)

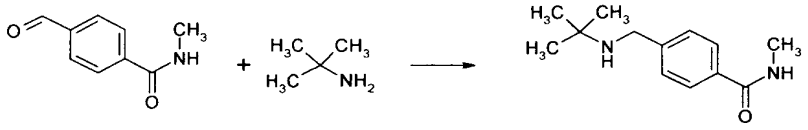
[M+H]+ = 534

DC: gel de sílica, diclorometano/etanol 9:1: valor Rf = 0,45.

Exemplo 78



78a)



78a é preparado de maneira análoga a 60a a partir de 0,82 g

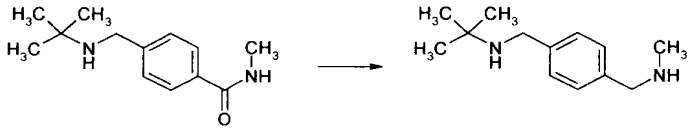
(5,00 mmols) de metilamida de ácido 4-formil-benzóico (EMKA), 0,53 ml (5,00 mmols) de terc-butilamina (Fluka), 0,37 ml (6,50 mmol) de ácido acético e 1,59 g (7,50 mmol) de triacetoxiborohidreto de sódio em 30 ml de tetrahidrofurano.

$C_{13}H_{20}N_2O$ (220.31)

[M+H]+ = 221

DC: gel de sílica, diclorometano/etanol 9:1: valor Rf = 0,15.

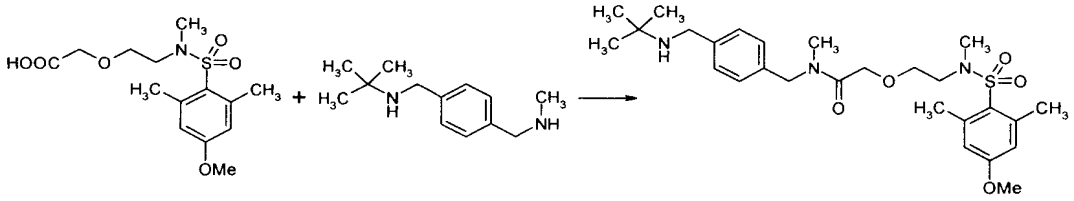
78b)



78b é preparado de maneira análoga a 38f a partir de 1,00 g (4,54 mmol) do produto de 78a e 9,10 ml (9,10 mmol) de hidreto de lítioalumínio 1 M em tetrahidrofurano (Aldrich) em 40 ml de tetrahidrofurano.

$C_{13}H_{22}N_2$ (206.33).

78c)



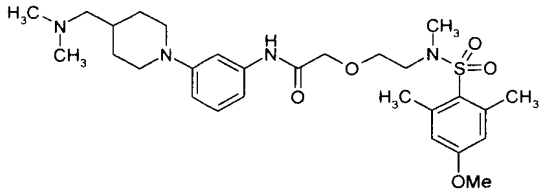
O exemplo 78 é preparado de maneira análoga a 1f a partir de 0,20 g (0,60 mmol) do produto de 53c, 0,12 g (0,60 mmol) do produto de 78b, 0,21 ml (1,50 mmol) de trietilamina e 0,23 g (0,72 mmol) de TBTU em 10 ml de tetrahidrofurano.

$C_{27}H_{41}N_3O_5S$ (519.70)

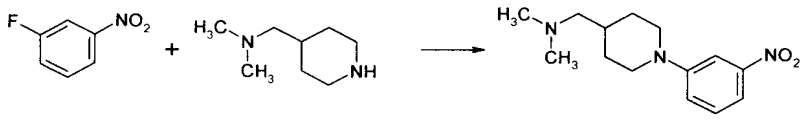
[M+H]+ = 520

HPLC (método 5): tempo de retenção = 1.58 min.

Exemplo 79



79a)



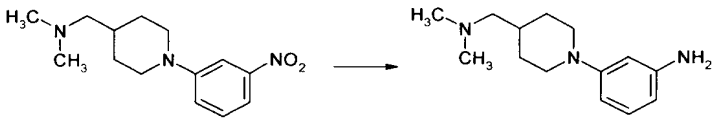
Uma mistura de 0,50 ml (4,70 mmol) de 1-flúor-3-nitrobenzeno (Fluka), 1,34 g (9,39 mmol) de 4-(N,N-dimetilaminometil)-piperidina (Eur. J. Med. Chem. Chim. Ther. 37, 2002, 487 – 502), 0,65 g (4,70 mmol) de carbonato de potássio e 6,6 ml de dimetilsulfóxido é agitada a 110°C por cinco dias. A seguir, a mistura de reação é vertida sobre gelo, o precipitado formado é filtrado. O produto obtido dessa maneira é seco no dessecador a vácuo durante a noite.

$C_{14}H_{21}N_3O_2$ (263.34)

[M+H]+ = 264

DC: gel de sílica, diclorometano/metanol 9:1: valor Rf = 0,20.

79b)

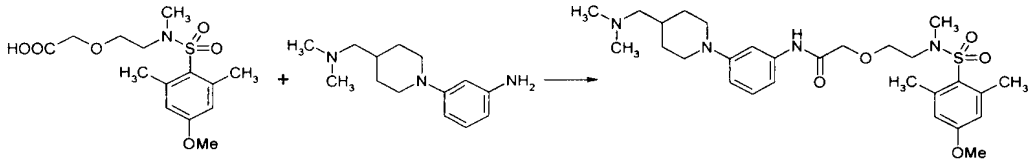


Uma mistura de 0,95 ml (3,60 mmol) do produto de 79a, 0,095 g de paládio sobre carvão (5%) e 72 ml de etanol é hidrogenada no autoclave à temperatura ambiente. O catalisador é filtrado, o filtrado concentrado no vácuo à secura.

$C_{14}H_{23}N_3$ (233.35)

[M+H]+ = 234

79c)



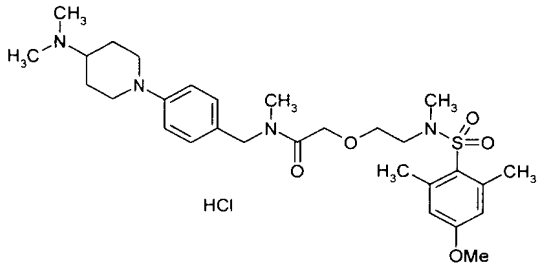
O exemplo 79 é preparado de maneira análoga a 1f a partir de 0,15 g (0,46 mmol) do produto de 53c, 0,11 g (0,46 mmol) do produto de 79b, 0,084 ml (0,60 mmol) de trietilamina e 0,18 g (0,56 mmol) de TBTU em 3 ml de dimetilformamida.

$C_{28}H_{42}N_4O_5S$ (546.72)

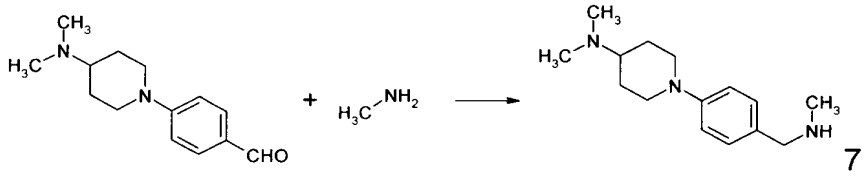
[M+H]+ = 547

HPLC (método 5): tempo de retenção = 1.49 min.

Exemplo 80



80a)



7

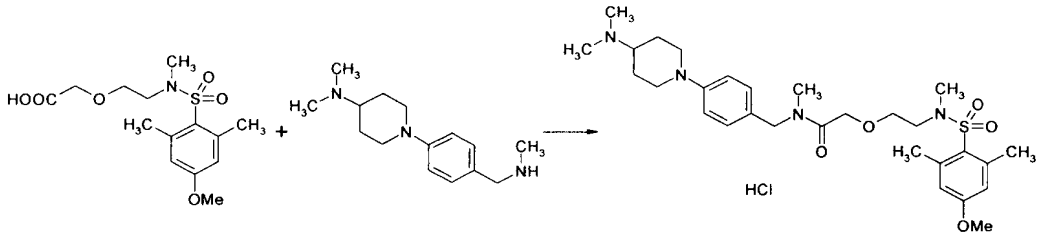
80a é preparado de maneira análoga a 33a a partir de 0,70 g (3,01 mmols) de 4-(4-dimetilamino-piperidin-1-il)-benzaldeído (Tetrahedron 57, 2001, 4781-4785), 3,00 ml (31,88 mmols) de metilamina a 33% em etanol (Aldrich), 0,20 g de níquel de Raney em 25 ml de etanol.

$C_{15}H_{25}N_3$ (247.38)

[M+H]+ = 248

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,16.

80b)



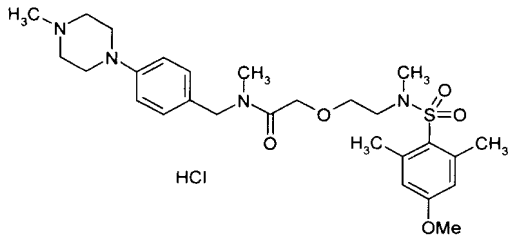
O exemplo 80 é preparado de maneira análoga a 1f a partir de 0,15 g (0,45 mmol) do produto de 53c, 0,11 g (0,45 mmol) do produto de 80a, 0,13 ml (0,90 mmol) de trietilamina e 0,17 g (0,54 mmol) de TBTU em 5 ml de dimetilformamida.

$C_{29}H_{44}N_4O_5S$ x HCl (597.21)

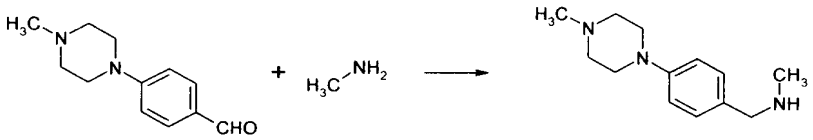
[M+H]+ = 561

HPLC (método 1): tempo de retenção = 2.33 min.

Exemplo 81



81a)



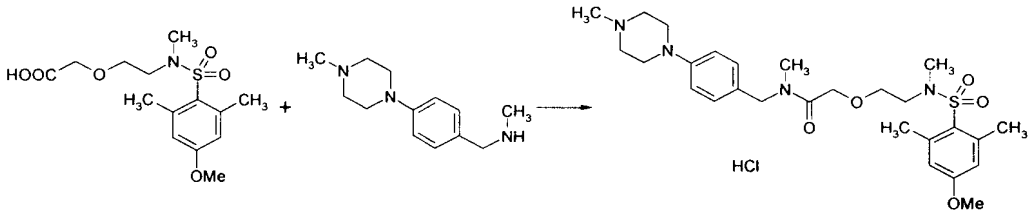
81a é preparado de maneira análoga a 33a a partir de 1,00 (4,90 mmols) de 4-(4-metil-piperazin-1-il)-benzaldeído (Chem. Pharm. Bull. 45, 1997, 1458-1469), 4,00 ml (42,50 mmols) de metilamina a 33% em etanol (Aldrich), 0,20 g de níquel de Raney em 30 ml de etanol.

$C_{13}H_{21}N_3$ (219.33)

[M+H]+ = 220

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,15.

81b)



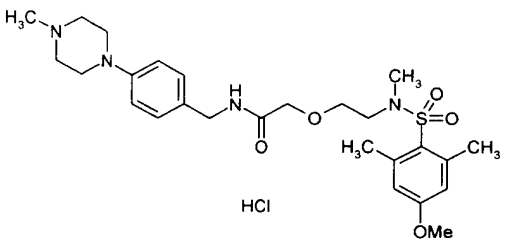
O exemplo 81 é preparado de maneira análoga a 1f a partir de 0,15 g (0,45 mmol) do produto de 53c, 0,099 g (0,45 mmol) do produto de 81a, 0,13 ml (0,90 mmol) de trietilamina e 0,17 g (0,54 mmol) de TBTU em 5 ml de dimetilformamida.

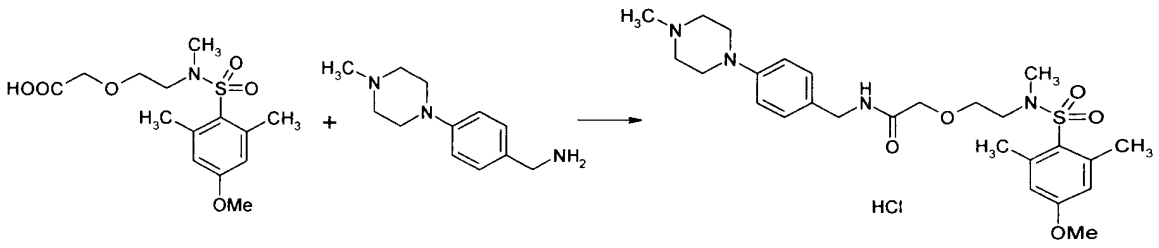
$C_{27}H_{40}N_4O_5S$ x HCl (569.16)

[M+H]+ = 533

HPLC (método 1): tempo de retenção = 2.28 min.

Exemplo 82





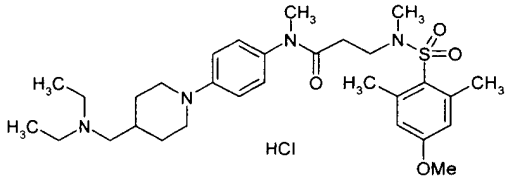
O exemplo 82 é preparado de maneira análoga a 1f a partir de 0,15 g (0,45 mmol) do produto de 53c, 0,092 g (0,45 mmol) do produto de 19b, 0,13 ml (0,90 mmol) de trietilamina e 0,17 g (0,54 mmol) de TBTU em 5 ml de dimetilformamida.

$C_{26}H_{38}N_4O_5S$ x HCl (555.13)

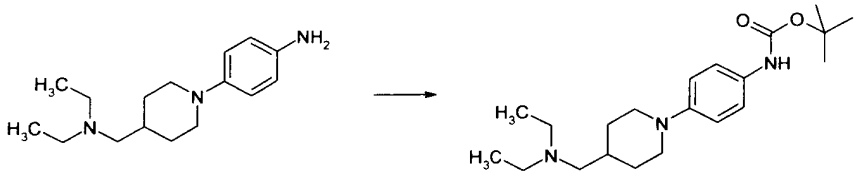
[M+H]+ = 519

HPLC (método 1): tempo de retenção = 2.29 min.

Exemplo 83



83a)



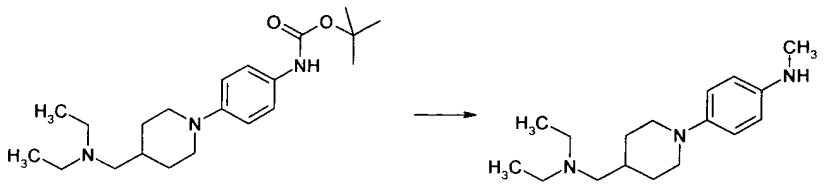
83a é preparado de maneira análoga a 51a a partir de 1,35 g (5,16 mmols) do produto de 41b, 1,24 g (5,68 mmols de anidrido boc e 0,80 ml (5,68 mmols) de trietilamina em 50 ml de diclorometano.

$C_{21}H_{35}N_3O_2$ (361.52)

[M+H]+ = 362

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,42.

83b)



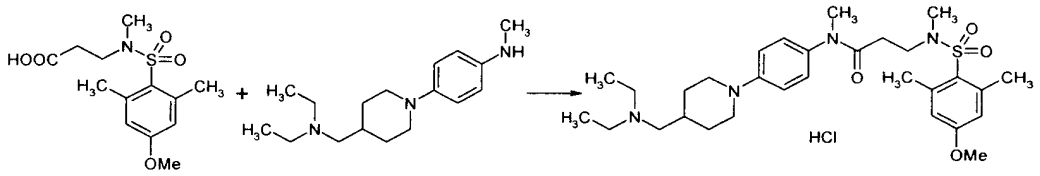
83b é preparado de maneira análoga a 51b a partir de 1,80 g (4,98 mmols) do produto de 83a e 0,57 g (15,00 mmols) de hidreto de lítioa-lumínio (Aldrich) em 25 ml de tetrahidrofurano.

$C_{17}H_{29}N_3$ (275.43)

[M+H]+ = 276

HPLC (método 1): tempo de retenção = 1.77 min.

83c)



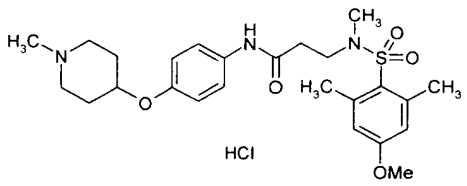
O exemplo 83 é preparado de maneira análoga a 1f a partir de 0,14 g (0,50 mmol) do produto de 22c, 0,15 g (0,50 mmol) do produto de 83b, 0,14 ml (1,00 mmol) de trietilamina e 0,18 g (0,55 mmol) de TBTU em 6 ml de dimetilformamida.

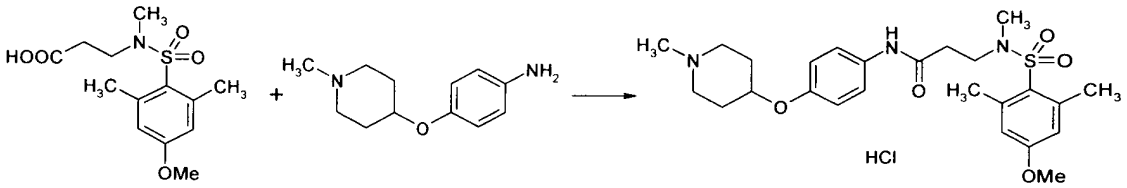
$C_{30}H_{46}N_4O_4S$ x HCl (595.24)

[M+H]+ = 559

HPLC (método 1): tempo de retenção = 2.46 min.

Exemplo 84





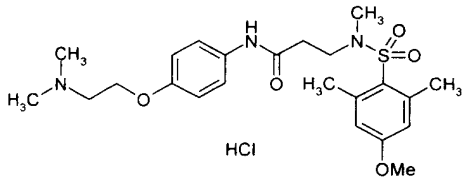
O exemplo 84 é preparado de maneira análoga a 1f a partir de 0,15 g (0,50 mmol) do produto de 22c, 0,10 g (0,50 mmol) de 4-(1-metilpiperidin-4-iloxi)-fenilamina (ART-CHEM), 0,14 ml (1,00 mmol) de trietilamina e 0,18 g (0,55 mmol) de TBTU em 6 ml de dimetilformamida.

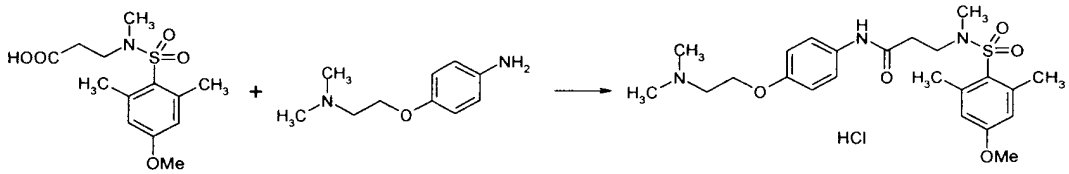
$C_{25}H_{35}N_3O_5S$ x HCl (526.09)

[M+H]+ = 490

HPLC (método 1): tempo de retenção = 2.40 min.

Exemplo 85





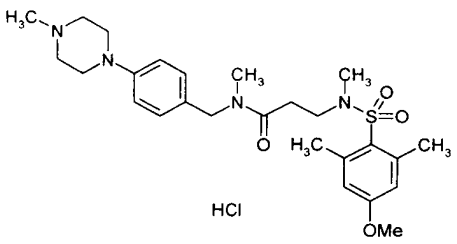
O exemplo 85 é preparado de maneira análoga a 1f a partir de 0,15 g (0,50 mmol) do produto de 22c, 0,09 g (0,50 mmol) de 4-(2-dimetilamino-etoxi)-fenilamina (Collect. Czech. Chem. Commun. 55, 1990, 282-295), 0,14 ml (1,00 mmol) de trietilamina e 0,18 g (0,55 mmol) de TBTU em 6 ml de dimetilformamida.

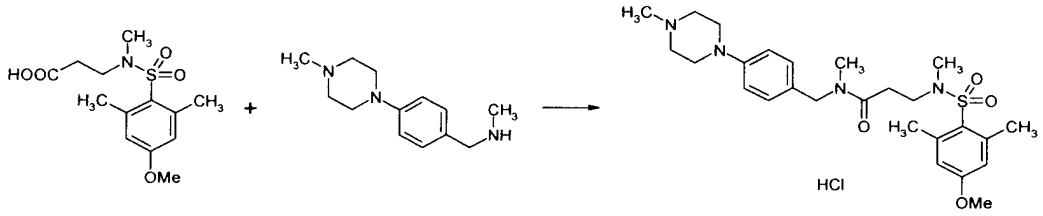
$C_{23}H_{33}N_3O_5S$ x HCl (500.05)

[M+H]+ = 464

HPLC (método 1): tempo de retenção = 2.35 min.

Exemplo 86





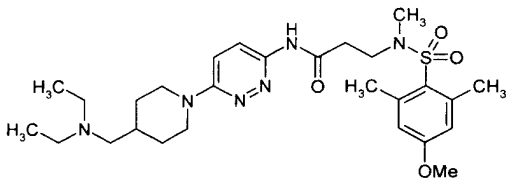
O exemplo 86 é preparado de maneira análoga a 1f a partir de 0,14 g (0,45 mmol) do produto de 22c, 0,099 g (0,45 mmol) do produto de 81a, 0,13 ml (0,90 mmol) de trietilamina e 0,17 g (0,54 mmol) de TBTU em 5 ml de dimetilformamida.

$C_{26}H_{38}N_4O_5S$ x HCl (539.13)

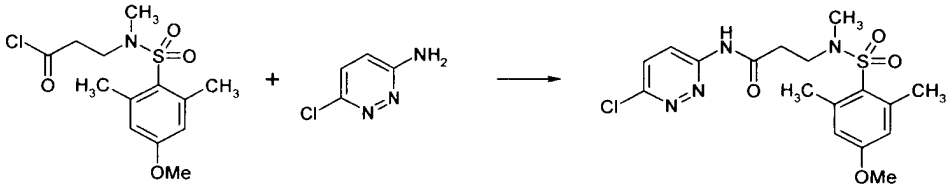
[M+H]+ = 503

HPLC (método 1): tempo de retenção = 2.43 min.

Exemplo 87



87a)



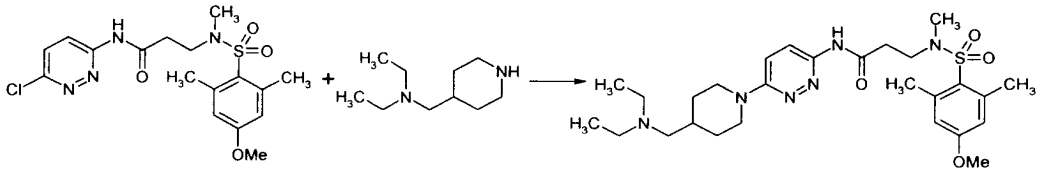
Uma mistura de 0,11 g (0,33 mmol) do produto de 27c, 0,043 g (0,33 mmol) de 3-amino-6-cloropiridazina (Acros), 0,12 ml (0,66 mmol) de DIPEA e 10 ml de diclorometano é agitada sob refluxo por três dias. A se-

guir, o precipitado é filtrado. O filtrado é concentrado no vácuo à secura e o produto bruto é purificado por meio de HPLC preparatória.

$C_{17}H_{21}ClN_4O_4S$ (412.89)

[M+H]+ = 413/415

87b)



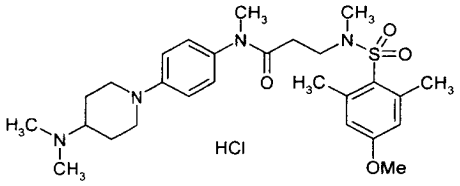
Uma mistura de 0,03, g (0,073 mmol) do produto de 87a e 0,013 g (0,073 mmol) de dietil-piperidin-4-ilmetil-amina (Chem. Pharm. Bull. 42. 1994, 74-84) é fundida a 173°C. A seguir, o produto é obtido da mistura de reação por meio de HPLC preparatória.

$C_{27}H_{42}N_6O_4S$ (546.73)

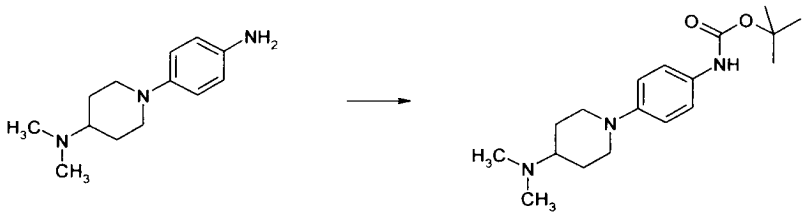
[M+H]+ = 547

HPLC (método 6): tempo de retenção = 2.12 min.

Exemplo 88



88a)



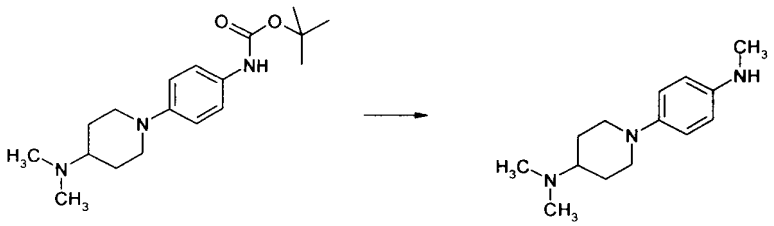
88a é preparado de maneira análoga a 51a a partir de 0,70 g (3,18 mmols) do produto de 27b, 0,80 g (3,65 mmols) de anidrido boc e 5,50 ml (11,00 mmols) de soda cáustica 2 M em 40 ml de dioxano e 20 ml de água.

$C_{17}H_{28}N_4O_2$ (320.43)

[M+H]+ = 321

DC: gel de sílica, diclorometano/metanol/amoníaco 4:1:0,2, valor Rf = 0,83.

88b)



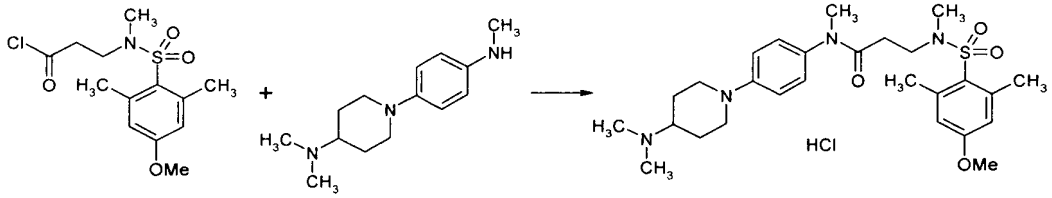
88b é preparado de maneira análoga a 51b a partir de 0,60 g (1,87 mmol) do produto de 88a e 0,21 g (5,60 mmols) de hidreto de lítioalumínio (Aldrich) em 20 ml de tetrahidrofurano.

$C_{13}H_{22}N_4$ (234.34)

[M+H]+ = 235

DC: gel de sílica, diclorometano/metanol/amoníaco 4:1:0,2, valor Rf = 0,62.

88c)



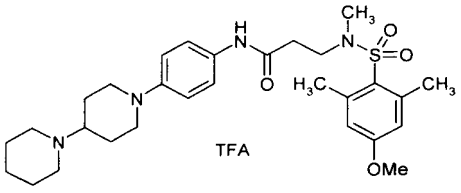
O exemplo 88 é preparado de maneira análoga a 27d a partir de 0,16 g (0,50 mmol) do produto de 27c, 0,12 g (0,50 mmol) do produto de 88b e 0,17 ml (1,00 mmol) de DIPEA em 5 ml de tetrahidrofurano.

$C_{26}H_{39}N_5O_4S$ x HCl (554.15)

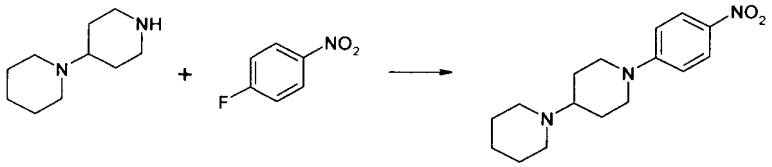
[M+H]+ = 518

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,61.

Exemplo 89



89a)



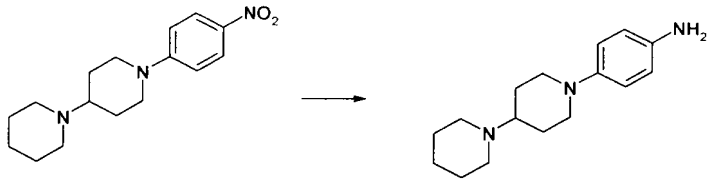
89a é preparado de maneira análoga a 8a a partir de 0,70 g (4,18 mmols) de 4-piperidinopiperidina (Aldrich), 0,44 ml (4,18 mmols) de 1-flúor-4-nitrobenzeno 9Acros) e 1,33 ml (9,61 mmols) de trietilamina em 12 ml de dimetilformamida.

$C_{16}H_{23}N_3O_2$ (289.37)

[M+H]+ = 290

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0.3

89b)



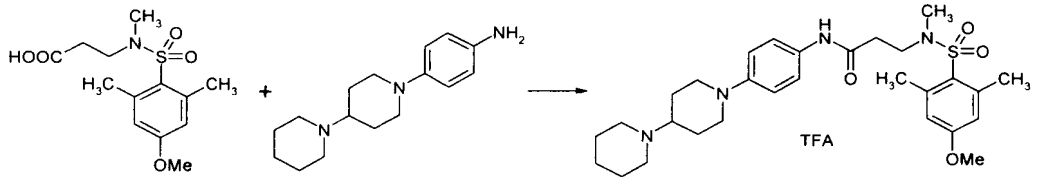
89b é preparado de maneira análoga a 8b a partir de 0,96 g (3,32 mmols) do produto de 89a e 0,093 g de paládio sobre carvão (5%) em 45 ml de etanol.

$C_{16}H_{25}N_3$ (259.39)

[M+H]+ = 260

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,2.

89c)



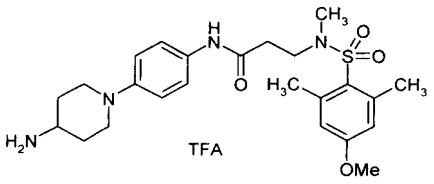
O exemplo 89 é preparado de maneira análoga a 1f a partir de 0,10 g (0,33 mmol) do produto de 22c, 0,086 g (0,33 mmol) do produto de 89b, 0,14 ml (1,00 mmol) de trietilamina e 0,11 g (0,33 mmol) de TBTU em 2 ml de tetrahidrofurano.

$C_{29}H_{42}N_4O_4S \times C_2HF_3O_2$ (656.76)

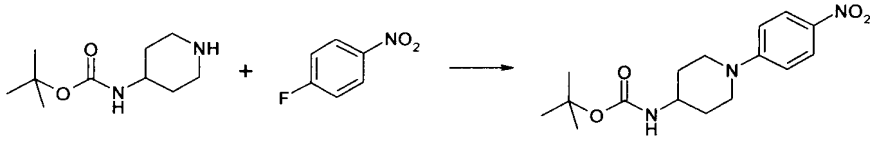
[M+H]+ = 543

HPLC (método 5): tempo de retenção = 1.47 min.

Exemplo 90



90a)

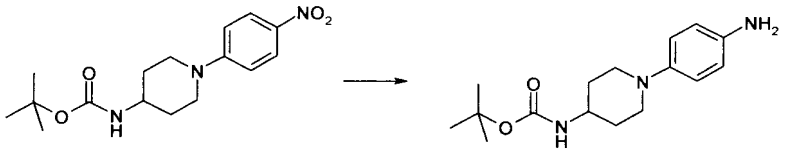


90a é preparado de maneira análoga a 8a a partir de 0,84 g (4,18 mmols) de 4-N-boc-aminopiperidina (Acros), 0,44 ml (4,18 mmols) de 1-flúor-4-nitrobenzeno (Acros) e 1,33 ml (9,61 mmols) de trietilamina em 12 ml de dimetilformamida.

$C_{16}H_{23}N_3O_4$ (321.37)

[M+H]+ = 322

90b)

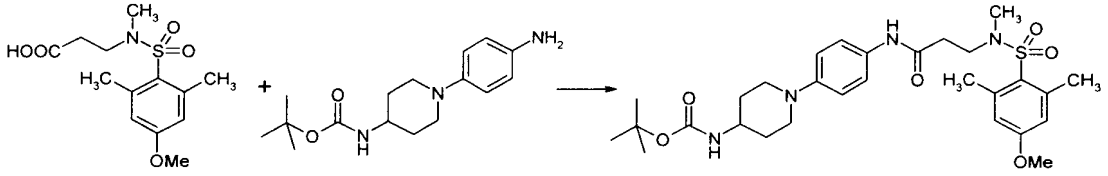


90b é preparado de maneira análoga a 8b a partir de 1,01 g (3,43 mmol) do produto de 90a e 0,11 g de paládio sobre carvão (5%) em 45 ml de etanol.

$C_{16}H_{25}N_3O_2$ (291.39)

[M+H]+ = 292

90c)



90c é preparado de maneira análoga a 1f a partir de 0,10 g (0,33

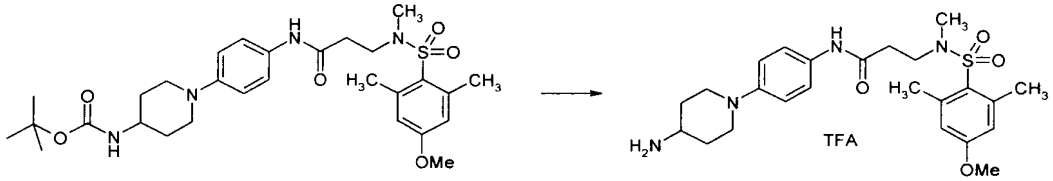
mmol) do produto de 22c, 0,097 g (0,33 mmol) do produto de 90b, 0,14 ml (1,00 mmol) de trietilamina e 0,11 g (0,33 mmol) de TBTU em 2 ml de tetra-hidrofurano.

$C_{29}H_{42}N_4O_6S$ (574.73)

[M+H]+ = 575

HPLC (método 5): tempo de retenção = 1.62 min.

90d)



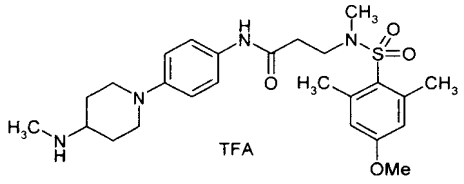
O exemplo 90 é preparado de maneira análoga a 18b a partir de 0,19 g (0,33 mmol) do produto de 90c e 0,33 ml de TFA em 0,5 ml de diclorometano.

$C_{24}H_{34}N_4O_4S \times C_2HF_3O_2$ (588.64)

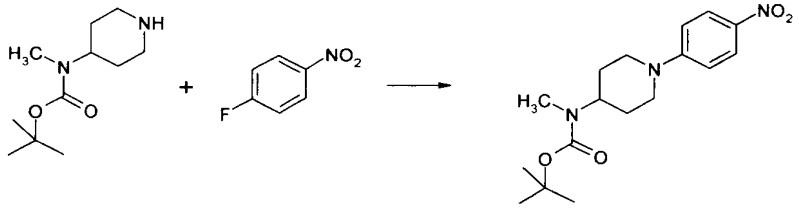
[M+H]+ = 475

HPLC (método 5): tempo de retenção = 1.41 min.

Exemplo 91



91a)



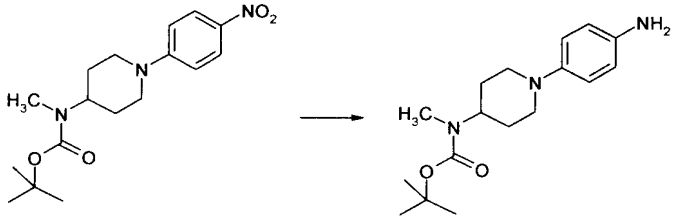
91a é preparado de maneira análoga a 8a a partir de 0,90 g (4,18 mmols) de éster terc-butílico de ácido metil-piperidin-4-il-carbâmico (Fluorochem), 0,44 ml (4,18 mmols) de 1-flúor-4-nitrobenzeno (Acros) e 1,33 ml (9,61 mmols) de trietilamina em 12 ml de dimetilformamida.

$C_{17}H_{25}N_3O_4$ (335.40)

[M+H]+ = 336

DC: gel de sílica, diclorometano/metanol 30:1, valor Rf = 0,6.

91b)



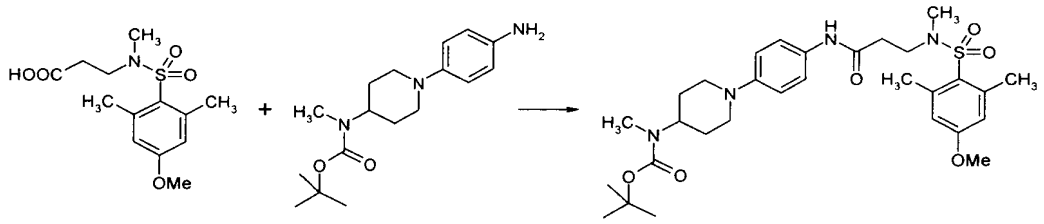
91b é preparado de maneira análoga a 8b a partir de 1,08 (3,22 mmol) do produto de 91a e 0,11 g de paládio sobre carvão (5%) em 45 ml de metanol.

$C_{17}H_{27}N_3O_2$ (305.42)

[M+H]+ = 306

DC: gel de sílica, diclorometano/metanol 30:1, valor Rf = 0,4.

91c)



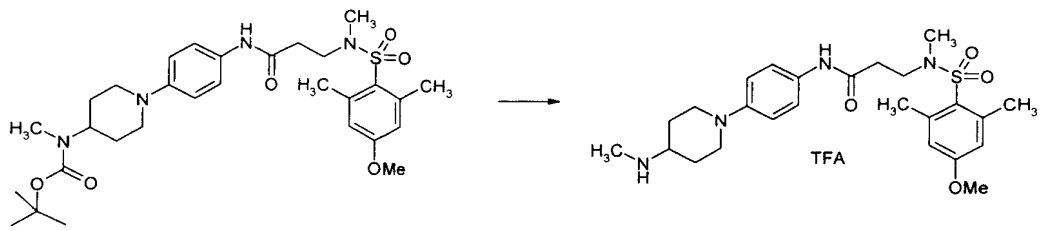
91c é preparado de maneira análoga a 1f a partir de 0,10 g (0,33 mmol) do produto de 22c, 0,10 g (0,33 mmol) do produto de 91b, 0,14 ml (1,00 mmol) de trietilamina e 0,11 g (0,33 mmol) de TBTU em 2 ml de tetra-hidrofurano.

$C_{30}H_{44}N_4O_6S$ (588.76)

[M+H]+ = 589

HPLC (método 5): tempo de retenção = 1.69 min.

91d)



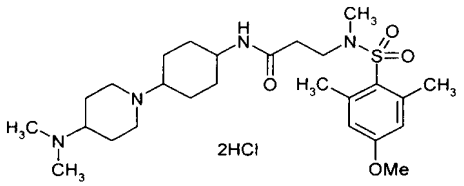
O exemplo 91 é preparado de maneira análoga a 18b a partir de 0,21 g (0,36 mmol) do produto de 91c e 0,36 ml de TFA em 0,6 ml de diclorometano.

$C_{25}H_{36}N_4O_4S \times C_2HF_3O_2$ (602.67)

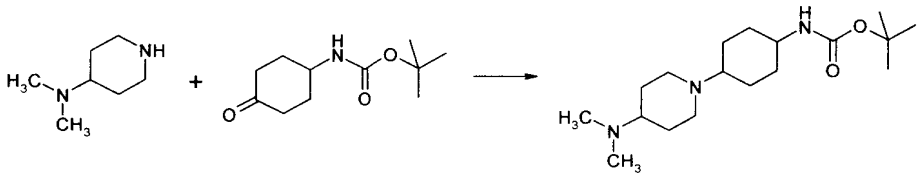
[M+H]+ = 489

HPLC (método 5): tempo de retenção = 1.42 min.

Exemplo 92



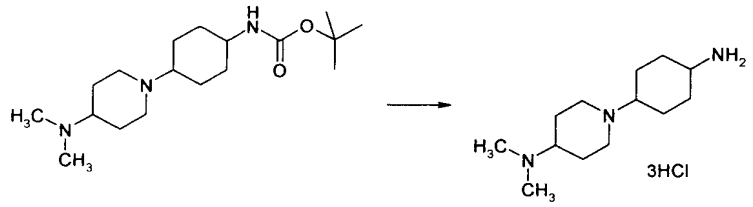
92a)



Uma mistura de 0,66 g (5,16 mmols) de 4-dimetilamino-piperidina (Alfa Aesar), 1,00 g (4,69 mmols) de éster terc-butílico de ácido (4-oxociclohexil)-carbâmico (Fluorochem), 1,19 g (5,16 mmols) de triacetoxiborohidreto de sódio e 20 ml de diclorometano é agitada sob nitrogênio à temperatura ambiente por quatro horas. A seguir, a mistura de reação é diluída com diclorometano, lavada com solução saturada de bicarbonato de sódio, seca sobre sulfato de sódio e concentrada no vácuo à secura.

$C_{18}H_{35}N_3O_2$ (325.49)

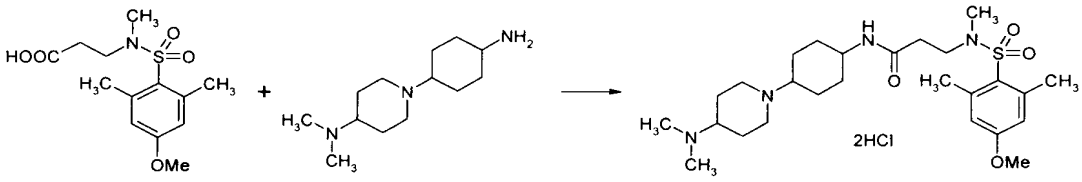
92b)



Uma mistura de 0,80 g (2,46 mmols) do produto de 92a, 4 ml de HCl 6 M, 3 ml de HCl a 37% e 3 ml de metanol é agitada a 50°C por duas horas. A seguir, a mistura de reação é concentrada no vácuo à secura.

$C_{13}H_{27}N_3$ x 3HCl (334.76).

92c)



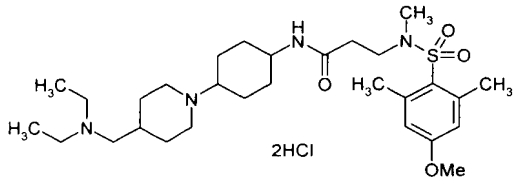
O exemplo 92 é preparado de maneira análoga a 1f a partir de 0,10 g (0,33 mmol) do produto de 22c, 0,13 g (0,40 mmol) do produto de 92b, 0,23 ml (1,66 mmol) de trietilamina e 0,13 g (9,40 mmol) de TBTU em 8 ml de dimetilformamida.

$C_{26}H_{44}N_4O_4S$ x 2HCl (581.64)

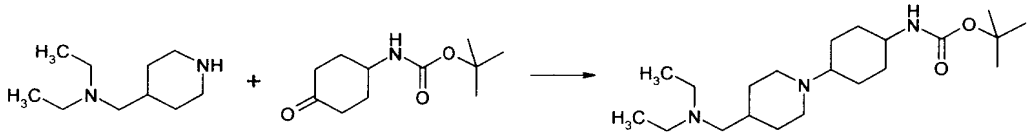
[M+H]+ = 509

HPLC (método 5): tempo de retenção = 1.36 min.

<u>Exemplo 93</u>



93a)

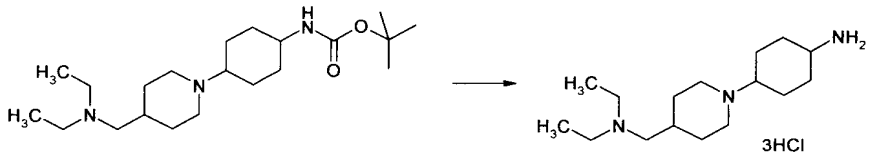


93a é preparado de maneira análoga a 92a a partir de 0,6 g (3,70 mmols) de dietil-piperidin-4-ilmetil-amina (Chem. Pharm. Bull. 42, 74-

84), 0,72 g (3,37 mmols) de éster terc-butílico de ácido (4-oxociclohexil)-carbâmico (Fluorochem) e 0,86 g (4,04 mmols) de triacetoxiborohidreto de sódio em 20 ml de diclorometano.

$C_{21}H_{41}N_3O_2$ (367,57).

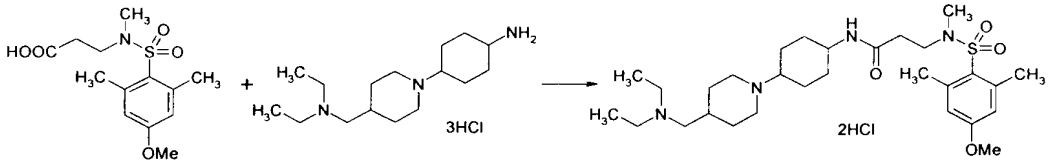
93b)



93b é preparado de maneira análoga a 92b a partir de 0,90 g (2,45 mmols) do produto de 93a, 4 ml de HCl 6M e 3 ml de HCl a 37% em 3 ml de metanol.

$C_{16}H_{33}N_3$ x 3HCl (376.84).

93c)



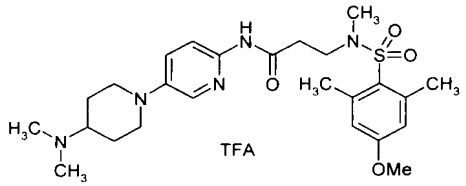
O exemplo 93 é preparado de maneira análoga a 1f a partir de 0,10 g (0,33 mmol) do produto de 22c, 0,14 g (0,37 mmol) do produto de 93b, 0,23 ml (1,66 mmol) de trietilamina e 0,13 g (0,40 mmol) de TBTU em 8 ml de dimetilformamida.

$C_{29}H_{50}N_4O_4S$ x 2HCl (623.72)

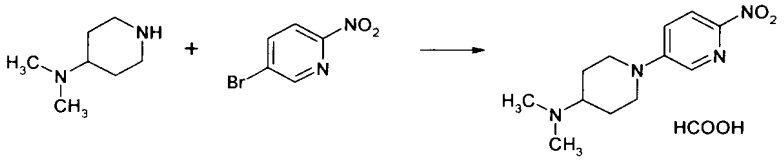
[M+H]+ = 551

HPLC (método 5): tempo de retenção = 1.39 min.

<u>Exemplo 94</u>



94a)

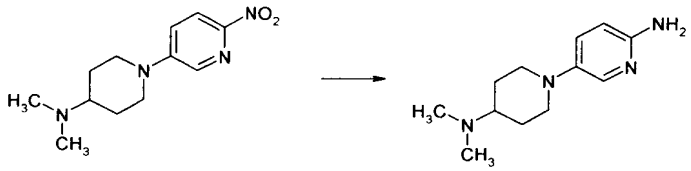


Uma mistura de 0,88 g (6,88 mmols) de 4-dimetilamino-piperidina (Alfa Aesar), 1,00 g (4,93 mmol) de 3-bromo-6-nitropiridina (Aldrich), 0,18 g (0,49 mmol) de iodeto de tetrabutil-amônio, 0,74 g (5,33 mmol) de carbonato de potássio e 5 ml de dimetilsulfóxido é agitada a 80°C por duas horas. A seguir, a mistura de reação é vertida em água e extraída com diclorometano. Os extratos orgânicos são lavados com solução saturada de bicarbonato de sódio e solução saturada de cloreto de sódio, secos sobre sulfato de sódio e concentrados no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de HPLC preparatória.

$C_{12}H_{18}N_4O_2 \times CH_2O_2$ (296.32)

HPLC (método 1): tempo de retenção = 1.49 min.

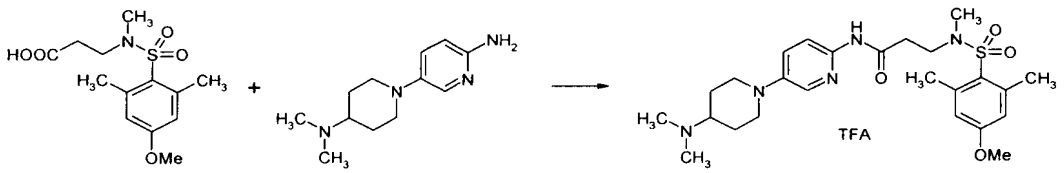
94b)



94b é preparado de maneira análoga a 8b a partir de 0,50 g (2,00 mmols) do produto de 94a e 0,08 g de paládio sobre carvão (10%) em 40 ml de metanol.

$C_{12}H_{20}N_4$ (220,31).

94c)



Uma mistura de 0,63 g (2,10 mmols) do produto de 22c, 0,91 g (9,00 mmols) de N-metil-morfolina, 0,45 g (2,04 mmols) do produto de 94b e 50 ml de tetrahidrofurano é agitada à temperatura ambiente por 10 minutos e a seguir, adicionada a 5,22 ml (9,00 mmols) de anidrido de ácido propilfosfô-

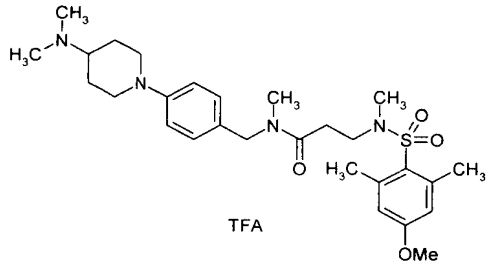
nico a 50% em acetato de etila (Fluka). Deixa-se agitar a mistura de reação à temperatura ambiente durante a noite e em seguida, concentra-se a mesma no vácuo à secura. O resíduo é adicionado à solução de carbonato de potássio 2 N e extraído com diclorometano. Os extratos orgânicos são lavados com água e solução saturada de cloreto de sódio, secos sobre sulfato de sódio e concentrados no vácuo à secura. O produto obtido dessa maneira é purificado por meio de HPLC preparatória.

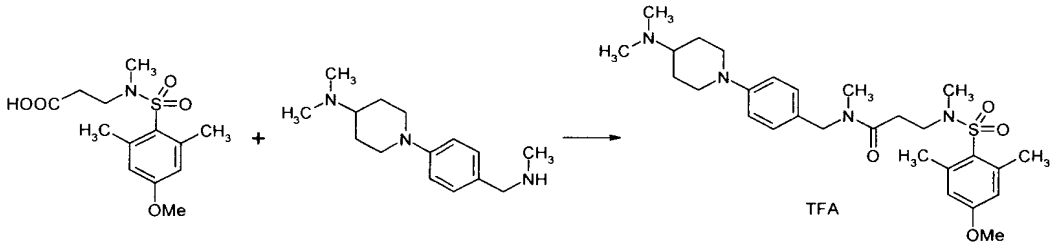
$C_{25}H_{37}N_5O_4S \times C_2HF_3O_2$ (617.68)

[M+H]+ = 504

HPLC (método 5): tempo de retenção = 1.38 min.

Exemplo 95





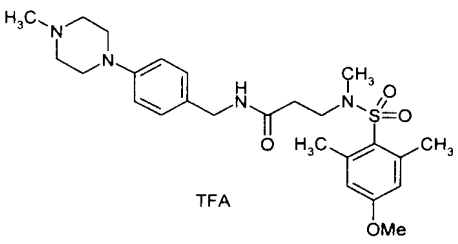
O exemplo 95 é preparado de maneira análoga a 1f a partir de 0,08 g (0,27 mmol) do produto de 22c, 0,066 g (0,27 mmol) do produto de 80a, 0,11 ml (0,80 mmol) de trietilamina e 0,085 g (0,27 mmol) de TBTU em 2 ml de tetrahidrofurano.

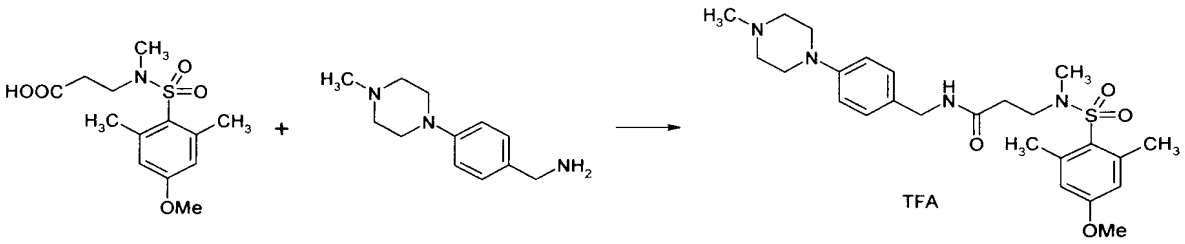
$C_{28}H_{42}N_4O_4S \times C_2HF_3O_2$ (644.75)

[M+H]+ = 531

HPLC (método 5): tempo de retenção = 1.50 min.

Exemplo 96





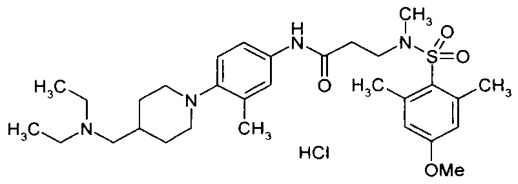
O exemplo 96 é preparado de maneira análoga a 1f a partir de 0,08 g (0,27 mmol) do produto de 22c, 0,054 g (0,27 mmol) do produto de 19b, 0,11 ml (0,80 mmol) de trietilamina e 0,085 g (0,27 mmol) de TBTU em 2 ml de tetrahidrofurano.

$C_{25}H_{36}N_4O_4S \times C_2HF_3O_2$ (602.67)

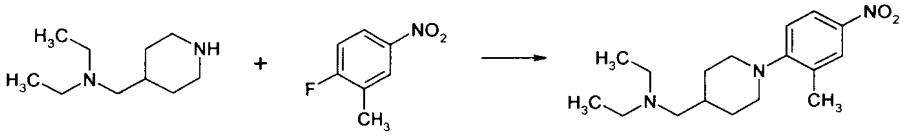
[M+H]+ = 489

HPLC (método 5): tempo de retenção = 1.49 min.

Exemplo 97



97a)

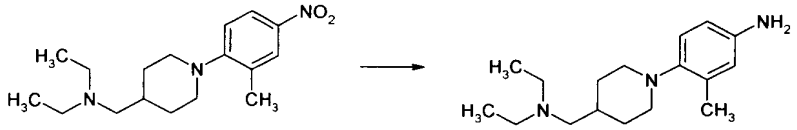


97a é preparado de maneira análoga a 8a a partir de 1,00 g (5,87 mmols) de dietil-piperidin-4-ilmetil-amina (Chem. Pharm. Bull. 42, 1994, 74-84), 0,91 g (5,87 mmols) de 1-flúor-2-metil-4-nitrobenzeno (ABCR) e 1,14 ml (8,20 mmols) de trietilamina em 12 ml de dimetilformamida.

$C_{17}H_{27}N_3O_2$ (305.42)

[M+H]+ = 306

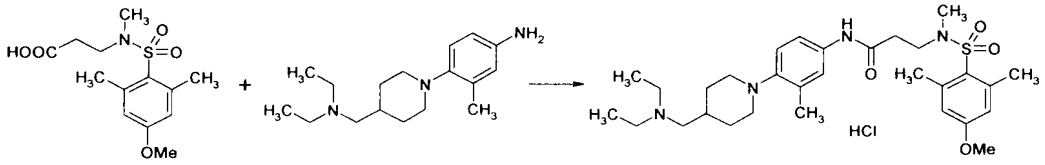
97b)



97b é preparado de maneira análoga a 8b a partir de 0,91 g (2,98 mmol) do produto de 97a e 0,20 g de paládio sobre carvão (10%) em 50 ml de metanol.

$C_{17}H_{29}N_3$ (275,43)

97c)



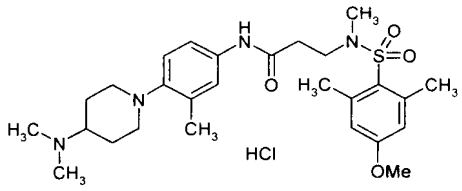
O exemplo 97 é preparado de maneira análoga a 1f a partir de 0,15 g (0,50 mmol) do produto de 22c, 0,14 g (0,50 mmol) do produto de 97b, 0,21 ml (1,50 mmol) de trietilamina e 0,16 g (0,50 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{30}H_{46}N_4O_4S$ x HCl (595.24)

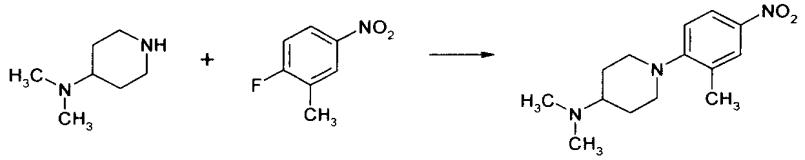
[M+H]+ = 559

HPLC (método 5): tempo de retenção = 1.44 min.

<u>Exemplo 98</u>



98a)

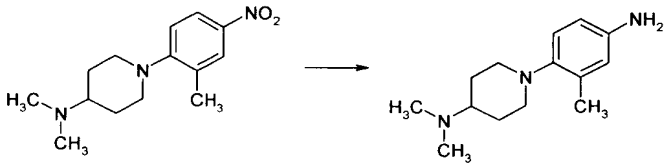


98a é preparado de maneira análoga a 8a a partir de 0,75 g (5,87 mmols) de 4-dimetilamino-piperidina (Alfar Aesar), 0,91 g (5,87 mmols)

de 1-flúor-2-metil-4-nitrobenzeno (ABCR) e 1,14 ml (8,20 mmols) de trietilamina em 12 ml de dimetilformamida.

$C_{14}H_{21}N_3O_2$ (263,34)

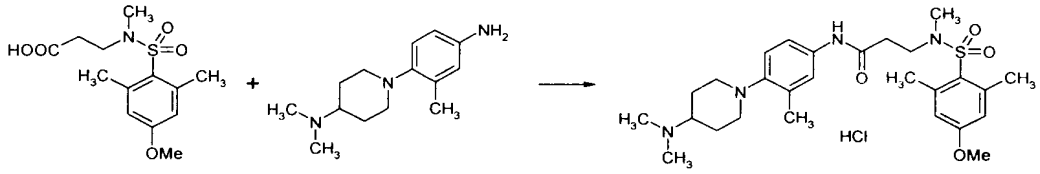
98b)



98b é preparado de maneira análoga a 8b a partir de 0,30 g (1,14 mmol) do produto de 98a e 0,10 g de paládio sobre carvão (10%) em 25 ml de metanol.

$C_{14}H_{23}N_3$ (233,35)

98c)



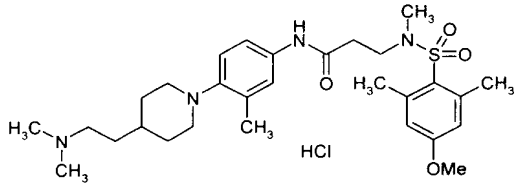
O exemplo 98 é preparado de maneira análoga a 1f a partir de 0,32 g (1,07 mmol) do produto de 22c, 0,25 g (1,07 mmol) do produto de 98b, 0,42 ml (3,00 mmol) de trietilamina e 0,34 g (1,07 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{27}H_{40}N_4O_4S$ x HCl (553.16)

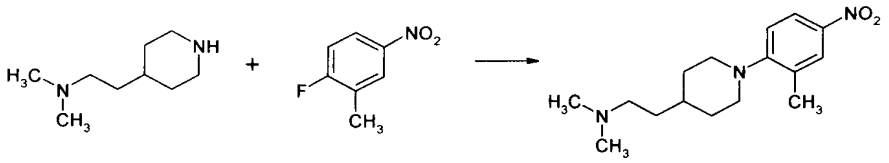
[M+H]+ = 517

HPLC (método 5): tempo de retenção = 1.52 min.

Exemplo 99



99a)

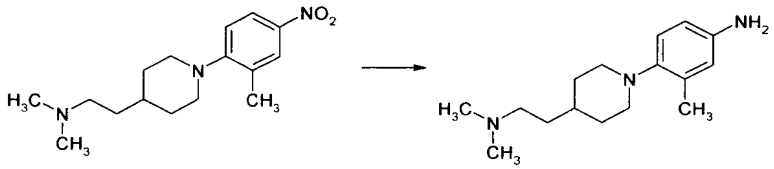


99a é preparado de maneira análoga a 8a a partir de 0,92 g (5,87 mmols) de dimetil-(2-piperidin-4-il-etil)-amina (J. Med. Chem. 36, 1993, 162-165), 0,91 g (5,87 mmols) de 1-flúor-2-metil-4-nitrobenzeno (ABCR) e 2,49 g (18,00 mmols) de carbonato de potássio em 12 ml de dimetilformamida.

$C_{16}H_{25}N_3O_2$ (291.39)

[M+H]+ = 292.

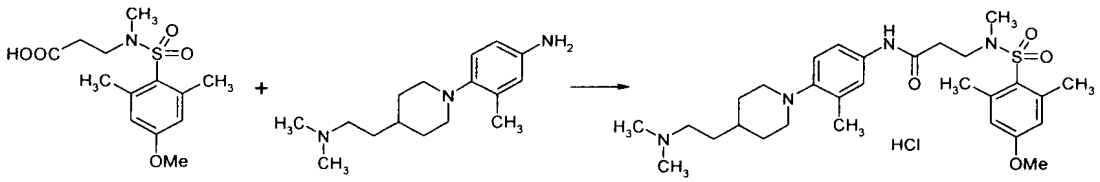
99b)



99b é preparado de maneira análoga a 8b a partir de 0,60 g (1,14 mmol) do produto de 99a e 0,20 g de paládio sobre carvão (10%) em 50 ml de metanol.

$C_{16}H_{27}N_3$ (261.41)

99c)



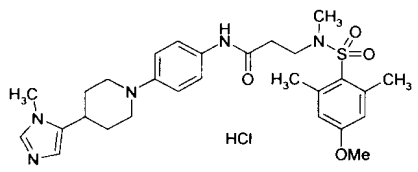
O exemplo 99 é preparado de maneira análoga a 1f a partir de 0,15 g (0,50 mmol) do produto de 22c, 0,13 g (0,50 mmol) do produto de 99b, 0,21 ml (1,50 mmol) de trietilamina e 0,16 g (0,50 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{29}H_{44}N_4O_4S$ x HCl (581.21)

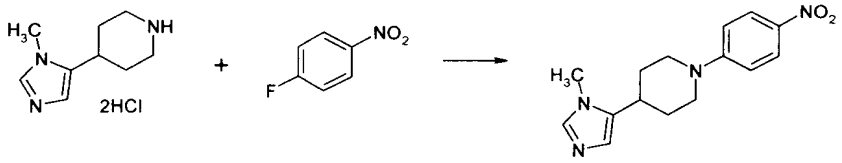
[M+H]+ = 545

HPLC (método 5): tempo de retenção = 1.42 min.

Exemplo 100



100a)

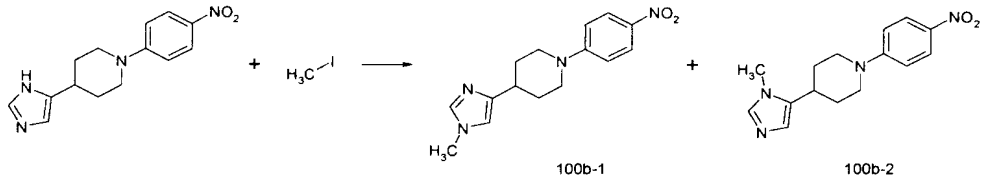


100a é preparado de maneira análoga a 8a a partir de 1,00 g (4,47 mmols) de 4-(3-metil-3H-imidazol-4-il)-piperidina (J. Med. Chem. 46, 2003, 5445-5457), 0,63 g (4,47 mmols) de 4-flúor-nitrobenzeno (ABCR) e 2,10 g (15,20 mmols) de carbonato de potássio em 50 ml de dimetilformamida.

$C_{14}H_{16}N_4O_2$ (272,3)

[M+H]+ = 273.

100b)



100b-1 e 100b-2 são preparados de maneira análoga a 62a a partir de 1,10 g (4,04 mmols) do produto de 100a, 0,60 g (4,23 mmols) de iodeto de metila e 0,46 g (4,10 msmol) de terc-butilato de potássio em 50 ml de dimetilsulfóxido. A mistura isomérica formada dessa maneira é separada por meio de cromatografia de coluna sobre gel de sílica (agente de eluição: diclorometano/metanol 100:1 a 30:1).

100b-1: $C_{15}H_{18}N_4O_2$ (286,33)

[M+H]+ = 287

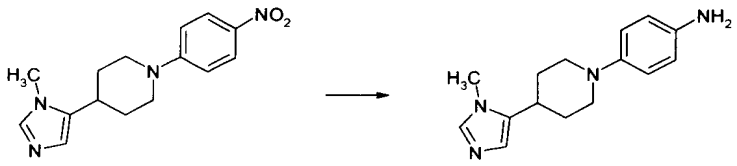
DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,50

100b-2: $C_{15}H_{18}N_4O_2$ (286,33)

[M+H]+ = 287

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,38.

100c)

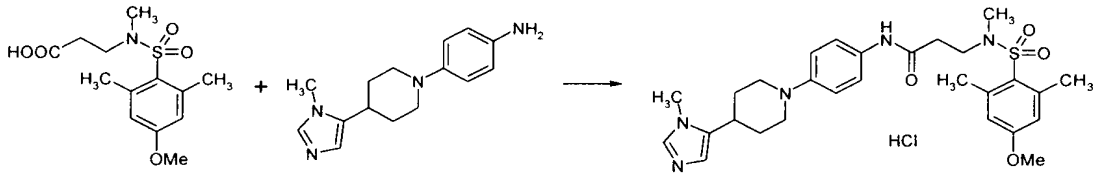


100c é preparado de maneira análoga a 8b a partir de 0,10 g (0,35 mmol) de 100b-2 e 0,20 g de paládio sobre carvão (10%) em 30 ml de metanol.

$C_{15}H_{20}N_4$ (256,35)

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,10.

100d)



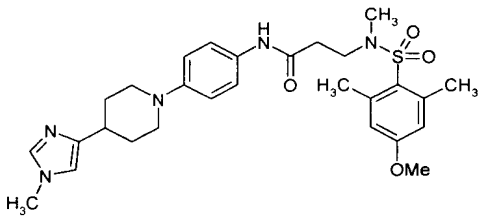
O exemplo 100 é preparado de maneira análoga a 1f a partir de 0,085 g (0,28 mmol) do produto de 22c, 0,070 g (0,27 mmol) do produto de 100c, 0,048 ml (0,35 mmol) de trietilamina e 0,095 g (0,30 mmol) de TBTU em 20 ml de tetrahidrofurano e 3 ml de dimetilformamida.

$C_{28}H_{37}N_5O_4S$ x HCl (576.15)

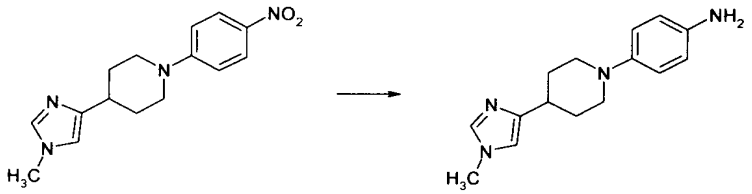
$[M+H]^+$ = 540

HPLC (método 5): tempo de retenção = 1.41 min.

Exemplo 101



101a)

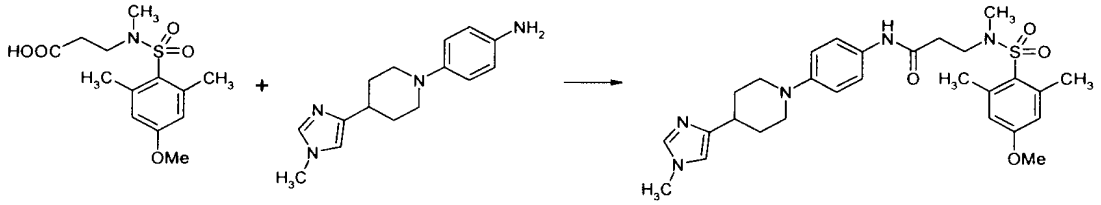


101a é preparado de maneira análoga a 8b a partir de 0,35 g (1,22 mmol) de 100b-1 e 0,50 g de paládio sobre carvão em 50 ml de metanol

$C_{15}H_{20}N_4$ (256,35)

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,14.

101b)



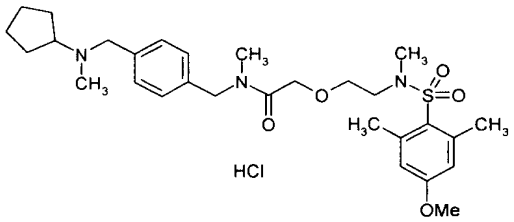
Exemplo 101 é preparado de maneira análoga a 1f a partir de 0,12 g (0,40 mmol) do produto de 22c, 0,10 g (0,39 mmol) do produto de 101a, 0,05 ml (0,50 mmol) de trietilamina e 0,14 g (0,42 mmol) de TBTU em 30 ml de tetrahidrofurano e 5 ml de dimetilformamida.

$C_{28}H_{37}N_5O_4S$ (539.69)

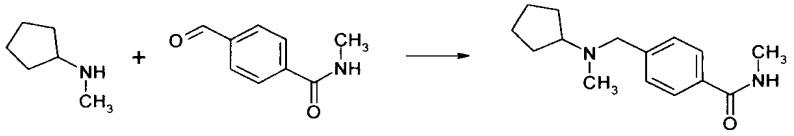
[M+H]+ = 540

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,47.

<u>Exemplo 102</u>



102a)

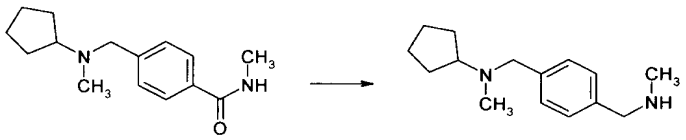


102a é preparado de maneira análoga a 60a a partir de 0,50 g

(5,00 mmols) de N-metilciclohexilamina (CHESS), 0,82 g (5,00 mmols) de metilamida de ácido 4-formil-benzóico (EMKA), 1,59 g (7,50 mmol) de triacetoxiborohidreto de sódio e 0,37 ml (6,50 mmols) de ácido acético em 30 ml de tetrahidrofurano.

$C_{15}H_{22}N_2$ (246,35)

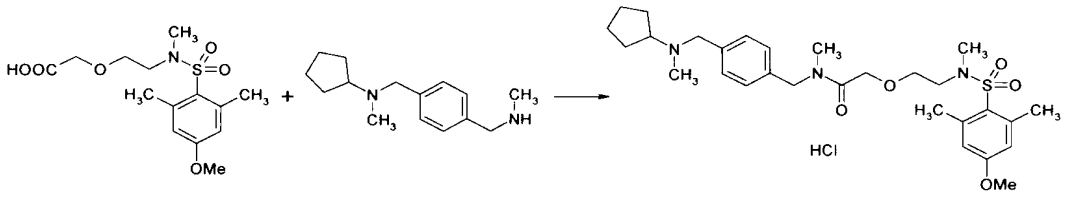
102b)



102b é preparado de maneira análoga a 38f a partir de 1,06 g (4,30 mmols) do produto de 102a e 8,60 ml (8,60 mmols) de hidreto de lítioalumínio 1 M em tetrahidrofurano (Aldrich) em 40 ml de tetrahidrofurano.

$C_{15}H_{24}N_2$ (232,36).

102c)



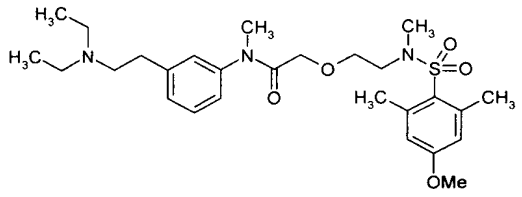
O exemplo 102 é preparado de maneira análoga a 1f a partir de 0,20 g (0,60 mmol) do produto de 53c, 0,14 g (0,60 mmol) do produto de 102b, 0,21 ml (1,50 mmol) de trietilamina e 0,23 (0,72 mmol) de TBTU em 10 ml de tetrahidrofurano.

$C_{29}H_{43}N_3O_5S$ x HCl (582.20)

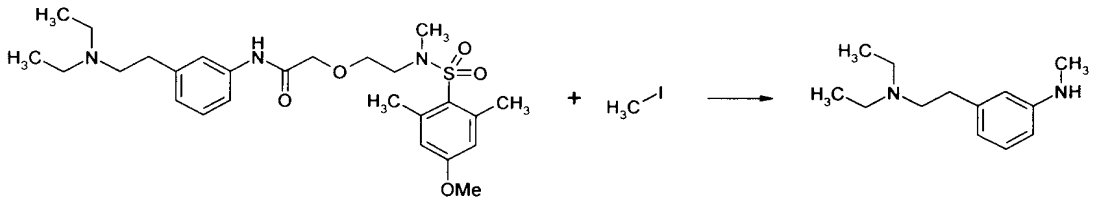
[M+H]+ = 546

HPLC (método 5): tempo de retenção = 1.58 min.

Exemplo 103



103a)

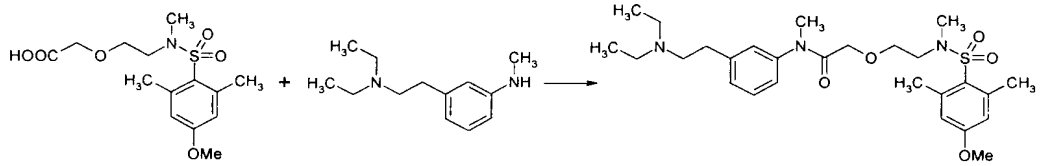


Uma mistura de 0,04 g (0,079 mmol) de 70, 4,8 mg (0,12 mmol) de hidreto de sódio a 60%, 1 ml de tetrahidrofurano e 0,5 ml de dimetilformamida é agitada à temperatura ambiente por 30 minutos. A seguir, acrescentam-se 4,9 µl (0,079 mmol) de iodeto de metila e deixa-se agitar à temperatura ambiente por mais duas horas. Em seguida, a mistura de reação é concentrada no vácuo à secura, o resíduo é adicionado à água e extraído com acetato de etila. Os extratos orgânicos são secos sobre sulfato de sódio e concentrados no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna (agente de eluição: diclorometano/metanol/amoníaco 95:5:0,5).

$C_{13}H_{22}N_2$ (206.33)

[M+H]+ = 207.

103b)



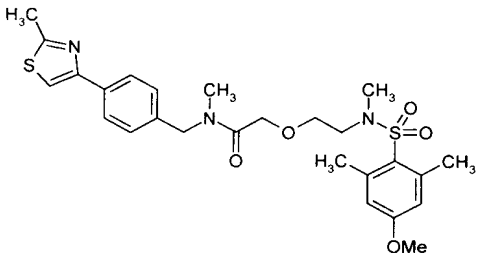
O exemplo 103 é preparado de maneira análoga a 1f a partir de 0,08 g (0,24 mmol) do produto de 53c, 0,05 g (0,24 mmol) do produto de 103a, 0,067 ml (0,48 mmol) de trietilamina e 0,093 g (0,29 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{27}H_{41}N_3O_5S$ (519.70)

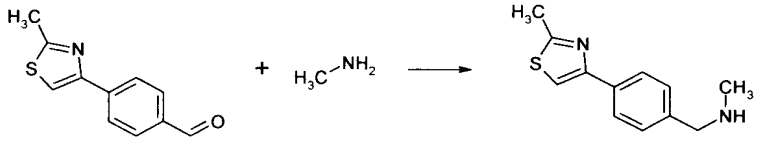
[M+H]+ = 520

HPLC (método 4): tempo de retenção = 3.2 min.

Exemplo 104



104a)

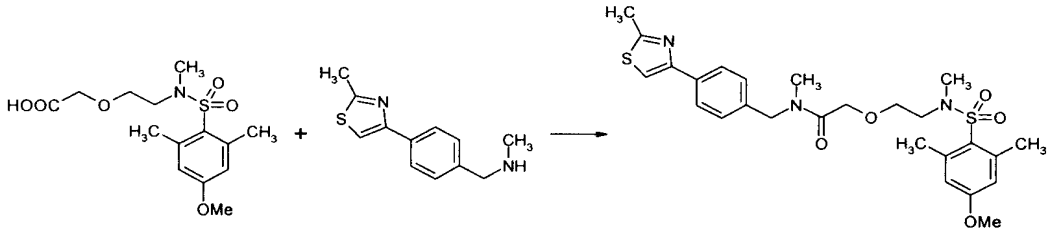


104a é preparado de maneira análoga a 60a a partir de 0,35 g (1,72 mmol) de 4-(2-metil-1,3-tiazol-4-il)-benzaldeído (Maybridge), 1,50 ml (3,00 mmol) de metilamina 2 M em tetrahidrofurano (Acros), 0,70 g (3,30 mmol) de triacetoxiborohidreto de sódio e 0,23 ml (4,00 mmol) de ácido acético em 20 ml de tetrahidrofurano.

$C_{12}H_{14}N_2S$ (218.32)

[M+H]+ = 219

104b)



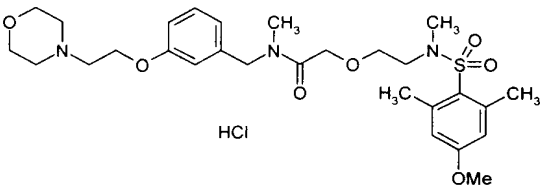
O exemplo 104 é preparado de maneira análoga a 1f a partir de 0,16 g (0,47 mmol) do produto de 53c, 0,10 g (0,46 mmol) do produto de 104a, 0,11 ml (1,09 mmol) de trietilamina e 0,16 g (0,48 mmol) de TBTU em 30 ml de tetrahidrofurano e 5 ml de dimetilformamida.

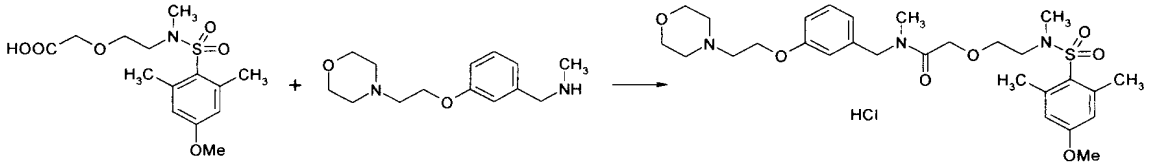
$C_{26}H_{33}N_3O_5S_2$ (531.69)

[M+H]+ = 532

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,166

Exemplo 105





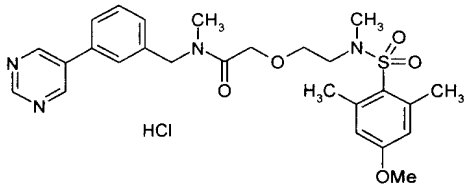
O exemplo 105 é preparado de maneira análoga a 1f a partir de 0,14 g (0,41 mmol) do produto de 53c, 0,10 g (0,40 mmol) de metil-[3-(2-morfolin-4-il-etoxi)-benzil]-amina (Maybridge), 0,14 ml (0,99 mmol) de trietilamina e 0,14 g (0,44 mmol) de TBTU em 30 ml de tetrahidrofurano e 5 ml de dimetilformamida.

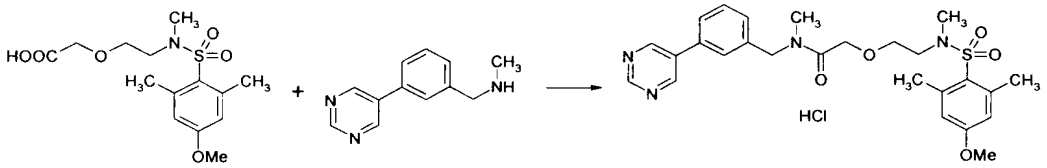
$C_{28}H_{41}N_3O_7S$ x HCl (600.17)

[M+H]+ = 564

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,59.

Exemplo 106





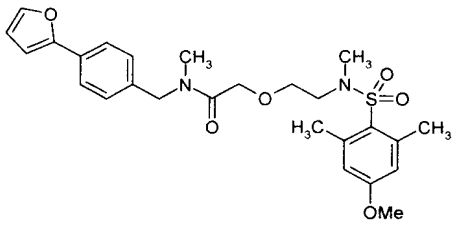
O exemplo 106 é preparado de maneira análoga a 1f a partir de 0,17 (0,51 mmol) do produto de 53c, 0,10 g (0,50 mmol) de metil-(3-pirimidin-5-il-benzil)-amina (Maybridge), 0,17 ml (1,19 mmol) de trietilamina e 0,17 g (0,53 mmol) de TBTU em 30 ml de tetrahidrofurano e 5 ml de dimetilformamida.

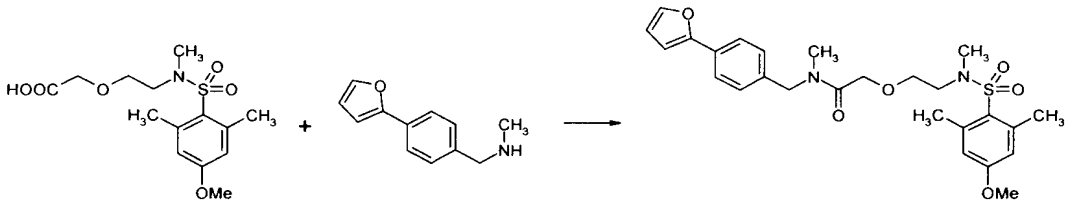
$C_{26}H_{32}N_4O_5S$ x HCl (549.08)

[M+H]+ = 513

HPLC (método 5): tempo de retenção = 1.78 min.

Exemplo 107





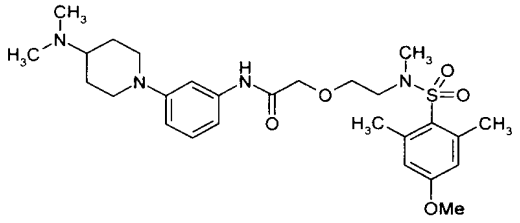
O exemplo 107 é preparado de maneira análoga a 1f a partir de 0,18 g (0,54 mmol) do produto de 53c, 0,10 g (0,53 mmol) de (4-furan-2-il-benzil)-metil-amina (Maybridge), 0,18 ml (1,29 mmol) de trietilamina e 0,18 g (0,56 mmol) de TBTU em 30 ml de tetrahidrofurano e 5 ml de dimetilformamida.

$C_{26}H_{32}N_2O_6S$ (500.61)

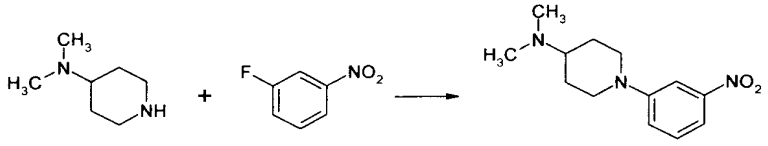
[M+H]+ = 501

HPLC (método 5): tempo de retenção = 2.09 min.

Exemplo 108



108a)

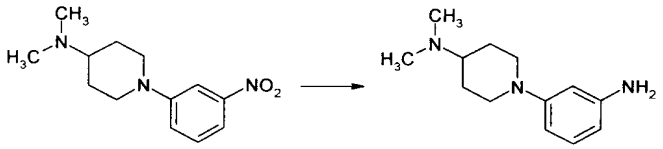


107a é preparado de maneira análoga a 79a a partir de 2,41 g (18,78 mmols) de 4-dimetilamino-piperidina (Alfa Aesar), 1,00 ml (9,39 mmols) de 1-flúor-3-nitrobenzeno (Fluka) e 1,30 g (9,39 mmols) de carbonato de potássio em 15 ml de dimetilsulfóxido.

$C_{13}H_{19}N_3O_2$ (249.31)

[M+H]+ = 250

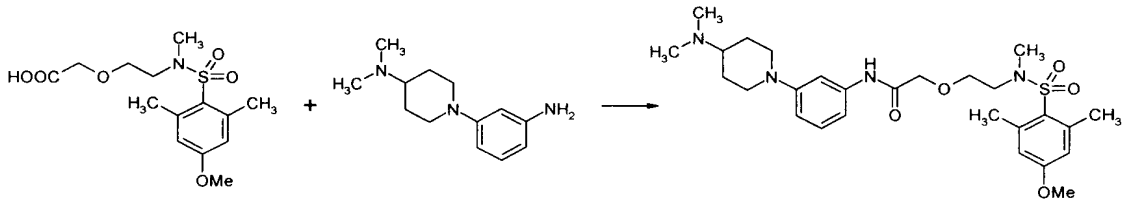
108b)



Uma mistura de 1,74 g (6,98 mmol) do produto de 108a, 12,00 g (68,92 mmol) de ditionita de sódio, 10,00 g (72,35 mmol) de carbonato de potássio, 60 ml de tetrahidrofurano e 30 ml de água é aquecida a 80°C por seis horas. Depois de resfriar, a fase orgânica é separada, lavada com solução saturada de cloreto de sódio, seca sobre sulfato de sódio e concentrada no vácuo à secura.

$C_{13}H_{21}N_3$ (219,33)

108c)



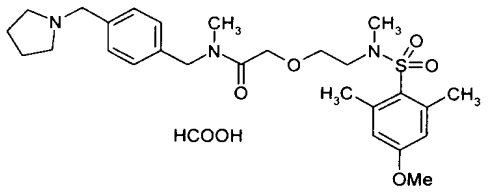
O exemplo 108 é preparado de maneira análoga a 1f a partir de 0,13 g (0,40 mmol) do produto de 53c, 0,10 g (0,47 mmol) do produto de 108b, 0,067 ml (0,48 mmol) de trietilamina e 0,15 g (0,48 mmol) de TBTU em 5 ml de dimetilformamida.

$C_{27}H_{40}N_4O_5S$ (532.70)

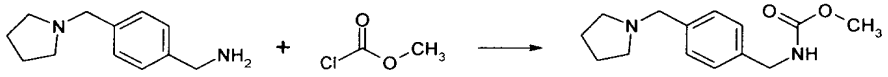
[M+H]+ = 533

HPLC (método 5): tempo de retenção = 1.56 min.

Exemplo 109



109a)



Uma mistura de 0,59 g (3,12 mmols) de 4-pirrolidin-1-ilmetil-benzilamina (Enamine-BB), 0,29 ml (3,75 mmols) de éster metílico de ácido clorofórmico (Fluka), 0,52 ml (3,75 mmols) de trietilamina e 10 ml de diclorometano é agitada à temperatura ambiente por duas horas. A mistura de reação é diluída com 10 ml de diclorometano, lavada duas vezes com água, seca sobre sulfato de sódio e concentrada no vácuo à secura.

$C_{14}H_{20}N_2O_2$ (248.32)

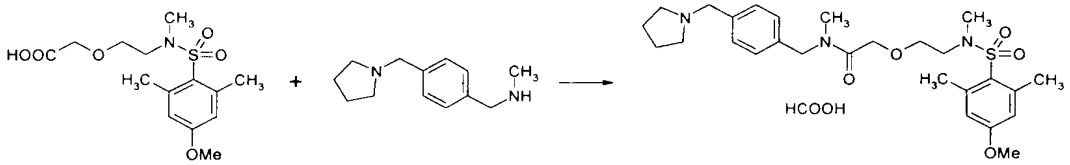
109b)



109b é preparado de maneira análoga a 51b a partir de 0,61 g (2,44 mmols) do produto de 109a e 5,00 ml (5,00 mmols) de hidreto de lítioalumínio 1 M em tetrahidrofurano (Aldrich) em 5 ml de tetrahidrofurano.

$C_{13}H_{20}N_2$ (204,31).

109c)



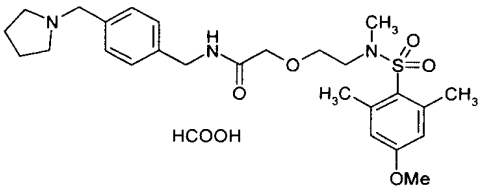
O exemplo 109 é preparado de maneira análoga a 1f a partir de 0,18 g (0,54 mmol) do produto de 53c, 0,17 g (0,81 mmol) do produto de 109b, 0,15 ml (1,07 mmol) de trietilamina e 0,21 g (0,65 mmol) de TBTU em 4 ml de dimetilformamida.

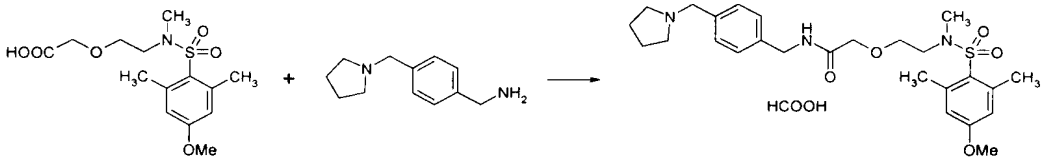
$C_{27}H_{39}N_3O_5S$ x CH_2O_2 (631.71)

[M+H]+ = 518

HPLC (método 5): tempo de retenção = 1.56 min.

Exemplo 110





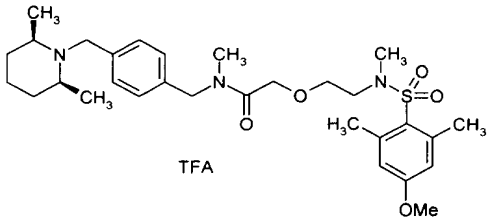
O exemplo 110 é preparado de maneira análoga a 1f a partir de 0,12 g (0,36 mmol) do produto de 53c, 0,096 g (0,51 mmol) de 4-pirrolidin-1-ilmetil-benzilamina (Enamine-BB), 0,10 ml (0,72 mmol) de trietilamina e 0,14 g (0,44 mmol) de TBTU em 4 ml de dimetilformamida.

$C_{26}H_{37}N_3O_5S$ x CH_2O_2 (617.68

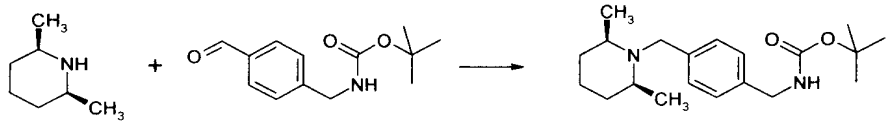
[M+H]+ = 504

HPLC (método 5): tempo de retenção = 1.56 min.

Exemplo 111



111a)



Uma mistura de 1,00 g (4,25 mmols) de éster terc-butílico de ácido (4-formilbenzil)-carbâmico (Acros) e 10 ml de diclorometano é adicionada sob resfriamento com banho de gelo, sucessivamente, a 1,15 ml (8,50

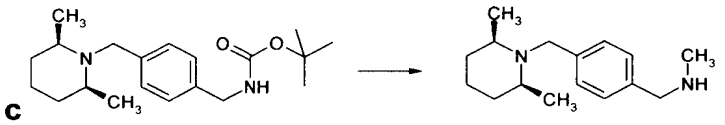
mmols) de cis-2,6-dimetilpiperidina (Aldrich) e 1,80 g (8,50 mmols) de triacetoxiborohidreto de sódio. A mistura de reação é agitada à temperatura ambiente por três dias, a seguir, é lentamente bruscamente resfriada com solução saturada de bicarbonato de sódio e extraída com diclorometano. Os extratos orgânicos são lavados com água e solução saturada de cloreto de sódio, secos sobre sulfato de sódio e concentrados no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna (agente de eluição: diclorometano/metanol 93:7).

$C_{20}H_{32}N_2O_2$ (332.48)

[M+H]+ = 333

HPLC (método 5): tempo de retenção = 1.47 min.

111b)



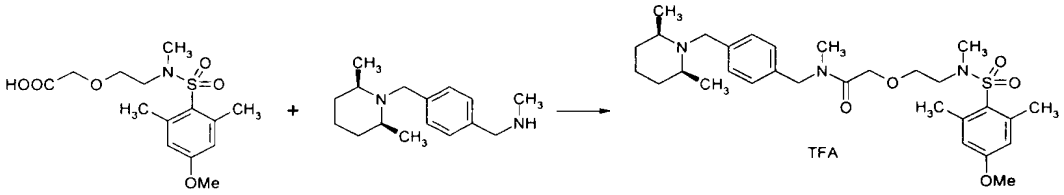
111b é preparado de maneira análoga a 51b a partir de 0,92 g (2,76 mmols) do produto de 111a e 8,27 ml (8,27 mmols) de hidreto de lítioalumínio 1 M em tetrahidrofurano (Aldrich) em 30 ml de tetrahidrofurano.

$C_{16}H_{26}N_2$ (246,39)

[M+H]+ = 247

HPLC (método 5): tempo de retenção = 1,03 min.

111c)



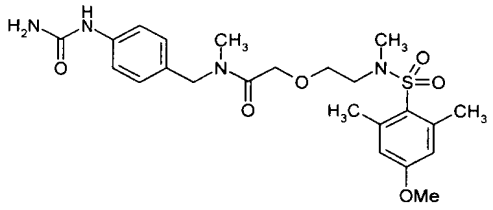
O exemplo 111 é preparado de maneira análoga a 1f a partir de 0,08 g (0,24 mmol) do produto de 53c, 0,059 g (0,24 mmol) do produto de 111b, 0,10 ml (0,72 mmol) de trietilamina e 0,078 g (0,24 mmol) de TBTU em 2 ml de tetrahidrofurano.

$C_{30}H_{45}N_3O_5S \times C_2HF_3O_2$ (673.78)

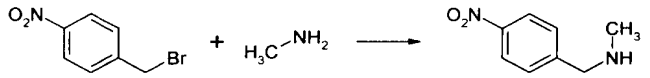
[M+H]+ = 560

HPLC (método 5): tempo de retenção = 1,59 min.

Exemplo 112



112a)

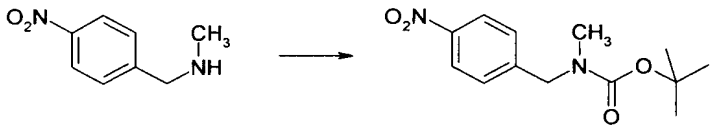


250,00 ml (500,00 mmols) de metilamina 2 M em metanol (Fluka) são lentamente adicionados a 54,00 g (250,00 mmols) de brometo de 4-nitrobenzila (Fluka) sob resfriamento com gelo. A mistura de reação é agitada por uma hora sob resfriamento com gelo e 30 minutos à temperatura ambiente e depois concentrada no vácuo à secura. O resíduo é misturado com éter dietílico e filtrado. O filtrado é concentrado no vácuo à secura, adicionado à solução de carbonato de sódio e extraído com éter dietílico. Os extratos orgânica são secos sobre sulfato de sódio e concentrados no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna (agente de eluição: diclorometano/metanol 5:0 a 5:1).

$C_8H_{10}N_2O_2$ (166.18)

[M+H]+ = 167

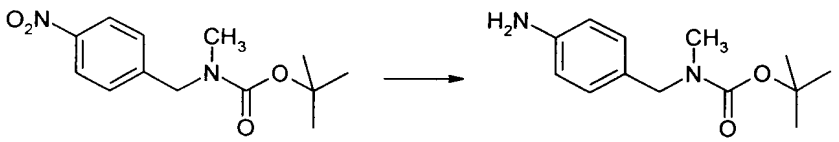
112b)



Uma mistura de 13,40 g (80,64 mmols) do produto de 112a e 25 ml de acetato de etila é lentamente adicionada a 17,68 g (81,00 mmols) de anidrido boc sob resfriamento com gelo. A mistura de reação é agitada à temperatura ambiente por três horas, depois lavada com água, seca sobre sulfato de sódio e concentrada no vácuo à secura.

$C_{13}H_{18}N_2O_4$ (266,29)

112c)



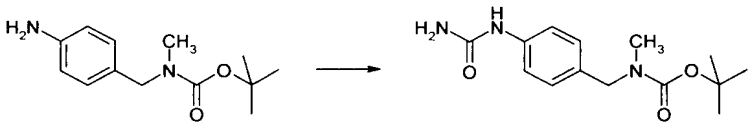
Uma mistura de 23,00 g (86,37 mmols) do produto de 112b, 2,30 g de níquel de Raney, 230 ml de etanol e 230 ml de acetato de etila é hidrogenada no autoclave à temperatura ambiente. O catalisador é filtrado, o filtrado concentrado no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de cromatografia de coluna (agente de eluição: éter de petróleo/acetato de etila 1:1).

$C_{13}H_{20}N_2O_2$ (236.31)

[M+H]+ = 237

DC: gel de sílica, éter de petróleo/acetato de etila 1:1, valor Rf = 0,55.

112d)

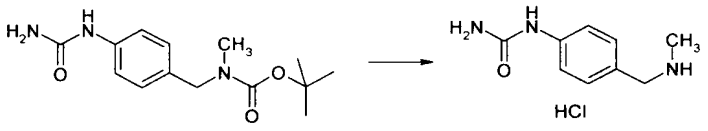


Uma mistura de 0,50 g (2,12 mmols) do produto de 112c, 0,48 g (3,56 mmols) de trimetil-sililisocianato (Fluka) e 15 ml de tetrahidrofurano é agitada sob refluxo durante o final de semana. Em seguida, a mistura de reação é concentrada no vácuo à secura.

$C_{14}H_{21}N_3O_3$ (279.33)

[2M+H]+ = 559

112e)

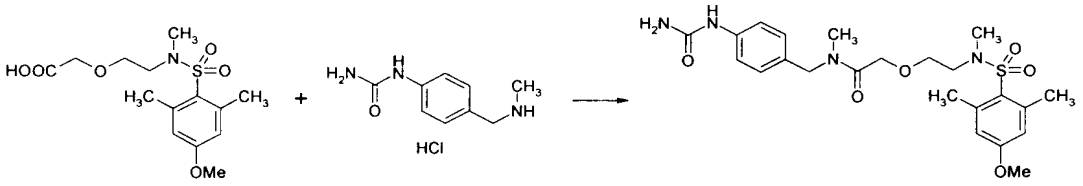


Uma mistura de 0,64 g (2,29 mmols) do produto de 112d e 10 ml de HCl metanólico é agitada por três horas à temperatura ambiente e duas horas a 50°C. Em seguida, a mistura de reação é concentrada no vácuo à secura. O resíduo é seco no vácuo durante a noite.

$C_9H_{13}N_3$ x HCl (215.68)

[M+H]+ = 180

112f)

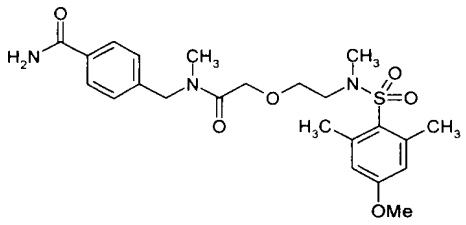


O exemplo 112 é preparado de maneira análoga a 1f a partir de 0,20 g (0,60 mmol) do produto de 53c, 0,13 g (0,60 mmol) do produto de 112e, 0,42 ml (3,02 mmols) de trietilamina e 0,22 g (0,66 mmol) de TBTU em 4 ml de dimetilformamida.

$C_{23}H_{32}N_4O_6S$ (492.59)

[M+H]+ = 493

Exemplo 113



113a)



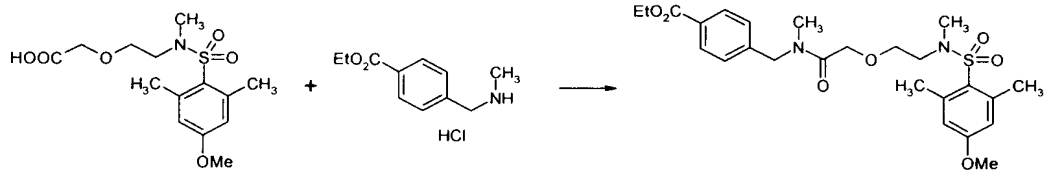
Uma mistura de 2,00 g (9,92 mmols) de cloridrato de ácido 4-metilaminometil-benzóico (J. Med. Chem. 26, 1983, 309-312) e 25 ml de HCl etanólico é agitada sob refluxo por 1,5 horas. A seguir, a mistura de reação é concentrada no vácuo à secura.

$C_{11}H_{15}NO_2$ x HCl (229.70)

[M+H]+ = 194

HPLC (método 6): tempo de retenção = 1,39 min.

113b)



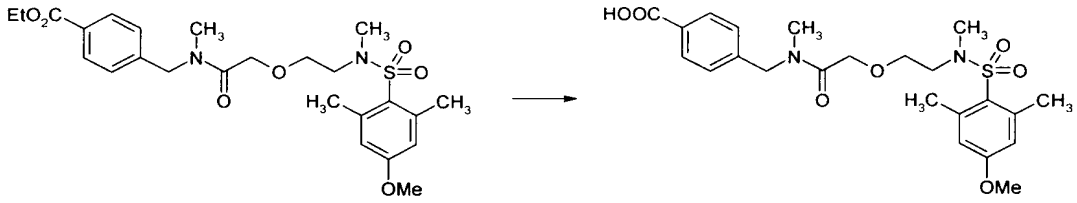
113b é preparado de maneira análoga a 1f a partir de 0,70 g (2,11 mmols) do produto de 53c, 0,49 g (2,11 mmols) do produto de 113a, 0,88 ml (6,34 mmols) de trietilamina e 0,78 g (2,32 mmols) de TBTU em 12 ml de dimetilformamida.

$C_{25}H_{34}N_2O_7S$ (506.61)

[M+H]+ = 507

HPLC (método 6): tempo de retenção = 3,95 min.

113c)



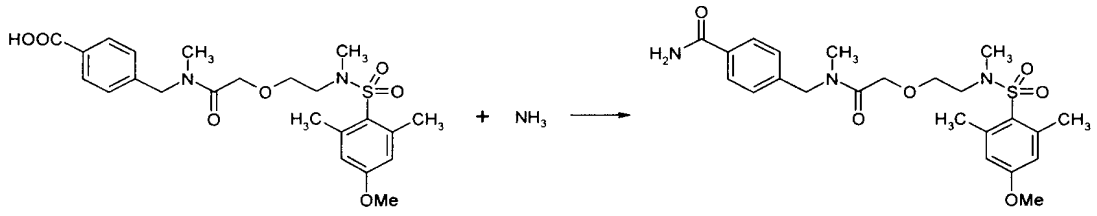
Uma mistura de 1,06 g (2,09 mmols) do produto de 133b, 7,00 ml (7,00 mmols) de soda cáustica 1 M, 15 ml de tetrahidrofurano e 1,5 ml de etanol é agitada a 50°C por quatro horas. A seguir, a mistura de reação é adicionada a 7 ml de HCl 1 M e concentrada no vácuo à secura. O resíduo é retomado em acetona, seco sobre sulfato de sódio e concentrado no vácuo à secura.

$C_{23}H_{30}N_2O_7S$ (478.56)

[M+H]+ = 479

HPLC (método 6): tempo de retenção = 3,21 min.

113d)



O exemplo 113 é preparado de maneira análoga a 1f a partir de

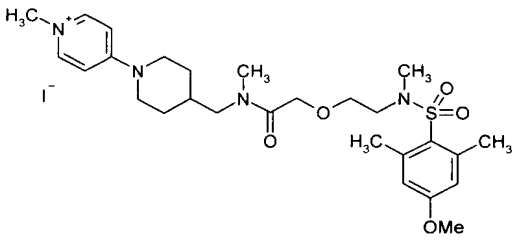
0,50 g (1,05 mmol) do produto de 113c, 4,00 ml (2,00 mmols) de amoníaco 0,5 M em dioxano, 0,44 ml (3,14 mmols) de trietilamina e 0,38 g (1,15 mmol) de TBTU em 4 ml de dimetilformamida.

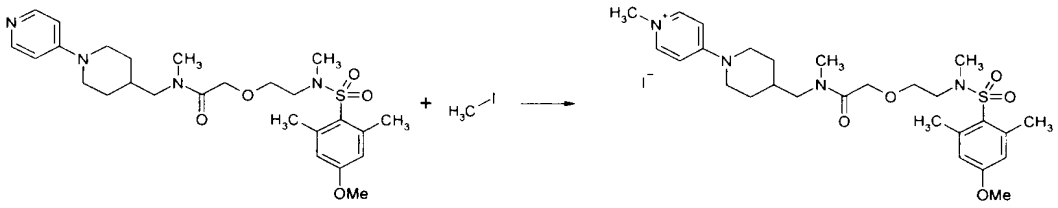
$C_{23}H_{31}N_3O_6S$ (477.57)

[M+H]+ = 478

HPLC (método 6): tempo de retenção = 2,92 min.

Exemplo 114





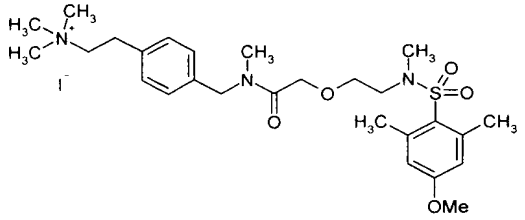
Uma mistura de 0,075 g (0,15 mmol) de 61, 0,1 g (0,71 mmol) de iodeto de metila e 5 ml de diclorometano é agitada à temperatura ambiente durante a noite. A seguir, a mistura de reação é concentrada no vácuo à secura.

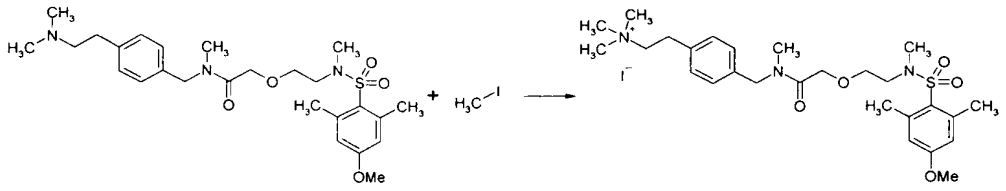
$C_{27}H_{41}N_4O_5S$ x I (660.61)

[M+H]+ = 533

HPLC (método 5): tempo de retenção = 1,55 min.

Exemplo 115





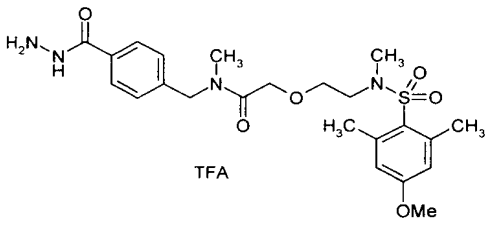
O exemplo 115 é preparado de maneira análoga a 114 a partir de 0,03 g (0,059 mmol) de 64 e 0,05 g (0,35 mmol) de iodeto de metila em 5 ml de diclorometano.

$C_{27}H_{42}N_3O_5S$ x I (647.61)

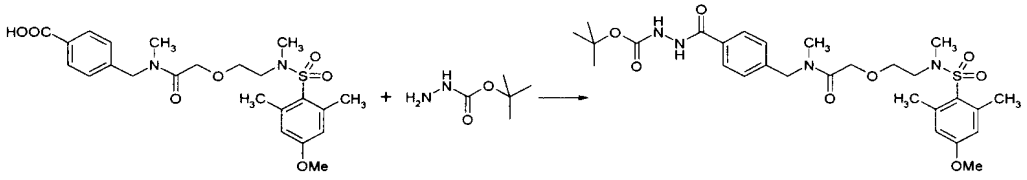
[M+H]+ = 520

HPLC (método 5): tempo de retenção = 1,55 min.

Exemplo 116



116a)



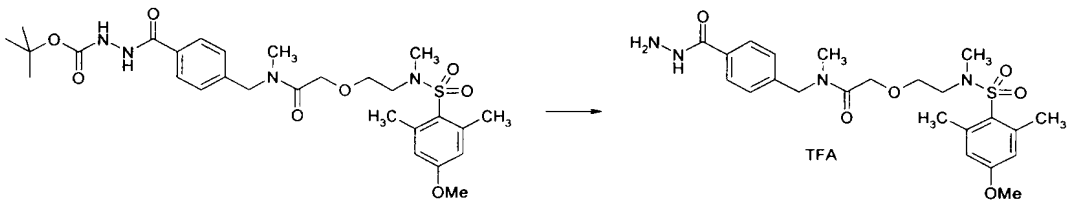
116a é preparado de maneira análoga a 1f a partir de 0,50 g (1,05 mmol) do produto de 113c, 0,14 g (1,05 mmol) de éster terc-butílico de ácido hidrazincarboxílico (Aldrich), 0,58 ml (4,18 mmols) de trietilamina e 0,38 g (1,15 mmol) de TBTU em 6 ml de dimetilformamida.

$C_{28}H_{40}N_4O_8S$ (592.71)

[M+H]+ = 593

HPLC (método 6): tempo de retenção = 3,46 min.

116b)



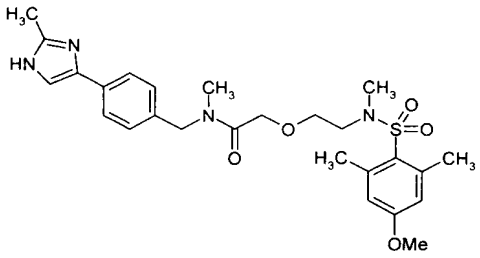
O exemplo 116 é preparado de maneira análoga a 112e a partir de 0,68 g (1,15 mmol) do produto de 116a e 10 ml de HCl metanólico.

$C_{23}H_{32}N_4O_6S \times C_2HF_3O_2$ (606.61)

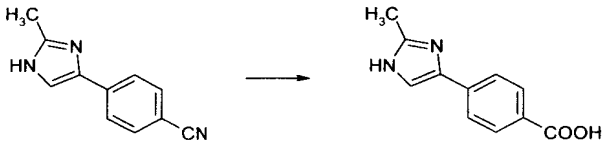
$[M+H]^+ = 493$

HPLC (método 6): tempo de retenção = 3,46 min.

Exemplo 117



117a)

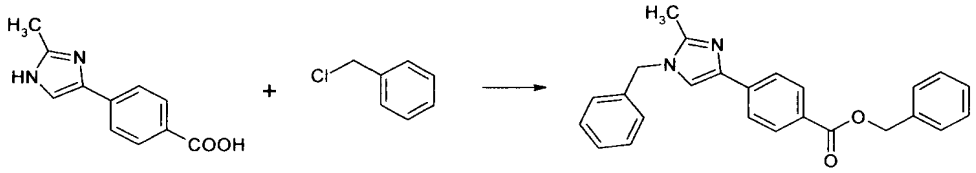


Uma mistura de 3,20 g (17,47 mmols) do produto de 63a, 50 ml de soda cáustica a 20% e 50 ml de etanol é agitada sob agitação durante a noite. A seguir, o etanol é removido no vácuo e o resíduo aquoso é neutralizado com HCl concentrado. O precipitado formado é filtrado e seco.

$C_{11}H_{10}N_2O_2$ (202,21)

$[M+H]^+ = 203$.

117b)



Uma mistura de 2,70 g (13,35 mmols) do produto de 117a, 8,00

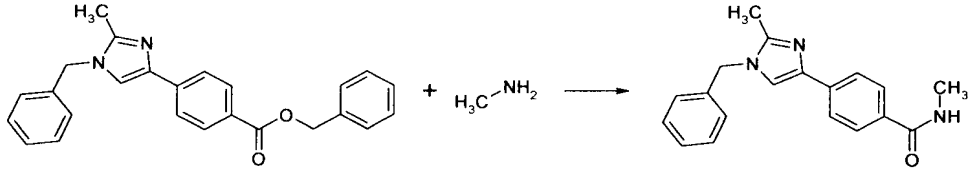
g (57,89 mmols) de carbonato de potássio e 100 ml de dimetilformamida é agitada a 60°C por uma hora. Depois de resfriar, a mistura de reação é adicionada a 3,50 g (27,65 mmols) de cloreto de benzila (Aldrich) à temperatura ambiente e em seguida, agitada a 60°C durante o final de semana. A mistura de reação é vertida sobre água e agitada à temperatura ambiente por uma hora. O precipitado formado é filtrado e seco.

$C_{25}H_{22}N_2O_2$ (382.45)

[M+H]+ = 383

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,64.

117c)

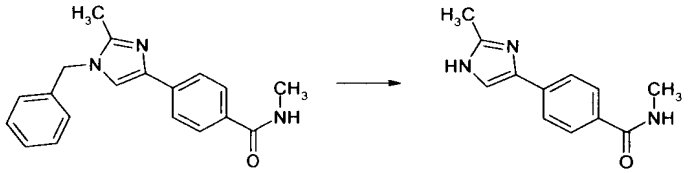


Uma mistura de 1,80 g (4,71 mmols) do produto de 117b e 100 ml de metilamina a 33% em etanol (Aldrich) é agitada no autoclave a 180°C por seis horas e a 160°C durante a noite. A seguir, a mistura de reação é concentrada no vácuo à secura. O produto obtido dessa maneira é purificado por meio de cromatografia de coluna (agente de eluição: diclorometano/metanol 19:1).

$C_{19}H_{19}N_3O$ (305.37)

[M+H]+ = 306

117d)

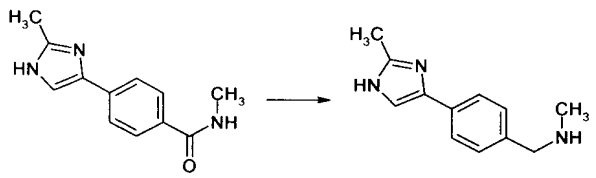


Uma mistura de 1,20 g (3,93 mmols) do produto de 117c, 0,20 g de paládio sobre carvão (20%) e 50 ml de metanol é hidrogenada no autoclave a 50°C. O catalisador é filtrado, o filtrado concentrado no vácuo à secura.

$C_{12}H_{13}N_3O$ (215.25)

[M+H]+ = 216.

117e)

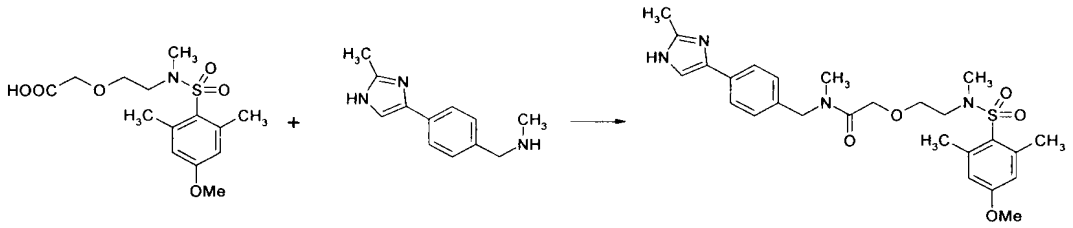


117e é preparado de maneira análoga a 38f a partir de 0,70 g (3,25 mmols) do produto de 117d e 10,00 ml (10,00 mmols) de hidreto de lítioalumínio 1 M em tetrahidrofurano (Aldrich) em 200 ml de tetrahidrofurano.

$C_{12}H_{15}N_3$ (201,27)

[M+H]+ = 202

117f)



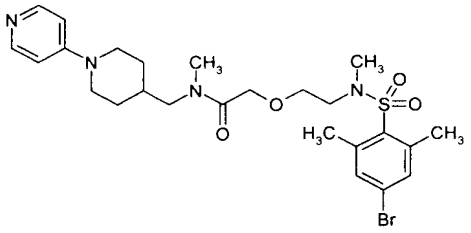
O exemplo 117 é preparado de maneira análoga a 1f a partir de 0,17 g (0,51 mmol) do produto de 53c, 0,10 g (0,50 mmol) do produto de 117e, 0,17 ml (1,19 mmol) de trietilamina e 0,17 g (0,53 mmol) de TBTU em 30 ml de tetrahidrofurano e 5 ml de dimetilformamida.

$C_{26}H_{34}N_4O_5S$ (514.64)

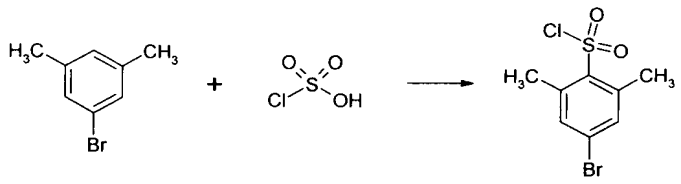
[M+H]+ = 515

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,28.

Exemplo 118



118a)

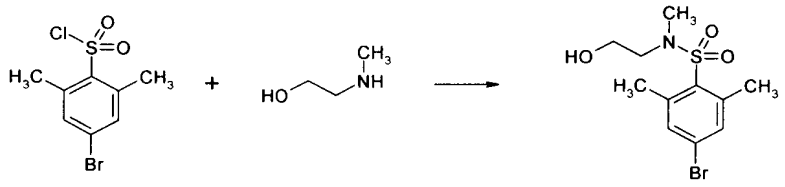


118a é preparado de maneira análoga a 13a a partir de 0,75 g (4,05 mmols) de 5-bromo-m-xileno (Aldrich), 0,55 ml (8,30 mmols) de ácido clorossulfônico (Aldrich) e 10 ml de diclorometano.

$C_8H_8BrClO_2S$ (283.57)

HPLC (método 6): tempo de retenção = 4,76 min.

118b)

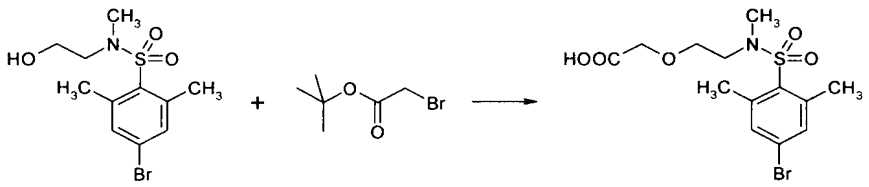


118b é preparado de maneira análoga a 3a a partir de 0,65 g (2,29 mmols) do produto de 118a e 0,28 ml (3,44 mmols) de N-metilaminoetanol (BASF) em 5 ml de tetrahidrofurano.

$C_{11}H_{16}BrNO_3S$ (322.22)

HPLC (método 6): tempo de retenção = 3,38 min.

118c)

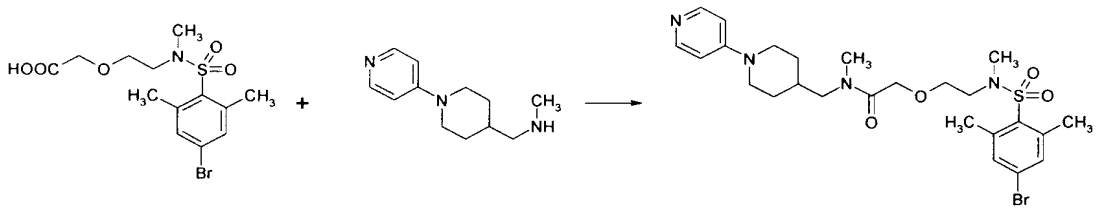


118c é inicialmente preparado de maneira análoga a 53b a partir de 0,74 g (2,29 mmols) do produto de 118b, 0,75 g (5,06 mmols) de éster terc-butílico de ácido 2-bromopropiônico (Fluka), 0,42 g (1,14 mmol) de iodeto de tetrabutilamônio (Aldrich) e 8,67 g (75,90 mmol) sde soda cáustica a 35% em 40 ml de tolueno. O éster terc-butílico é agitado, em seguida, junto com 2 ml de HCl 4 M em dioxano (Aldrich) em 4 ml de dioxano à temperatura ambiente durante a noite. A seguir, o produto é obtido através de concentração da mistura de reação no vácuo.

$C_{13}H_{18}BrNO_5S$ (380.26)

HPLC (método 6): tempo de retenção = 3,48 min.

118d)



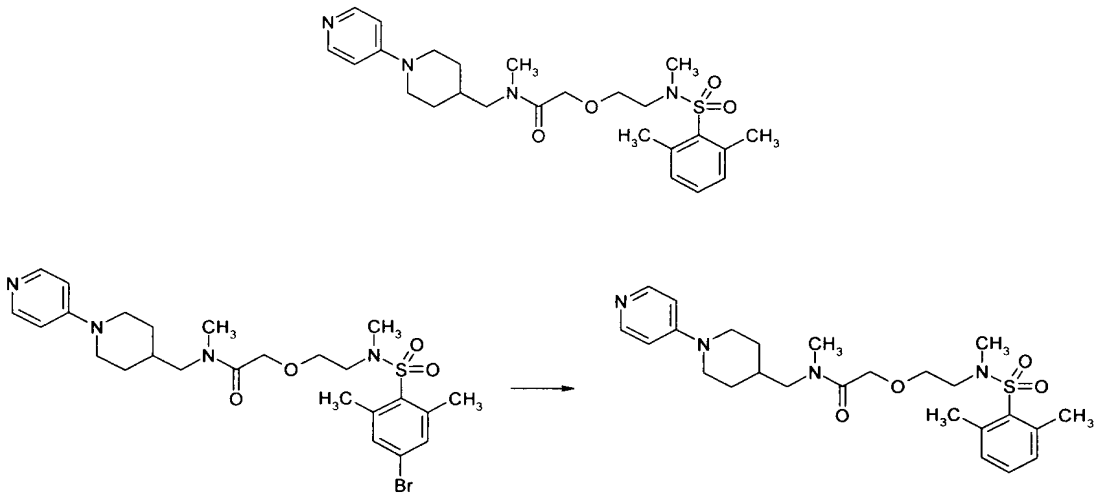
O exemplo 118 é preparado de maneira análoga a 1f a partir de 0,10 g (0,26 mmol) do produto de 118c, 0,054 g (0,26 mmol) do produto de 61b, 0,11 ml (0,79 mmol) de trietilamina e 0,084 g (0,26 mmol) de TBTU em 10 ml de tetrahidrofurano e 3 ml de dimetilformamida.

$C_{25}H_{35}BrN_4O_4S$ (567.54)

[M+H]+ = 568/569/571

HPLC (método 6): tempo de retenção = 2,77 min.

Exemplo 119



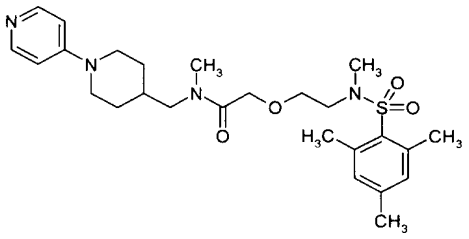
Uma mistura de 0,03 g (0,053 mmol) de 118 e 0,03 g de paládio sobre carvão em 5 ml de metanol é hidrogenada no autoclave à temperatura ambiente. O catalisador é filtrado, o filtrado é concentrado no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de HPLC preparatória.

$C_{25}H_{36}N_4O_4S$ (488.64)

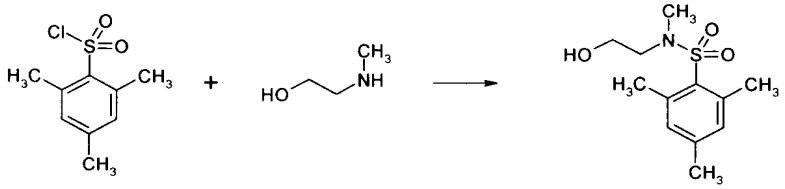
[M+H]+ = 489

HPLC (método 6): tempo de retenção = 2,45 min.

Exemplo 120



120a)

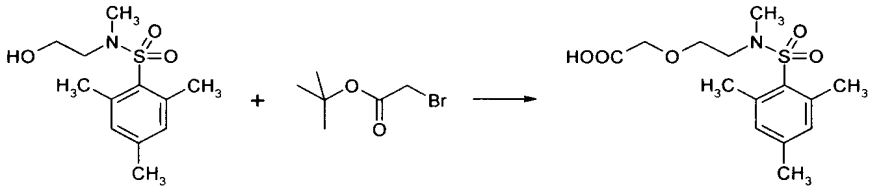


120a é preparado de maneira análoga a 3a a partir de 0,50 g (2,29 mmols) de cloreto de ácido 2,4,6-trimetilbenzeno-sulfônico (Fluka) e 0,19 g (2,52 mmols) de N-metilaminoetanol (Fluka) e 0,19 g (2,52 mmols) de N-metilaminoetanol (BASF) em 5 ml de tetrahidrofurano.

$C_{12}H_{19}NO_3S$ (257.35)

[M+H]+ = 258

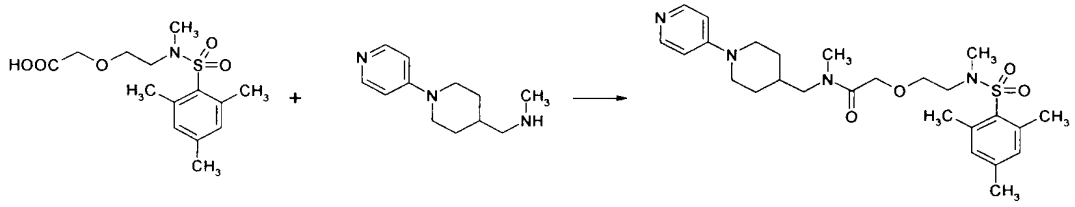
120b)



120b é preparado de maneira análoga a 118c a partir de 0,56 g (2,18 mmols) do produto de 120a, 0,48 ml (3,26 mmols) de éster terc-butílico de ácido 2-bromopropiônico (Fluka), 0,18 g (0,65 mmol) de cloreto de tetra-butilamônio (Fluka) e 7,46 g (65,28 mmols) de soda cáustica a 35% em 20 ml de tolueno e subsequente agitação em 2 ml de HCl 4 M em dioxano.

$C_{14}H_{21}NO_5S$ (315.39).

120c)



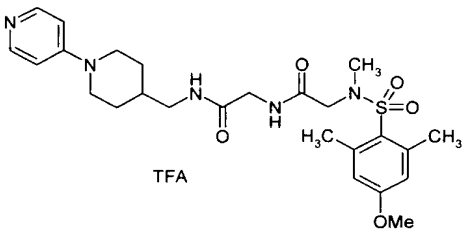
O exemplo 120 é preparado de maneira análoga a 1f a partir de 0,10 g (0,32 mmol) do produto de 120b, 0,065 g (0,32 mmol) do produto de 61b, 0,13 ml (0,95 mmol) de trietilamina e 0,20 g (0,63 mmol) de TBTU em 10 ml de tetrahidrofurano.

$C_{26}H_{38}N_4O_4S$ (502.67)

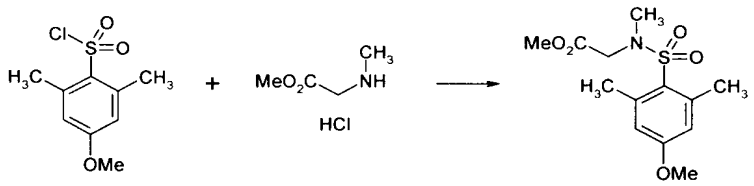
[M+H]+ = 503

HPLC (método 5): tempo de retenção = 1,57 min.

Exemplo 121



121a)

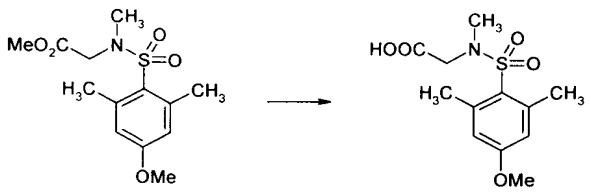


Uma mistura de 0,98 g (7,05 mmols) de cloridrato de sarcosin metiléster (Fluka), 1,65 g (7,05 mmols) do produto de 13a e 50 ml de piridina é agitada à temperatura ambiente por uma hora. A seguir, a mistura de reação é concentrada no vácuo à secura. A seguir o resíduo é retomado em HCl 1 M e extraído com acetato de etila. Os extratos orgânicos são secos sobre sulfato de sódio e concentrados no vácuo à secura.

$C_{13}H_{19}NO_5S$ (301.36)

[M+H]+ = 302

121b)

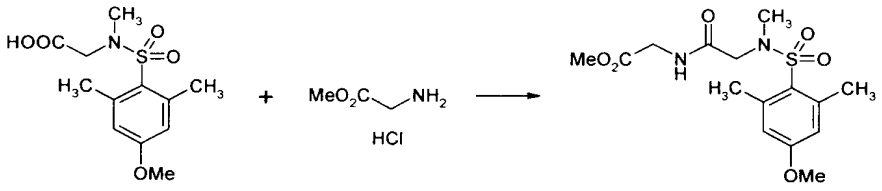


Uma mistura de 1,90 g (6,29 mmols) do produto de 121a, 6,45 ml (12,90 mmols) de soda cáustica 2 M e 9 ml de metanol é agitada à temperatura ambiente por três dias. O metanol é removido no vácuo, o resíduo aquoso é vertido sobre HCl 1 M. O precipitado formado é filtrado e seco no dessecador a vácuo durante a noite.

$C_{12}H_{17}NO_5S$ (287.33)

[M+H]+ = 288.

121c)



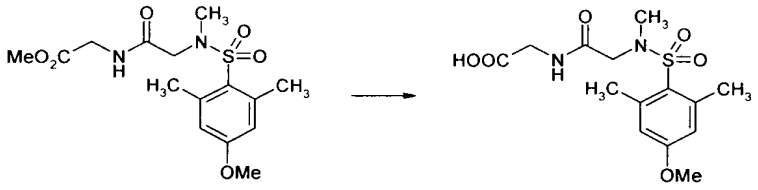
121c é preparado de maneira análoga a 1f a partir de 0,20 g (0,70 mmol) do produto de 121b, 0,087 g (0,70 mmol) de cloridrato de éster glicin metílico (Aldrich), 0,29 ml (2,09 mmols) de trietilamina e 0,22 g (0,70 mmol) de TBTU em 5 ml de tetrahidrofurano.

$C_{15}H_{22}N_2O_6S$ (358.41)

[M+H]+ = 359

HPLC (método 5): tempo de retenção = 1,72 min.

121d)

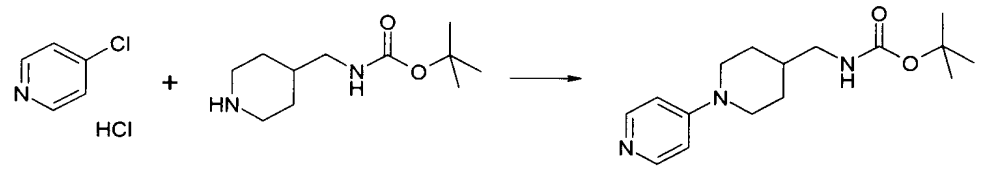


121d é preparado de maneira análoga a 121b a partir de 0,23 g (0,63 mmol) do produto de 121c e 0,64 ml (1,29 mmol) de soda cáustica 2 M em 1 ml de metanol.

$C_{14}H_{20}N_2O_6S$ (344.38)

[M+H]+ = 345

121e)



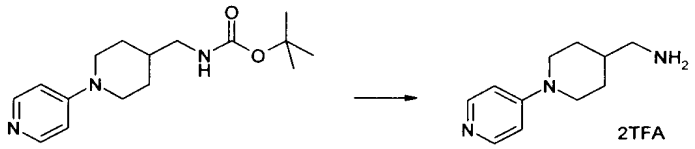
121e é preparado de maneira análoga a 28c a partir de 3,00 g (14,00 mmols) de éster terc-butílico de ácido piperidin-4-ilmetil-carbâmico (EMKA), 2,10 g (14,00 mmols) de cloridrato de 4-cloropiridina (Aldrich) e 7,80 ml (56,32 mmols) de trietilamina em 15 ml de isopropanol.

$C_{16}H_{25}N_3O_2$ (291.39)

[M+H]+ = 292

HPLC (método 5): tempo de retenção = 1,40 min.

121f)



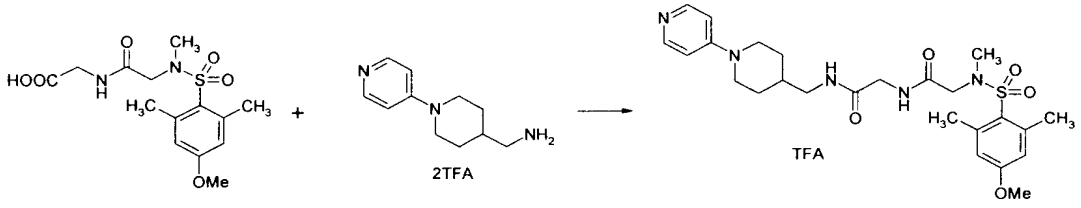
121f é preparado de maneira análoga a 18b a partir de 1,44 g (4,95 mmols) do produto de 121e e 4,95 ml de TFA em 8 ml de diclorometano.

$C_{11}H_{17}N_3 \times 2C_2HF_3O_2$ (419.32)

[M+H]+ = 192

HPLC (método 5): tempo de retenção = 0,36.

121g)



O exemplo 121 é preparado de maneira análoga a 1f a partir de 0,09 g (0,26 mmol) do produto de 121d, 0,11 g (0,26 mmol) do produto de 121f, 0,15 ml (1,05 mmol) de trietilamina e 0,084 g (0,26 mmol) de TBTU em

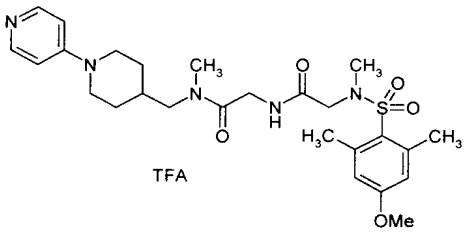
1,9 ml de tetrahidrofurano.

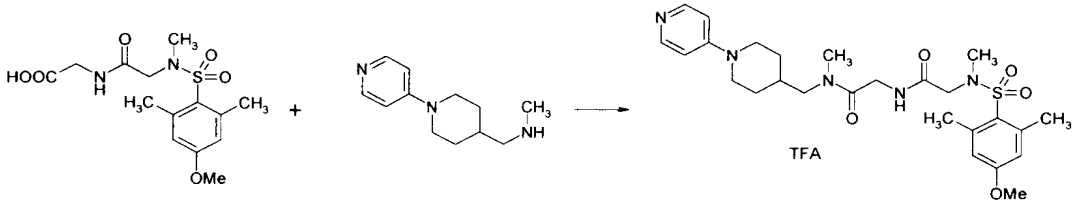
$C_{25}H_{35}N_5O_5S$ x $C_2HF_3O_2$ (631.67)

[M+H]+ = 518

HPLC (método 5): tempo de retenção = 1,46 min.

Exemplo 122





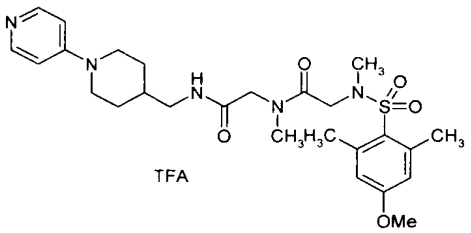
O exemplo 122 é preparado de maneira análoga a 1f a partir de 0,09 g (0,26 mmol) do produto de 121d, 0,054 g (0,26 mmol) do produto de 61b, 0,11 ml (0,78 mmol) de trietilamina e 0,084 g (0,26 mmol) de TBTU em 1,9 ml de tetrahidrofurano.

$C_{26}H_{37}N_5O_5S$ x $C_2HF_3O_2$ (645.69)

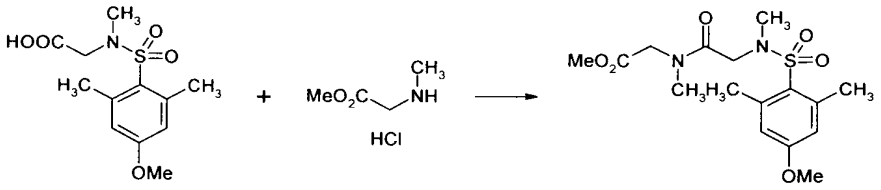
[M+H]+ = 532

HPLC (método 5): tempo de retenção = 1,50 min.

Exemplo 123



123a)



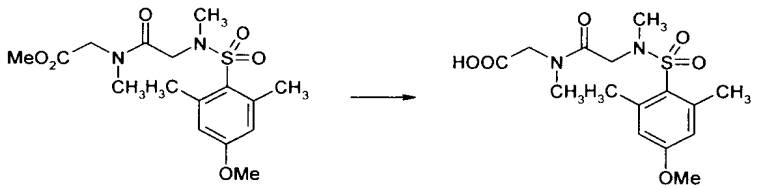
123a é preparado de maneira análoga a 1f a partir de 0,20 g (0,70 mmol) do produto de 121b, 0,097 g (0,70 mmol) de cloridrato de sarcosin metiléster (Fluka), 0,29 ml (2,09 mmols) de trietilamina e 0,22 g (0,70 mmol) de TBTU em 5 ml de tetrahidrofurano.

$C_{16}H_{24}N_2O_6S$ (372.44)

[M+H]+ = 373

HPLC (método 5): tempo de retenção = 1,78 min.

123b)

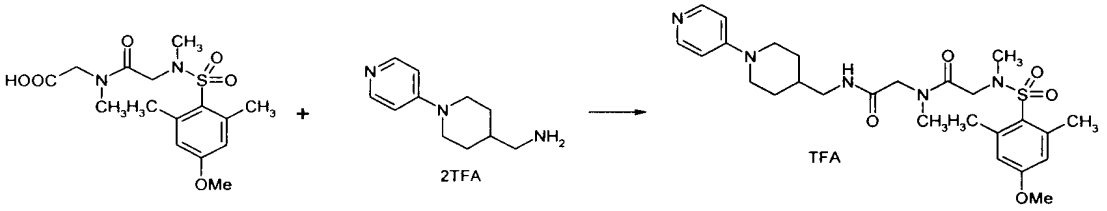


123b é preparado de maneira análoga a 121b a partir de 0,23 g (0,60 mmol) do produto de 123a e 0,62 ml (1,24 mmol) de soda cáustica 2 M em 1 ml de metanol.

$C_{15}H_{22}N_2O_6S$ (258.41)

[M+H]+ = 359

123c)



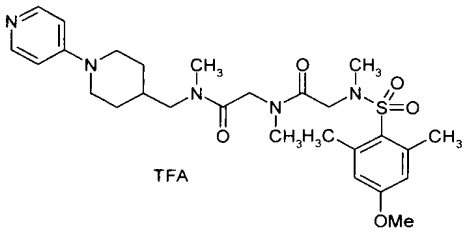
O exemplo 123 é preparado de maneira análoga a 1f a partir de 0,094 g (0,26 mmol) do produto de 123b, 0,11 g (0,26 mmol) do produto de 121f, 0,15 ml (1,05 mmol) de trietilamina e 0,084 g (0,26 mmol) de TBTU em 1,9 ml de tetrahidrofurano.

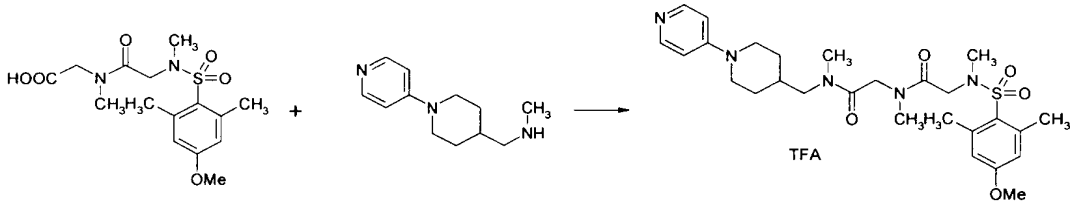
$C_{26}H_{37}N_5O_5S \times C_2HF_3O_2$ (645.69)

[M+H]+ = 532

HPLC (método 5): tempo de retenção = 1,47 min.

Exemplo 124





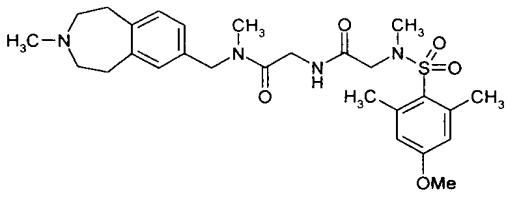
O exemplo 124 é preparado de maneira análoga a 1f a partir de 0,094 (0,26 mmol) do produto de 123b, 0,054 g (0,26 mmol) do produto de 61b, 0,11 ml (0,78 mmol) de trietilamina e 0,084 g (0,26 mmol) de TBTU em 1,9 ml de tetrahidrofurano.

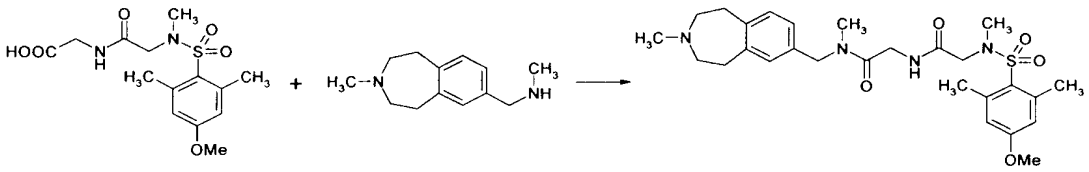
$C_{27}H_{39}N_5O_5S \times C_2HF_3O_2$ (659.72)

[M+H]+ = 549

HPLC (método 5): tempo de retenção = 1,49 min.

Exemplo 125





O exemplo 125 é preparado de maneira análoga a 1f a partir de 0,09 g (0,26 mmol) do produto de 121d, 0,076 g (0,26 mmol) do produto de 54b, 0,11 ml (0,78 mmol) de trietilamina e 0,084 g (0,26 mmol) de TBTU em

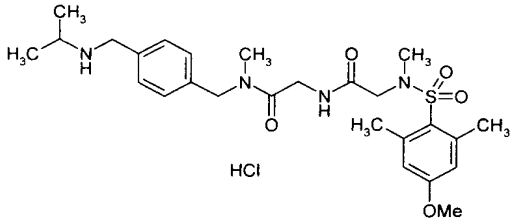
1,9 ml de tetrahidrofurano.

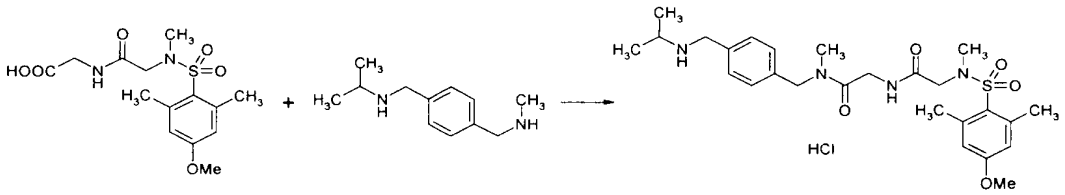
$C_{27}H_{38}N_4O_5S$ (530.68)

[M+H]+ = 531

HPLC (método 1): tempo de retenção = 2,43 min.

Exemplo 126





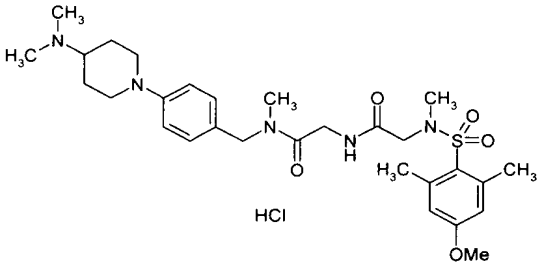
O exemplo 126 é preparado de maneira análoga a 1f a partir de 0,09 g (0,26 mmol) do produto de 121d, 0,05 g (0,26 mmol) do produto de 59b, 0,11 ml (0,78 mmol) de trietilamina e 0,084 g (0,26 mmol) de TBTU em 1,9 ml de tetrahidrofurano.

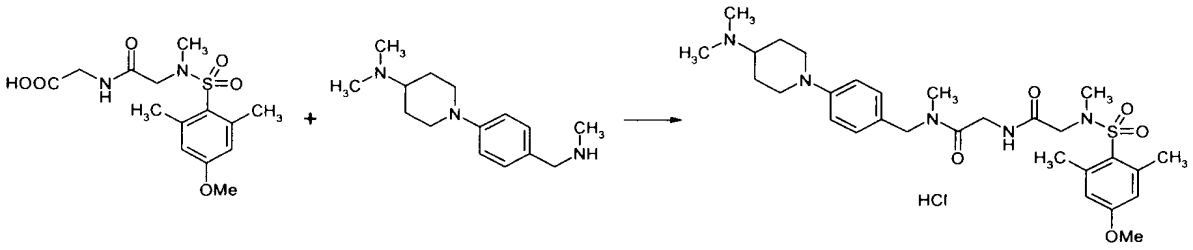
$C_{26}H_{38}N_4O_5S$ x HCl (555.13)

[M+H]+ = 519

HPLC (método 1): tempo de retenção = 2,42 min.

Exemplo 127





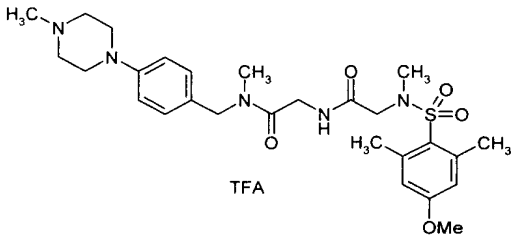
O exemplo 127 é preparado de maneira análoga a 1f a partir de 0,09 g (0,26 mmol) do produto de 121d, 0,065 g (0,26 mmol) do produto de 80a, 0,11 ml (0,78 mmol) de trietilamina e 0,084 g (0,26 mmol) de TBTU em 1,9 ml de tetrahidrofurano.

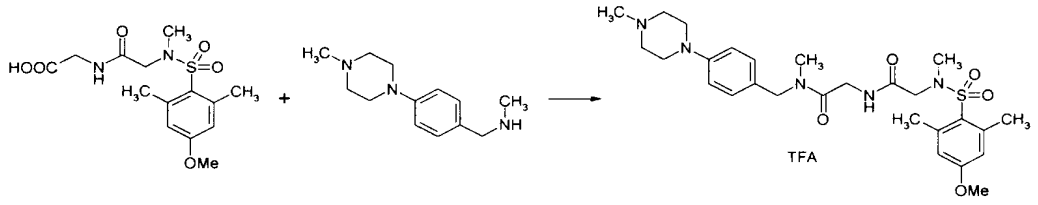
$C_{29}H_{43}N_5O_5S$ x HCl (610.21)

[M+H]+ = 574

HPLC (método 1): tempo de retenção = 2,38 min.

Exemplo 128





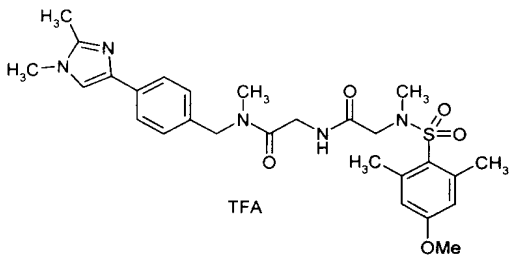
O exemplo 128 é preparado de maneira análoga a 1f a partir de 0,09 g (0,26 mmol) do produto de 121d, 0,057 g (0,26 mmol) do produto de 81a, 0,11 ml (0,78 mmol) de trietilamina e 0,084 g (0,26 mmol) de TBTU em 1,9 ml de tetrahidrofurano.

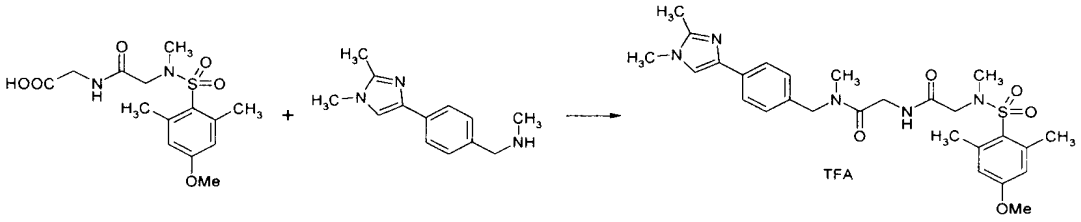
$C_{27}H_{39}N_5O_5S$ x $C_2HF_3O_2$ (610.21)

[M+H]+ = 546

HPLC (método 5): tempo de retenção = 1,51 min.

Exemplo 129





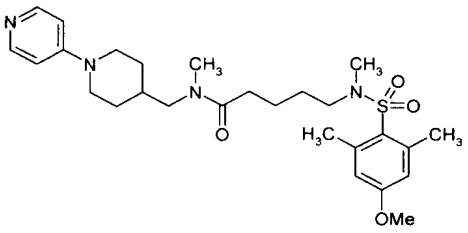
O exemplo 129 é preparado de maneira análoga a 1f a partir de 0,09 (0,26 mmol) do produto de 121d, 0,056 g (0,26 mmol) do produto de 67c, 0,11 ml (0,78 mmol) de trietilamina e 0,084 g (0,26 mmol) de TBTU em 1,9 ml de tetrahidrofurano.

$C_{27}H_{35}N_5O_5S \times C_2HF_3O_2$ (655.69)

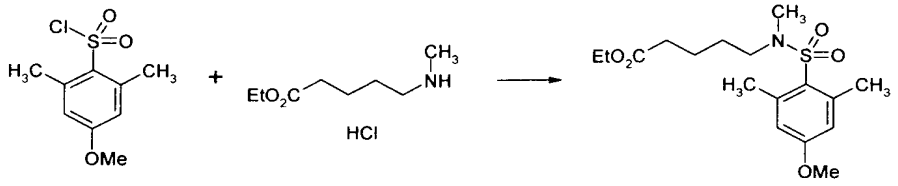
[M+H]+ = 542

HPLC (método 5): tempo de retenção = 1,52 min.

Exemplo 130



130a)



130a é preparado de maneira análoga a 10d a partir de 0,50 g (2,13 mmols) do produto de 13a, 0,42 g (2,13 mmols) de éster etílico de áci-

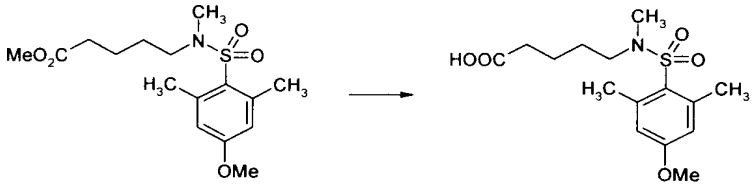
do 5-metilaminovalérico (J. Am. Chem. Soc. 55, 1933, 1233-1241) e 1,18 ml (8,52 mmols) de trietilamina em 15 ml de tetrahidrofurano.

$C_{17}H_{27}NO_5S$ (357.47)

[M+H]+ = 358

HPLC (método 6): tempo de retenção = 4,10 min.

130b)



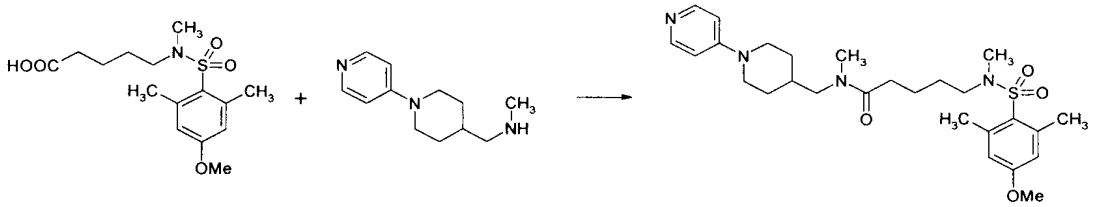
130b é preparado de maneira análoga a 121b a partir de 0,62 (1,73 mmol) do produto de 130a e 7,00 ml (7,00 mmols) de soda cáustica 1 M em 1,5 ml de metanol e 15 ml de tetrahidrofurano.

$C_{15}H_{23}NO_5S$ (329.41)

[M+H]+ = 330

HPLC (método 6): tempo de retenção = 3,24 min.

130c)



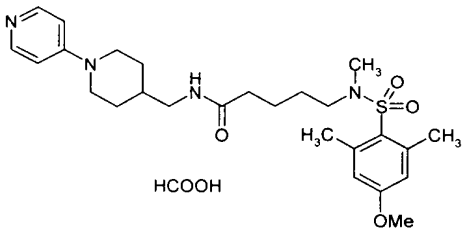
O exemplo 130 é preparado de maneira análoga a 1f a partir de 0,18 g (0,54 mmol) do produto de 130b, 0,10 g (0,49 mmol) do produto de 61b, 0,14 ml (0,97 mmol) de trietilamina e 0,18 g (0,54 mmol) de TBTU em 3 de dimetilformamida.

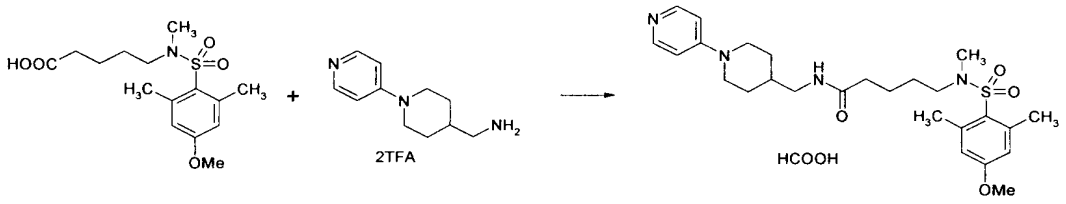
$C_{27}H_{40}N_4O_4S$ (516.70)

[M+H]+ = 517

HPLC (método 6): tempo de retenção = 2,65 min.

Exemplo 131





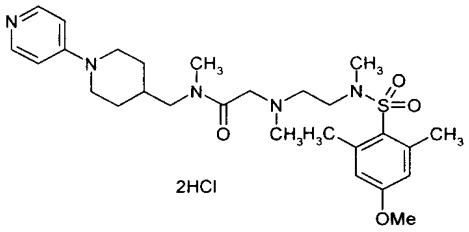
O exemplo 131 é preparado de maneira análoga a 1f a partir de 0,069 g (0,21 mmol) do produto de 130b, 0,088 g (0,21 mmol) do produto de 121f, 0,087 ml (0,63 mmol) de trietilamina e 0,077 g (0,23 mmol) de TBTU em 1 ml de dimetilformamida.

$C_{26}H_{38}N_4O_4S \times CH_2O_2$ (548.71)

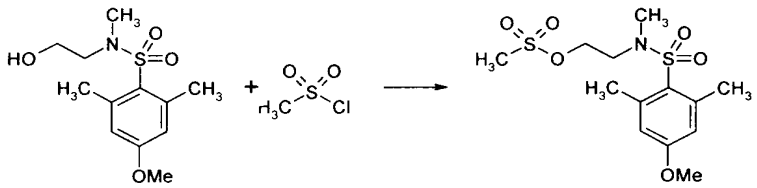
[M+H]+ = 503

HPLC (método 6): tempo de retenção = 2.52 min.

Exemplo 132



132a)



Uma mistura de 2,50 g (9,15 mmols) do produto de 53a, 1,39 ml (10,00 mmols) de trietilamina e 50 ml de tetrahidrofurano é adicionada à temperatura ambiente a 0,77 ml (10,00 mmols) de cloreto de ácido metanossulfônico (Aldrich). A seguir, a mistura de reação é agitada à temperatura ambi-

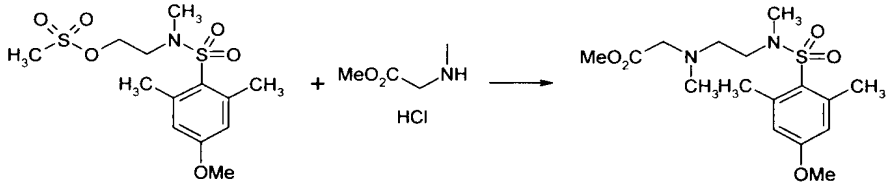
ente durante a noite. O precipitado formado é filtrado. O filtrado é concentrado no vácuo à secura. O resíduo é retomado em acetato de etila e lavado com água e solução saturada de cloreto de sódio, seco sobre sulfato de sódio e concentrado no vácuo à secura.

$C_{13}H_{21}NO_6S_2$ (351.44)

[M+H]+ = 352

DC: gel de sílica, diclorometano/metanol 9,5:0,5, valor Rf = 0,95.

132b)

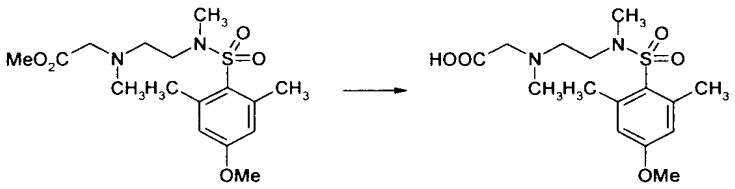


Uma mistura de 0,50 g (1,42 mmol) do produto de 132a, 0,20 g (1,42 mmol) de cloridrato de sarcosin metiléster (Aldrich), 0,52 ml (3,00 mmol) de DIPEA e 5 ml de dimetilformamida é agitada a 80°C por 24 horas. A mistura de reação é concentrada no vácuo. O resíduo é retomado com diclorometano e lavado com água e solução saturada de bicarbonato de sódio, seco sobre sulfato de sódio e concentrado no vácuo à secura. O produto bruto obtida dessa maneira é purificado por meio de cromatografia de coluna (agente de eluição: diclorometano/0-3 % de metanol).

$C_{16}H_{26}N_2O_5S$ (358.45)

[M+H]+ = 359

132c)

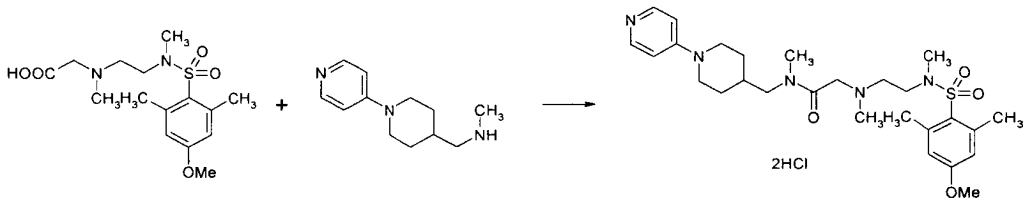


132c é preparado de maneira análoga a 1c a partir de 0,29 g (0,81 mmol) do produto de 132b e 0,17 g (4,00 mmols) de monohidrato de hidróxido de lítio (Aldrich) em 5 ml de tetrahidrofurano e 4 ml de água.

$C_{15}H_{24}N_2O_5S$ (344.43)

HPLC (método 1): tempo de retenção = 2,32 min.

132d)



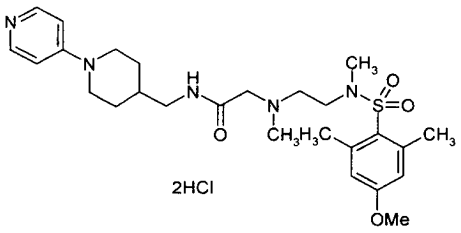
O exemplo 132 é preparado de maneira análoga a 1f a partir de 0,10 g (0,29 mmol) do produto de 132c, 0,06 g (0,29 mmol) do produto de 61b, 0,084 ml (0,60 mmol) de trietilamina e 0,096 g (0,30 mmol) de TBTU em 10 ml de dimetilformamida.

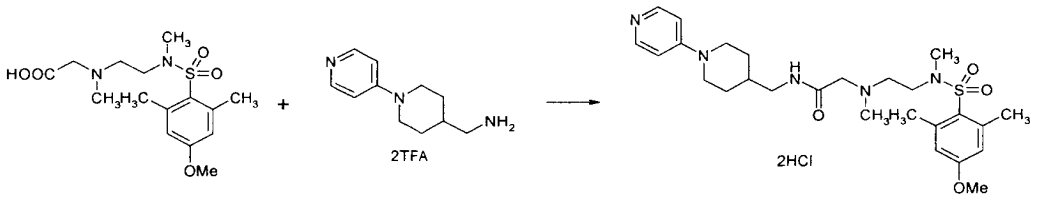
$C_{27}H_{41}N_5O_4S$ x 2HCl (604.63)

[M+H]+ = 532

HPLC (método 5): tempo de retenção = 1,39 min.

Exemplo 133





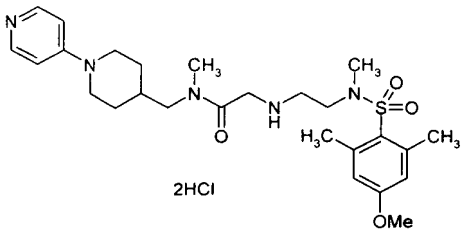
O exemplo 133 é preparado de maneira análoga a 1f a partir de 0,10 g (0,29 mmol) do produto de 132c, 0,12 g (0,29 mmol) do produto de 121f, 0,17 ml (1,20 mmol) de trietilamina e 0,096 g (0,30 mmol) de TBTU em 60 ml de dimetilformamida.

$C_{26}H_{39}N_5O_4S$ x 2HCl (590.61)

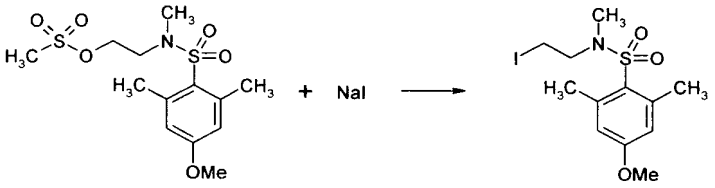
[M+H]+ = 518

HPLC (método 5): tempo de retenção = 1,37 min.

Exemplo 134



134a)



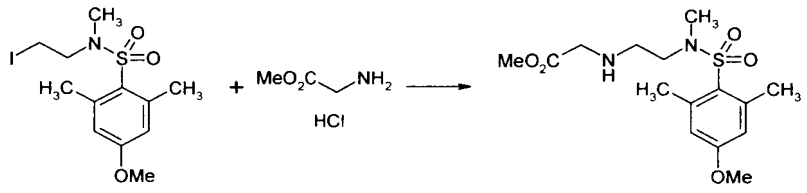
Uma mistura de 1,60 g (4,55 mmols) do produto de 132a, 2,10 g (14,00 mmols) de iodeto de sódio e 30 ml de acetona é agitada sob refluxo por oito horas. A seguir, a mistura de reação é filtrada sobre gel de sílica. O filtrado é concentrado no vácuo à secura. O resíduo é retomado em acetato de etila, lavado com água, seco sobre sulfato de sódio e concentrado no vácuo à secura.

$C_{12}H_{18}INO_3S$ (383.25)

[M+H]+ = 384

HPLC (método 1): tempo de retenção = 3,75 min.

134b)



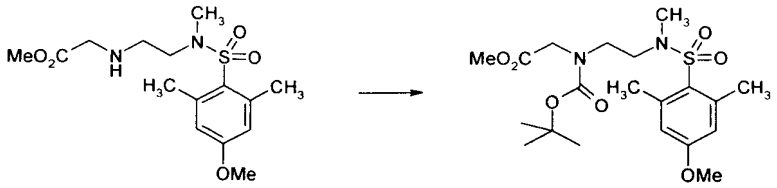
134b é preparado de maneira análoga a 132b a partir de 1,30 g (3,39 mmols) do produto de 134a, 1,28 g (10,20 mmols) de cloridrato de éster glicin metílico (Aldrich) e 3,48 ml (20,00 mmols) de DIPEA em 15 ml de acetonitrila.

$C_{15}H_{24}N_2O_5S$ (344.43)

[M+H]+ = 345

DC: gel de sílica, diclorometano/metanol 9,5:0,5, valor Rf = 0,38.

134c)



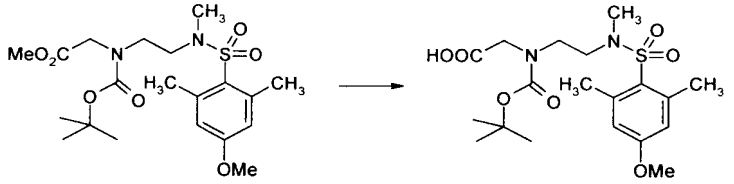
Uma mistura de 0,46 g (1,34 mmol) do produto de 134b, 0,33 g (1,50 mmol) de anidrido boc, 0,21 ml (1,50 mmol) de trietilamina e 30 ml de diclorometano é agitada à temperatura ambiente durante a noite. Em seguida, a mistura de reação é diluída com diclorometano e lavada com solução saturada de bicarbonato de sódio e solução saturada de cloreto de sódio, seca sobre sulfato de sódio e concentrada no vácuo à secura.

$C_{20}H_{32}N_2O_7S$ (444.54)

[M+H]+ = 445

DC: gel de sílica, diclorometano/metanol 9,5:0,5, valor Rf = 0,45.

134d)

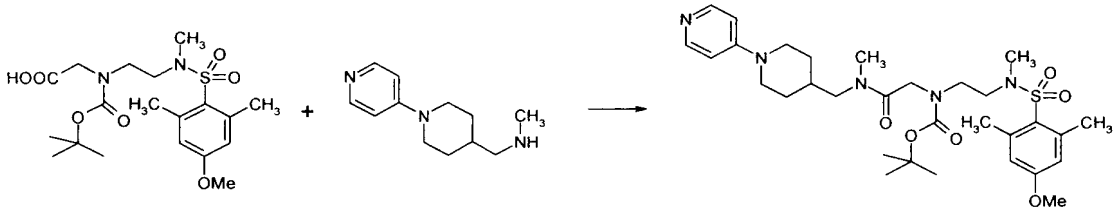


134d é preparado de maneira análoga a 1c a partir de 0,59 g (1,33 mmol) do produto de 134c e 0,28 g (6,60 mmols) de monohidrato de hidróxido de lítio (Aldrich) em 7 ml de tetrahidrofurano e 6,6 ml de água.

$C_{19}H_{30}N_2O_7S$ (430,52)

[M+H]+ = 431

134e)



134e é preparado de maneira análoga a 1f a partir de 0,15 g (0,35 mmol) do produto de 134d, 0,072 g (0,35 mmol) do produto de 61b, 0,098 ml (0,70 mmol) de trietilamina e 0,11 g (0,35 mmol) de TBTU em 7 ml

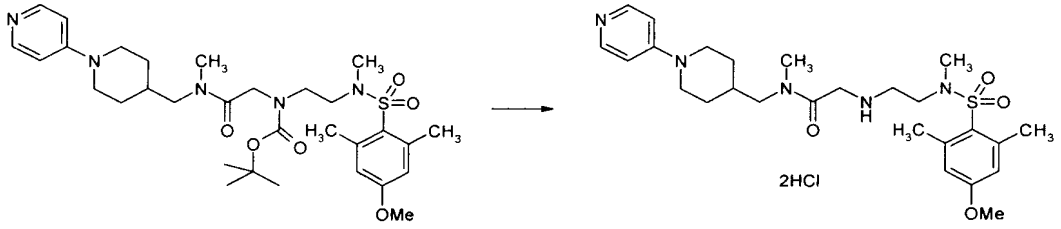
de dimetilformamida.

$C_{31}H_{47}N_5O_6S$ (617,80)

[M+H]+ = 618

HPLC (método 1): tempo de retenção = 2,62 min.

134f)



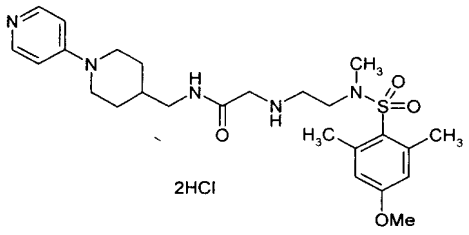
O exemplo 134 é preparado de maneira análoga a 18b a partir de 0,16 g (0,26 mmol) do produto de 134e e 3 ml de TFA em 3 ml de diclorometano.

$C_{26}H_{39}N_5O_4S$ x 2HCl (590.61)

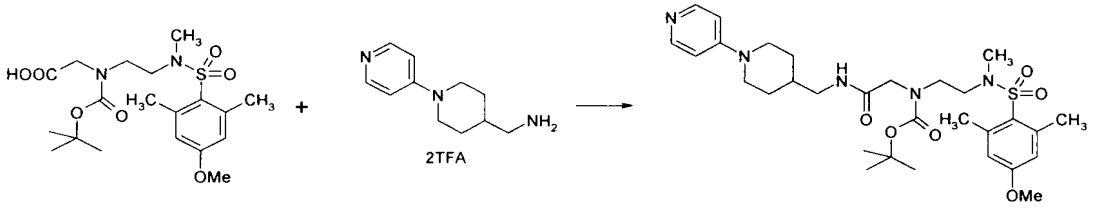
[M+H]+ = 518

HPLC (método 5): tempo de retenção = 1,40 min.

Exemplo 135



135a)



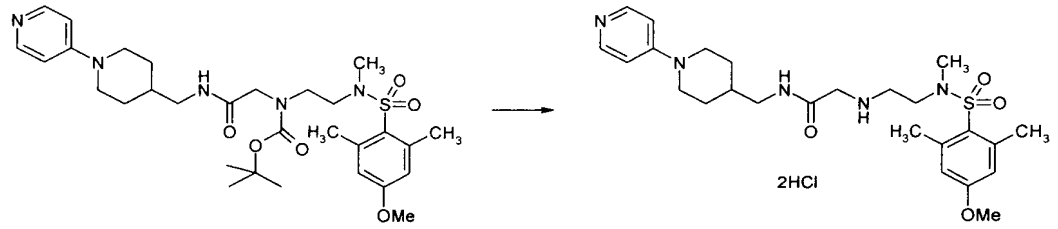
135a é preparado de maneira análoga a 1f a partir de 0,15 g (0,35 mmol) do produto de 134d, 0,15 (0,35 mmol) do produto de 121f, 0,20 ml (1,40 mmol) de trietilamina e 0,11 g (0,35 mmol) de TBTU em 7 ml de dimetilformamida.

$C_{30}H_{45}N_5O_6S$ (603.77)

[M+H]+ = 604

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,48.

135b)



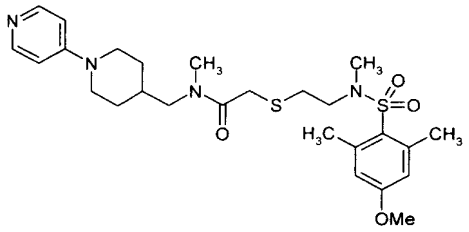
O exemplo 135 é preparado de maneira análoga a 18b a partir de 0,16 g (0,27 mmol) do produto de 135a e 5 ml de TFA em 5 ml de diclorometano.

$C_{25}H_{37}N_5O_4S$ x 2HCl (576.58)

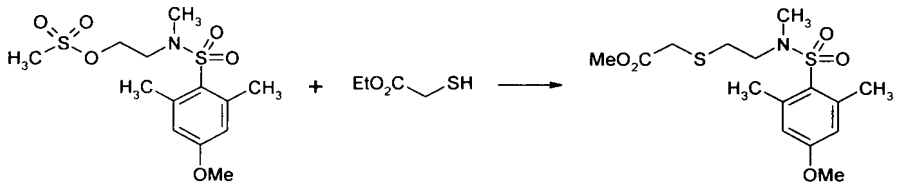
[M+H]+ = 504

HPLC (método 1): tempo de retenção = 2,17 min.

Exemplo 136



136a)

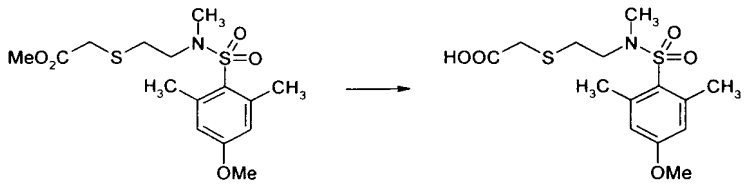


Uma mistura de 0,21 g (0,60 mmol) do produto de 132a, 0,065 ml (0,60 mmol) de éster etílico de ácido mercaptoacético (Aldrich), 0,17 g (1,20 mmol) de carbonato de potássio e 10 ml de acetonitrila é agitada à temperatura ambiente por 24 horas. O precipitado é filtrado, o filtrado é concentrado no vácuo. O produto bruto obtido dessa maneira é purificado por meio de HPLC preparatória.

$C_{16}H_{25}NO_5S_2$ (375.51)

[M+H]+ = 376

136b)

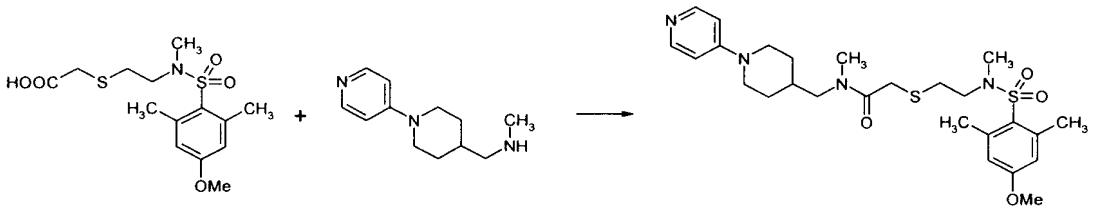


136b é preparado de maneira análoga a 121b a partir de 0,070 g (0,19 mmol) do produto de 136a e 2,00 ml (2,00 mmols) de soda cáustica 1 M em 5 ml de tetrahidrofurano.

$C_{14}H_{21}NO_5S_2$ (347.45)

[M+H]+ = 348

136c)



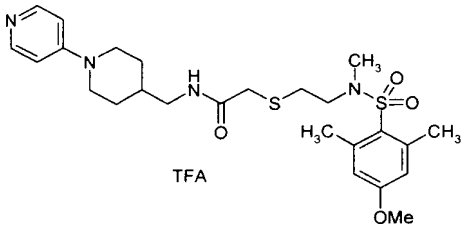
O exemplo 136 é preparado de maneira análoga a 1f a partir de 0,064 g (0,18 mmol) do produto de 136b, 0,038 g (0,18 mmol) do produto de 61b, 0,079 ml (0,46 mmol) de DIPEA e 0,059 g (0,18 mmol) de TBTU em 5 ml de dimetilformamida.

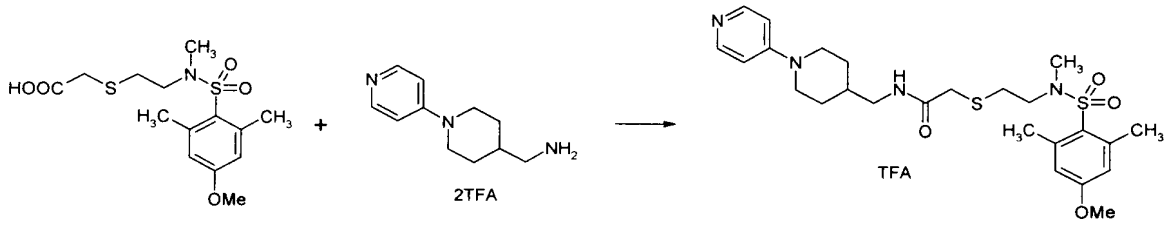
$C_{26}H_{38}N_4O_4S_2$ (534.74)

[M+H]+ = 535

HPLC (método 6): tempo de retenção = 2,68 min.

Exemplo 137





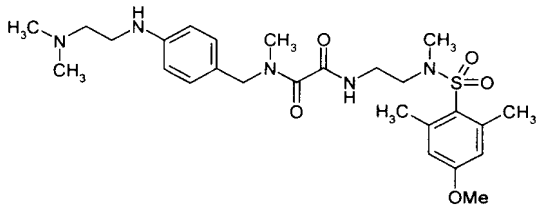
O exemplo 137 é preparado de maneira análoga a 1f a partir de 0,073 g (0,21 mmol) do produto de 136b, 0,088 g (0,21 mmol) do produto de 121f, 0,11 ml (0,63 mmol) de DIPEA e 0,087 g (0,27 mmol) de TBTU em 5 ml de dimetilformamida.

$C_{25}H_{36}N_4O_4S_2 \times C_2HF_3O_2$ (634.73)

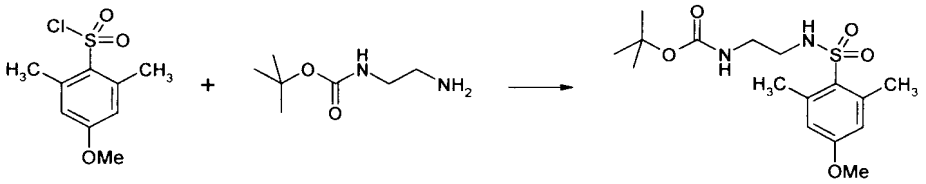
[M+H]+ = 521

HPLC (método 6): tempo de retenção = 2,57 min.

Exemplo 138



138a)



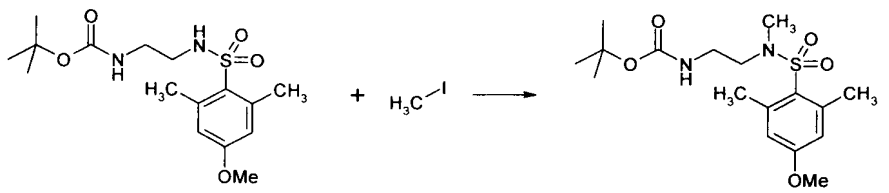
138a é preparado de maneira análoga a 3a a partir de 2,0 g (8,52 mmols) do produto de 13a, 1,37 g (8,55 mmols) de N-boc-etilenodiamina (Fluka) e 1,0 g (9,89 mmols) de trietilamina em 50 ml de tetrahidrofurano.

$C_{16}H_{26}N_2O_5S$ (358.45)

[M+H]+ = 357

HPLC (método 6): tempo de retenção = 3,63 min.

138b)



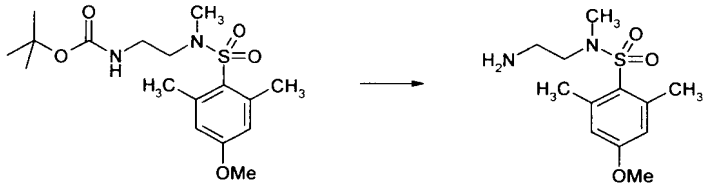
138b é preparado de maneira análoga a 3b a partir de 3,38 g (9,43 mmols) do produto de 138a, 0,53 ml (8,55 mmols) de iodeto de metila, 1,77 g (12,83 mmols) de carbonato de potássio anidro em 30 ml de dimetilsulfóxido.

$C_{17}H_{28}N_2O_5S$ (372.48)

[M+H]+ = 373

HPLC (método 6): tempo de retenção = 3,89 min.

138c)



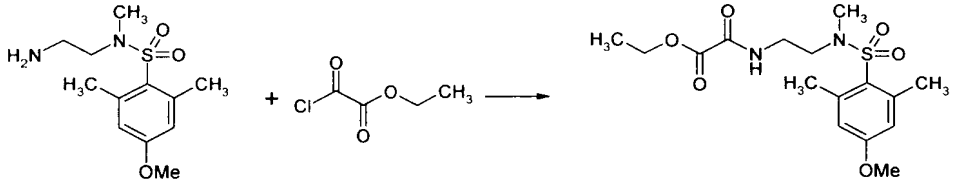
138b é preparado de maneira análoga a 28d a partir de 3,61 g (9,69 mmols) do produto de 138b e 10 ml de TFA em 50 ml de diclorometano.

$C_{127}H_{20}N_2O_3S$ (272.36)

[M+H]+ = 273

HPLC (método 6): tempo de retenção = 1,95 min.

138d)



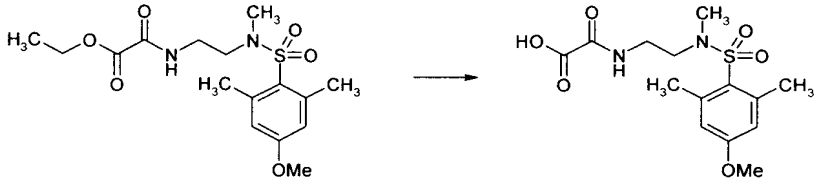
Uma mistura de 0,50 g (1,84 mmols) do produto de 138c, 0,56 ml (5,51 mmols) de trietilamina e 25 ml de diclorometano é adicionada sob resfriamento com gelo, a 0,38 ml (2,75 mmols) de cloreto de éster monoetílico de ácido oxálico (Fluka) em 5 ml de diclorometano e agitada à temperatu-

ra ambiente por duas horas. Em seguida, a mistura de reação é diluída com diclorometano, lavada com solução aquosa de ácido cítrico a 10%, solução saturada de sulfato de sódio e com água, seca sobre sulfato de sódio e concentrada no vácuo à secura.

$C_{16}H_{24}N_2O_6S$ (372.44)

[M+H]+ = 373

138e)

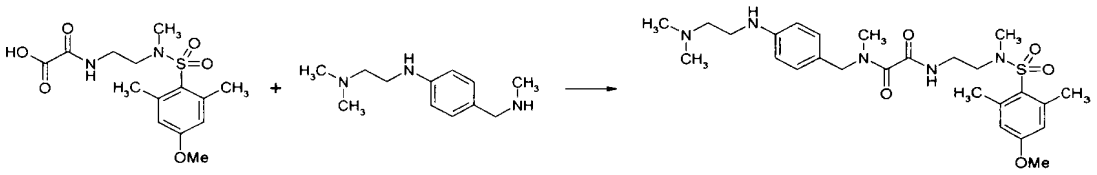


Uma mistura de 0,60 g (1,60 mmol) do produto de 138d, 5,6 ml de soda cáustica 1 M e 6 ml de etanol é agitada à temperatura ambiente por quatro horas e depois é concentrada no vácuo à secura. O resíduo é adicionado a 8 ml de ácido clorídrico 1 M e extraído com acetato de etila. Os extratos orgânicos combinados são lavados com água e com solução saturada de cloreto de sódio, secos sobre sulfato de sódio e concentrados no vácuo à secura.

$C_{14}H_{20}N_2O_6S$ (344.38)

[M+H]+ = 345

138f)



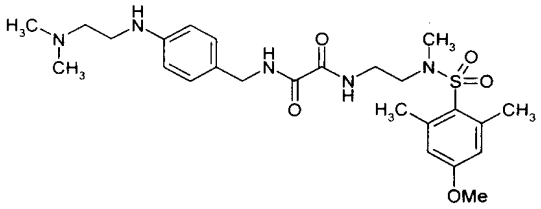
O exemplo 138 é preparado de maneira análoga a 1f a partir de 40,0 mg (0,12 mmol) do produto de 138e, 48,2 mg (0,12 mmol) de N,N-dimetil-N'-(4-metilaminometil-fenil)-etan-1,2-diamina (análogo a J. Chem. Soc. 1960, 3163-3165), 0,038 ml (0,29 mmol) de DIPEA e 38,9 mg (0,12 mmol) de TBTU em 1,5 ml de dimetilformamida.

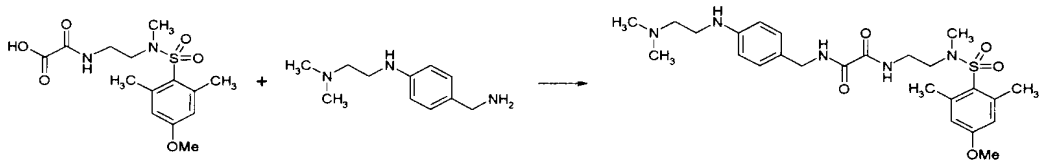
$C_{26}H_{39}N_5O_5S$ (533.68)

[M+H]+ = 534

HPLC (método 6): tempo de retenção = 1,61 min.

Exemplo 139





O exemplo 139 é preparado de maneira análoga a 1f a partir de 40,0 mg (0,12 mmol) do produto de 138e, 22,5 mg (0,12 mmol) de N-(4-aminometil-fenil)-N',N'-dimetiletan-1,2-diamina (análogo a J. Chem. Soc. 1960, 3163-3165), 0,038 ml (0,29 mmol) de DIPEA e 38,9 mg (0,12 mmol) de TBTU em 1,5 ml de dimetilformamida.

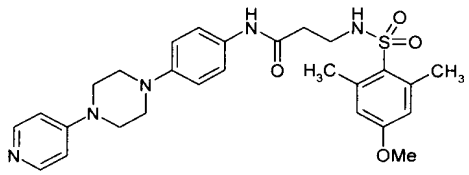
$C_{25}H_{37}N_5O_5S$ (519.66)

[M+H]+ = 520

HPLC (método 6): tempo de retenção = 1,53 min.

Os seguintes compostos foram preparados de maneira análoga ao exemplo 22:

Exemplo 140

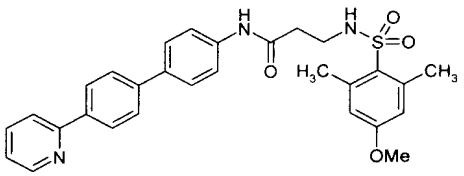


$C_{27}H_{33}N_5O_4S \times C_2HF_3O_2$ (637.67)

[M+H]+ = 524

HPLC (método 6): tempo de retenção = 2,43 min.

Exemplo 141

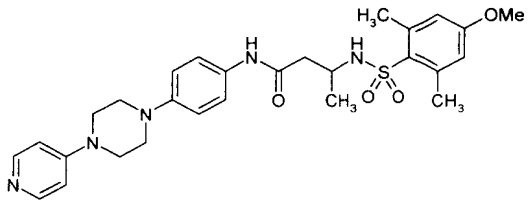


$C_{29}H_{29}N_3O_4S$ x $C_2HF_3O_2$ (629.65)

[M+H]+ = 516

HPLC (método 6): tempo de retenção = 3,39 min.

Exemplo 142

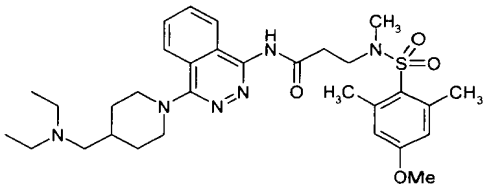


$C_{28}H_{35}N_5O_4S$ (537.67)

[M+H]+ = 538

HPLC (método 6): tempo de retenção = 2,45 min.

Exemplo 143

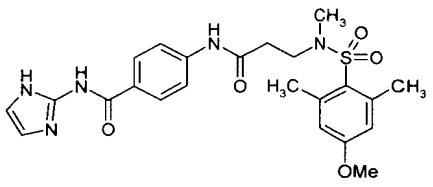


$C_{31}H_{44}N_6O_4S$ x $C_2HF_3O_2$ (710.81)

[M+H]+ = 597

HPLC (método 6): tempo de retenção = 2,30 min.

Exemplo 144

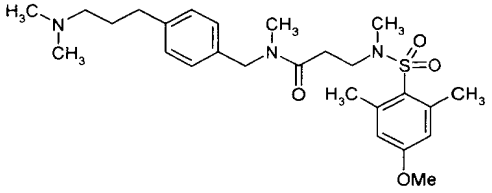


$C_{23}H_{27}N_5O_5S$ x $C_2HF_3O_2$ (599.58)

[M+H]+ = 486

HPLC (método 6): tempo de retenção = 2,46 min.

Exemplo 145

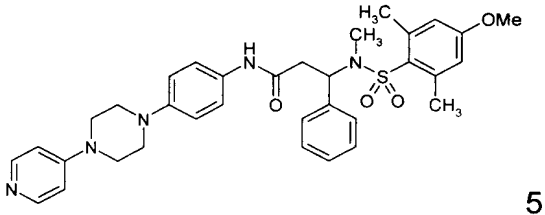


$C_{26}H_{39}N_3O_4S$ (489.67)

[M+H]+ = 490

HPLC (método 6): tempo de retenção = 2,66 min.

Exemplo 146

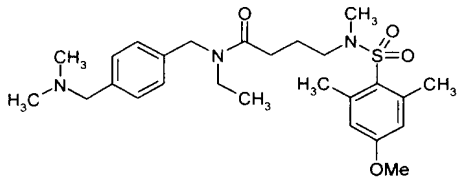


$C_{34}H_{39}N_5O_4S$ (613.77)

[M+H]+ = 614

HPLC (método 6): tempo de retenção = 3,07 min.

Exemplo 147

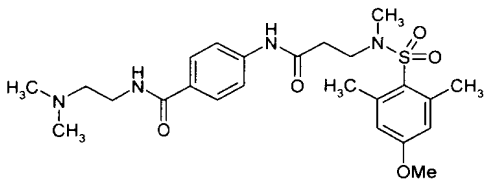


$C_{26}H_{39}N_3O_4S$ x $C_2HF_3O_2$ (603.70)

[M+H]+ = 490

HPLC (método 6): tempo de retenção = 2,60 min.

Exemplo 148

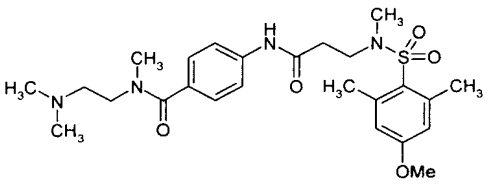


$C_{24}H_{34}N_4O_5S$ x CH_2O_2 (536.64)

[M+H]+ = 491

HPLC (método 6): tempo de retenção = 2,29 min.

Exemplo 149

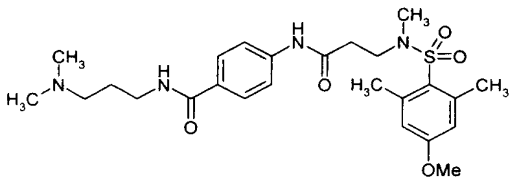


$C_{25}H_{36}N_4O_5S$ x CH_2O_2 (550.67)

[M+H]+ = 505

HPLC (método 6): tempo de retenção = 2,32 min.

Exemplo 150

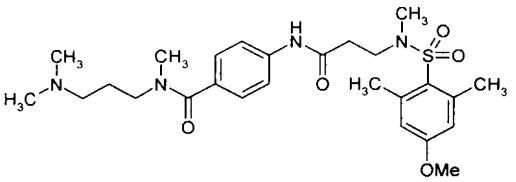


$C_{25}H_{36}N_4O_5S$ (504.64)

[M+H]+ = 505

HPLC (método 6): tempo de retenção = 2,31 min.

Exemplo 151

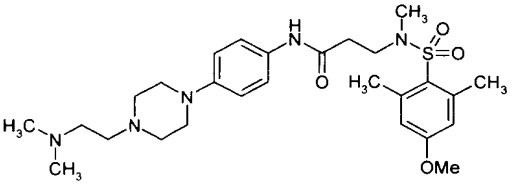


$C_{26}H_{38}N_4O_5S$ x CH_2O_2 (564,70)

[M+H]+ = 519

HPLC (método 6): tempo de retenção = 2,34 min.

Exemplo 152

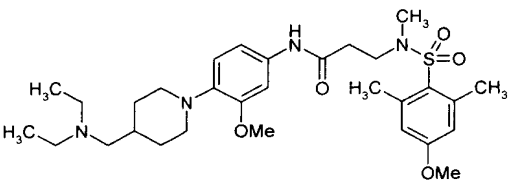


$C_{27}H_{41}N_5O_4S$ x $2C_2HF_3O_2$ (759,76)

[M+H]+ = 532

HPLC (método 5): tempo de retenção = 1,40 min.

Exemplo 153

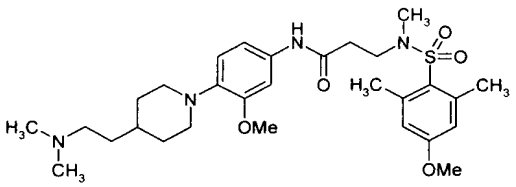


$C_{30}H_{46}N_4O_5S$ x HCl (611.24)

[M+H]+ = 575

HPLC (método 1): tempo de retenção = 2,12 min.

Exemplo 154

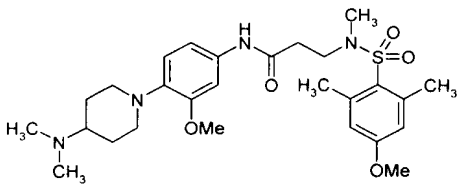


$C_{29}H_{44}N_4O_5S$ x HCl (597.21)

[M+H]+ = 561

HPLC (método 8: tempo de retenção = 3,12 min.

Exemplo 155

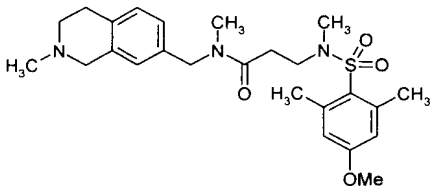


$C_{27}H_{40}N_4O_5S$ x HCl (569.16)

[M+H]+ = 533

HPLC (método 11): tempo de retenção = 1,67 min.

Exemplo 156

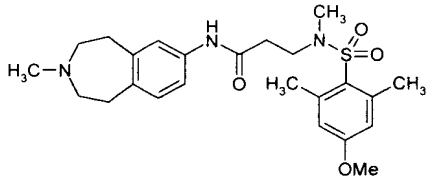


$C_{25}H_{35}N_3O_4S$ x HCl (510.09)

[M+H]+ = 474

HPLC (método 7): tempo de retenção = 1,90 min.

Exemplo 157

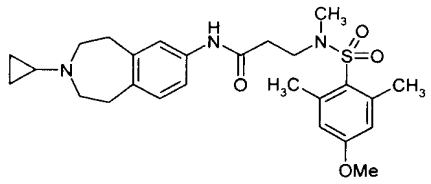


$C_{24}H_{33}N_3O_4S$ x $C_2HF_3O_2$ (573.63)

[M+H]+ = 460

HPLC (método 5): tempo de retenção = 1,52 min.

Exemplo 158

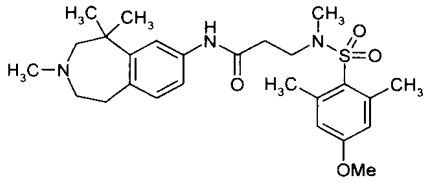


$C_{26}H_{35}N_3O_4S \times C_2HF_3O_2$ (599.66)

[M+H]+ = 486

HPLC (método 5): tempo de retenção = 1,55 min.

Exemplo 159

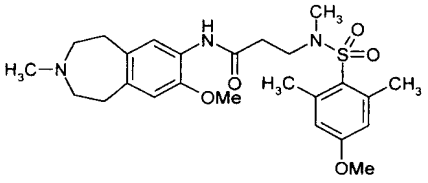


$C_{26}H_{37}N_3O_4S \times C_2HF_3O_2$ (601.68)

[M+H]+ = 488

HPLC (método 5): tempo de retenção = 1,54 min.

Exemplo 160

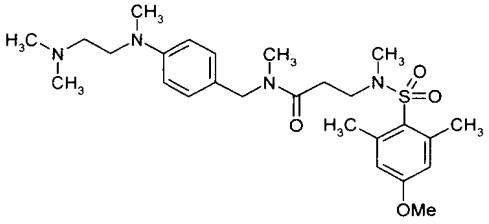


$C_{25}H_{35}N_3O_5S \times C_2HF_3O_2$ (603.65)

[M+H]+ = 490

HPLC (método 5): tempo de retenção = 1,54 min.

Exemplo 161

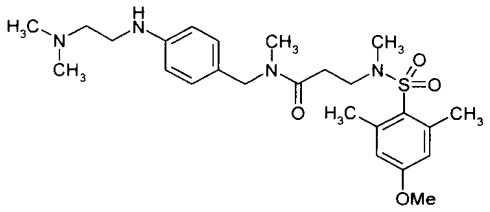


$C_{26}H_{40}N_4O_4S \times HCl$ (541.15)

[M+H]+ = 505

HPLC (método 5): tempo de retenção = 1,59 min.

Exemplo 162

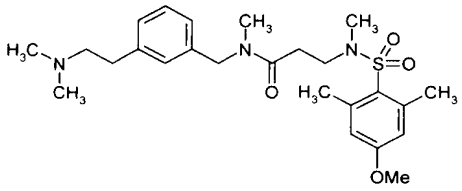


$C_{25}H_{38}N_4O_4S$ x HCl (527.12)

[M+H]+ = 491

HPLC (método 5): tempo de retenção = 1,55 min.

Exemplo 163

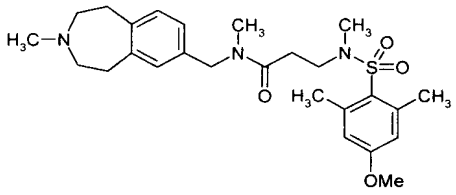


$C_{25}H_{37}N_3O_4S$ x HCl (512.11)

[M+H]+ = 476

HPLC (método 5): tempo de retenção = 1,56 min.

Exemplo 164

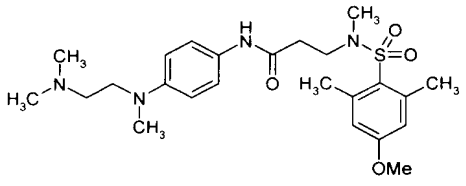


$C_{26}H_{37}N_3O_4S$ x HCl (524.12)

[M+H]+ = 488

HPLC (método 5): tempo de retenção = 1,54 min.

Exemplo 165

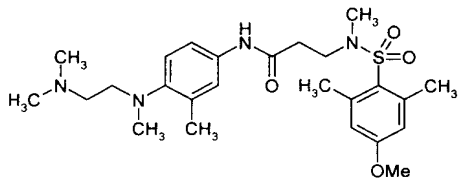


$C_{24}H_{36}N_4O_4S$ x HCl (513.09)

[M+H]+ = 477

HPLC (método 7): tempo de retenção = 1,88 min.

Exemplo 166

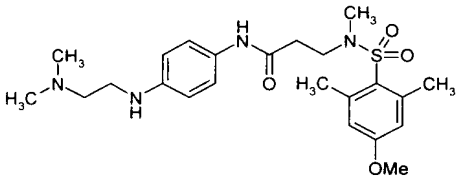


$C_{25}H_{38}N_4O_4S$ x HCl (527.12)

[M+H]+ = 491

HPLC (método 7): tempo de retenção = 1,92 min.

Exemplo 167

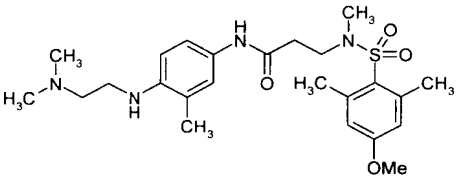


$C_{23}H_{34}N_4O_4S$ x HCl (499.07)

[M+H]+ = 463

HPLC (método 7): tempo de retenção = 1,79 min.

Exemplo 168

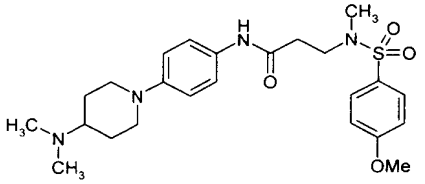


$C_{24}H_{36}N_4O_4S$ x HCl (513.09)

[M+H]+ = 477

HPLC (método 7): tempo de retenção = 1,86 min.

Exemplo 169

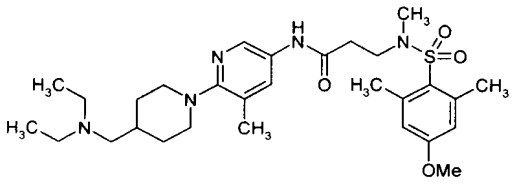


$C_{24}H_{34}N_4O_4S$ x $C_2HF_3O_2$ (588.64)

[M+H]+ = 475

HPLC (método 5): tempo de retenção = 1,39 min.

Exemplo 170

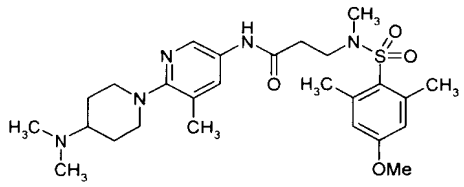


$C_{29}H_{45}N_5O_4S$ x 2HCl (632.69)

[M+H]+ = 560

DC: gel de sílica, diclorometano/etanol 9:1, valor Rf = 0,22.

Exemplo 171

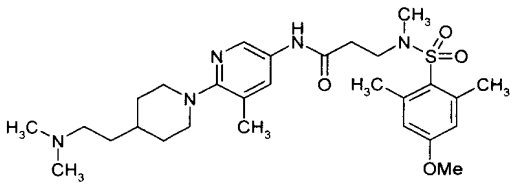


$C_{26}H_{39}N_5O_4S$ x 2HCl (590.61)

[M+H]+ = 518

DC: gel de sílica, diclorometano/etanol 4:1, valor Rf = 0,68.

Exemplo 172

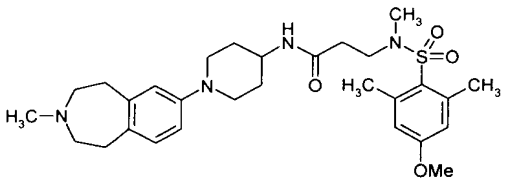


$C_{28}H_{43}N_5O_4S$ x 2HCl (618.66)

[M+H]+ = 546

HPLC (método 5): tempo de retenção = 1,26 min.

Exemplo 173

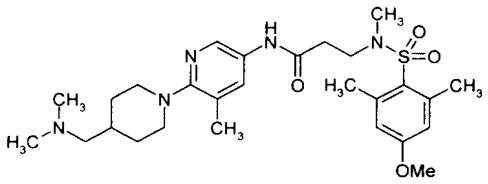


$C_{29}H_{42}N_4O_4S$ (542.73)

[M+H]+ = 543

HPLC (método 4): tempo de retenção = 2,8 min.

Exemplo 174

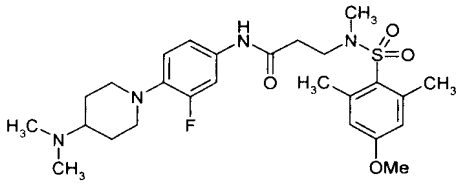


$C_{27}H_{41}N_5O_4S$ x 2HCl (604.63)

[M+H]+ = 532

HPLC (método 5): tempo de retenção = 1,39 min.

Exemplo 175

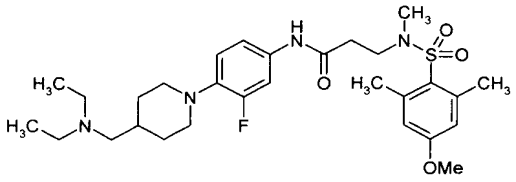


$C_{26}H_{37}FN_4O_4S$ x HCl (557.12)

[M+H]+ = 521

DC: gel de sílica, diclorometano/etanol 9:1, valor Rf = 0,25.

Exemplo 176

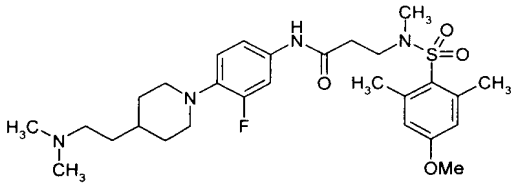


$C_{29}H_{43}FN_4O_4S$ x HCl (599.20)

[M+H]+ = 563

DC: gel de sílica, diclorometano/etanol 9:1, valor Rf = 0,40.

Exemplo 177

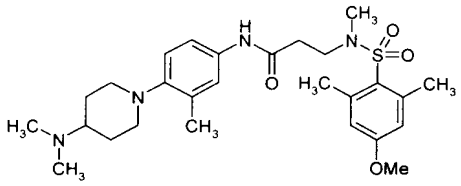


$C_{28}H_{41}FN_4O_4S$ x HCl (585.17)

[M+H]+ = 549

DC: gel de sílica, diclorometano/etanol 9:1, valor Rf = 0,35.

Exemplo 178

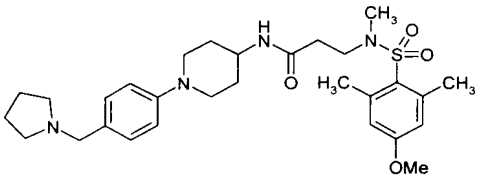


$C_{27}H_{40}N_4O_4S$ (516.70)

[M+H]+ = 517

DC: gel de sílica, diclorometano/etanol/amoníaco 8:2:0,01 valor Rf = 0,41.

Exemplo 179

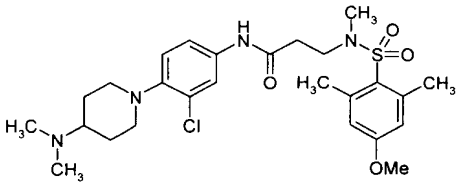


$C_{29}H_{42}N_4O_4S$ x HCl (579.19)

[M+H]+ = 543

DC: gel de sílica, diclorometano/etanol/amoníaco 8:2:0,01 valor Rf = 0,47.

Exemplo 180

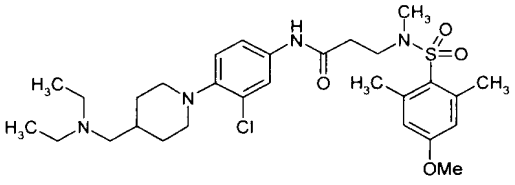


$C_{26}H_{37}ClN_4O_4S$ x HCl (573.58)

[M+H]+ = 537/539

DC: gel de sílica, diclorometano/etanol 9:1, valor Rf = 0,26.

Exemplo 181

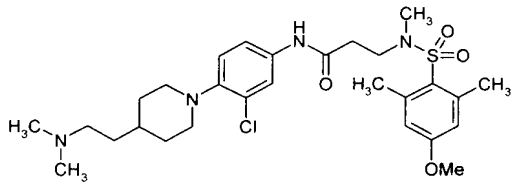


$C_{29}H_{43}ClN_4O_4S$ x HCl (615.66)

[M+H]+ = 579/581

DC: gel de sílica, diclorometano/etanol 9:1, valor Rf = 0,45.

Exemplo 182

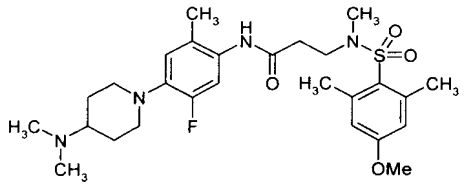


$C_{28}H_{41}ClN_4O_4S$ x HCl (601.63)

[M+H]+ = 565/567

DC: gel de sílica, diclorometano/etanol 9:1, valor Rf = 0,30.

Exemplo 183

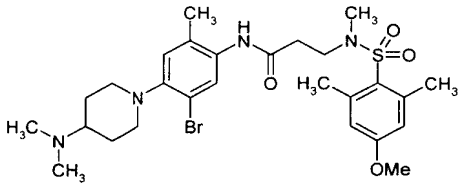


$C_{27}H_{39}FN_4O_4S$ x HCl (571.15)

[M+H]+ = 535

DC: gel de sílica, diclorometano/etanol/amoníaco 8:2:0,01 valor Rf = 0,26.

Exemplo 184

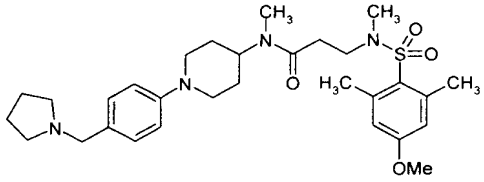


$C_{27}H_{39}BrN_4O_4S$ x HCl (632.05)

[M+H]+ = 595/597

DC: gel de sílica, diclorometano/etanol/amoníaco 8:2:0,01 valor Rf = 0,51.

Exemplo 185

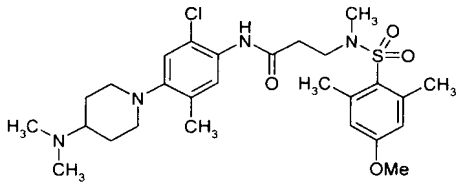


$C_{30}H_{44}N_4O_4S$ x HCl (593.22)

[M+H]+ = 557

DC: gel de sílica, diclorometano/etanol/amoníaco 8:2:0,01 valor Rf = 0,63.

Exemplo 186

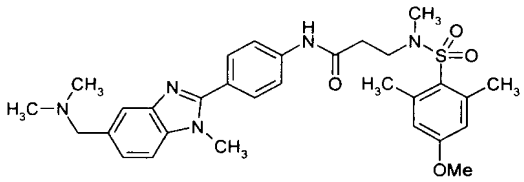


$C_{27}H_{39}ClN_4O_4S$ x HCl (587.60)

[M+H]+ = 551

DC: gel de sílica, diclorometano/etanol/amoníaco 8:2:0,01 valor Rf = 0,58.

Exemplo 187

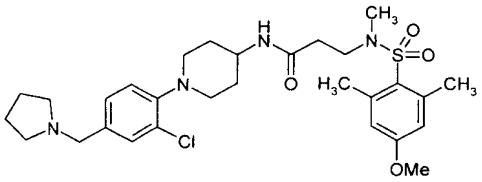


$C_{30}H_{37}N_5O_4S$ x HCl (600.17)

[M+H]+ = 564

HPLC (método 4): tempo de retenção = 3,0 min.

Exemplo 188

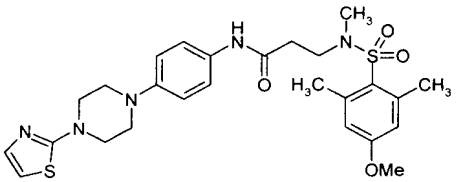


$C_{29}H_{41}ClN_4O_4S$ x HCl (613.64)

[M+H]+ = 577/579

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,24.

Exemplo 189

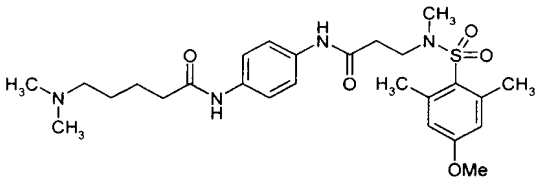


$C_{26}H_{33}N_5O_4S_2$ (543.70)

[M+H]+ = 544

HPLC (método 6): tempo de retenção = 3,11 min.

Exemplo 190

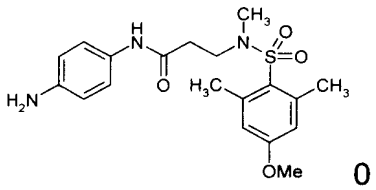


$C_{26}H_{38}N_4O_5S$ (518.67)

[M+H]+ = 519

HPLC (método 6): tempo de retenção = 2,44 min.

Exemplo 191

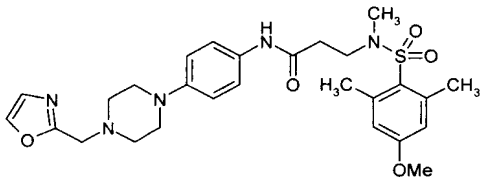


$C_{19}H_{25}N_3O_4S \times C_2HF_3O_2$ (505.51)

[M+H]+ = 392

HPLC (método 6): tempo de retenção = 2,04 min.

Exemplo 192

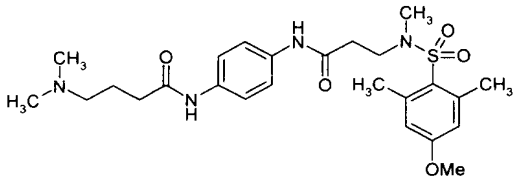


$C_{27}H_{35}N_5O_5S$ (541.66)

[M+H]+ = 542

HPLC (método 6): tempo de retenção = 2,51 min.

Exemplo 193

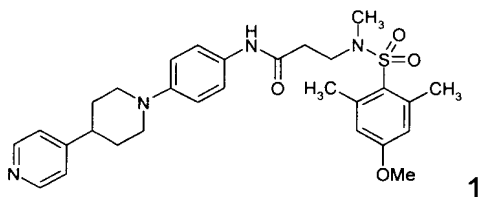


$C_{25}H_{36}N_4O_5S$ (504.64)

[M+H]+ = 505

HPLC (método 6): tempo de retenção = 2,43.

Exemplo 194



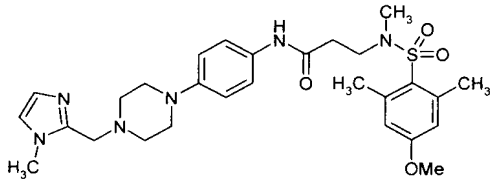
1

$C_{29}H_{36}N_4O_4S$ (536.69)

[M+H]+ = 537

HPLC (método 6): tempo de retenção = 2,19.

Exemplo 195

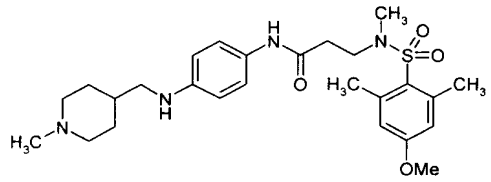


$C_{28}H_{38}N_6O_4S$ (554.71)

[M+H]+ = 555

HPLC (método 6): tempo de retenção = 2,37.

Exemplo 196

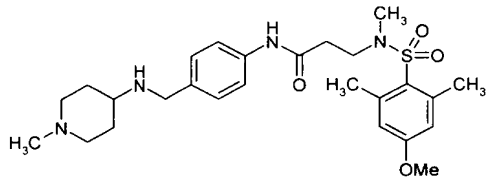


$C_{26}H_{38}N_4O_4S$ (502.67)

[M+H]+ = 503

HPLC (método 6): tempo de retenção = 2,36.

Exemplo 197

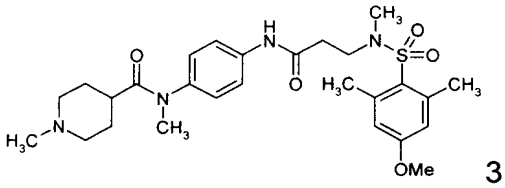


$C_{26}H_{38}N_4O_4S$ (502.67)

[M+H]+ = 503

HPLC (método 6): tempo de retenção = 2,00 min.

Exemplo 198



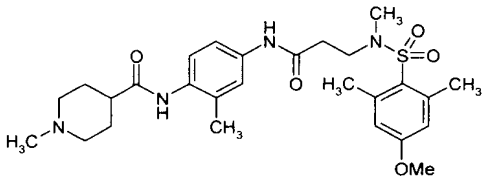
3

$C_{27}H_{38}N_4O_5S \times C_2HF_3O_2$ (644.70)

[M+H]+ = 531

HPLC (método 6): tempo de retenção = 2,45.

Exemplo 199

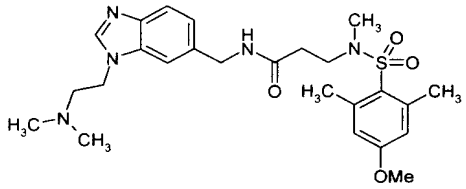


$C_{27}H_{38}N_4O_5S$ (530.68)'

[M+H]+ = 531

HPLC (método 6): tempo de retenção = 2,53 min.

Exemplo 200

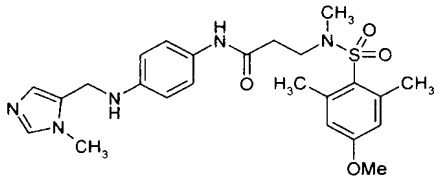


$C_{25}H_{35}N_5O_4S$ (501.64)

[M+H]+ = 502

HPLC (método 6): tempo de retenção = 2,05 min.

Exemplo 201

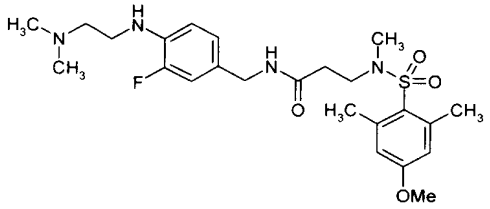


$C_{24}H_{31}N_5O_4S$ (485.60)

[M+H]+ = 486

HPLC (método 6): tempo de retenção = 2,41.

Exemplo 202

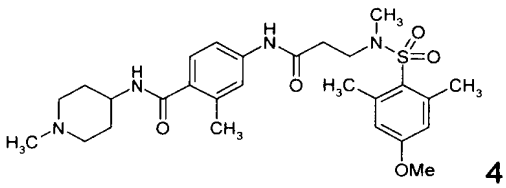


$C_{24}H_{35}FN_4O_4S \times CH_2O_2$ (540.65)

[M+H]+ = 495

HPLC (método 6): tempo de retenção = 2,50 min.

Exemplo 203



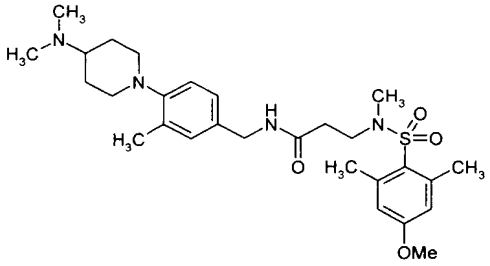
4

$C_{27}H_{38}N_4O_5S$ (530.68)

[M+H]+ = 531

HPLC (método 6): tempo de retenção = 2,36 min.

Exemplo 204

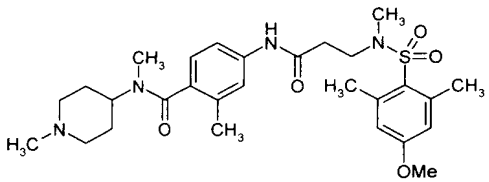


$C_{28}H_{42}N_4O_4S$ (530.72)

[M+H]+ = 531

HPLC (método 6): tempo de retenção = 2,60 min.

Exemplo 205

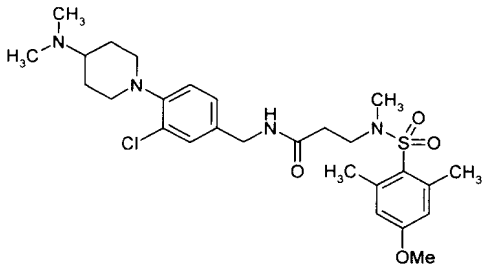


$C_{28}H_{40}N_4O_5S$ (544.71)

[M+H]+ = 545

HPLC (método 6): tempo de retenção = 2,21 min.

Exemplo 206

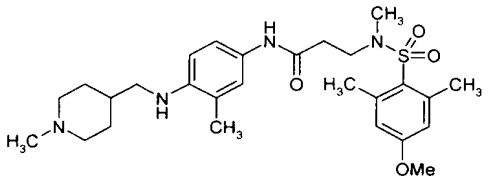


$C_{27}H_{39}ClN_4O_4S$ (551.14)

[M+H]+ = 551/553

HPLC (método 6): tempo de retenção = 2,65 min.

Exemplo 207

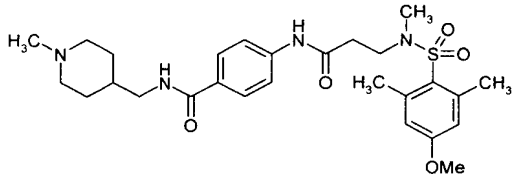


$C_{27}H_{40}N_4O_4S \times C_2HF_3O_2$ (630.72)

[M+H]+ = 517

HPLC (método 6): tempo de retenção = 2,51 min.

Exemplo 208

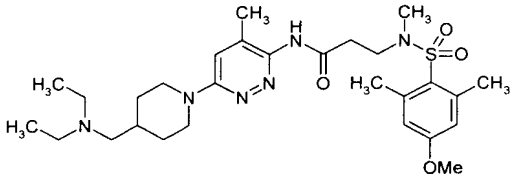


$C_{27}H_{38}N_4O_5S \times CH_2O_2$ (576.71)

[M+H]+ = 531

HPLC (método 6): tempo de retenção = 2,33 min.

Exemplo 209

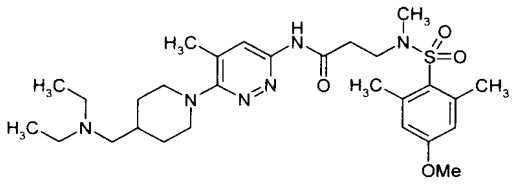


$C_{28}H_{44}N_6O_4S$ x $C_2HF_3O_2$ (674.78)

[M+H]+ = 561

HPLC (método 6): tempo de retenção = 2,14.

Exemplo 210

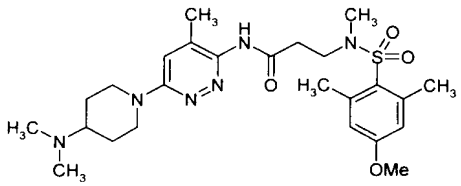


$C_{28}H_{44}N_6O_4S$ x $C_2HF_3O_2$ (674.78)

[M+H]+ = 561

HPLC (método 6): tempo de retenção = 2,43 min.

Exemplo 211

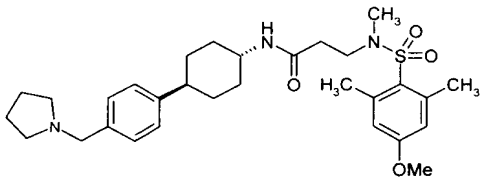


$C_{25}H_{38}N_6O_4S$ x $C_2HF_3O_2$ (632.70)

[M+H]+ = 519

HPLC (método 6): tempo de retenção = 2,11 min.

Exemplo 212

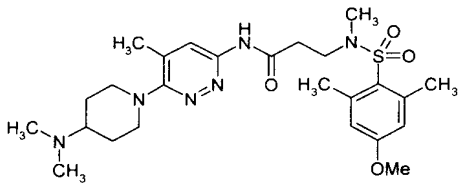


$C_{30}H_{43}N_3O_4S$ x $C_2HF_3O_2$ (655.77)

[M+H]+ = 542

HPLC (método 6): tempo de retenção = 2,75.

Exemplo 213

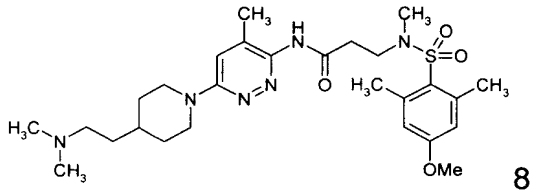


$C_{25}H_{38}N_6O_4S$ x $C_2HF_3O_2$ (632.70)

[M+H]+ = 519

HPLC (método 6): tempo de retenção = 2,30.

Exemplo 214



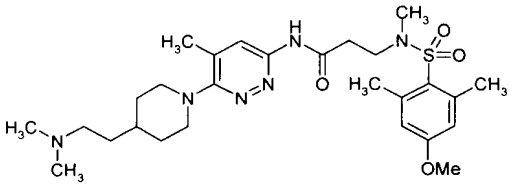
8

$C_{27}H_{42}N_6O_4S \times C_2HF_3O_2$ (660.75)

[M+H]+ = 547

HPLC (método 6): tempo de retenção = 2,08.

Exemplo 215

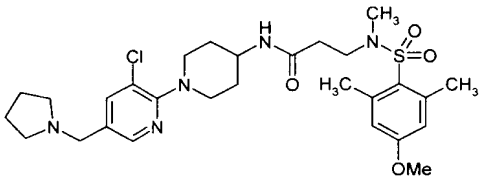


$C_{27}H_{42}N_6O_4S \times C_2HF_3O_2$ (660.75)

[M+H]+ = 547

HPLC (método 6): tempo de retenção = 2,34.

Exemplo 216

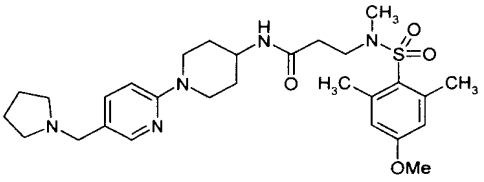


$C_{28}H_{40}ClN_5O_4S \times CH_2O_2$ (624.19)

[M+H]+ = 578/580

HPLC (método 6): tempo de retenção = 2,64 min.

Exemplo 217

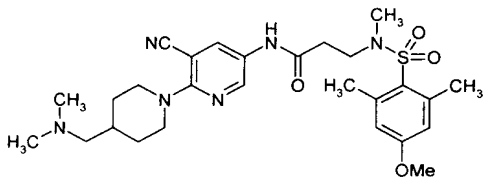


$C_{28}H_{41}N_5O_4S \times CH_2O_2$ (589.75)

[M+H]+ = 544

HPLC (método 6): tempo de retenção = 2,09 min.

Exemplo 218

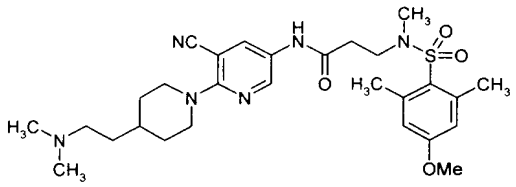


$C_{27}H_{38}N_6O_4S$ x CH_2O_2 (588,72)

[M+H]+ = 543

HPLC (Método 9): Tempo de retenção = 1,67 min

Exemplo 219

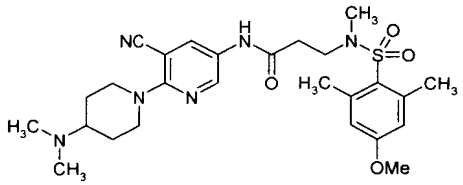


$C_{28}H_{40}N_6O_4S$ (556,72)

[M+H]+ = 557

HPLC (Método 9): Tempo de retenção = 1,71 min

Exemplo 220

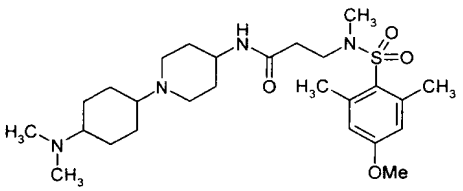


$C_{26}H_{36}N_6O_4S$ x CH_2O_2 (574,69)

[M+H]+ = 529

HPLC (Método 9): Tempo de retenção = 1,61 min

Exemplo 221

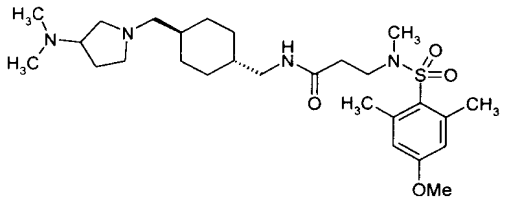


$C_{26}H_{44}N_4O_4S$ (508,72)

[M+H]+ = 509

HPLC (Método 9): Tempo de retenção = 1,23 min

Exemplo 222

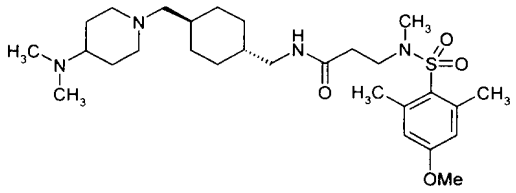


$C_{27}H_{46}N_4O_4S \times 2C_2HF_3O_2$ (750,79)

[M+H]+ = 523

HPLC (Método 9): Tempo de retenção = 1,30 min

Exemplo 223

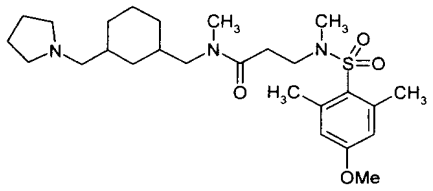


$C_{28}H_{48}N_4O_4S \times 2C_2HF_3O_2$ (764,82)

[M+H]+ = 537

HPLC (Método 9): Tempo de retenção = 1,31 min

Exemplo 224

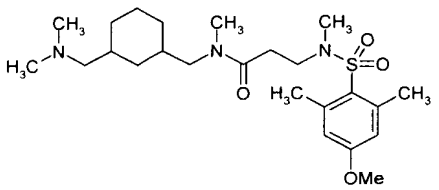


$C_{26}H_{43}N_3O_4S$ (493,70)

[M+H]+ = 494

HPLC (Método 9): Tempo de retenção = 1,72 min

Exemplo 225

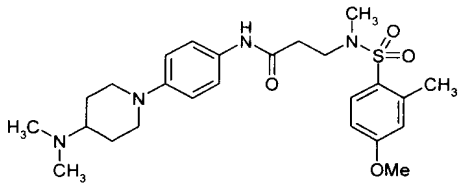


$C_{24}H_{41}N_3O_4S \times C_2HF_3O_2$ (581,69)

[M+H]+ = 468

HPLC (Método 9): Tempo de retenção = 1,69 min

Exemplo 226

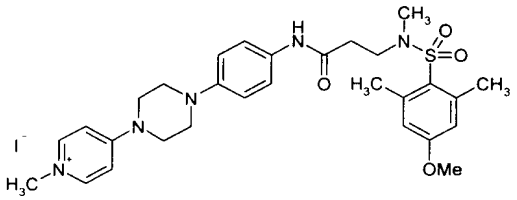


$C_{25}H_{36}N_4O_4S \times C_2HF_3O_2$ (602,67)

[M+H]+ = 489

HPLC (Método 5): Tempo de retenção = 1,39 min

Exemplo 227

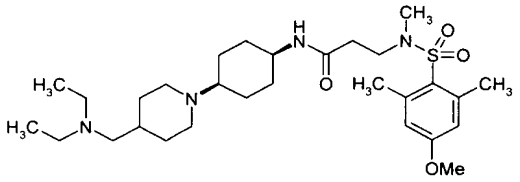


$C_{29}H_{38}N_5O_4S \times I$ (679,61)

[M+H]+ = 552

HPLC (Método 5): Tempo de retenção = 1,55 min

Exemplo 228

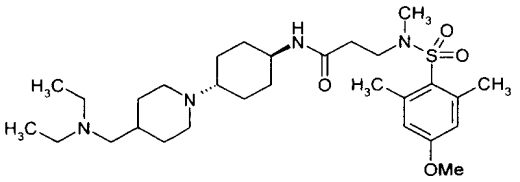


$C_{29}H_{50}N_4O_4S$ (550,80)

[M+H]+ = 551

HPLC (Método 5): Tempo de retenção = 1,38 min

Exemplo 229

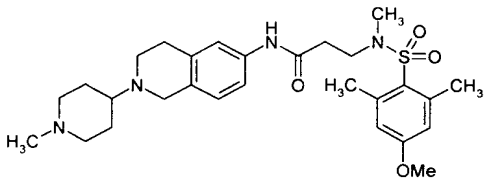


$C_{29}H_{50}N_4O_4S$ (550,80)

[M+H]+ = 551

HPLC (Método 5): Tempo de retenção = 1,40 min

Exemplo 230

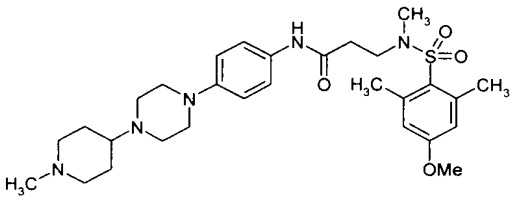


$C_{28}H_{40}N_4O_4S$ x 2HCl (601,63)

[M+H]+ = 529

HPLC (Método 5): Tempo de retenção = 1,41 min

Exemplo 231

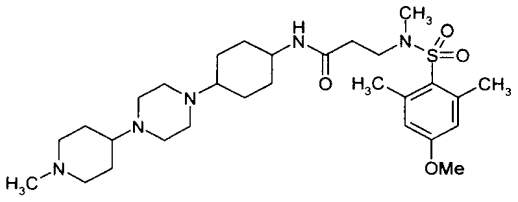


$C_{29}H_{43}N_5O_4S$ (557,75)

[M+H]+ = 558

HPLC (Método 1): Tempo de retenção = 1,90 min

Exemplo 232

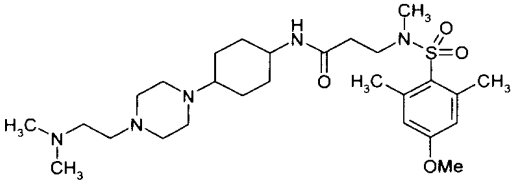


$C_{29}H_{49}N_5O_4S$ (563,80)

[M+H]+ = 564

HPLC (Método 5): Tempo de retenção = 1,33 min

Exemplo 233

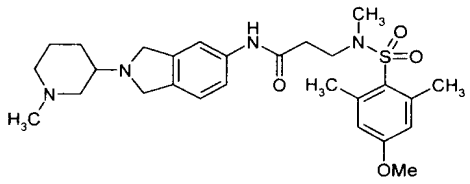


$C_{27}H_{47}N_5O_4S$ x 2HCl (610,68)

[M+H]+ = 538

HPLC (Método 7): Tempo de retenção = 1,74 min

Exemplo 234

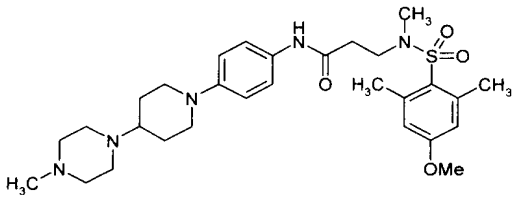


$C_{27}H_{38}N_4O_4S$ (610,68)

[M+H]+ = 515

HPLC (Método 5): Tempo de retenção = 1,41 min

Exemplo 235

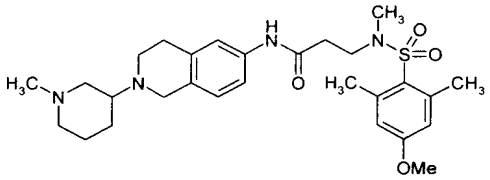


$C_{29}H_{43}N_5O_4S$ (557,75)

[M+H]+ = 558

HPLC (Método 5): Tempo de retenção = 1,43 min

Exemplo 236

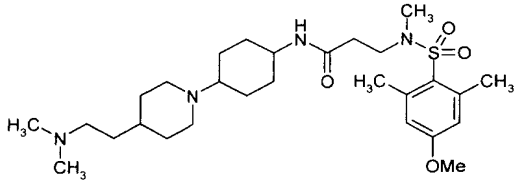


$C_{28}H_{40}N_4O_4S \times 2C_2HF_3O_2$ (756,75)

[M+H]+ = 529

HPLC (Método 5): Tempo de retenção = 1,42 min

Exemplo 237

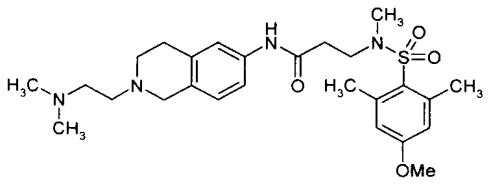


$C_{28}H_{48}N_4O_4S \times 2HCl$ (609,69)

[M+H]+ = 537

HPLC (Método 7): Tempo de retenção = 1,70 min

Exemplo 238

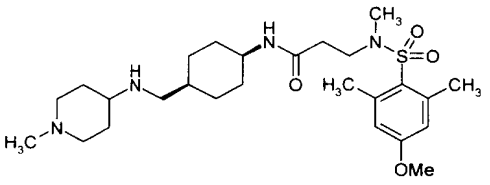


$C_{26}H_{38}N_4O_4S \times 2C_2HF_3O_2$ (730,72)

[M+H]+ = 503

HPLC (Método 5): Tempo de retenção = 1,40 min

Exemplo 239

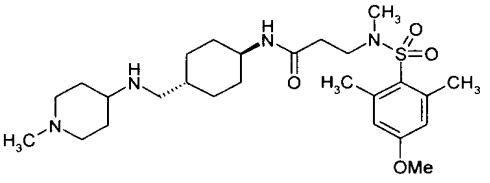


$C_{26}H_{44}N_4O_4S \times 2HCl$ (581,64)

[M+H]+ = 509

HPLC (Método 5): Tempo de retenção = 1,38 min

Exemplo 240

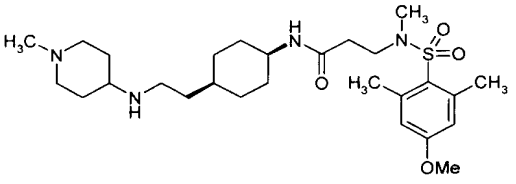


$C_{26}H_{44}N_4O_4S \times 2HCl$ (581.64)

[M+H]+ = 509

HPLC (Método 5): Tempo de retenção = 1,40 min

Exemplo 241

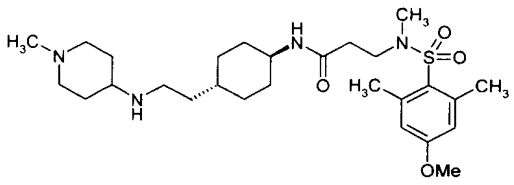


$C_{27}H_{46}N_4O_4S \times 2HCl$ (595.67)

[M+H]+ = 523

DC: Gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, Valor RF = 0,13

Exemplo 242

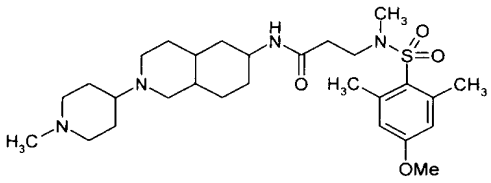


$C_{27}H_{46}N_4O_4S$ x 2HCl (595.67)

[M+H]+ = 523

DC: Gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, Valor RF = 0,13

Exemplo 243

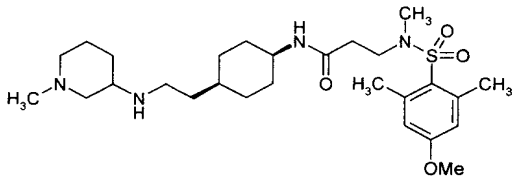


$C_{28}H_{46}N_4O_4S$ x 2HCl (607,68)

[M+H]+ = 535

HPLC (Método 5): Tempo de retenção = 1,10 min

Exemplo 244

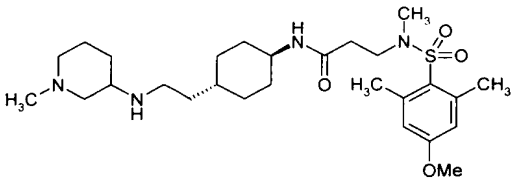


$C_{27}H_{46}N_4O_4S$ x 2HCl (595,67)

[M+H]+ = 523

DC: Gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, Valor RF = 0,25

Exemplo 245

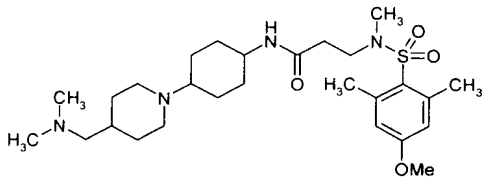


$C_{27}H_{46}N_4O_4S$ x 2HCl (595,67)

[M+H]+ = 523

DC: Gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, Valor RF = 0,25

Exemplo 246

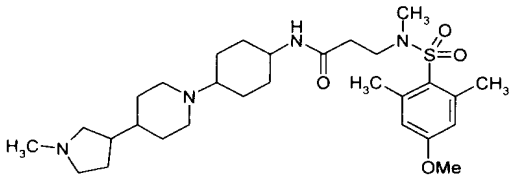


$C_{27}H_{46}N_4O_4S \times 2C_2HF_3O_2$ (750,79)

[M+H]+ = 523

HPLC (Método 5): Tempo de retenção = 1,38 min

Exemplo 247

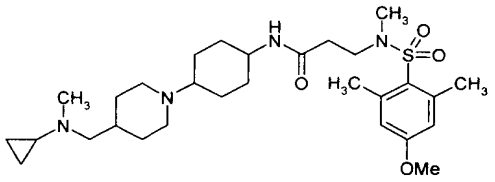


$C_{29}H_{48}N_4O_4S \times 2C_2HF_3O_2$ (776,83)

[M+H]+ = 549

HPLC (Método 5): Tempo de retenção = 1,39 min

Exemplo 248

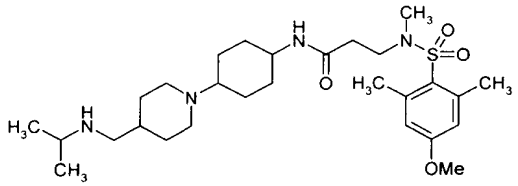


$C_{29}H_{48}N_4O_4S \times 2C_2HF_3O_2$ (776,83)

[M+H]+ = 549

HPLC (Método 5): Tempo de retenção = 1,39 min

Exemplo 249

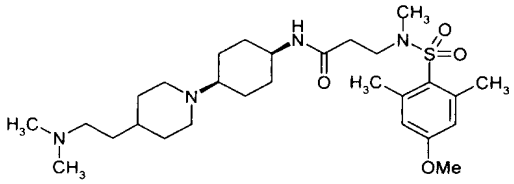


$C_{28}H_{48}N_4O_4S \times 2HCl$ (609.69)

[M+H]+ = 537

HPLC (Método 5): Tempo de retenção = 1,38 min

Exemplo 250

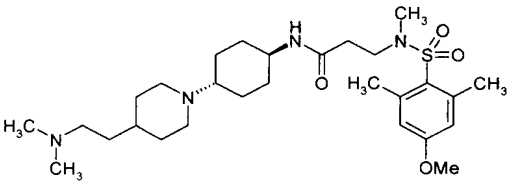


$C_{28}H_{48}N_4O_4S$ x 2HCl (609.69)

[M+H]+ = 537

HPLC (Método 11): Tempo de retenção = 1,60 min

Exemplo 251

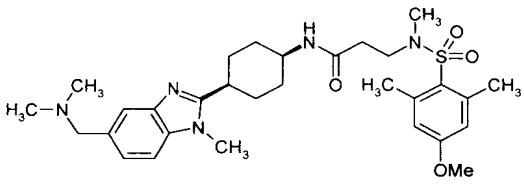


$C_{28}H_{48}N_4O_4S$ x 2HCl (609,69)

[M+H]+ = 537

HPLC (Método 7): Tempo de retenção = 1,71 min

Exemplo 252

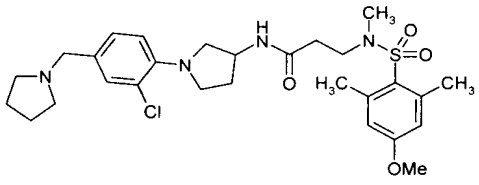


$C_{30}H_{43}N_5O_4S$ x HCl (606.22)

[M+H]+ = 570

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,29.

Exemplo 253

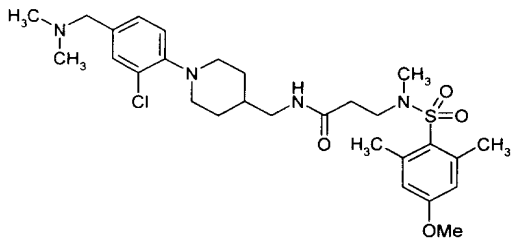


$C_{28}H_{39}ClN_4O_4S$ x HCl (599.61)

[M+H]+ = 563/565

HPLC (método 5): tempo de retenção = 1,59 min.

Exemplo 254

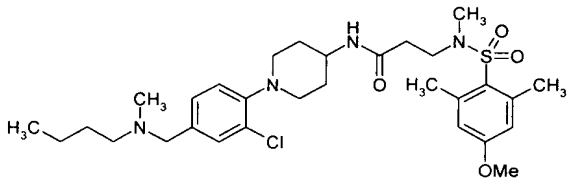


$C_{28}H_{41}ClN_4O_4S$ x HCl (601,63)

[M+H]+ = 565/567

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, valor Rf = 0,46.

Exemplo 255

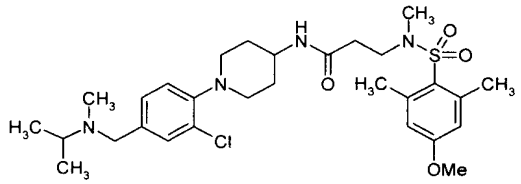


$C_{30}H_{45}ClN_4O_4S$ x HCl (629.68)

[M+H]+ = 593/595

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,42.

Exemplo 256

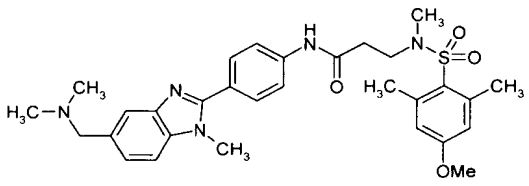


$C_{29}H_{43}ClN_4O_4S$ x HCl (615,66)

[M+H]+ = 579/581

DC: gel de sílica, diclorometano/metanol 9:1, valor Rf = 0,23.

Exemplo 257

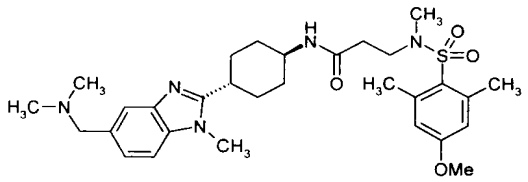


$C_{30}H_{37}N_5O_4S$ x HCl (600.17)

[M+H]+ = 564

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,1, Valor Rf = 0,67

Exemplo 258

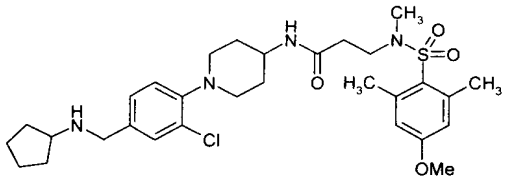


$C_{30}H_{43}N_5O_4S$ (569.76)

[M+H]+ = 570

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,2, Valor Rf = 0,65

Exemplo 259

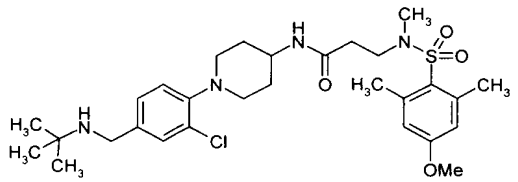


$C_{30}H_{43}ClN_4O_4S$ x HCl (627.67)

[M+H]+ = 591/593

DC: Kieselgel, Dichlormethan / Methanol 9:1, Valor Rf = 0,20

Exemplo 260

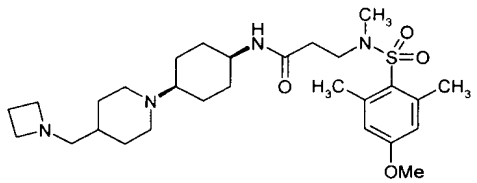


$C_{29}H_{43}ClN_4O_4S$ x HCl (615.66)

[M+H]+ = 579/581

DC: Gel de sílica, diclorometano/metanol 9:1, Valor Rf = 0,17

Exemplo 261

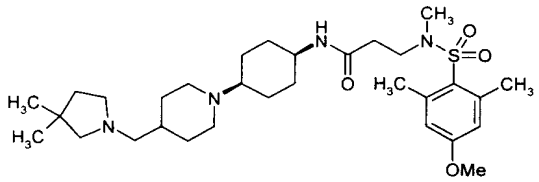


$C_{28}H_{46}N_4O_4S$ x 2HCl (607.68)

[M+H]+ = 535

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,2, Valor Rf = 0,23

Exemplo 262

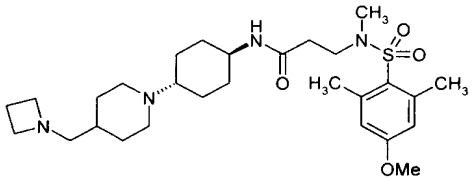


$C_{31}H_{52}N_4O_4S$ x 2HCl (649.76)

[M+H]+ = 577

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,2, Valor Rf = 0,69

Exemplo 263

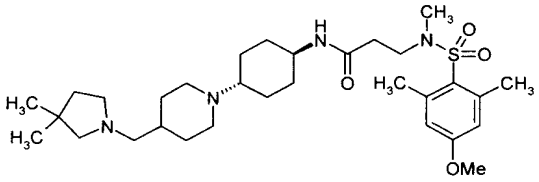


$C_{28}H_{46}N_4O_4S$ (534.76)

[M+H]+ = 535

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,2, Valor Rf = 0,58

Exemplo 264

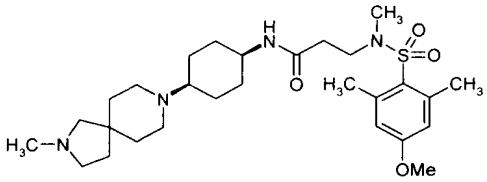


$C_{31}H_{52}N_4O_4S$ (576.84)

[M+H]+ = 577

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,2, Valor Rf = 0,56

Exemplo 265

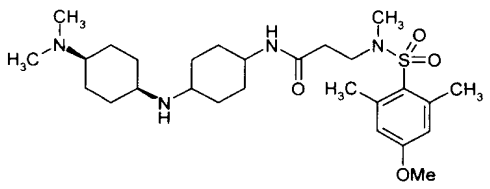


$C_{28}H_{46}N_4O_4S$ x 2HCl (607.68)

[M+H]+ = 535

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,2, Valor Rf = 0,58

Exemplo 266

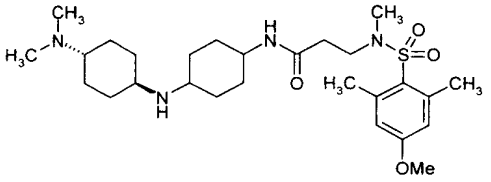


$C_{27}H_{46}N_4O_4S$ (522.74)

[M+H]+ = 523

HPLC (Método 9): Tempo de retenção = 1.30 min

Exemplo 267

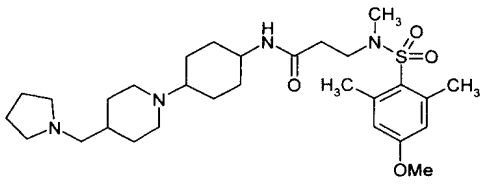


$C_{27}H_{46}N_4O_4S$ (522.74)

[M+H]+ = 523

HPLC (Método 9): Tempo de retenção = 1.28 min

Exemplo 268

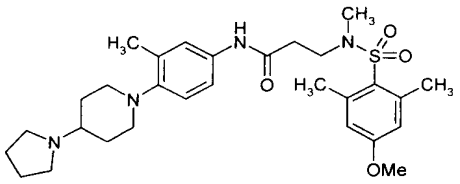


$C_{29}H_{48}N_4O_4S \times CH_2O_2$ (594.81)

[M+H]+ = 549

HPLC (Método 6): Tempo de retenção = 1.96 min

Exemplo 269

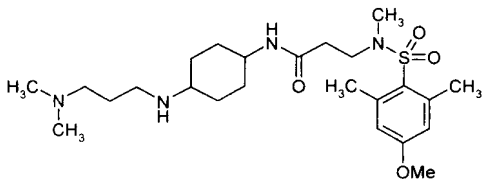


$C_{309}H_{44}N_4O_4S$ (556.76)

[M+H]+ = 557

HPLC (Método 9): Tempo de retenção = 1.71 min

Exemplo 270

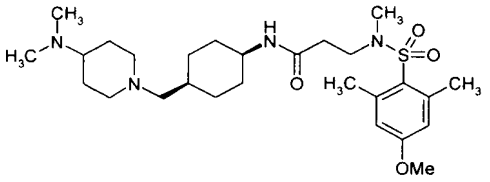


$C_{24}H_{42}N_4O_4S \times C_2HF_3O_2$ (596.70)

[M+H]+ = 483

HPLC (Método 9): Tempo de retenção = 1.23 min

Exemplo 271

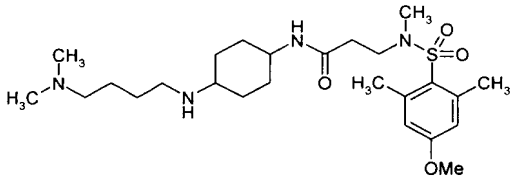


$C_{27}H_{46}N_4O_4S$ (522.74)

[M+H]+ = 523

HPLC (Método 9): Tempo de retenção = 1.23 min

Exemplo 272

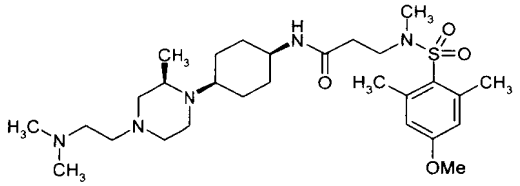


$C_{25}H_{44}N_4O_4S$ (496.71)

[M+H]+ = 497

HPLC (Método 9): Tempo de retenção = 1.25 min

Exemplo 273

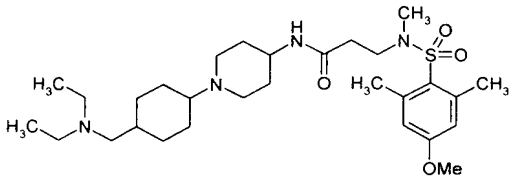


$C_{28}H_{49}N_5O_4S \times 2HCl$ (624.71)

[M+H]+ = 552

HPLC (Método 10): Tempo de retenção = 1.06 min

Exemplo 274

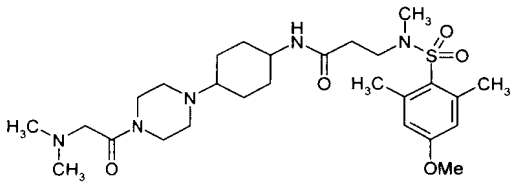


$C_{29}H_{50}N_4O_4S$ x CH_2O_2 (596.82)

[M+H]+ = 551

HPLC (Método 9): Tempo de retenção = 1.31 min

Exemplo 275

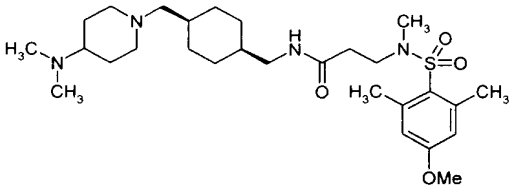


$C_{27}H_{45}N_5O_5S$ x CH_2O_2 (597.77)

[M+H]+ = 552

HPLC (Método 9): Tempo de retenção = 1.20 min

Exemplo 276

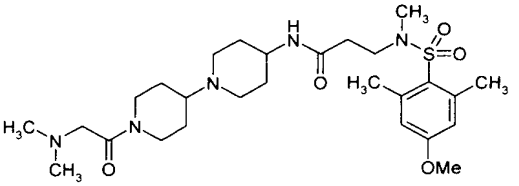


$C_{28}H_{48}N_4O_4S$ (536.77)

[M+H]+ = 537

HPLC (Método 6): Tempo de retenção = 1.32 min

Exemplo 277

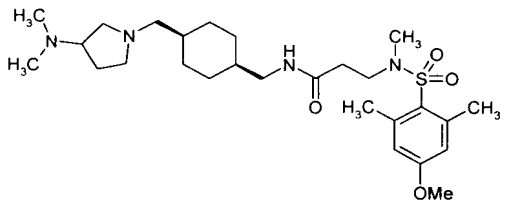


$C_{27}H_{45}N_5O_5S$ x $C_2HF_3O_2$ (665.77)

[M+H]+ = 552

HPLC (Método 9): Tempo de retenção = 1.18 min

Exemplo 278

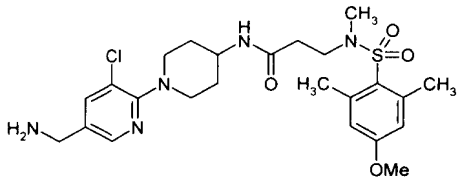


$C_{27}H_{46}N_4O_4S$ x 2 $C_2HF_3O_2$ (750.79)

[M+H]+ = 523

HPLC (Método 9): Tempo de retenção = 1.29 min

Exemplo 279

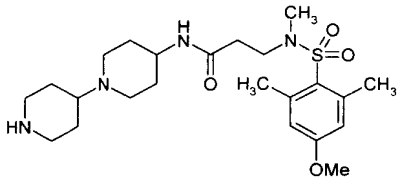


$C_{24}H_{34}ClN_5O_4S$ (524.08)

[M+H]+ = 524/526

HPLC (Método 9): Tempo de retenção = 1.60 min

Exemplo 280

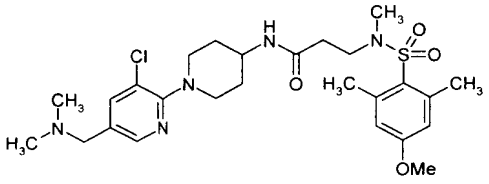


$C_{23}H_{38}N_4O_4S$ x $2C_2HF_3O_2$ (694.69)

[M+H]+ = 467

HPLC (Método 9): Tempo de retenção = 1.16 min

Exemplo 281

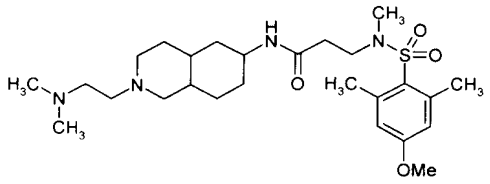


$C_{26}H_{38}ClN_5O_4S$ x $C_2HF_3O_2$ (666.15)

[M+H]+ = 552/554

HPLC (Método 9): Tempo de retenção = 1.68 min

Exemplo 282

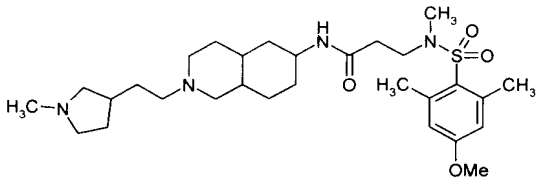


$C_{26}H_{44}N_4O_4S$ x 2HCl (581.64)

[M+H]+ = 509

HPLC (Método 5): Tempo de retenção = 1.36 min

Exemplo 283

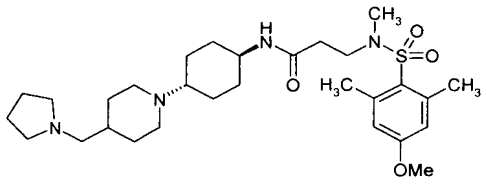


$C_{29}H_{48}N_4O_4S$ x 2HCl (621.70)

[M+H]+ = 549

HPLC (Método 5): Tempo de retenção = 1.38 min

Exemplo 284

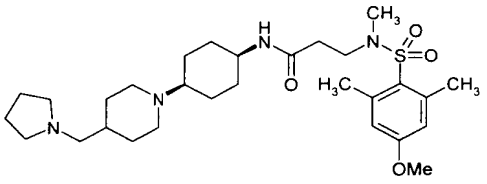


$C_{29}H_{48}N_4O_4S$ (548.78)

[M+H]+ = 549

HPLC (Método 5): Tempo de retenção = 1.38 min

Exemplo 285

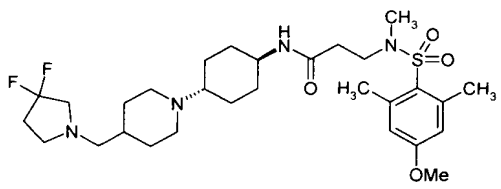


$C_{29}H_{48}N_4O_4S$ (548.78)

[M+H]+ = 549

HPLC (Método 5): Tempo de retenção = 1.36 min

Exemplo 286

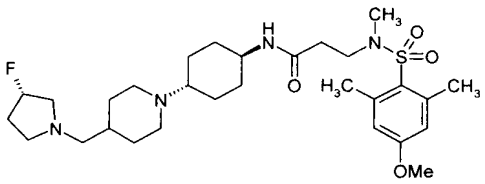


$C_{29}H_{46}F_2N_4O_4S$ (584.76)

[M+H]+ = 585

HPLC (Método 5): Tempo de retenção = 1.38 min

Exemplo 287

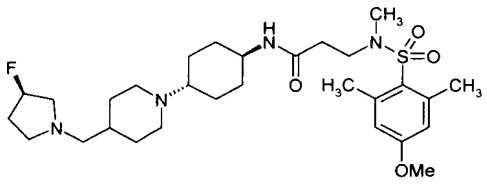


$C_{29}H_{47}FN_4O_4S$ (566.77)

[M+H]+ = 567

HPLC (Método 5): Tempo de retenção = 1.38 min

Exemplo 288

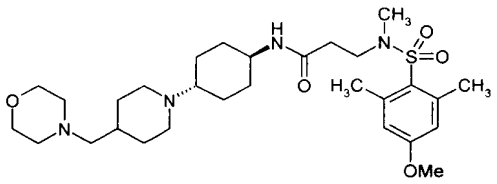


$C_{29}H_{47}FN_4O_4S$ (566.77)

[M+H]+ = 567

HPLC (Método 5): Tempo de retenção = 1.36 min

Exemplo 289

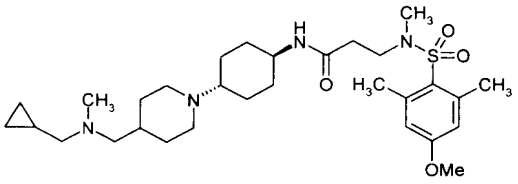


$C_{29}H_{48}N_4O_5S$ (564.78)

[M+H]+ = 565

HPLC (Método 5): Tempo de retenção = 1.37 min

Exemplo 290

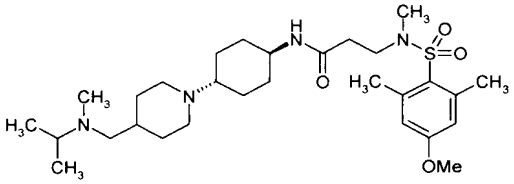


$C_{30}H_{50}N_4O_4S$ (562.81)

[M+H]+ = 563

HPLC (Método 5): Tempo de retenção = 1.39 min

Exemplo 291

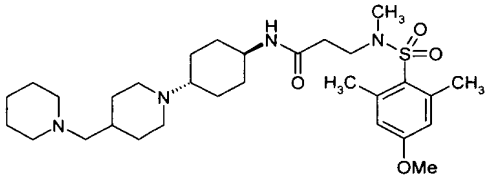


$C_{29}H_{50}N_4O_4S$ (550.80)

[M+H]+ = 551

HPLC (Método 5): Tempo de retenção = 1.36 min

Exemplo 292

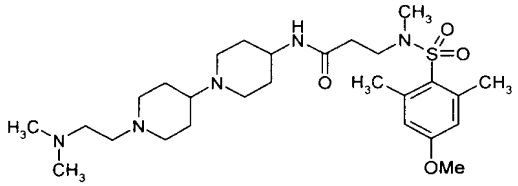


$C_{30}H_{50}N_4O_4S$ (562.81)

[M+H]+ = 563

HPLC (Método 5): Tempo de retenção = 1.28 min

Exemplo 293

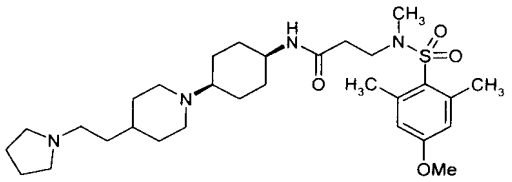


$C_{27}H_{47}N_5O_4S \times 3C_2HF_3O_2$ (879.83)

[M+H]+ = 538

HPLC (Método 5): Tempo de retenção = 1.33 min

Exemplo 294

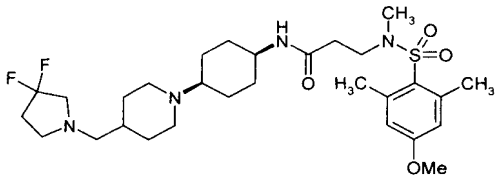


$C_{30}H_{50}N_4O_4S$ x 2HCl (635.73)

[M+H]+ = 563

HPLC (Método 5): Tempo de retenção = 1.37 min

Exemplo 295

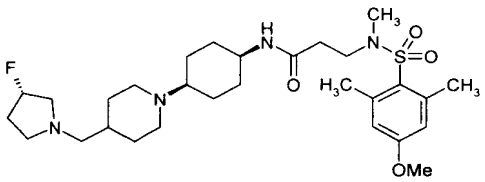


$C_{29}H_{46}F_2N_4O_4S$ x $2C_2HF_3O_2$ (584.76)

[M+H]+ = 585

HPLC (Método 5): Tempo de retenção = 1.38 min

Exemplo 296

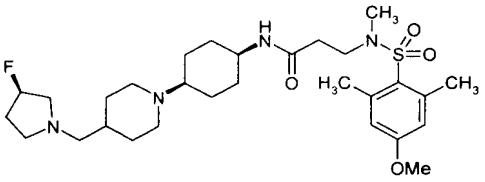


$C_{29}H_{47}FN_4O_4S$ x $2C_2HF_3O_2$ (794.82)

[M+H]+ = 567

HPLC (Método 5): Tempo de retenção = 1.35 min

Exemplo 297

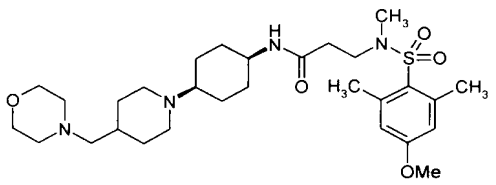


$C_{29}H_{47}FN_4O_4S$ x $2C_2HF_3O_2$ (794.82)

[M+H]+ = 567

HPLC (Método 5): Tempo de retenção = 1.36 min

Exemplo 298

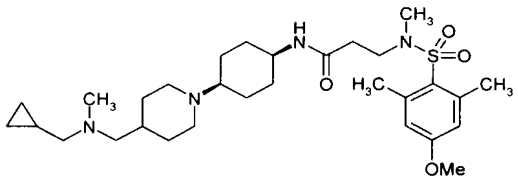


$C_{29}H_{48}N_4O_5S$ (564.78)

[M+H]+ = 565

HPLC (Método 5): Tempo de retenção = 1.36 min

Exemplo 299

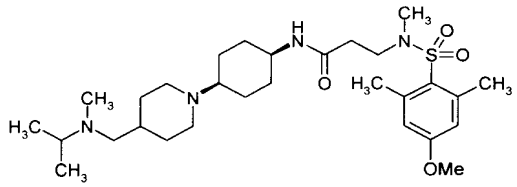


$C_{30}H_{50}N_4O_4S$ (562.81)

[M+H]+ = 563

HPLC (Método 5): Tempo de retenção = 1.37 min

Exemplo 300

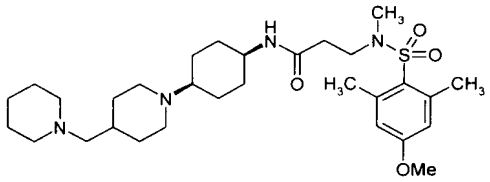


$C_{29}H_{50}N_4O_4S$ (550.80)

[M+H]+ = 551

HPLC (Método 5): Tempo de retenção = 1.37 min

Exemplo 301

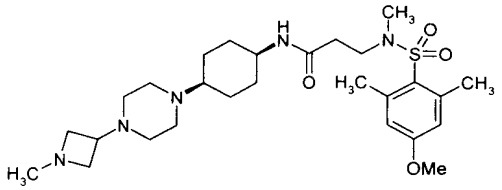


$C_{30}H_{50}N_4O_4S$ (562.81)

[M+H]+ = 563

HPLC (Método 5): Tempo de retenção = 1.37 min

Exemplo 302

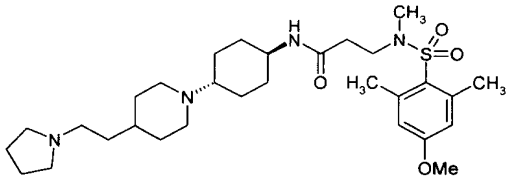


$C_{30}H_{50}N_4O_4S$ x $3C_2HF_3O_2$ (877.81)

[M+H]+ = 536

HPLC (Método 5): Tempo de retenção = 1.34 min

Exemplo 303

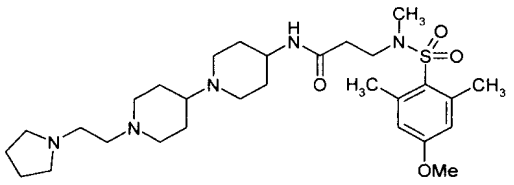


$C_{30}H_{50}N_4O_4S$ (562.81)

[M+H]+ = 563

HPLC (Método 5): Tempo de retenção = 1.37 min

Exemplo 304

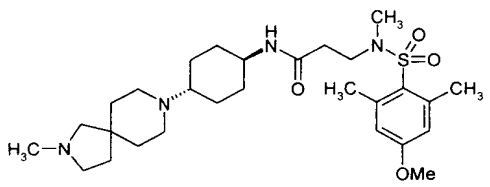


$C_{29}H_{49}N_5O_4S$ x $3C_2HF_3O_2$ (905.87)

[M+H]+ = 564

HPLC (Método 5): Tempo de retenção = 1.08 min

Exemplo 305

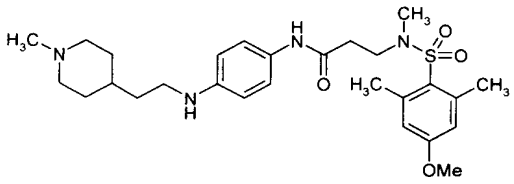


$C_{28}H_{46}N_4O_4S$ x 2HCl (607.68)

[M+H]+ = 535

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,2, Valor Rf = 0,19

Exemplo 306

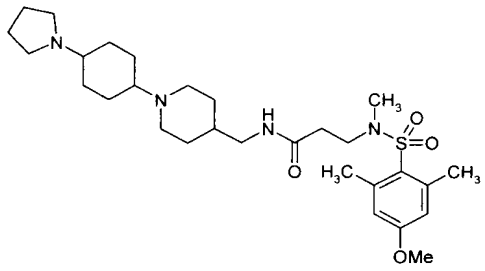


$C_{27}H_{40}N_4O_4S \times C_2HF_3O_4$ (630.72)

[M+H]+ = 517

HPLC (Método 9): Tempo de retenção = 1.40 min

Exemplo 307

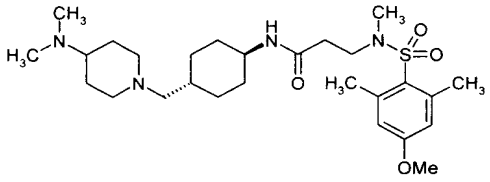


$C_{29}H_{48}N_4O_4S$ (548.78)

[M+H]+ = 549

HPLC (Método 6): Tempo de retenção = 1.24 min

Exemplo 308

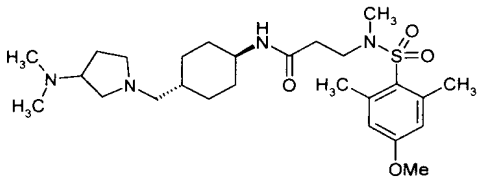


$C_{27}H_{46}N_4O_4S$ (522.74)

[M+H]+ = 523

HPLC (Método 9): Tempo de retenção = 1.29 min

Exemplo 309

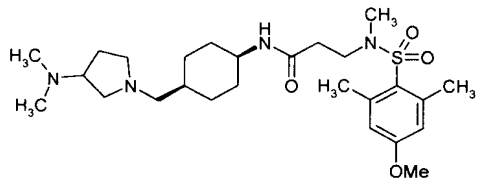


$C_{26}H_{44}N_4O_4S$ (508.72)

[M+H]+ = 509

HPLC (Método 9): Tempo de retenção = 1.30 min

Exemplo 310

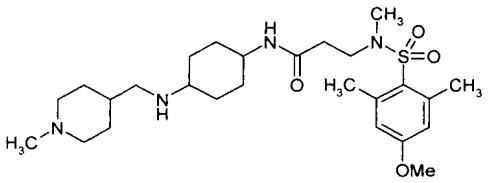


$C_{26}H_{44}N_4O_4S$ (508.72)

[M+H]+ = 509

HPLC (Método 9): Tempo de retenção = 1.23 min

Exemplo 311

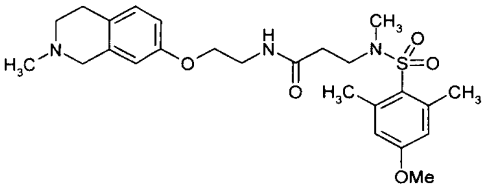


$C_{26}H_{44}N_4O_4S$ (508.72)

[M+H]+ = 509

HPLC (Método 6): Tempo de retenção = 1.20 min

Exemplo 312

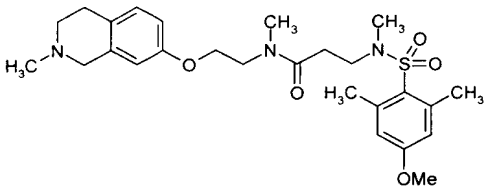


$C_{25}H_{35}N_3O_5S$ x HCl (526.09)

[M+H]+ = 490

HPLC (Método 10): Tempo de retenção = 1.16 min

Exemplo 313

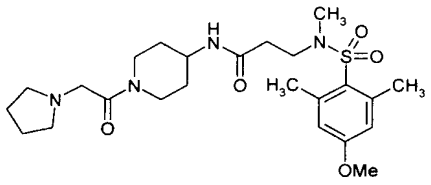


$C_{26}H_{37}N_3O_5S$ x HCl (540.12)

[M+H]+ = 504

HPLC (Método 10): Tempo de retenção = 1.22 min

Exemplo 314

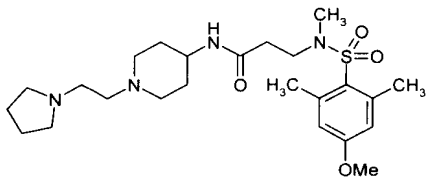


$C_{24}H_{38}N_4O_5S$ x $C_2HF_3O_2$ (608.67)

[M+H]+ = 495

HPLC (Método 9): Tempo de retenção = 1.47 min

Exemplo 315

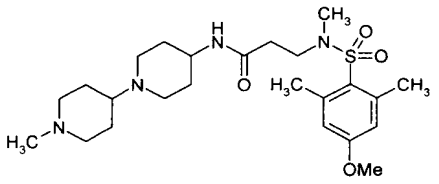


$C_{24}H_{40}N_4O_4S$ (480.66)

[M+H]+ = 481

HPLC (Método 9): Tempo de retenção = 1.21 min

Exemplo 316

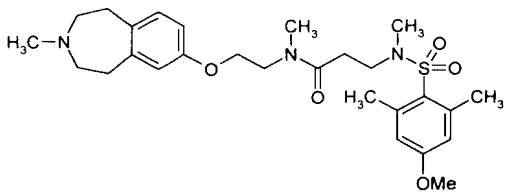


$C_{24}H_{40}N_4O_4S$ x $C_2HF_3O_2$ (594.69)

[M+H]+ = 481

HPLC (Método 9): Tempo de retenção = 1.19 min

Exemplo 317

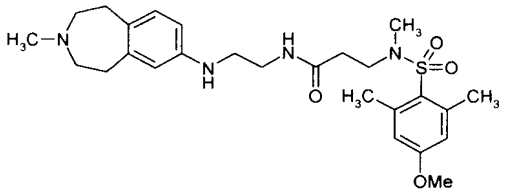


$C_{27}H_{39}N_3O_5S$ x HCl (554.14)

[M+H]+ = 518

HPLC (Método 5): Tempo de retenção = 1.36 min

Exemplo 593

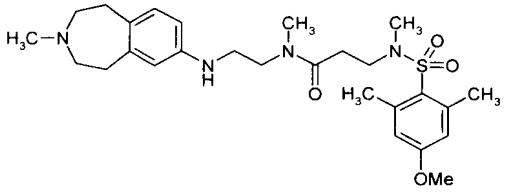


$C_{26}H_{38}N_4O_4S$ x HCl (539.13)

[M+H]+ = 503

HPLC (Método 5): Tempo de retenção = 1.29 min

Exemplo 594

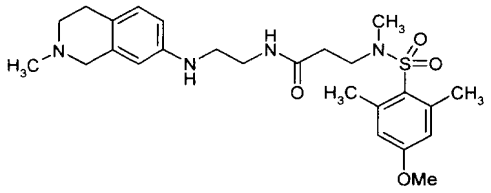


$C_{27}H_{40}N_4O_4S$ x HCl (553.16)

[M+H]+ = 517

HPLC (Método 5): Tempo de retenção = 1.35 min

Exemplo 595

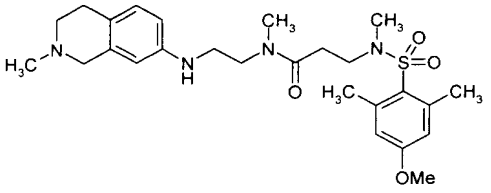


$C_{25}H_{36}N_4O_4S$ x HCl (525.10)

[M+H]+ = 489

HPLC (Método 5): Tempo de retenção = 1.31 min

Exemplo 596

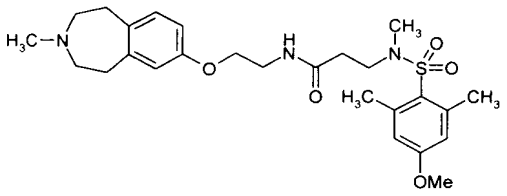


$C_{26}H_{38}N_4O_4S$ x HCl (539.13)

[M+H]+ = 503

HPLC (Método 5): Tempo de retenção = 1.35 min

Exemplo 597

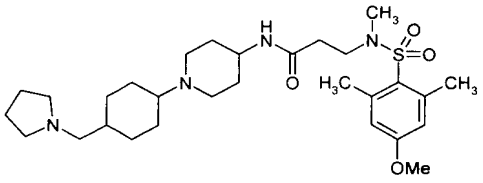


$C_{26}H_{37}N_3O_5S$ x HCl (540.12)

[M+H]+ = 504

HPLC (Método 10): Tempo de retenção = 1.18 min

Exemplo 598

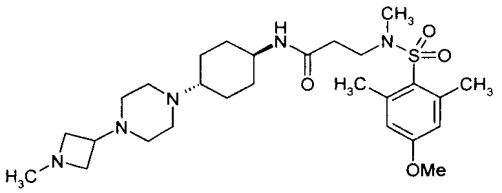


$C_{29}H_{48}N_4O_4S$ x $C_2HF_3O_2$ (662.81)

[M+H]+ = 549

HPLC (Método 9): Tempo de retenção = 1.27 min

Exemplo 599

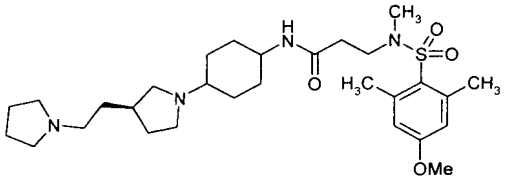


$C_{27}H_{45}N_5O_4S$ x 3HCl (645.13)

[M+H]+ = 536

HPLC (Método 5): Tempo de retenção = 1.14 min

Exemplo 600

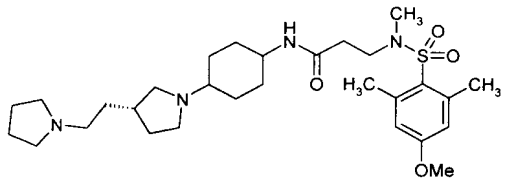


$C_{29}H_{48}N_4O_4S$ x 2HCl (621.70)

[M+H]+ = 549

HPLC (Método 5): Tempo de retenção = 1.16 min

Exemplo 601

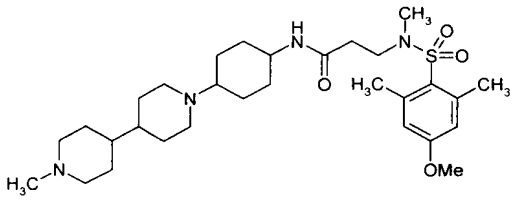


$C_{29}H_{48}N_4O_4S$ (548.78)

[M+H]+ = 549

HPLC (Método 5): Tempo de retenção = 1.16 min

Exemplo 602

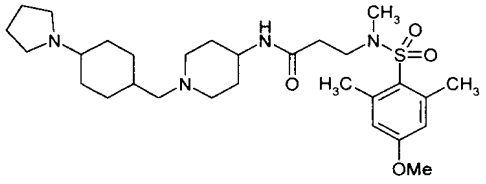


$C_{30}H_{50}N_4O_4S \times C_2HF_3O_2$ (676.83)

[M+H]+ = 563

HPLC (Método 9): Tempo de retenção = 1.14 min

Exemplo 608

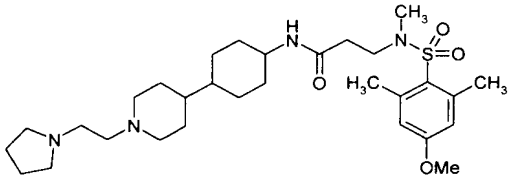


$C_{29}H_{48}N_4O_4S \times C_2HF_3O_2$ (662.81)

[M+H]+ = 549

HPLC (Método 9): Tempo de retenção = 1.30 min

Exemplo 609

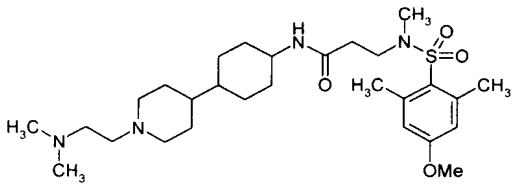


$C_{30}H_{50}N_4O_4S \times 2HCl$ (635.73)

[M+H]+ = 563

HPLC (Método 11): Tempo de retenção = 1.70 min

Exemplo 610

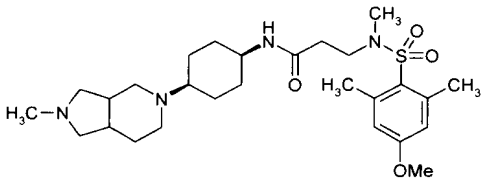


$C_{28}H_{48}N_4O_4S$ x 2HCl (609.69)

[M+H]+ = 537

HPLC (Método 11): Tempo de retenção = 1.67 min

Exemplo 611

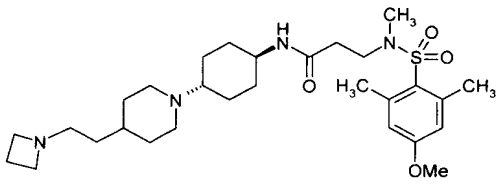


$C_{27}H_{44}N_4O_4S$ x 2HCl (593.65)

[M+H]+ = 521

HPLC (Método 11): Tempo de retenção = 1,61 min

Exemplo 636

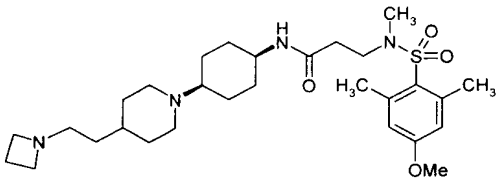


$C_{29}H_{48}N_4O_4S$ x 2HCl (621.70)

[M+H]+ = 549

HPLC (Método 4): Tempo de retenção = 2.39 min

Exemplo 637



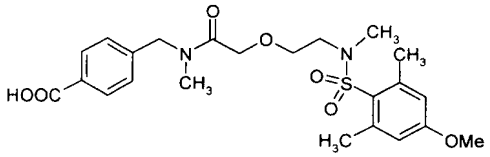
$C_{29}H_{48}N_4O_4S$ x 2HCl (621.70)

[M+H]+ = 549

HPLC (Método 4): Tempo de retenção = 2.34 min

Die folgenden Verbindungen wurden analog zu Exemplo 53 hergestellt:

Exemplo 318

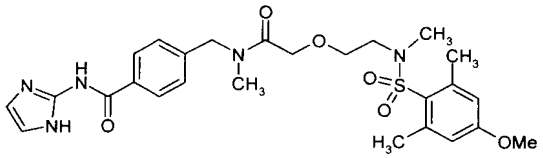


$C_{23}H_{30}N_2O_7S$ (478.56)

[M+H]+ = 479

HPLC (Método 6): Tempo de retenção = 3.21 min

Exemplo 319

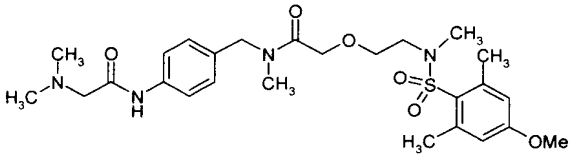


$C_{26}H_{33}N_5O_6S$ (543.64)

[M+H]+ = 544

HPLC (Método 6): Tempo de retenção = 2.51 min

Exemplo 320

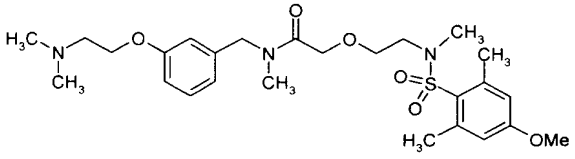


$C_{26}H_{38}N_4O_6S$ (534.67)

[M+H]+ = 535

HPLC (Método 6): Tempo de retenção = 2.48 min

Exemplo 321

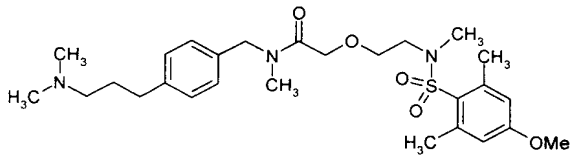


$C_{26}H_{398}N_3O_6S$ (521.67)

[M+H]+ = 522

HPLC (Método 6): Tempo de retenção = 2.60 min

Exemplo 322

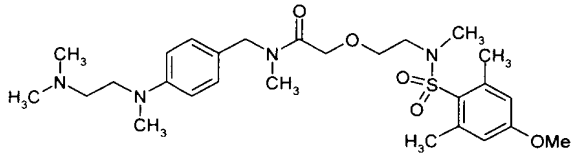


$C_{27}H_{41}N_3O_5S$ (519.70)

[M+H]+ = 520

HPLC (Método 6): Tempo de retenção = 2.61 min

Exemplo 323

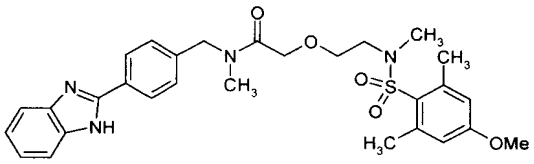


$C_{27}H_{42}N_4O_5S$ x HCl (571.17)

[M+H]+ = 535

HPLC (Método 5): Tempo de retenção = 1.57 min

Exemplo 324

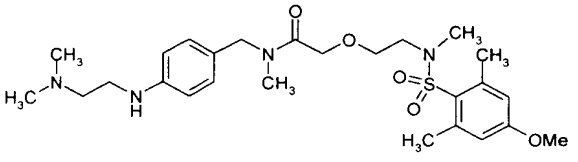


$C_{29}H_{34}N_4O_5S$ x $C_2HF_3O_2$ (664.69)

[M+H]+ = 551

HPLC (Método 5): Tempo de retenção = 1.60 min

Exemplo 325

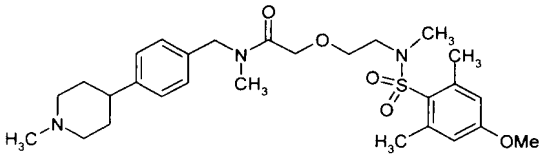


$C_{26}H_{40}N_4O_5S$ x HCl (557.15)

[M+H]+ = 521

HPLC (Método 5): Tempo de retenção = 1.53 min

Exemplo 326

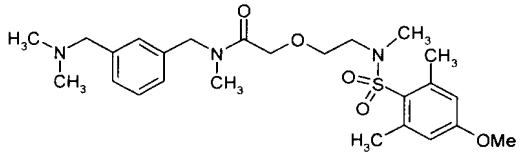


$C_{28}H_{41}N_3O_5S \times C_2HF_3O_2$ (645.73)

[M+H]+ = 532

HPLC (Método 5): Tempo de retenção = 1.54 min

Exemplo 327

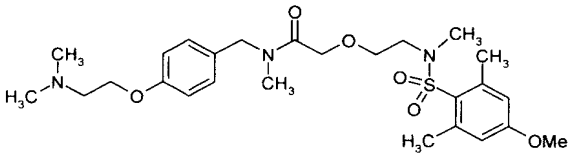


$C_{25}H_{37}N_3O_5S \times HCl$ (528.11)

[M+H]+ = 492

HPLC (Método 5): Tempo de retenção = 1.53 min

Exemplo 328

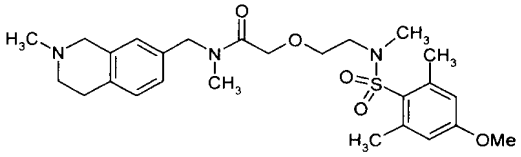


$C_{26}H_{39}N_3O_6S \times C_2HF_3O_2$ (635.69)

[M+H]+ = 522

HPLC (Método 5): Tempo de retenção = 1.53 min

Exemplo 329

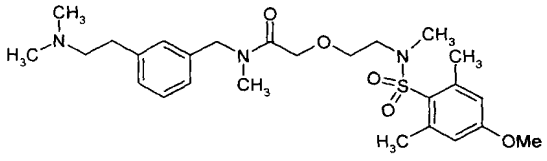


$C_{26}H_{37}N_3O_5S \times HCl$ (540.12)

[M+H]+ = 504

HPLC (Método 7): Tempo de retenção = 1.93 min

Exemplo 330

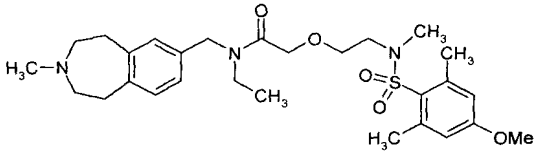


$C_{26}H_{39}N_3O_5S$ x HCl (542.13)

[M+H]+ = 506

HPLC (Método 5): Tempo de retenção = 1.54 min

Exemplo 331

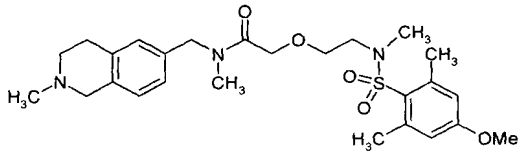


$C_{28}H_{41}N_3O_5S$ x HCl (568.17)

[M+H]+ = 532

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, Valor Rf = 0,30

Exemplo 332

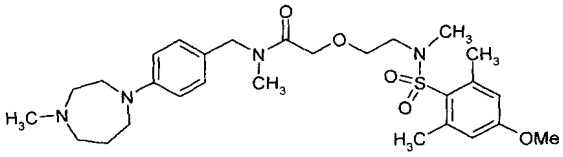


$C_{26}H_{37}N_3O_5S$ x HCl (540.12)

[M+H]+ = 504

HPLC (Método 5): Tempo de retenção = 1.51 min

Exemplo 333

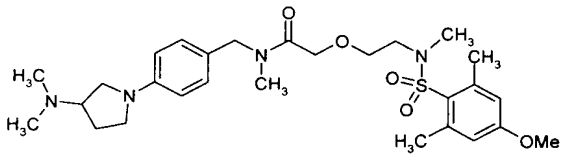


$C_{28}H_{42}N_4O_5S$ x HCl (583,18)

[M+H]+ = 547

HPLC (Método 5): Tempo de retenção = 1,54 min

Exemplo 334

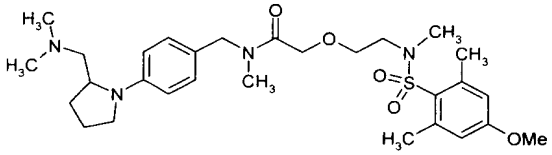


$C_{28}H_{42}N_4O_5S$ x HCl (583,18)

[M+H]+ = 547

HPLC (Método 10): Tempo de retenção = 1,24 min

Exemplo 335

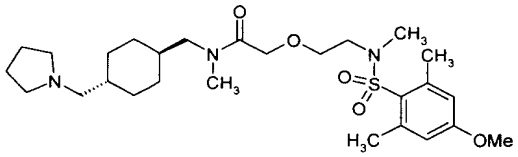


$C_{29}H_{44}N_4O_5S$ x HCl (597.21)

[M+H]+ = 561

HPLC (Método 5): Tempo de retenção = 1.55 min

Exemplo 336

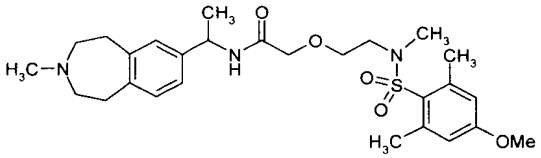


$C_{27}H_{45}N_3O_5S$ x HCl (560,19)

[M+H]+ = 524

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,01, Valor Rf = 0,39

Exemplo 337

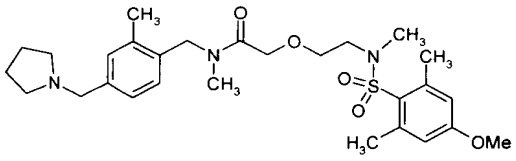


$C_{27}H_{39}N_3O_5S$ x HCl (554.14)

[M+H]+ = 518

HPLC (Método 4): Tempo de retenção = 3.4 min

Exemplo 338

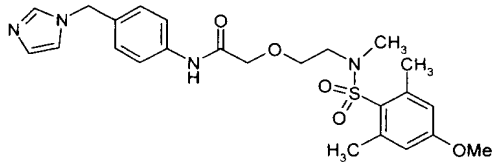


$C_{28}H_{41}N_3O_5S$ x HCl (568,17)

[M+H]+ = 532

DC: Gel de sílica, diclorometano/metanol 9:1, Valor Rf = 0,14

Exemplo 339

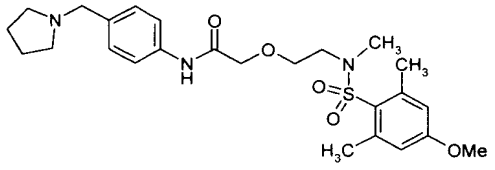


$C_{24}H_{30}N_4O_5S$ x $C_2HF_3O_2$ (600.61)

[M+H]+ = 487

HPLC (Método 6): Tempo de retenção = 2.58 min

Exemplo 340

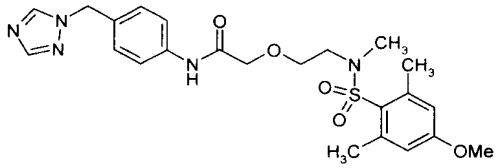


$C_{25}H_{35}N_3O_5S$ x $C_2HF_3O_2$ (603,65)

[M+H]+ = 490

HPLC (Método 6): Tempo de retenção = 2,61 min

Exemplo 341

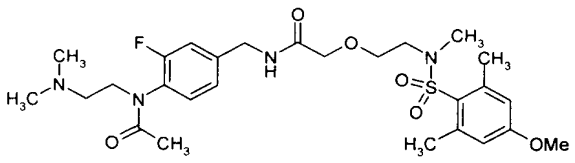


$C_{23}H_{29}N_5O_5S$ x $C_2HF_3O_2$ (601,60)

[M+H]+ = 488

HPLC (Método 6): Tempo de retenção = 3,28 min

Exemplo 342

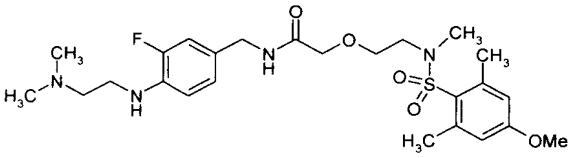


$C_{27}H_{39}FN_4O_6S$ (566.69)

[M+H]+ = 567

HPLC (Método 6): Tempo de retenção = 2.59 min

Exemplo 343

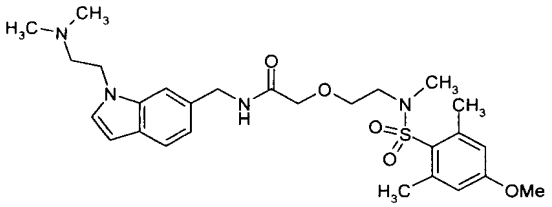


$C_{25}H_{37}FN_4O_5S$ (524.65)

[M+H]+ = 525

HPLC (Método 6): Tempo de retenção = 2.59 min

Exemplo 344

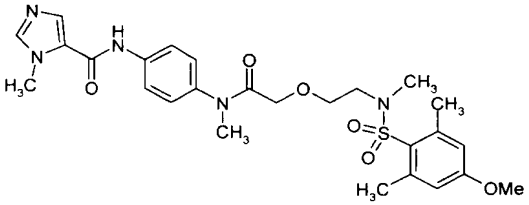


$C_{27}H_{38}N_4O_5S$ (530.68)

[M+H]+ = 531

HPLC (Método 6): Tempo de retenção = 2.65 min

Exemplo 345

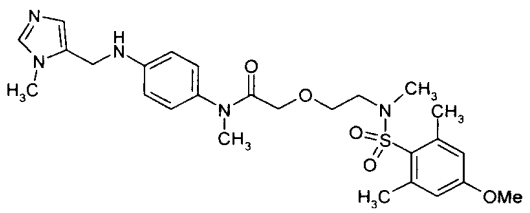


$C_{26}H_{33}N_5O_6S$ (543.64)

[M+H]+ = 544

HPLC (Método 6): Tempo de retenção = 2.39 min

Exemplo 346

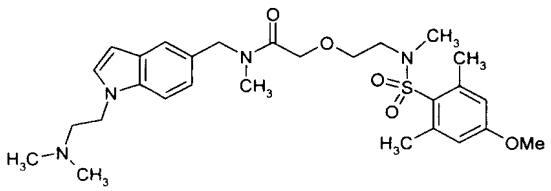


$C_{26}H_{35}N_5O_5S$ (529.65)

[M+H]+ = 530

HPLC (Método 6): Tempo de retenção = 2.43 min

Exemplo 347

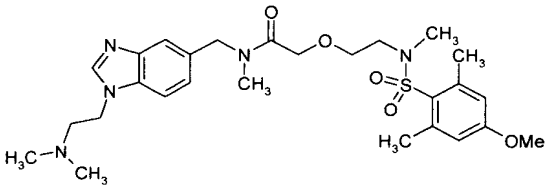


$C_{28}H_{40}N_4O_5S$ (544.71)

[M+H]+ = 545

HPLC (Método 6): Tempo de retenção = 2.65 min

Exemplo 348

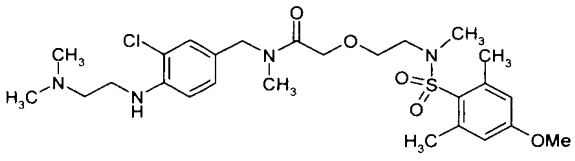


$C_{27}H_{39}N_5O_5S$ (545.70)

[M+H]+ = 546

HPLC (Método 6): Tempo de retenção = 2.19 min

Exemplo 349

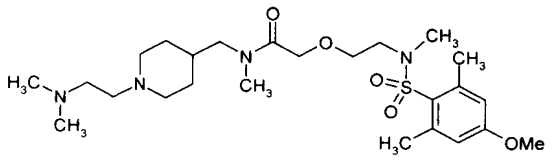


$C_{26}H_{39}ClN_4O_5S$ (555.13)

[M+H]+ = 555/557

HPLC (Método 6): Tempo de retenção = 2.63 min

Exemplo 350

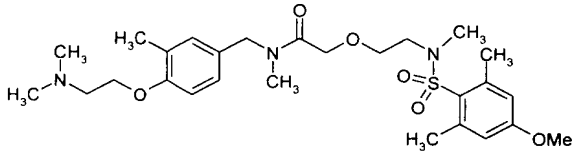


$C_{25}H_{44}N_4O_5S$ (512.71)

[M+H]+ = 513

HPLC (Método 6): Tempo de retenção = 1.94 min

Exemplo 351

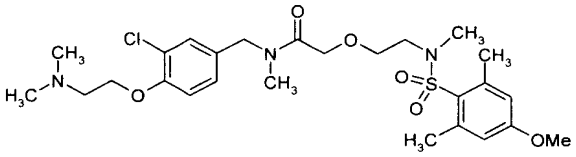


$C_{27}H_{41}N_3O_6S$ (535.70)

[M+H]+ = 536

HPLC (Método 6): Tempo de retenção = 2.56 min

Exemplo 352

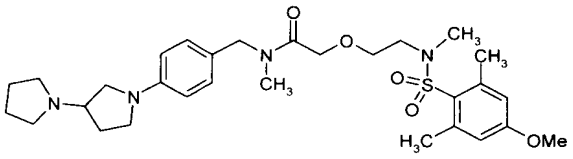


$C_{26}H_{38}ClN_3O_6S \times CH_2O_2$ (602.14)

[M+H]+ = 556/558

HPLC (Método 6): Tempo de retenção = 2.65 min

Exemplo 353

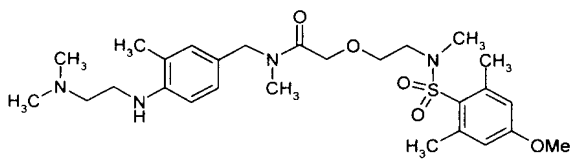


$C_{30}H_{44}N_4O_5S$ (572.76)

[M+H]+ = 573

HPLC (Método 6): Tempo de retenção = 2.69 min

Exemplo 354

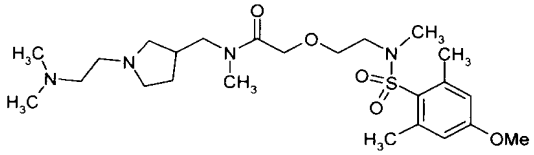


$C_{27}H_{42}N_4O_5S$ (534.71)

[M+H]+ = 535

HPLC (Método 6): Tempo de retenção = 2.54 min

Exemplo 355

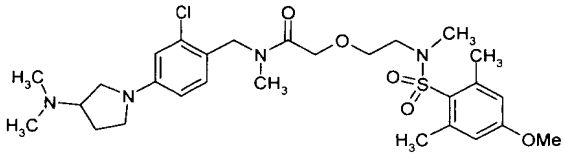


$C_{24}H_{42}N_4O_5S$ (498.68)

[M+H]+ = 499

HPLC (Método 6): Tempo de retenção = 1.95 min

Exemplo 356

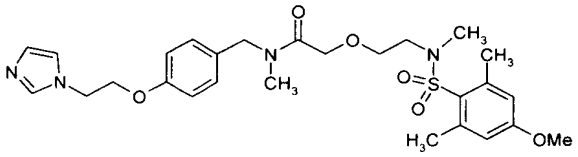


$C_{28}H_{41}ClN_4O_5S$ (581.17)

[M+H]+ = 581/583

HPLC (Método 6): Tempo de retenção = 2.77 min

Exemplo 357

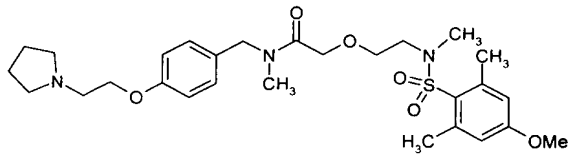


$C_{27}H_{36}N_4O_6S$ (544.66)

[M+H]+ = 545

HPLC (Método 6): Tempo de retenção = 2.59 min

Exemplo 358

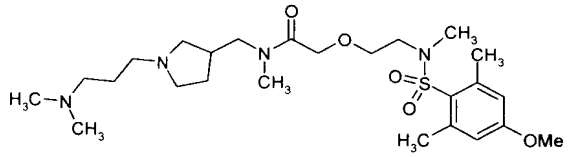


$C_{28}H_{41}N_3O_6S$ (547.71)

[M+H]+ = 548

HPLC (Método 6): Tempo de retenção = 2.59 min

Exemplo 359

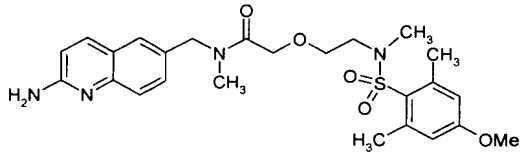


$C_{25}H_{44}N_4O_5S$ (512.71)

[M+H]+ = 513

HPLC (Método 6): Tempo de retenção = 1.94 min

Exemplo 360

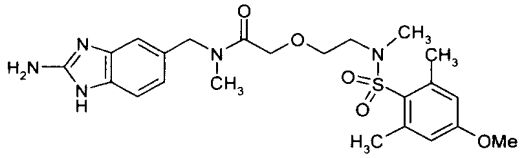


$C_{25}H_{32}N_4O_5S$ (500.61)

[M+H]+ = 501

HPLC (Método 6): Tempo de retenção = 2.41 min

Exemplo 361

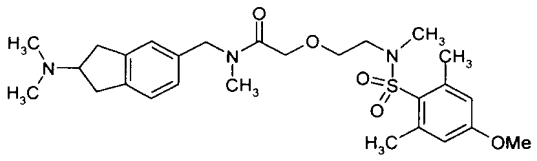


$C_{23}H_{31}N_5O_5S$ (489,59)

[M+H]+ = 490

HPLC (Método 6): Tempo de retenção = 2,46 min

Exemplo 362

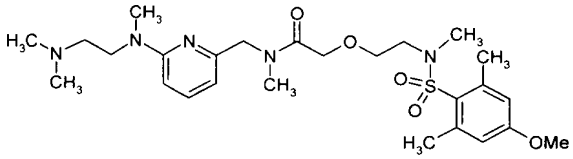


$C_{27}H_{39}N_3O_5S \times C_2HF_3O_2$ (631,71)

[M+H]+ = 518

HPLC (Método 6): Tempo de retenção = 2,54 min

Exemplo 363

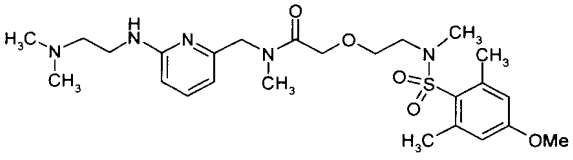


$C_{26}H_{41}N_5O_5S \times CH_2O_2$ (581.73)

[M+H]+ = 536

HPLC (Método 6): Tempo de retenção = 2.58 min

Exemplo 364

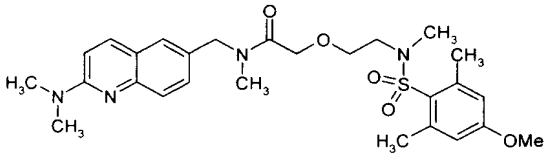


$C_{25}H_{39}N_5O_5S \times CH_2O_2$ (567,70)

[M+H]+ = 522

HPLC (Método 6): Tempo de retenção = 2,31 min

Exemplo 365

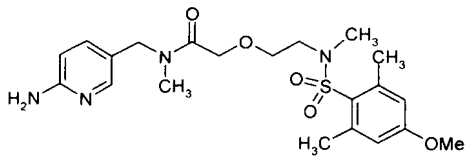


$C_{27}H_{36}N_4O_5S \times C_2HF_3O_2$ (642,69)

[M+H]+ = 529

HPLC (Método 6): Tempo de retenção = 2,56 min

Exemplo 366

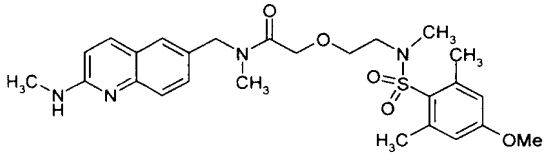


$C_{21}H_{30}N_4O_5S$ (450.55)

[M+H]+ = 451

HPLC (Método 6): Tempo de retenção = 2.31 min

Exemplo 367

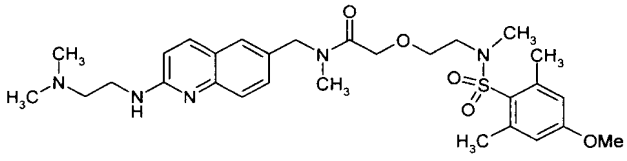


$C_{26}H_{34}N_4O_5S$ (514,64)

[M+H]+ = 515

HPLC (Método 6): Tempo de retenção = 2,51 min

Exemplo 368

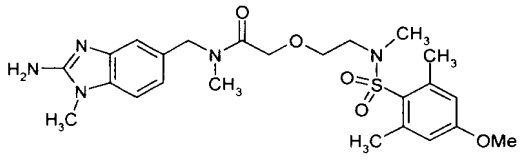


$C_{29}H_{41}N_5O_5S$ x $C_2HF_3O_2$ (685,76)

[M+H]+ = 572

HPLC (Método 6): Tempo de retenção = 2,14 min

Exemplo 369

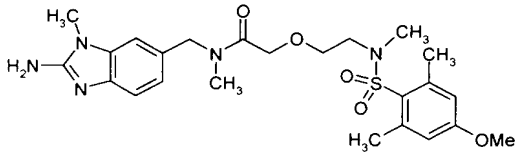


$C_{24}H_{33}N_5O_5S$ x $C_2HF_3O_2$ (617.64)

[M+H]+ = 504

HPLC (Método 9): Tempo de retenção = 1,61 min

Exemplo 370

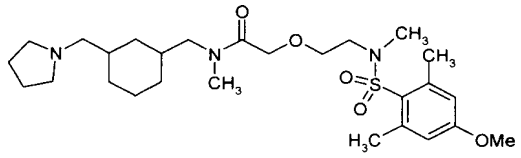


$C_{24}H_{33}N_5O_5S \times C_2HF_3O_2$ (617,64)

[M+H]+ = 504

HPLC (Método 9): Tempo de retenção = 1,59 min

Exemplo 371

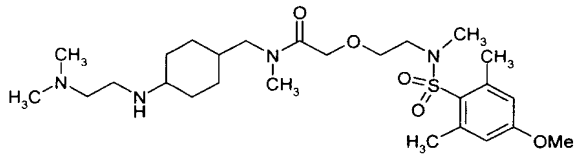


$C_{27}H_{45}N_3O_5S \times C_2HF_3O_2$ (637,75)

[M+H]+ = 524

HPLC (Método 9): Tempo de retenção = 1,70 min

Exemplo 372

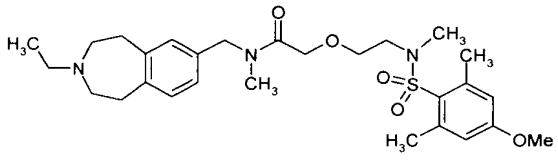


$C_{26}H_{46}N_4O_5S$ (526,73)

[M+H]+ = 527

HPLC (Método 5): Tempo de retenção = 1,43 min

Exemplo 373

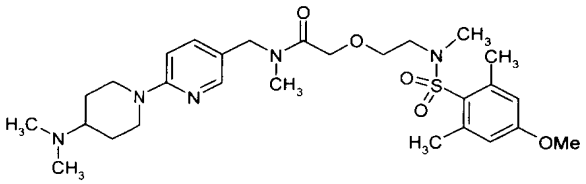


$C_{28}H_{41}N_3O_5S \times C_2HF_3O_2$ (645,73)

[M+H]+ = 532

HPLC (Método 5): Tempo de retenção = 1,56 min

Exemplo 374

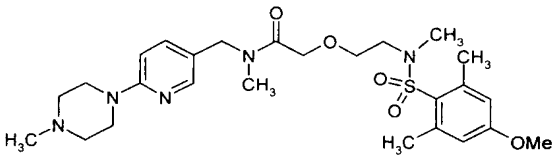


$C_{28}H_{43}N_5O_5S \times C_2HF_3O_2$ (675,76)

[M+H]+ = 562

HPLC (Método 5): Tempo de retenção = 1,41 min

Exemplo 375

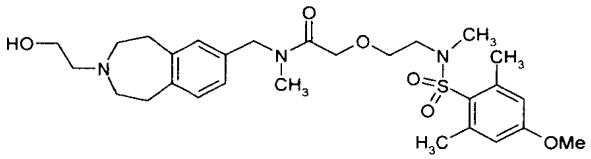


$C_{26}H_{39}N_5O_5S \times C_2HF_3O_2$ (647.71)

[M+H]+ = 534

HPLC (Método 5): Tempo de retenção = 1,42 min

Exemplo 376

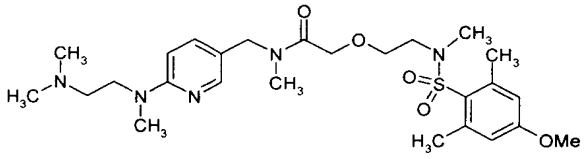


$C_{28}H_{41}N_3O_6S$ (547.71)

[M+H]+ = 548

HPLC (Método 5): Tempo de retenção = 1.53 min

Exemplo 377

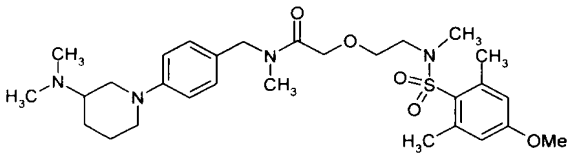


$C_{26}H_{41}N_5O_5S$ (535.70)

[M+H]+ = 536

HPLC (Método 5): Tempo de retenção = 1.42 min

Exemplo 378

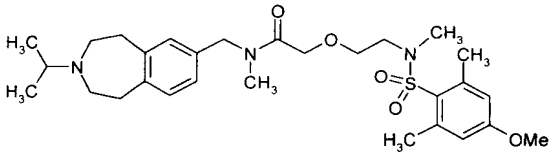


$C_{29}H_{44}N_4O_5S$ x HCl (597.21)

[M+H]+ = 561

HPLC (Método 7): Tempo de retenção = 1.91 min

Exemplo 379

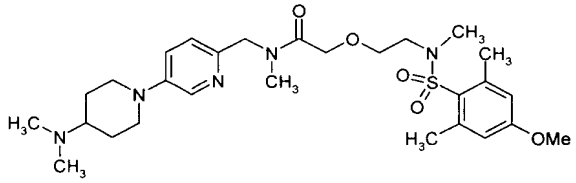


$C_{29}H_{43}N_3O_5S$ x $C_2HF_3O_2$ (659.76)

[M+H]+ = 546

HPLC (Método 5): Tempo de retenção = 1.59 min

Exemplo 380

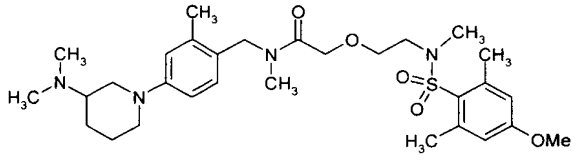


$C_{28}H_{43}N_5O_5S$ x $2C_2HF_3O_2$ (789.78)

[M+H]+ = 562

HPLC (Método 5): Tempo de retenção = 1.40 min

Exemplo 381

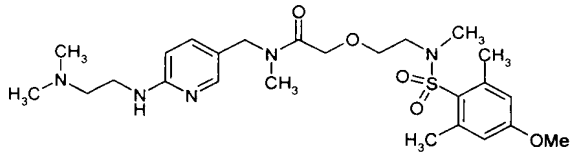


$C_{30}H_{46}N_4O_5S$ x $C_2HF_3O_2$ (688.80)

[M+H]+ = 575

HPLC (Método 5): Tempo de retenção = 1.56 min

Exemplo 382

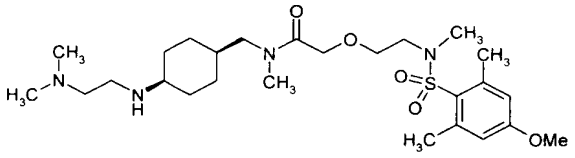


$C_{25}H_{39}N_5O_5S$ x 2HCl (594.60)

[M+H]+ = 522

HPLC (Método 5): Tempo de retenção = 1.40 min

Exemplo 383

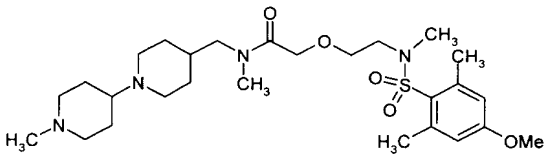


$C_{26}H_{46}N_4O_5S$ x 2HCl (599.65)

[M+H]+ = 527

HPLC (Método 5): Tempo de retenção = 1.41 min

Exemplo 384

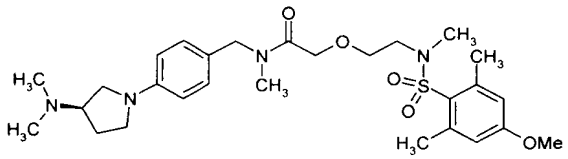


$C_{27}H_{46}N_4O_5S$ x HCl (575.20)

[M+H]+ = 539

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,01, Valor Rf = 0,35

Exemplo 385

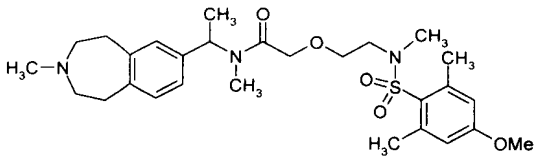


$C_{28}H_{42}N_4O_5S$ x HCl (583.18)

[M+H]+ = 547

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, Valor Rf = 0,32

Exemplo 386

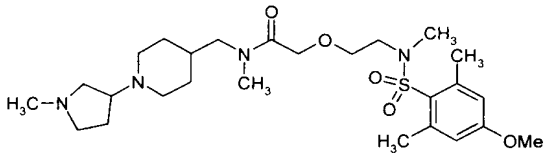


$C_{28}H_{41}N_3O_5S$ x HCl (568.17)

[M+H]+ = 532

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, Valor Rf = 0,35

Exemplo 387

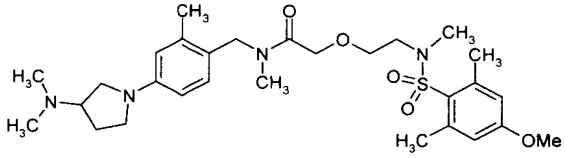


$C_{26}H_{44}N_4O_5S$ x HCl (561.18)

[M+H]+ = 525

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,01, Valor Rf = 0,12

Exemplo 388

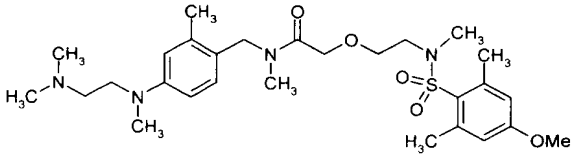


$C_{29}H_{44}N_4O_5S$ x HCl (597.21)

[M+H]+ = 561

DC: Gel de sílica, diclorometano/metanol 9:1, Valor Rf = 0,30

Exemplo 389

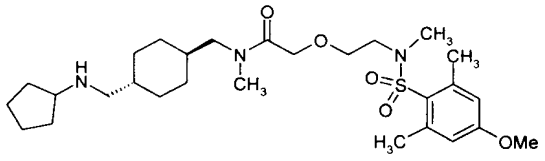


$C_{28}H_{44}N_4O_5S$ x HCl (585.20)

[M+H]+ = 549

DC: Gel de sílica, diclorometano/metanol 9:1, Valor Rf = 0,15

Exemplo 390

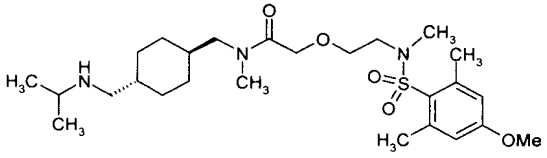


$C_{28}H_{47}N_3O_5S$ x HCl (574.22)

[M+H]+ = 538

DC: Gel de sílica, diclorometano/metanol 9:1, Valor Rf = 0,05

Exemplo 391

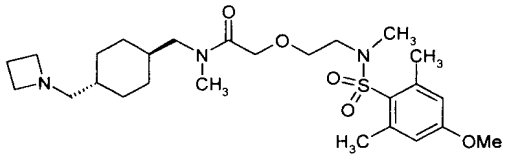


$C_{26}H_{45}N_3O_5S$ x HCl (548.18)

[M+H]+ = 512

HPLC (Método 5): Tempo de retenção = 1.56 min

Exemplo 392

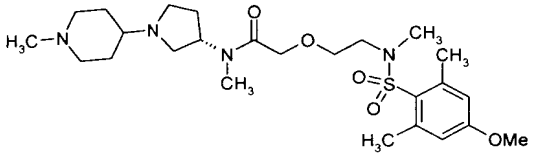


$C_{26}H_{43}N_3O_5S$ x HCl (546.16)

[M+H]+ = 510

DC: Gel de sílica, diclorometano/metanol 9:1, Valor Rf = 0,05

Exemplo 393

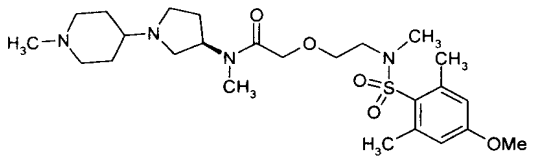


$C_{25}H_{42}N_4O_5S$ x 2HCl (583.61)

[M+H]+ = 511

DC: Gel de sílica, diclorometano/etanol/amoníaco 9:1:0,1, Valor Rf = 0,22

Exemplo 394

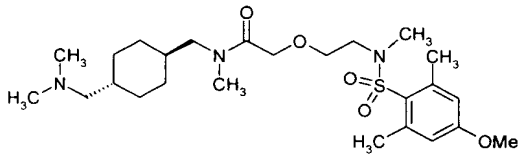


$C_{25}H_{42}N_4O_5S$ x 2HCl (583.61)

[M+H]+ = 511

HPLC (Método 5): Tempo de retenção = 1.37 min

Exemplo 395

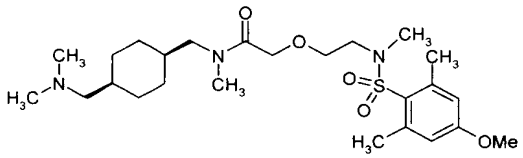


$C_{25}H_{43}N_3O_5S$ x HCl (534.15)

[M+H]+ = 498

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,01, Valor Rf = 0,58

Exemplo 396

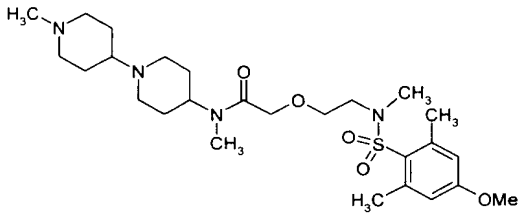


$C_{25}H_{43}N_3O_5S$ x HCl (534.15)

[M+H]+ = 498

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,01, Valor Rf = 0,57

Exemplo 397

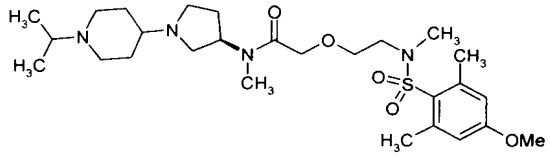


$C_{26}H_{44}N_4O_5S$ x 2HCl (597.64)

[M+H]+ = 525

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,2, Valor Rf = 0,52

Exemplo 398

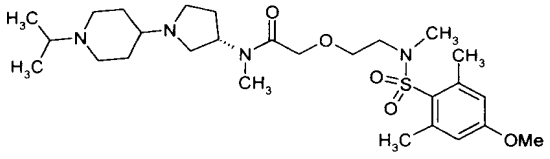


$C_{27}H_{46}N_4O_5S$ x 2HCl (611.67)

[M+H]+ = 539

HPLC (Método 12): Tempo de retenção = 2.45 min

Exemplo 399

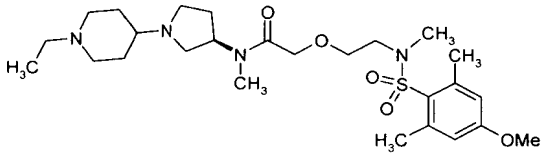


$C_{27}H_{46}N_4O_5S$ x 2HCl (611.67)

[M+H]+ = 539

HPLC (Método 12): Tempo de retenção = 2.35 min

Exemplo 400

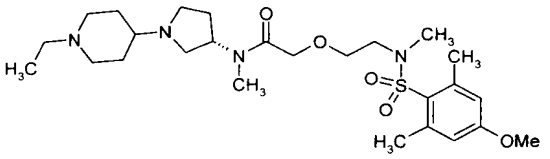


$C_{26}H_{44}N_4O_5S$ x 2HCl (597.64)

[M+H]+ = 525

HPLC (Método 12): Tempo de retenção = 2.3 min

Exemplo 401

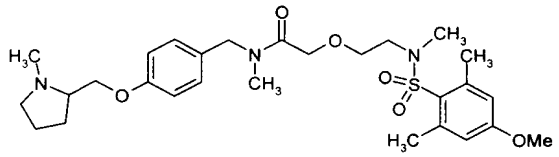


$C_{26}H_{44}N_4O_5S$ x 2HCl (597.64)

[M+H]+ = 525

HPLC (Método 12): Tempo de retenção = 2.3 min

Exemplo 402

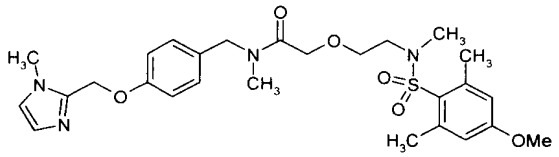


$C_{28}H_{41}N_3O_6S$ (547.71)

[M+H]+ = 548

HPLC (Método 9): Tempo de retenção = 1.7 min

Exemplo 403

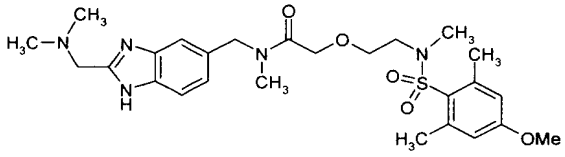


$C_{27}H_{36}N_4O_6S$ (544.66)

[M+H]+ = 545

HPLC (Método 9): Tempo de retenção = 1.69 min

Exemplo 404

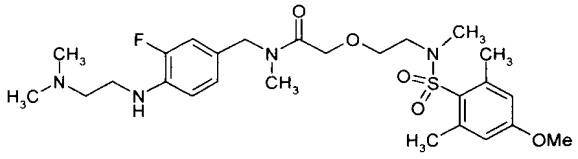


$C_{26}H_{37}N_5O_5S$ (531.67)

[M+H]+ = 532

HPLC (Método 6): Tempo de retenção = 1.56 min

Exemplo 405

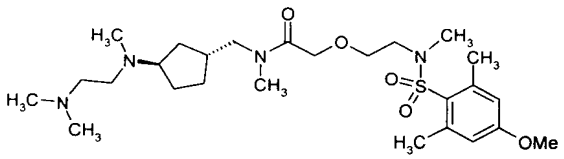


$C_{26}H_{39}FN_4O_5S$ (538.68)

[M+H]+ = 539

HPLC (Método 6): Tempo de retenção = 2.60 min

Exemplo 406

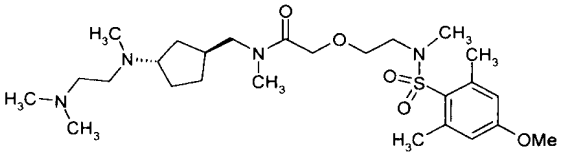


$C_{26}H_{46}N_4O_5S$ x 2HCl (599.65)

[M+H]+ = 527

HPLC (Método 7): Tempo de retenção = 1.78 min

Exemplo 407

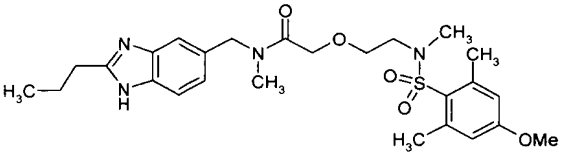


$C_{26}H_{46}N_4O_5S$ x 2HCl (599.65)

[M+H]+ = 527

HPLC (Método 7): Tempo de retenção = 1.77 min

Exemplo 408

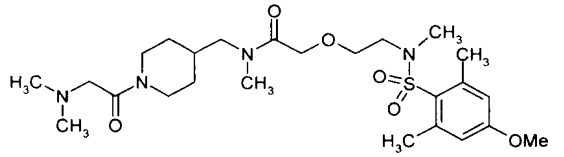


$C_{26}H_{36}N_4O_5S$ (516.65)

[M+H]+ = 517

HPLC (Método 9): Tempo de retenção = 1.65 min

Exemplo 409

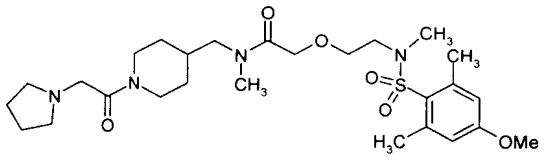


$C_{25}H_{42}N_4O_6S$ x $C_2HF_3O_2$ (640.71)

[M+H]+ = 527

HPLC (Método 9): Tempo de retenção = 1.55 min

Exemplo 410

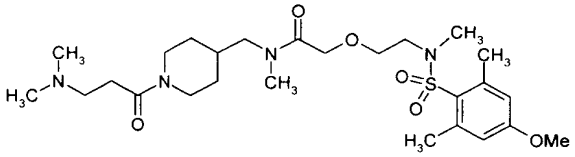


$C_{27}H_{44}N_4O_6S \times C_2HF_3O_2$ (666.75)

[M+H]+ = 553

HPLC (Método 9): Tempo de retenção = 1.57 min

Exemplo 411

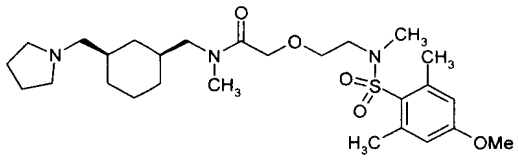


$C_{26}H_{44}N_4O_6S \times C_2HF_3O_2$ (654.74)

[M+H]+ = 541

HPLC (Método 9): Tempo de retenção = 1.57 min

Exemplo 412

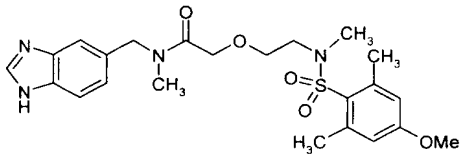


$C_{27}H_{45}N_3O_5S \times C_2HF_3O_2$ (637.75)

[M+H]+ = 524

HPLC (Método 6): Tempo de retenção = 1.71 min

Exemplo 413

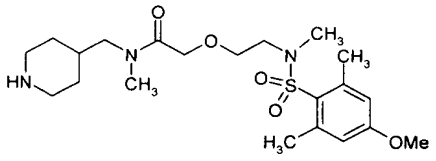


$C_{23}H_{30}N_4O_5S$ (474.57)

[M+H]+ = 475

HPLC (Método 9): Tempo de retenção = 1.53 min

Exemplo 414

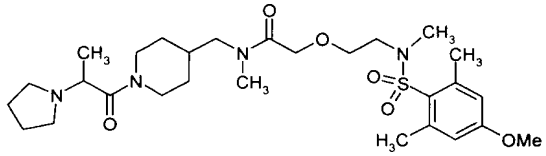


$C_{21}H_{35}N_3O_5S$ (441.59)

[M+H]+ = 442

HPLC (Método 9): Tempo de retenção = 1.48 min

Exemplo 415

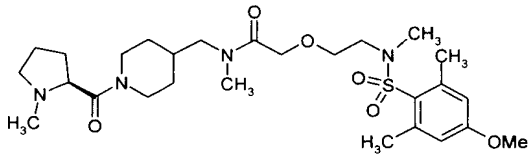


$C_{28}H_{46}N_4O_6S \times C_2HF_3O_2$ (680.78)

[M+H]+ = 567

HPLC (Método 9): Tempo de retenção = 1.60 min

Exemplo 416

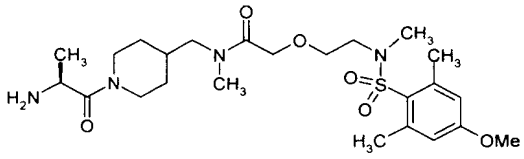


$C_{27}H_{44}N_4O_6S \times C_2HF_3O_2$ (666.75)

[M+H]+ = 553

HPLC (Método 9): Tempo de retenção = 1.57 min

Exemplo 417

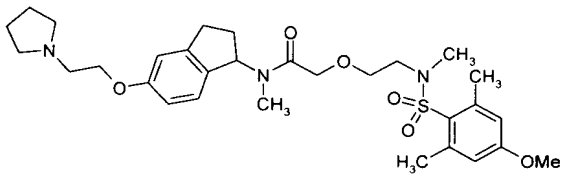


$C_{24}H_{40}N_4O_6S \times C_2HF_3O_2$ (626.69)

[M+H]+ = 513

HPLC (Método 9): Tempo de retenção = 1.53 min

Exemplo 418

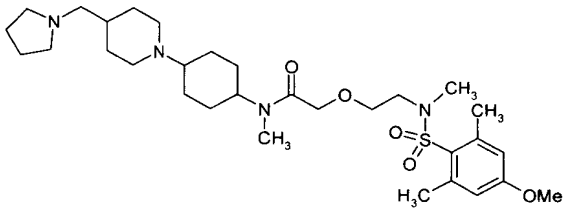


$C_{30}H_{43}N_3O_6S \times CH_2O_2$ (619.77)

[M+H]+ = 574

HPLC (Método 9): Tempo de retenção = 1.73 min

Exemplo 419

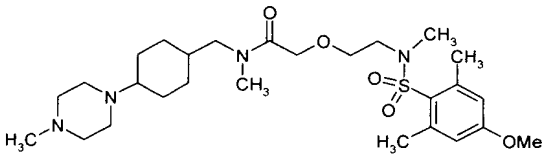


$C_{31}H_{52}N_4O_5S \times C_2HF_3O_2$ (706.86)

[M+H]+ = 593

HPLC (Método 9): Tempo de retenção = 1.34 min

Exemplo 420

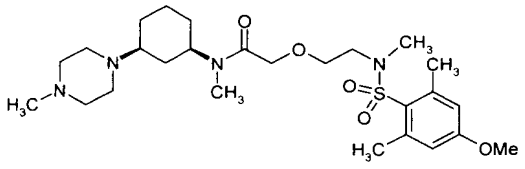


$C_{27}H_{46}N_4O_5S$ (538.74)

[M+H]+ = 539

HPLC (Método 9): Tempo de retenção = 1.43 min

Exemplo 421

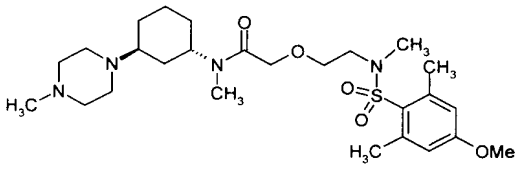


$C_{26}H_{44}N_4O_5S \times C_2HF_3O_2$ (638.74)

[M+H]+ = 525

HPLC (Método 6): Tempo de retenção = 1.53 min

Exemplo 422

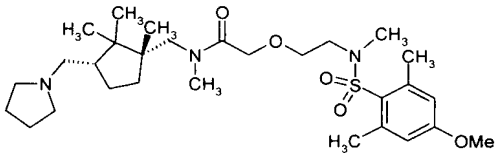


$C_{26}H_{44}N_4O_5S \times C_2HF_3O_2$ (638.74)

[M+H]+ = 525

HPLC (Método 6): Tempo de retenção = 1.41 min

Exemplo 423

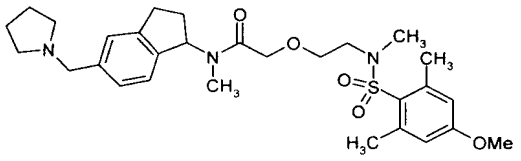


$C_{29}H_{49}N_3O_5S \times C_2HF_3O_2$ (665.81)

[M+H]+ = 552

HPLC (Método 9): Tempo de retenção = 1.74 min

Exemplo 424

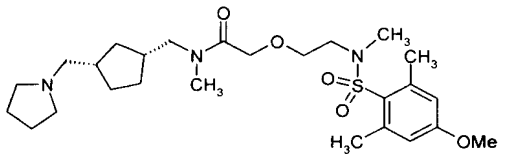


$C_{29}H_{41}N_3O_5S$ (543.72)

[M+H]+ = 544

HPLC (Método 6): Tempo de retenção = 1.73 min

Exemplo 425

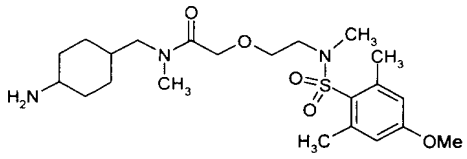


$C_{26}H_{43}N_3O_5S \times C_2HF_3O_2$ (623.73)

[M+H]+ = 510

HPLC (Método 9): Tempo de retenção = 1.63 min

Exemplo 426

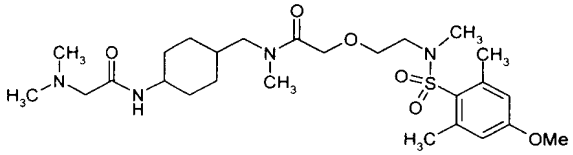


$C_{22}H_{37}N_3O_5S$ (455.61)

[M+H]+ = 456

HPLC (Método 6): Tempo de retenção = 1.55 min

Exemplo 427

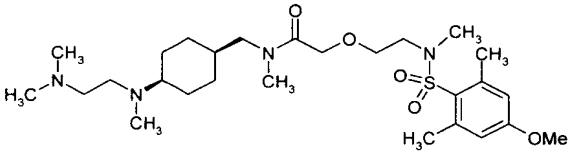


$C_{26}H_{44}N_4O_6S$ (540.72)

[M+H]+ = 541

HPLC (Método 6): Tempo de retenção = 1.59 min

Exemplo 428

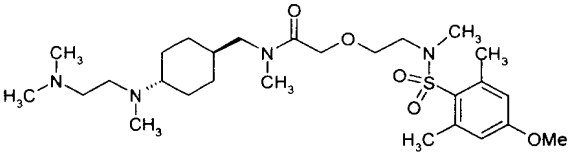


$C_{27}H_{48}N_4O_5S$ x 2HCl (613.68)

[M+H]+ = 541

HPLC (Método 7): Tempo de retenção = 1.65 min

Exemplo 429

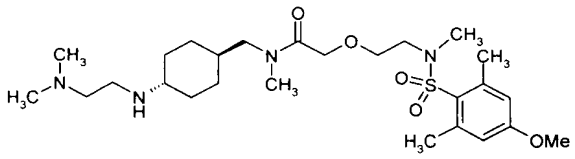


$C_{27}H_{48}N_4O_5S$ x 2HCl (613.68)

[M+H]+ = 541

HPLC (Método 11): Tempo de retenção = 1.64 min

Exemplo 430

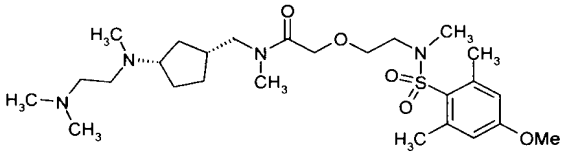


$C_{26}H_{46}N_4O_5S$ x $2C_2HF_3O_2$ (754.78)

[M+H]+ = 527

HPLC (Método 5): Tempo de retenção = 1.16 min

Exemplo 431

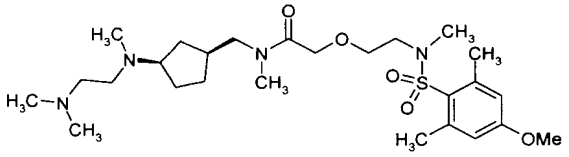


$C_{26}H_{46}N_4O_5S$ x 2HCl (599.65)

[M+H]+ = 527

HPLC (Método 7): Tempo de retenção = 1.82 min

Exemplo 432

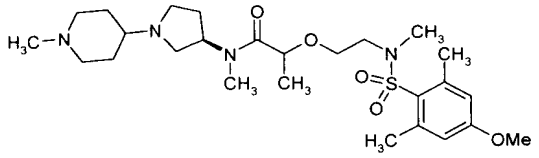


$C_{26}H_{46}N_4O_5S$ x 2HCl (599.65)

[M+H]+ = 527

HPLC (Método 7): Tempo de retenção = 1.82 min

Exemplo 433

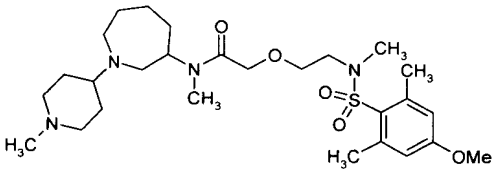


$C_{26}H_{44}N_4O_5S$ x 2HCl (597.64)

[M+H]+ = 525

HPLC (Método 12): Tempo de retenção = 2.3 min

Exemplo 434

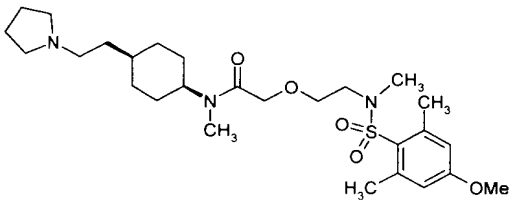


$C_{27}H_{46}N_4O_5S$ x 2HCl (611.67)

[M+H]+ = 539

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,2, Valor Rf = 0,65

Exemplo 435

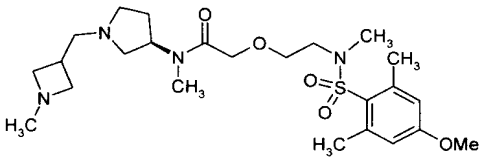


$C_{27}H_{45}N_3O_5S$ (523.73)

[M+H]+ = 524

HPLC (Método 6): Tempo de retenção = 1.29 min

Exemplo 436

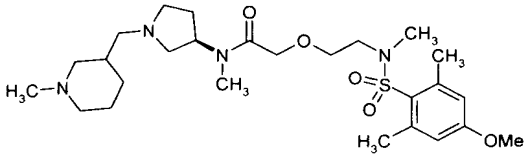


$C_{24}H_{40}N_4O_5S$ x CH_2O_2 (542.69)

[M+H]+ = 497

HPLC (Método 9): Tempo de retenção = 1.25 min

Exemplo 437

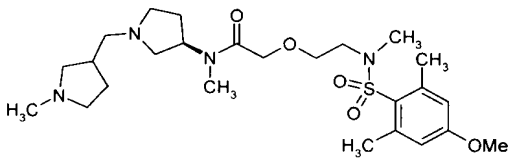


$C_{26}H_{44}N_4O_5S$ x CH_2O_2 (570.74)

[M+H]+ = 525

HPLC (Método 9): Tempo de retenção = 1.31 min

Exemplo 438

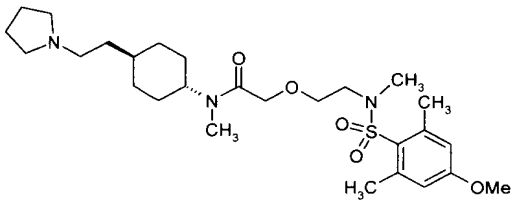


$C_{25}H_{42}N_4O_5S$ x CH_2O_2 (556.72)

[M+H]+ = 511

HPLC (Método 9): Tempo de retenção = 1.31 min

Exemplo 439

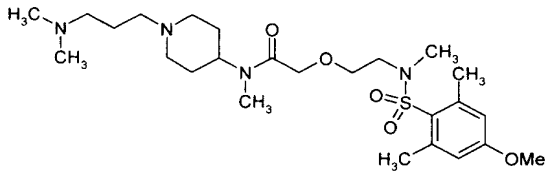


$C_{27}H_{45}N_3O_5S$ (523.73)

[M+H]+ = 524

HPLC (Método 6): Tempo de retenção = 1.67 min

Exemplo 440

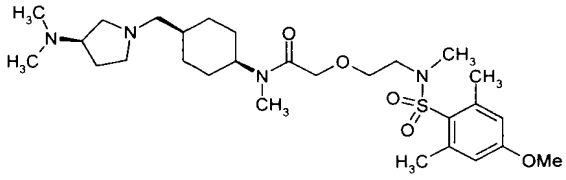


$C_{25}H_{44}N_4O_5S$ x $C_2HF_3O_2$ (626.73)

[M+H]+ = 513

HPLC (Método 9): Tempo de retenção = 1.29 min

Exemplo 441

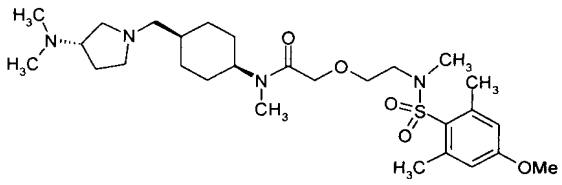


$C_{28}H_{48}N_4O_5S$ x 2 HCl (625.69)

[M+H]+ = 553

HPLC (Método 9): Tempo de retenção = 1.35 min

Exemplo 442

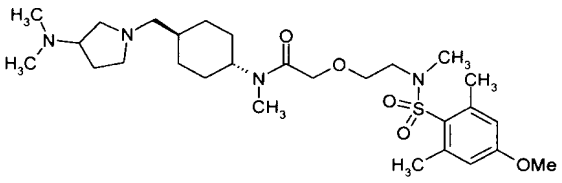


$C_{28}H_{48}N_4O_5S$ x 2 HCl (625.69)

[M+H]+ = 553

HPLC (Método 9): Tempo de retenção = 1.32 min

Exemplo 443

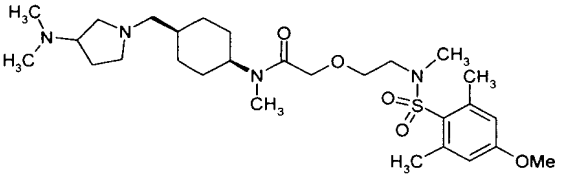


$C_{28}H_{48}N_4O_5S$ (552.77)

[M+H]+ = 553

HPLC (Método 9): Tempo de retenção = 1.37 min

Exemplo 444

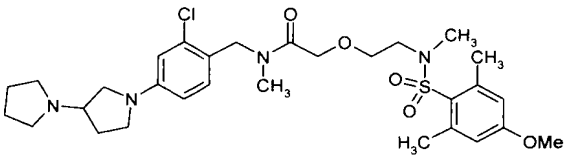


$C_{28}H_{48}N_4O_5S$ x CH_2O_2 (598.80)

[M+H]+ = 553

HPLC (Método 9): Tempo de retenção = 1.35 min

Exemplo 445

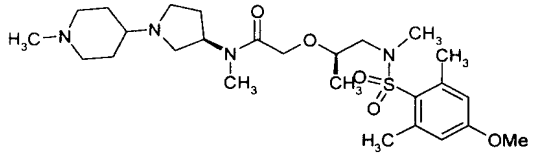


$C_{30}H_{43}ClN_4O_5S$ (607.21)

[M+H]+ = 608

HPLC (Método 6): Tempo de retenção = 1.80 min

Exemplo 446

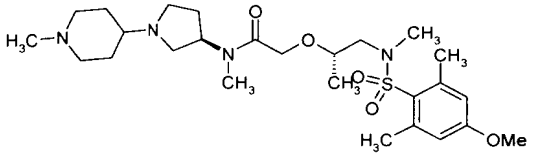


$C_{26}H_{44}N_4O_5S$ x 2HCl (597.64)

[M+H]+ = 525

HPLC (Método 12): Tempo de retenção = 2.4 min

Exemplo 447

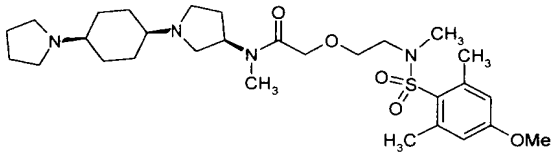


$C_{26}H_{44}N_4O_5S$ x 2HCl (597.64)

[M+H]+ = 525

HPLC (Método 12): Tempo de retenção = 2.4 min

Exemplo 448

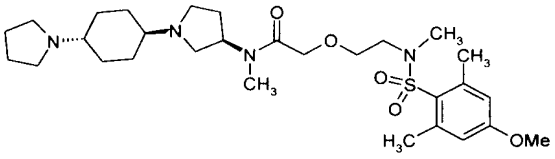


$C_{29}H_{48}N_4O_5S$ x 2HCl (637.70)

[M+H]+ = 565

HPLC (Método 12): Tempo de retenção = 2.3 min

Exemplo 449

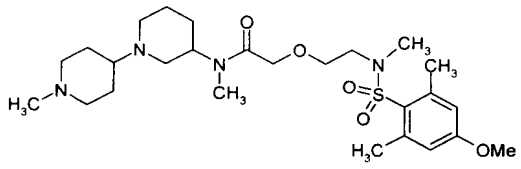


$C_{29}H_{48}N_4O_5S$ x 2HCl (637.70)

[M+H]+ = 565

HPLC (Método 12): Tempo de retenção = 2.92 min

Exemplo 450

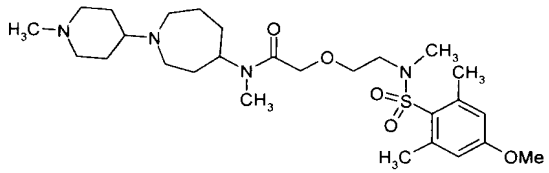


$C_{26}H_{44}N_4O_5S$ x 2HCl (597.64)

[M+H]+ = 525

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,2, Valor Rf = 0,60

Exemplo 451

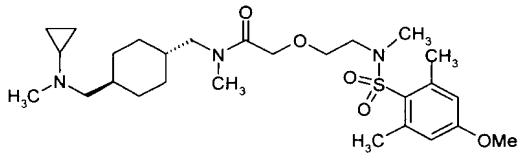


$C_{27}H_{46}N_4O_5S$ x 2HCl (611.67)

[M+H]+ = 539

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,2, Valor Rf = 0,62

Exemplo 452

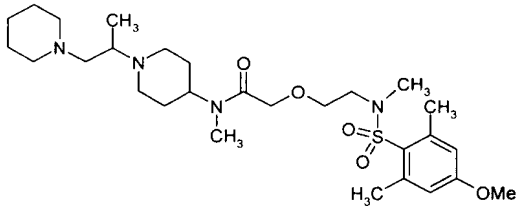


$C_{27}H_{45}N_3O_5S$ x HCl (560.19)

[M+H]+ = 524

HPLC (Método 12): Tempo de retenção = 3.01 min

Exemplo 453

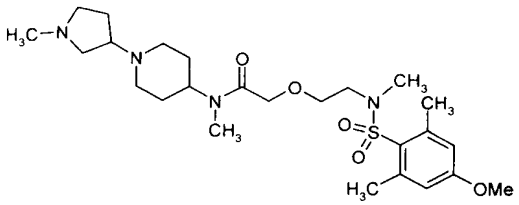


$C_{28}H_{48}N_4O_5S$ x 2HCl (625.69)

[M+H]+ = 553

HPLC (Método 12): Tempo de retenção = 2.45 min

Exemplo 454

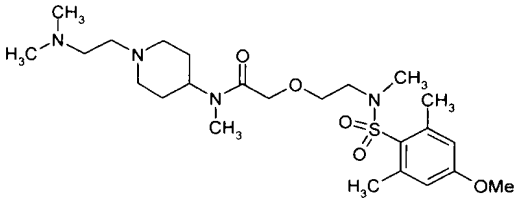


$C_{25}H_{42}N_4O_5S$ x 2HCl (583.61)

[M+H]+ = 511

HPLC (Método 12): Tempo de retenção = 2.33 min

Exemplo 455

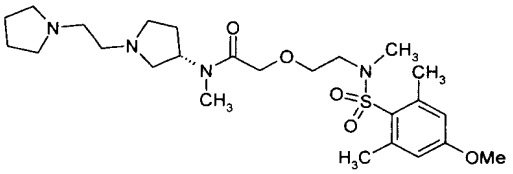


$C_{24}H_{42}N_4O_5S$ x $C_2HF_3O_2$ (612.70)

[M+H]+ = 499

HPLC (Método 9): Tempo de retenção = 1.32 min

Exemplo 456

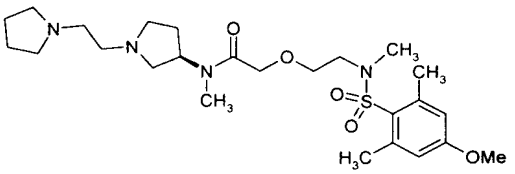


$C_{25}H_{42}N_4O_5S$ x $2C_2HF_3O_2$ (738.74)

[M+H]+ = 511

HPLC (Método 9): Tempo de retenção = 1.24 min

Exemplo 457

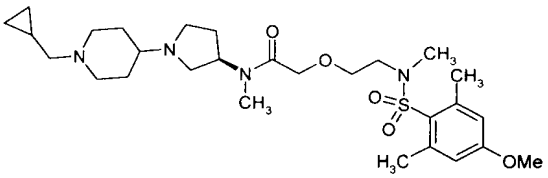


$C_{25}H_{42}N_4O_5S$ x $2C_2HF_3O_2$ (738.74)

[M+H]+ = 511

HPLC (Método 9): Tempo de retenção = 1.27 min

Exemplo 458

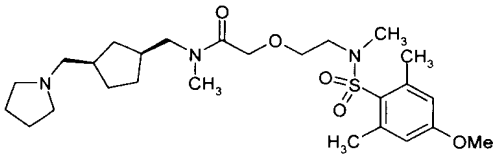


$C_{28}H_{46}N_4O_5S$ x CH_2O_2 (596.78)

[M+H]+ = 551

HPLC (Método 6): Tempo de retenção = 1.31 min

Exemplo 459

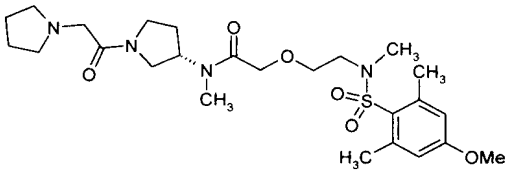


$C_{26}H_{43}N_3O_5S$ x $C_2HF_3O_2$ (623.73)

[M+H]+ = 510

HPLC (Método 9): Tempo de retenção = 1.62 min

Exemplo 460

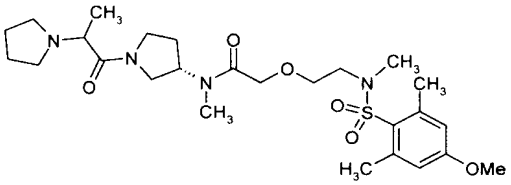


$C_{25}H_{40}N_4O_6S$ x $C_2HF_3O_2$ (638.70)

[M+H]+ = 525

HPLC (Método 9): Tempo de retenção = 1.49 min

Exemplo 461

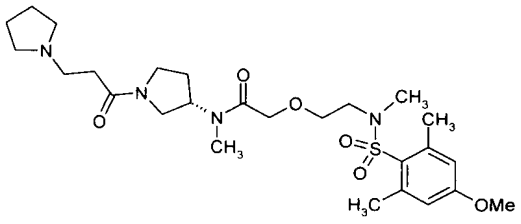


$C_{26}H_{42}N_4O_6S$ x $C_2HF_3O_2$ (652.72)

[M+H]+ = 539

HPLC (Método 9): Tempo de retenção = 1.51 min

Exemplo 462

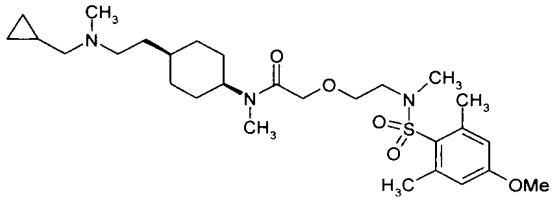


$C_{26}H_{42}N_4O_6S \times C_2HF_3O_2$ (652.72)

[M+H]+ = 539

HPLC (Método 9): Tempo de retenção = 1.52 min

Exemplo 463

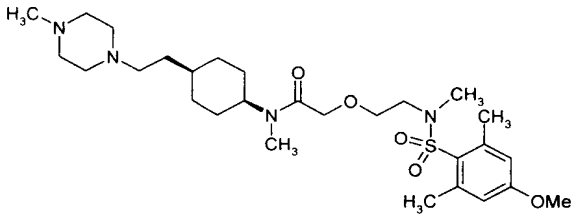


$C_{28}H_{47}N_3O_5S$ (537.76)

[M+H]+ = 538

HPLC (Método 9): Tempo de retenção = 1.71 min

Exemplo 464

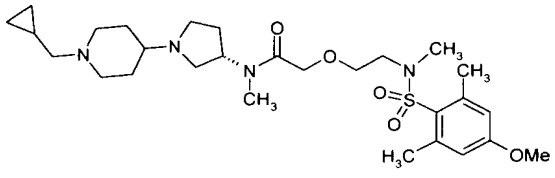


$C_{28}H_{48}N_4O_5S$ (552.77)

[M+H]+ = 553

HPLC (Método 9): Tempo de retenção = 1.39 min

Exemplo 465

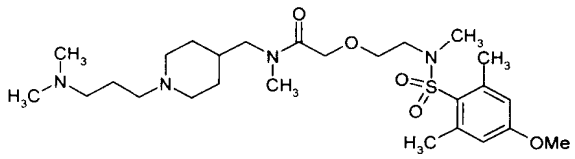


$C_{28}H_{46}N_4O_5S \times CH_2O_2$ (596.78)

[M+H]+ = 551

HPLC (Método 6): Tiempo de retención = 1.32 min

Exemplo 466

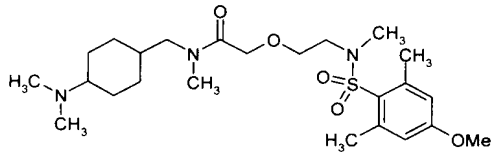


$C_{26}H_{46}N_4O_5S$ (526.73)

[M+H]+ = 527

HPLC (Método 9): Tiempo de retención = 1.27 min

Exemplo 467

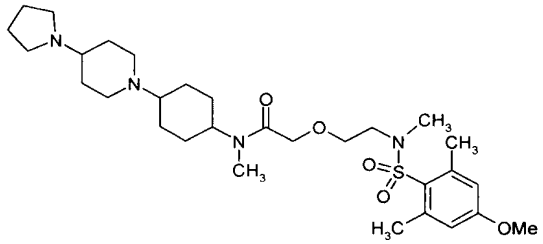


$C_{24}H_{41}N_3O_5S$ (483.67)

[M+H]+ = 484

HPLC (Método 6): Tiempo de retención = 1.60 min

Exemplo 468

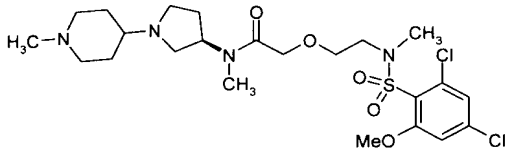


$C_{30}H_{50}N_4O_5S$ x CH_2O_2 (624.83)

[M+H]+ = 579

HPLC (Método 6): Tiempo de retención = 1.31 min

Exemplo 469

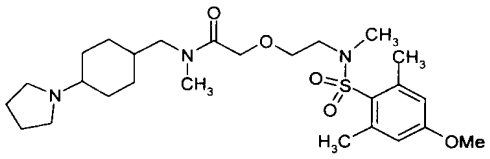


$C_{23}H_{36}Cl_2N_4O_5S$ (551.53)

[M+H]+ = 551/553/555

HPLC (Método 9): Tiempo de retención = 1.30 min

Exemplo 470

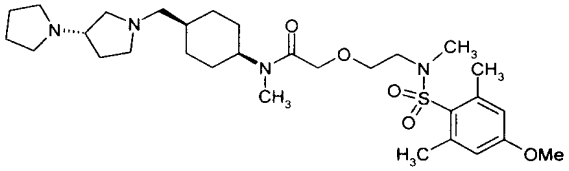


$C_{26}H_{43}N_3O_5S$ (509.70)

[M+H]+ = 510

HPLC (Método 6): Tempo de retenção = 1.67 min

Exemplo 471

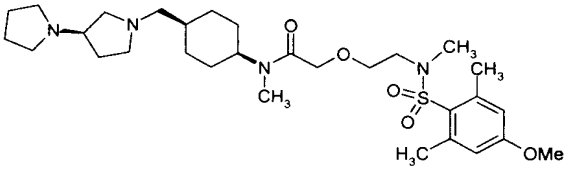


$C_{30}H_{50}N_4O_5S \times C_2HF_3O_2$ (692.83)

[M+H]+ = 579

HPLC (Método 9): Tempo de retenção = 1.39 min

Exemplo 472

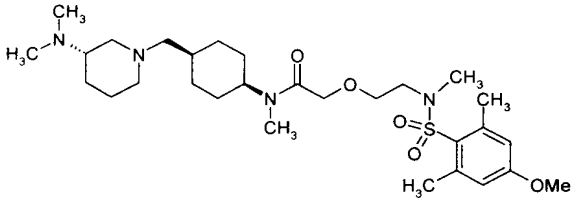


$C_{30}H_{50}N_4O_5S \times C_2HF_3O_2$ (692.83)

[M+H]+ = 579

HPLC (Método 9): Tempo de retenção = 1.39 min

Exemplo 473

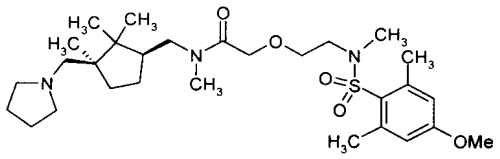


$C_{29}H_{50}N_4O_5S \times C_2HF_3O_2$ (680.82)

[M+H]+ = 567

HPLC (Método 9): Tempo de retenção = 1.40 min

Exemplo 474

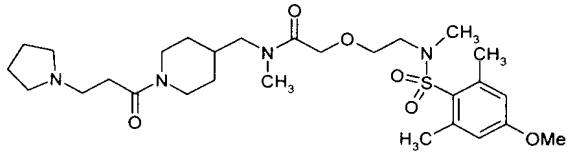


$C_{29}H_{49}N_3O_5S$ (551.78)

[M+H]+ = 552

HPLC (Método 9): Tempo de retenção = 1.72 min

Exemplo 475

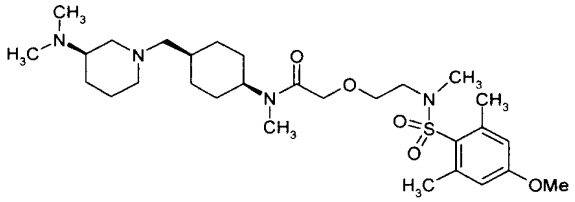


$C_{28}H_{46}N_4O_6S \times C_2HF_3O_2$ (680.78)

[M+H]+ = 567

HPLC (Método 9): Tempo de retenção = 1.60 min

Exemplo 476

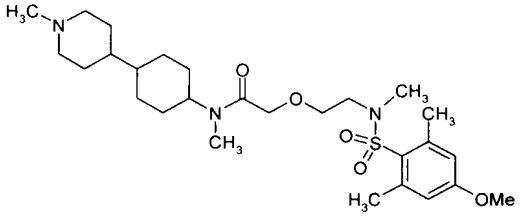


$C_{29}H_{50}N_4O_5S \times C_2HF_3O_2$ (680.82)

[M+H]+ = 567

HPLC (Método 9): Tempo de retenção = 1.41 min

Exemplo 477

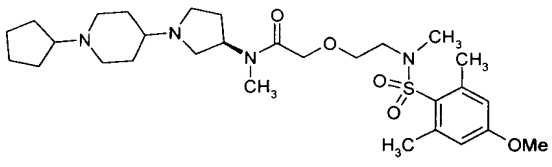


$C_{27}H_{45}N_3O_5S \times C_2HF_3O_2$ (637.75)

[M+H]+ = 524

HPLC (Método 9): Tempo de retenção = 1.69 min

Exemplo 478

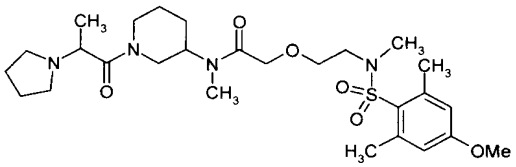


$C_{29}H_{48}N_4O_5S$ x 2HCl (637.70)

[M+H]+ = 565

HPLC (Método 12): Tempo de retenção = 2.4 min

Exemplo 479

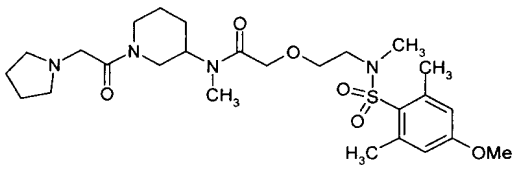


$C_{27}H_{44}N_4O_6S$ x $C_2HF_3O_2$ (666.75)

[M+H]+ = 553

HPLC (Método 9): Tempo de retenção = 1,61 min

Exemplo 480

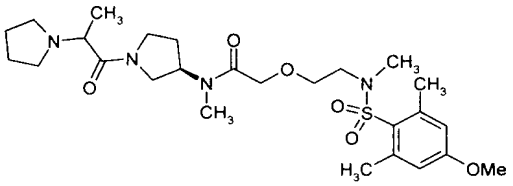


$C_{26}H_{42}N_4O_6S$ x $C_2HF_3O_2$ (652.72)

[M+H]+ = 539

HPLC (Método 9): Tempo de retenção = 1.60 min

Exemplo 481

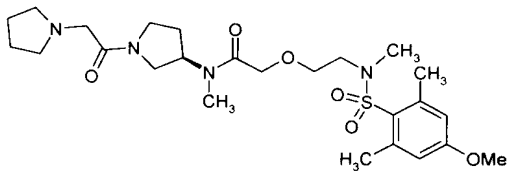


$C_{26}H_{42}N_4O_6S$ (538.70)

[M+H]+ = 539

HPLC (Método 9): Tempo de retenção = 1.47 min

Exemplo 482

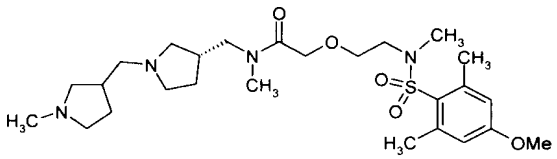


$C_{25}H_{40}N_4O_6S$ (524.67)

[M+H]+ = 525

HPLC (Método 9): Tempo de retenção = 1.48 min

Exemplo 575

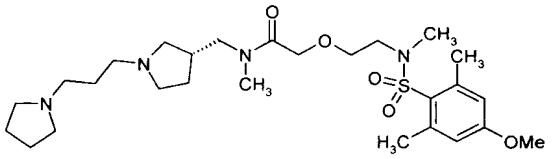


$C_{26}H_{44}N_4O_5S$ (524.72)

[M+H]+ = 525

HPLC (Método 9): Tempo de retenção = 1.30 min

Exemplo 576

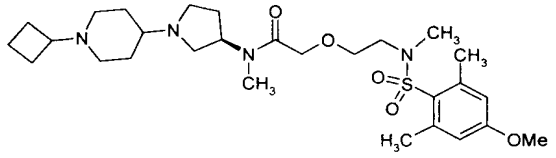


$C_{27}H_{46}N_4O_5S$ (538.74)

[M+H]+ = 539

HPLC (Método 9): Tempo de retenção = 1.34 min

Exemplo 577

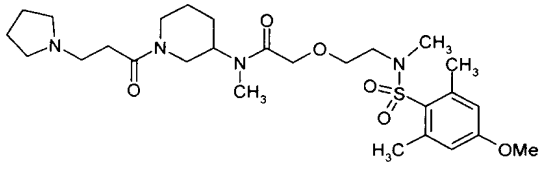


$C_{28}H_{46}N_4O_5S$ x 2HCl (623.68)

[M+H]+ = 551

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,2, Valor Rf = 0,71

Exemplo 578

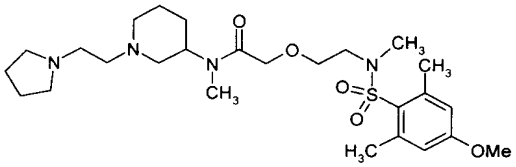


$C_{27}H_{44}N_4O_6S \times C_2HF_3O_2$ (666.75)

[M+H]+ = 553

HPLC (Método 9): Tempo de retenção = 1.62 min

Exemplo 579

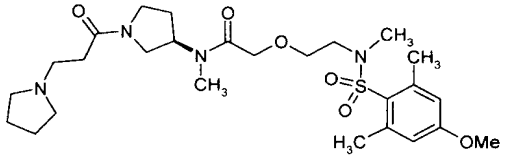


$C_{26}H_{44}N_4O_5S \times 2C_2HF_3O_2$ (752.76)

[M+H]+ = 525

HPLC (Método 9): Tempo de retenção = 1.33 min

Exemplo 580

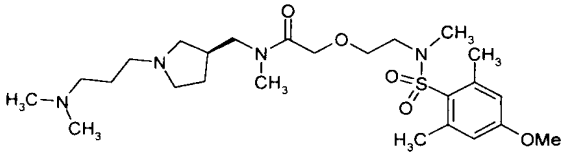


$C_{26}H_{42}N_4O_6S \times C_2HF_3O_2$ (652.72)

[M+H]+ = 539

HPLC (Método 9): Tempo de retenção = 1.50 min

Exemplo 581

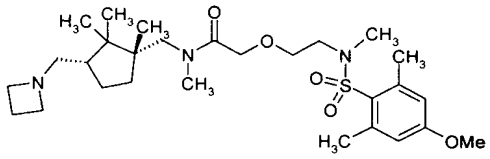


$C_{25}H_{44}N_4O_5S$ (512.71)

[M+H]+ = 513

HPLC (Método 9): Tempo de retenção = 1.27 min

Exemplo 582

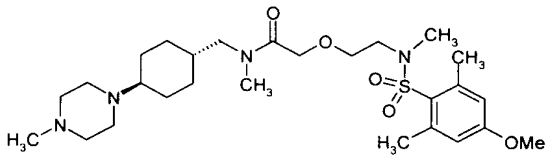


$C_{28}H_{47}N_3O_5S \times C_2HF_3O_2$ (651.78)

[M+H]+ = 538

HPLC (Método 9): Tempo de retenção = 1.71 min

Exemplo 583

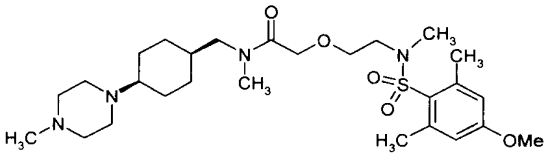


$C_{27}H_{46}N_4O_5S$ (538.74)

[M+H]+ = 539

HPLC (Método 9): Tempo de retenção = 1.37 min

Exemplo 584

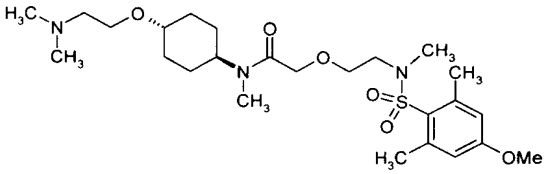


$C_{27}H_{46}N_4O_5S$ (538.74)

[M+H]+ = 539

HPLC (Método 9): Tempo de retenção = 1.44 min

Exemplo 585

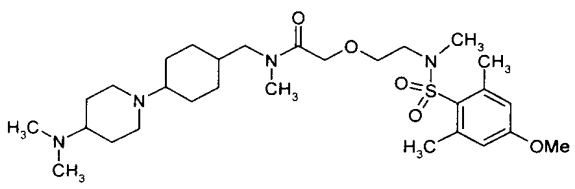


$C_{25}H_{43}N_3O_6S \times HCl$ (550.15)

[M+H]+ = 514

HPLC (Método 5): Tempo de retenção = 1.34 min

Exemplo 586

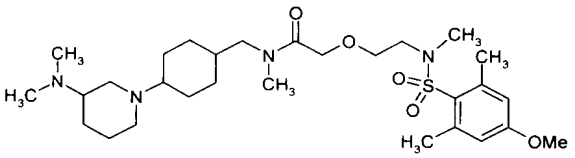


$C_{29}H_{50}N_4O_5S$ x 2HCl (639.72)

[M+H]+ = 567

HPLC (Método 5): Tempo de retenção = 1.21 min

Exemplo 587

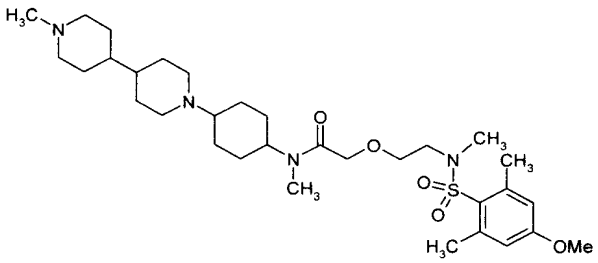


$C_{29}H_{50}N_4O_5S$ x 2HCl (639.72)

[M+H]+ = 567

HPLC (Método 5): Tempo de retenção = 1.20 min

Exemplo 588

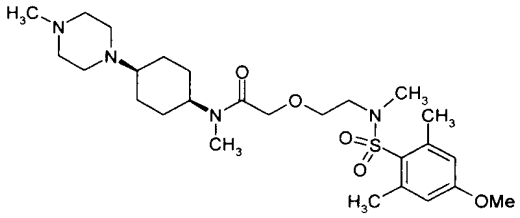


$C_{32}H_{54}N_4O_5S$ x $C_2HF_3O_2$ (720.88)

[M+H]+ = 607

HPLC (Método 9): Tempo de retenção = 1.37 min

Exemplo 589

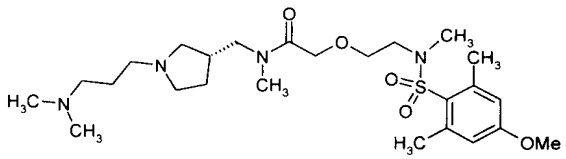


$C_{26}H_{44}N_4O_5S$ x $2C_2HF_3O_2$ (752.76)

[M+H]+ = 525

HPLC (Método 9): Tempo de retenção = 1.41 min

Exemplo 590

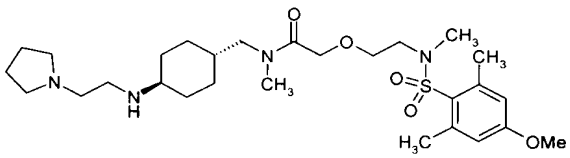


$C_{25}H_{44}N_4O_5S$ (512.71)

[M+H]+ = 513

HPLC (Método 9): Tempo de retenção = 1.35 min

Exemplo 591

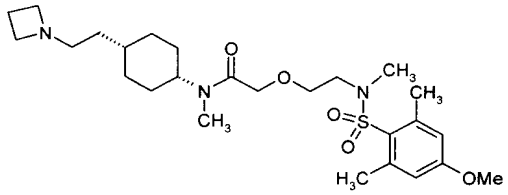


$C_{28}H_{48}N_4O_5S \times 2C_2HF_3O_2$ (780.82)

[M+H]+ = 553

HPLC (Método 9): Tempo de retenção = 1.40 min

Exemplo 592

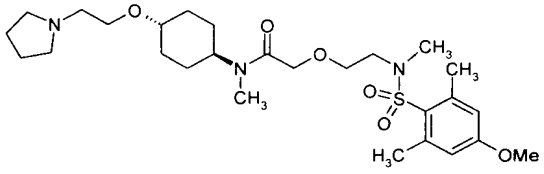


$C_{26}H_{43}N_3O_5S$ (509.70)

[M+H]+ = 510

HPLC (Método 9): Tempo de retenção = 1.70 min

Exemplo 612

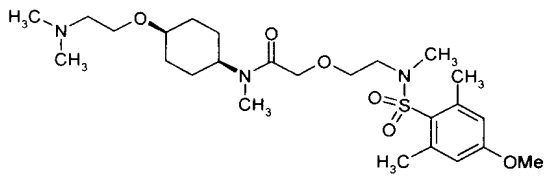


$C_{27}H_{45}N_3O_6S \times HCl$ (576.19)

[M+H]+ = 540

HPLC (Método 5): Tempo de retenção = 1.37 min

Exemplo 613

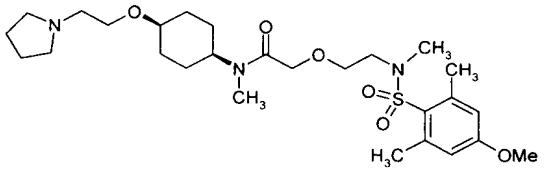


$C_{25}H_{43}N_3O_6S$ x HCl (550.15)

[M+H]+ = 514

HPLC (Método 5): Tempo de retenção = 1.36 min

Exemplo 614

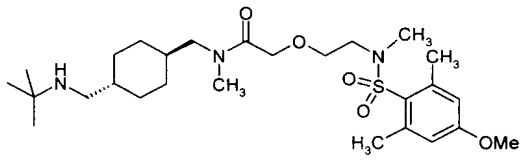


$C_{27}H_{45}N_3O_6S$ x HCl (576.19)

[M+H]+ = 540

HPLC (Método 5): Tempo de retenção = 1.38 min

Exemplo 615

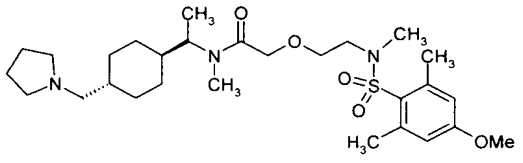


$C_{27}H_{47}N_3O_5S$ x HCl (562.21)

[M+H]+ = 526

HPLC (Método 4): Tempo de retenção = 3.0 min

Exemplo 616

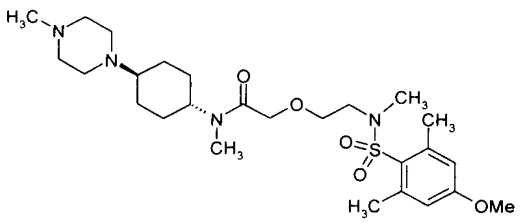


$C_{28}H_{47}N_3O_5S$ x HCl (574.22)

[M+H]+ = 538

HPLC (Método 4): Tempo de retenção = 3.1 min

Exemplo 617

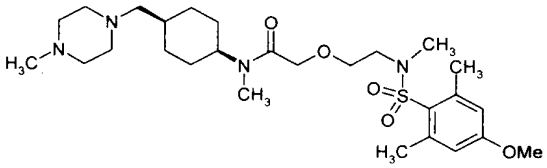


$C_{26}H_{44}N_4O_5S$ (524.72)

[M+H]+ = 525

HPLC (Método 9): Tempo de retenção = 1.32 min

Exemplo 618

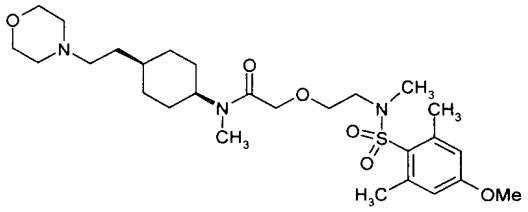


$C_{27}H_{46}N_4O_5S$ (538.74)

[M+H]+ = 539

HPLC (Método 9): Tempo de retenção = 1.57 min

Exemplo 619

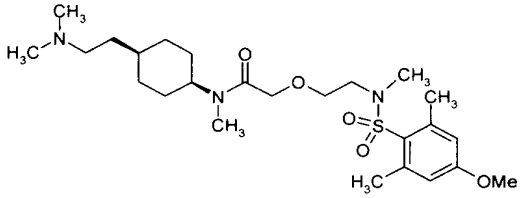


$C_{27}H_{45}N_3O_6S$ (539.73)

[M+H]+ = 540

HPLC (Método 9): Tempo de retenção = 1.65 min

Exemplo 620

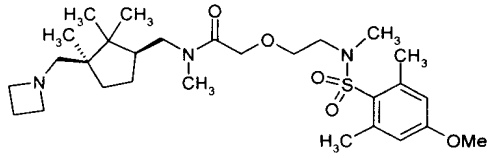


$C_{25}H_{43}N_3O_5S$ (497.69)

[M+H]+ = 498

HPLC (Método 9): Tempo de retenção = 1.65 min

Exemplo 621

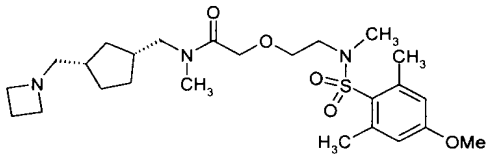


$C_{28}H_{47}N_3O_5S$ x HCl (574.22)

[M+H]+ = 538

HPLC (Método 9): Tempo de retenção = 1.68 min

Exemplo 622

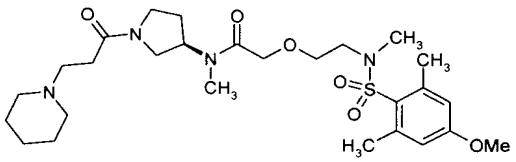


$C_{25}H_{41}N_3O_5S$ x $C_2HF_3O_2$ (609.70)

[M+H]+ = 496

HPLC (Método 9): Tempo de retenção = 1.62 min

Exemplo 623

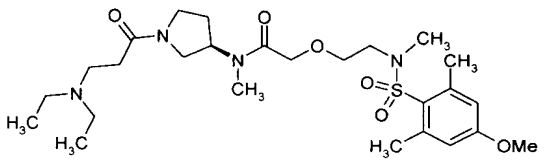


$C_{27}H_{44}N_4O_6S$ x $C_2HF_3O_2$ (666.76)

[M+H]+ = 553

HPLC (Método 9): Tempo de retenção = 1.57 min

Exemplo 624

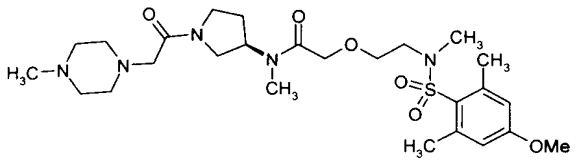


$C_{26}H_{44}N_4O_6S$ x $C_2HF_3O_2$ (654.75)

[M+H]+ = 541

HPLC (Método 9): Tempo de retenção = 1.56 min

Exemplo 625

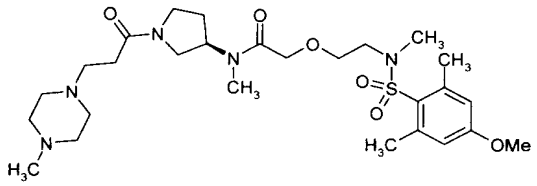


$C_{26}H_{43}N_5O_6S \times C_2HF_3O_2$ (667.74)

[M+H]+ = 554

HPLC (Método 9): Tempo de retenção = 1.00 min

Exemplo 626

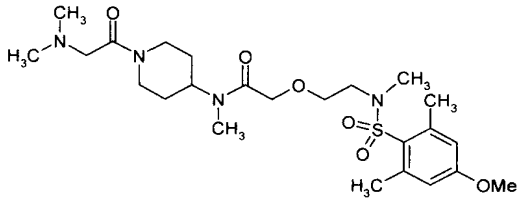


$C_{27}H_{45}N_5O_6S \times C_2HF_3O_2$ (681.77)

[M+H]+ = 568

HPLC (Método 9): Tempo de retenção = 1.03 min

Exemplo 627

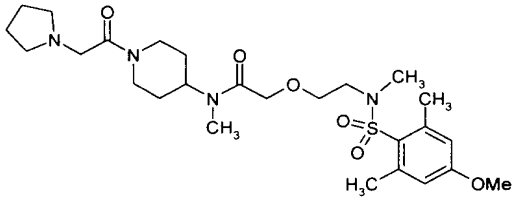


$C_{24}H_{40}N_4O_6S \times C_2HF_3O_2$ (626.69)

[M+H]+ = 513

HPLC (Método 9): Tempo de retenção = 1.50 min

Exemplo 628

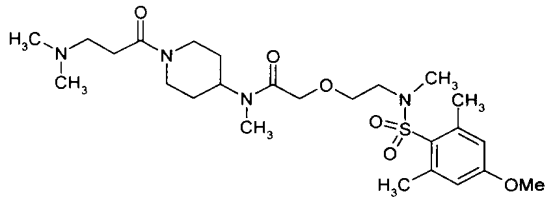


$C_{26}H_{42}N_4O_6S \times C_2HF_3O_2$ (654.72)

[M+H]+ = 539

HPLC (Método 9): Tempo de retenção = 1.55 min

Exemplo 629

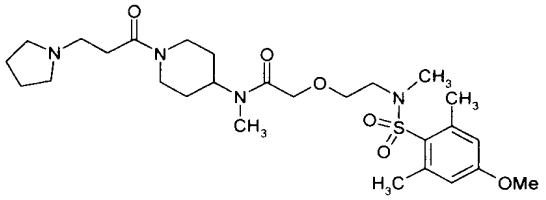


$C_{25}H_{42}N_4O_6S$ x $C_2HF_3O_2$ (640.71)

[M+H]+ = 527

HPLC (Método 9): Tempo de retenção = 1.63 min

Exemplo 630

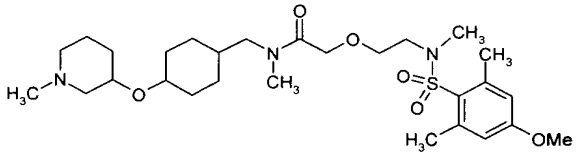


$C_{27}H_{44}N_4O_6S$ (552.73)

[M+H]+ = 553

HPLC (Método 9): Tempo de retenção = 1.65 min

Exemplo 638

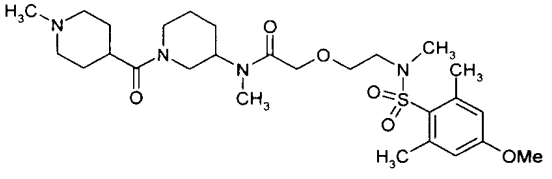


$C_{28}H_{47}N_3O_6S$ x HCl (590.22)

[M+H]+ = 554

HPLC (Método 5): Tempo de retenção = 1.44 min

Exemplo 639

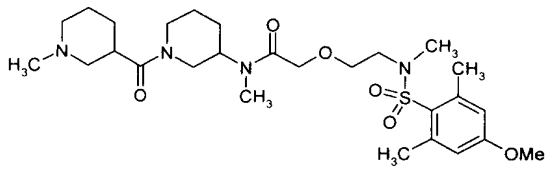


$C_{27}H_{44}N_4O_6S$ x $C_2HF_3O_2$ (666.75)

[M+H]+ = 553

HPLC (Método 9): Tempo de retenção = 1.59 min

Exemplo 640

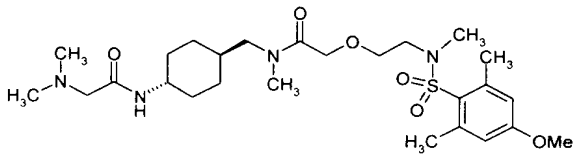


$C_{27}H_{44}N_4O_6S \times C_2HF_3O_2$ (666.75)

[M+H]+ = 553

HPLC (Método 9): Tempo de retenção = 1,61 min

Exemplo 641

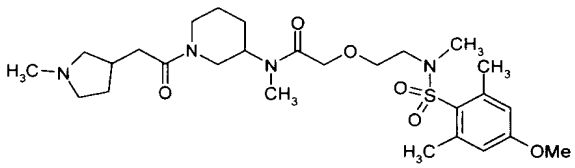


$C_{26}H_{44}N_4O_6S \times C_2HF_3O_2$ (590.22)

[M+H]+ = 541

HPLC (Método 9): Tempo de retenção = 1.56 min

Exemplo 642

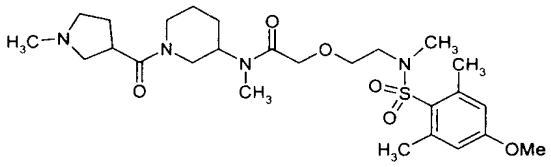


$C_{27}H_{44}N_4O_6S \times C_2HF_3O_2$ (666.75)

[M+H]+ = 553

HPLC (Método 9): Tempo de retenção = 1.55 min

Exemplo 643

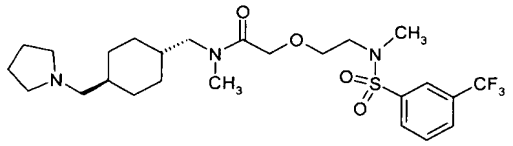


$C_{26}H_{42}N_4O_6S \times C_2HF_3O_2$ (652.72)

[M+H]+ = 539

HPLC (Método 9): Tempo de retenção = 1.55 min

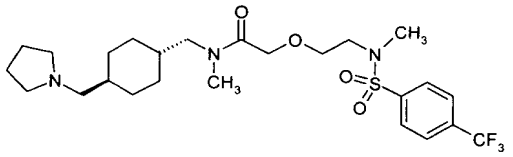
Exemplo 644



$C_{25}H_{38}F_3N_3O_4S$ (533.66)

[M+H]+ = 534

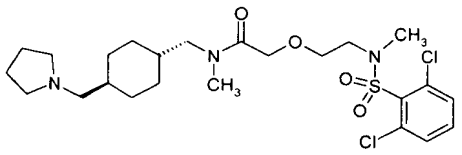
Exemplo 645



$C_{25}H_{38}F_3N_3O_4S$ (533.66)

[M+H]+ = 534

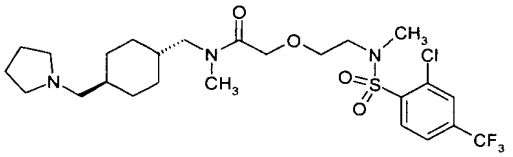
Exemplo 646



$C_{24}H_{37}Cl_2N_3O_4S$ (534.55)

[M+H]+ = 535

Exemplo 647

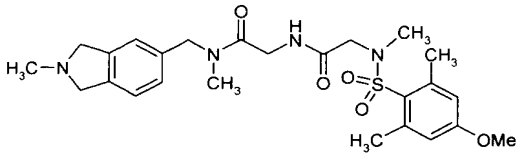


$C_{25}H_{37}ClF_3N_3O_4S$ (568.10)

[M+H]+ = 569

Die folgenden Verbindungen wurden analog zu Exemplo 121 hergestellt:

Exemplo 483

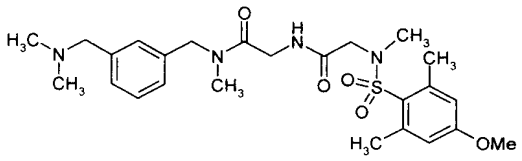


$C_{25}H_{34}N_4O_5S \times C_2HF_3O_2$ (616.65)

[M+H]+ = 503

HPLC (Método 6): Tempo de retenção = 2.30 min

Exemplo 484

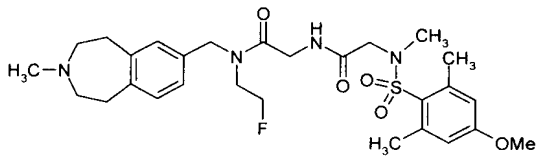


$C_{25}H_{36}N_4O_5S$ x HCl (541.10)

[M+H]+ = 505

HPLC (Método 5): Tempo de retenção = 1.49 min

Exemplo 485

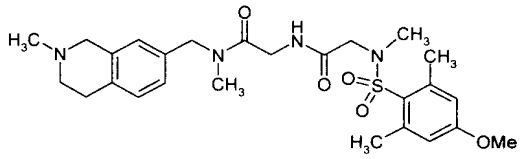


$C_{28}H_{39}FN_4O_5S$ x $C_2HF_3O_2$ (676.72)

[M+H]+ = 563

HPLC (Método 5): Tempo de retenção = 1.55 min

Exemplo 486

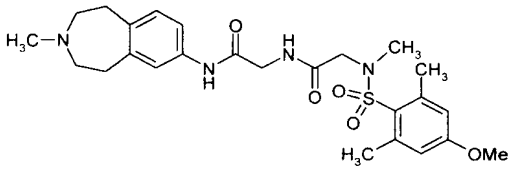


$C_{26}H_{36}N_4O_5S$ x HCl (553.11)

[M+H]+ = 517

HPLC (Método 11): Tempo de retenção = 1.73 min

Exemplo 487

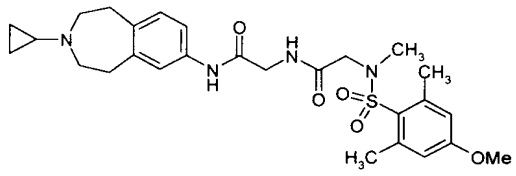


$C_{25}H_{34}N_4O_5S$ x $C_2HF_3O_2$ (616.65)

[M+H]+ = 503

HPLC (Método 5): Tempo de retenção = 1.49 min

Exemplo 488

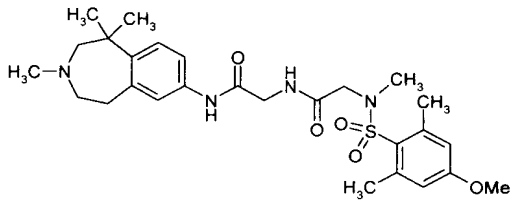


$C_{27}H_{36}N_4O_5S$ x $C_2HF_3O_2$ (642.69)

[M+H]+ = 529

HPLC (Método 5): Tempo de retenção = 1.50 min

Exemplo 489

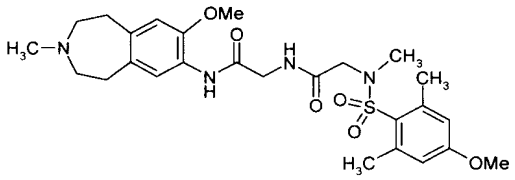


$C_{27}H_{38}N_4O_5S$ x $C_2HF_3O_2$ (644.70)

[M+H]+ = 531

HPLC (Método 5): Tempo de retenção = 1.54 min

Exemplo 490

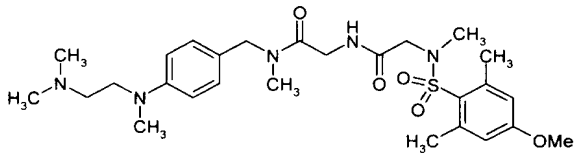


$C_{26}H_{36}N_4O_6S$ x $C_2HF_3O_2$ (646.68)

[M+H]+ = 533

HPLC (Método 5): Tempo de retenção = 1.51 min

Exemplo 491

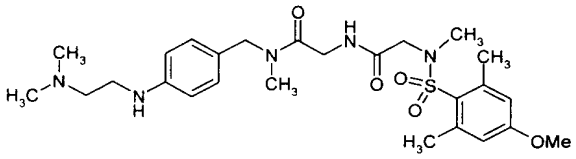


$C_{27}H_{41}N_5O_5S$ x HCl (584.17)

[M+H]+ = 548

HPLC (Método 5): Tempo de retenção = 1.53 min

Exemplo 492

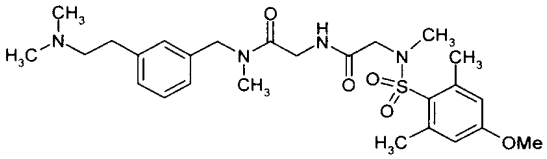


$C_{26}H_{39}N_5O_5S$ x HCl (570.15)

[M+H]+ = 534

HPLC (Método 5): Tempo de retenção = 1.52 min

Exemplo 493

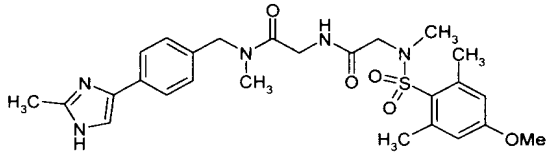


$C_{26}H_{38}N_4O_5S$ x HCl (555.13)

[M+H]+ = 519

HPLC (Método 5): Tempo de retenção = 1.51 min

Exemplo 494

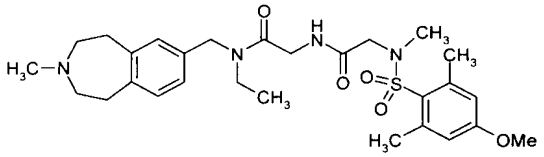


$C_{26}H_{33}N_5O_5S$ (527.64)

[M+H]+ = 528

HPLC (Método 4): Tempo de retenção = 3.0 min

Exemplo 495

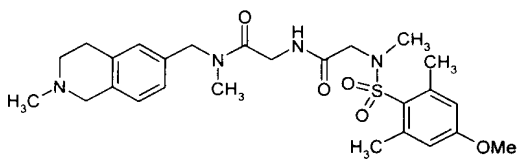


$C_{28}H_{40}N_4O_5S$ x HCl (581.17)

[M+H]+ = 545

HPLC (Método 4): Tempo de retenção = 3.1 min

Exemplo 496

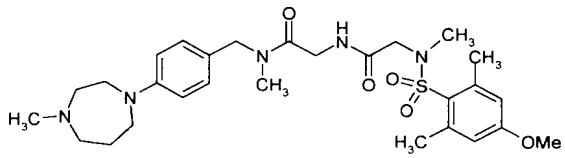


$C_{26}H_{36}N_4O_5S$ x HCl (553.11)

[M+H]+ = 517

HPLC (Método 5): Tempo de retenção = 1.48 min

Exemplo 497

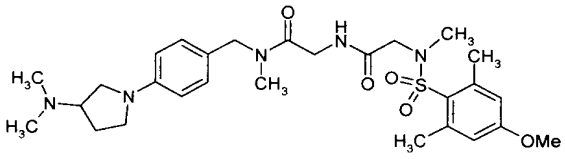


$C_{28}H_{41}N_5O_5S$ x HCl (596.18)

[M+H]+ = 560

HPLC (Método 5): Tempo de retenção = 1.52 min

Exemplo 498

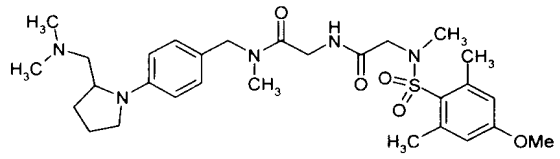


$C_{28}H_{41}N_5O_5S$ x HCl (596.18)

[M+H]+ = 560

HPLC (Método 5): Tempo de retenção = 1.52 min

Exemplo 499

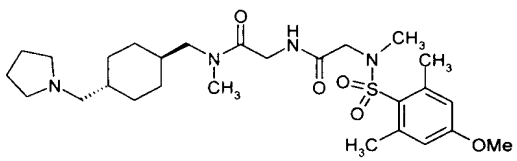


$C_{29}H_{43}N_5O_5S$ x HCl (610.21)

[M+H]+ = 574

HPLC (Método 5): Tempo de retenção = 1.57 min

Exemplo 500

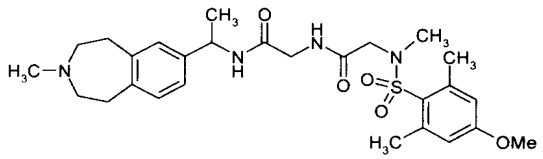


$C_{27}H_{44}N_4O_5S$ x HCl (573.19)

[M+H]+ = 537

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,01, Valor Rf = 0,66

Exemplo 501

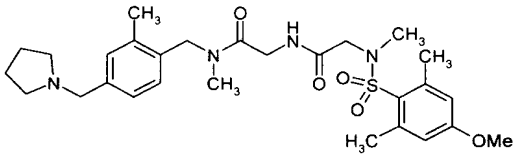


$C_{27}H_{38}N_4O_5S$ x HCl (567.14)

[M+H]+ = 531

HPLC (Método 4): Tempo de retenção = 3.0 min

Exemplo 502

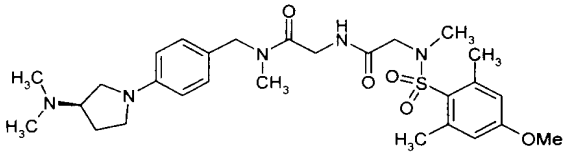


$C_{28}H_{40}N_4O_5S$ x HCl (581.17)

[M+H]+ = 545

DC: Gel de sílica, diclorometano/metanol 9:1, Valor Rf = 0,18

Exemplo 503

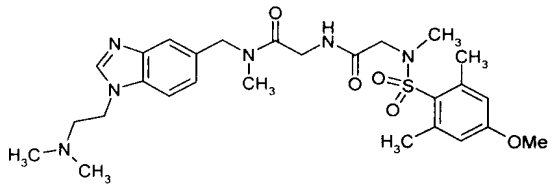


$C_{28}H_{41}N_5O_5S$ x HCl (596.18)

[M+H]+ = 560

DC: Kieselgel, Ethylacetat / Methanol / Ammoniak 9:1:0,1, Valor Rf = 0,42

Exemplo 504

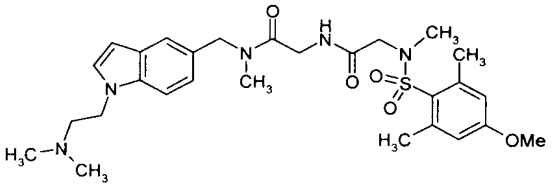


$C_{27}H_{38}N_6O_5S$ (558.69)

[M+H]+ = 559

HPLC (Método 6): Tempo de retenção = 2.23 min

Exemplo 505

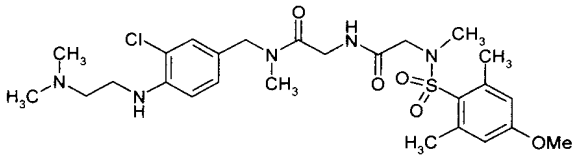


$C_{28}H_{39}N_5O_5S$ (557.71)

[M+H]+ = 558

HPLC (Método 6): Tempo de retenção = 2.35 min

Exemplo 506

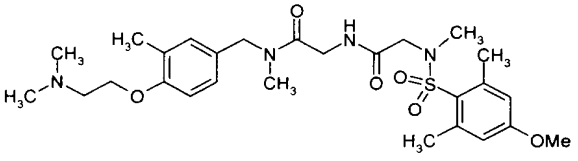


$C_{26}H_{38}ClN_5O_5S \times CH_2O_2$ (614.16)

[M+H]+ = 568/570

HPLC (Método 6): Tempo de retenção = 2.55 min

Exemplo 507

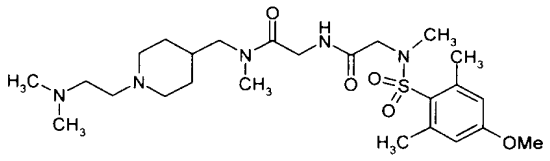


$C_{27}H_{40}N_4O_6S$ (548.70)

[M+H]+ = 549

HPLC (Método 6): Tempo de retenção = 2.49 min

Exemplo 508

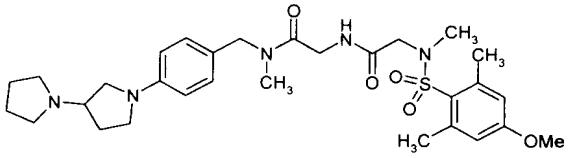


$C_{25}H_{43}N_5O_5S$ (525.71)

[M+H]+ = 526

HPLC (Método 6): Tempo de retenção = 1.85 min

Exemplo 509

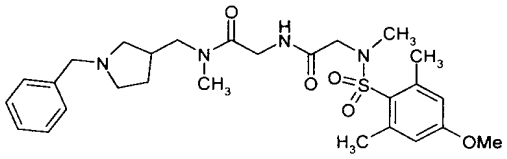


$C_{30}H_{43}N_5O_5S$ (585.76)

[M+H]+ = 586

HPLC (Método 6): Tempo de retenção = 2.66 min

Exemplo 510

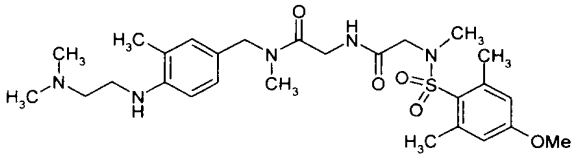


$C_{27}H_{38}N_4O_5S$ (530.68)

[M+H]+ = 531

HPLC (Método 6): Tempo de retenção = 2.52 min

Exemplo 511

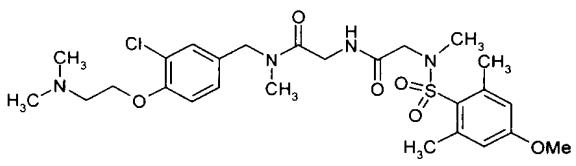


$C_{27}H_{41}N_5O_5S$ (547.71)

[M+H]+ = 548

HPLC (Método 6): Tempo de retenção = 2.44 min

Exemplo 512

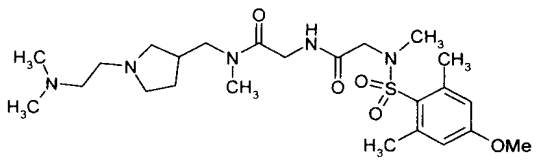


$C_{26}H_{37}ClN_4O_6S$ (569.11)

[M+H]+ = 570

HPLC (Método 6): Tempo de retenção = 2.56 min

Exemplo 513

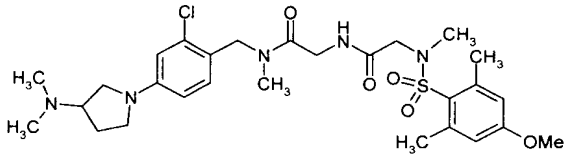


$C_{24}H_{41}N_5O_5S$ (511.68)

[M+H]+ = 512

HPLC (Método 6): Tempo de retenção = 1.80 min

Exemplo 514

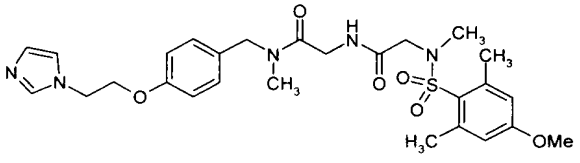


$C_{28}H_{40}ClN_5O_5S$ (594.17)

[M+H]+ = 594/596

HPLC (Método 6): Tempo de retenção = 2.68 min

Exemplo 515

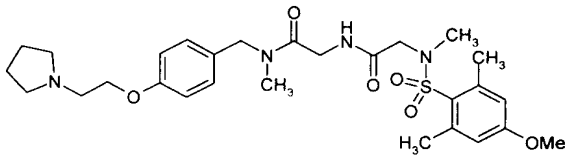


$C_{27}H_{35}N_5O_6S$ (557.66)

[M+H]+ = 558

HPLC (Método 6): Tempo de retenção = 2.51 min

Exemplo 516

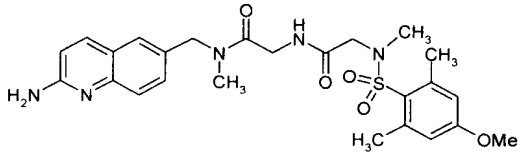


$C_{28}H_{40}N_4O_6S$ (560.71)

[M+H]+ = 561

HPLC (Método 6): Tempo de retenção = 2,51 min

Exemplo 517

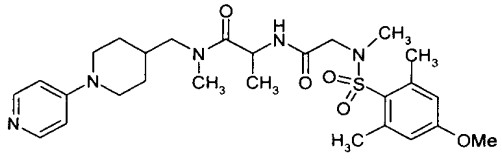


$C_{25}H_{31}N_5O_5S$ (513.61)

[M+H]+ = 514

HPLC (Método 6): Tempo de retenção = 2,35 min

Exemplo 518

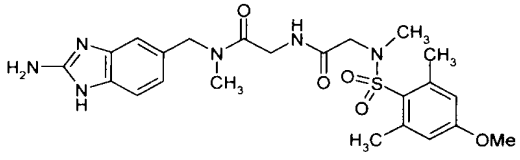


$C_{27}H_{39}N_5O_5S \times C_2HF_3O_2$ (659.72)

[M+H]+ = 546

HPLC (Método 6): Tempo de retenção = 2,44 min

Exemplo 519

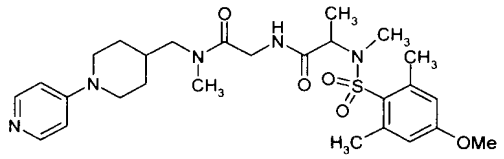


$C_{23}H_{30}N_6O_5S$ (502.59)

[M+H]+ = 503

HPLC (Método 6): Tempo de retenção = 2.37 min

Exemplo 520

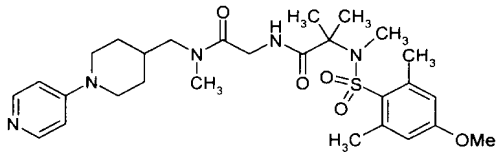


$C_{27}H_{39}N_5O_5S \times C_2HF_3O_2$ (659.72)

[M+H]+ = 546

HPLC (Método 6): Tempo de retenção = 2.52 min

Exemplo 521

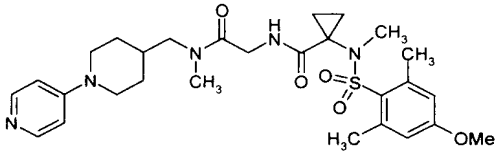


$C_{28}H_{41}N_5O_5S \times C_2HF_3O_2$ (673.75)

[M+H]+ = 560

HPLC (Método 6): Tempo de retenção = 2.58 min

Exemplo 522

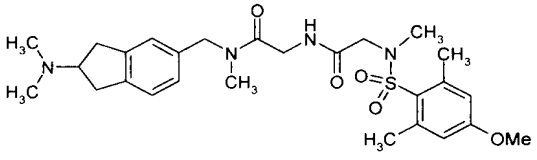


$C_{28}H_{39}N_5O_5S \times C_2HF_3O_2$ (671.73)

[M+H]+ = 558

HPLC (Método 6): Tempo de retenção = 2.57 min

Exemplo 523

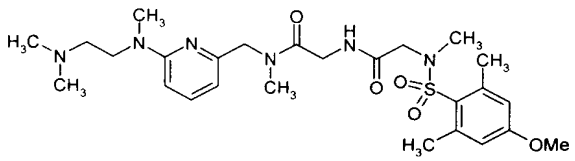


$C_{27}H_{38}N_4O_5S \times C_2HF_3O_2$ (644.70)

[M+H]+ = 531

HPLC (Método 6): Tempo de retenção = 2,45 min

Exemplo 524

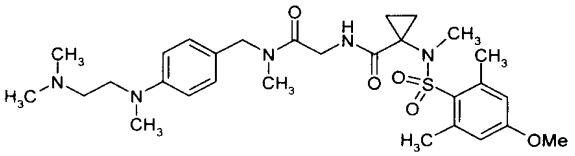


$C_{26}H_{40}N_6O_5S$ (548.70)

[M+H]+ = 549

HPLC (Método 6): Tempo de retenção = 2.52 min

Exemplo 525

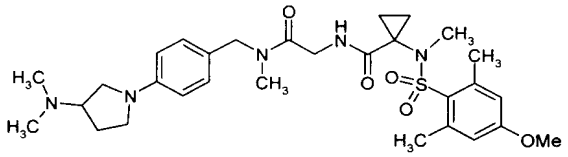


$C_{29}H_{43}N_5O_5S \times C_2HF_3O_2$ (687.77)

[M+H]+ = 574

HPLC (Método 6): Tempo de retenção = 2.72 min

Exemplo 526

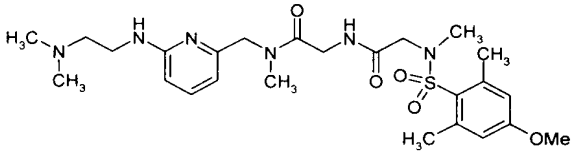


$C_{30}H_{43}N_5O_5S$ (585.76)

[M+H]+ = 586

HPLC (Método 6): Tempo de retenção = 2.70 min

Exemplo 527

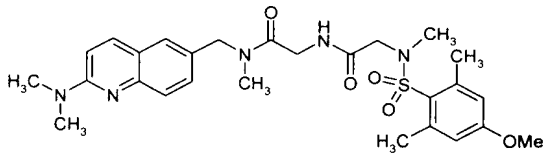


$C_{25}H_{38}N_6O_5S \times CH_2O_2$ (580.70)

[M+H]+ = 535

HPLC (Método 6): Tempo de retenção = 2.16 min

Exemplo 528

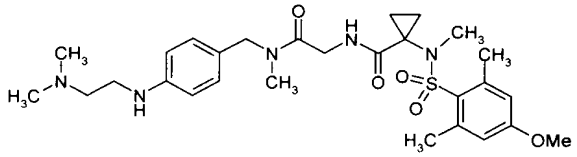


$C_{27}H_{35}N_5O_5S \times C_2HF_3O_2$ (655.69)

[M+H]+ = 542

HPLC (Método 6): Tempo de retenção = 2.48 min

Exemplo 529

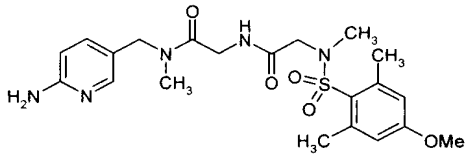


$C_{28}H_{41}N_5O_5S \times C_2HF_3O_2$ (673.75)

[M+H]+ = 560

HPLC (Método 6): Tempo de retenção = 2.61 min

Exemplo 530

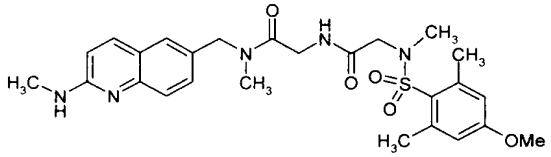


$C_{21}H_{29}N_5O_5S$ (463.55)

[M+H]+ = 464

HPLC (Método 9): Tempo de retenção = 1.47 min

Exemplo 531

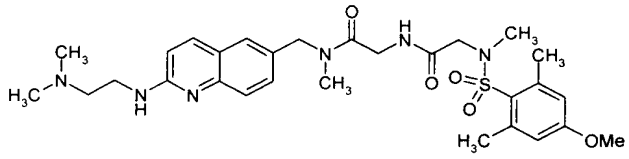


$C_{26}H_{33}N_5O_5S$ (527.64)

[M+H]+ = 528

HPLC (Método 9): Tempo de retenção = 1.60 min

Exemplo 532

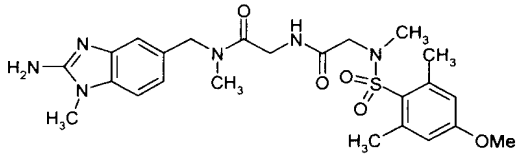


$C_{29}H_{40}N_6O_5S$ (584.73)

[M+H]+ = 585

HPLC (Método 9): Tempo de retenção = 1.37 min

Exemplo 533

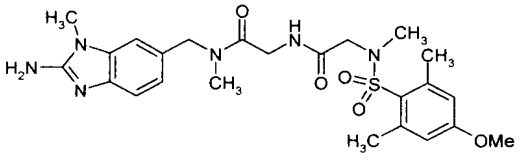


$C_{24}H_{32}N_6O_5S \times C_2HF_3O_2$ (630.64)

[M+H]+ = 517

HPLC (Método 9): Tempo de retenção = 1.58 min

Exemplo 534

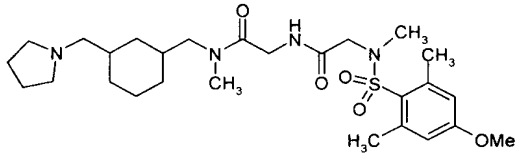


$C_{24}H_{32}N_6O_5S \times C_2HF_3O_2$ (630.64)

[M+H]+ = 517

HPLC (Método 9): Tempo de retenção = 1.57 min

Exemplo 535

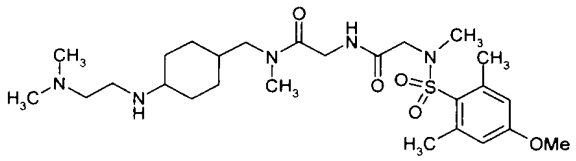


$C_{27}H_{44}N_4O_5S \times C_2HF_3O_2$ (650.75)

[M+H]+ = 537

HPLC (Método 9): Tempo de retenção = 1.68 min

Exemplo 536

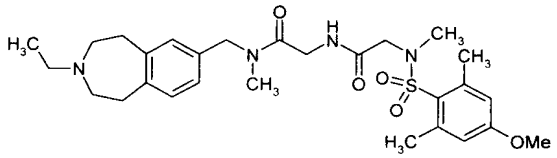


$C_{26}H_{45}N_5O_5S$ x 2HCl (612.65)

[M+H]+ = 540

HPLC (Método 5): Tempo de retenção = 1.39 min

Exemplo 537

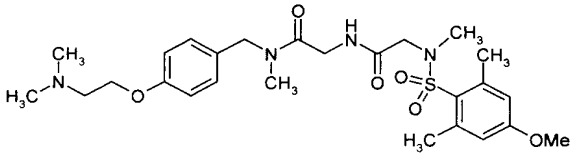


$C_{28}H_{40}N_4O_5S$ x $C_2HF_3O_2$ (658.73)

[M+H]+ = 545

HPLC (Método 5): Tempo de retenção = 1.53 min

Exemplo 538

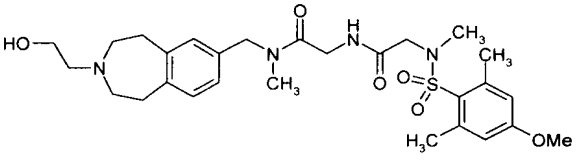


$C_{26}H_{38}N_4O_6S$ x $C_2HF_3O_2$ (648.69)

[M+H]+ = 535

HPLC (Método 5): Tempo de retenção = 1.43 min

Exemplo 539

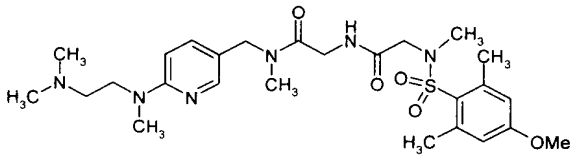


$C_{28}H_{40}N_4O_6S$ (560.71)

[M+H]+ = 561

HPLC (Método 5): Tempo de retenção = 1.50 min

Exemplo 540

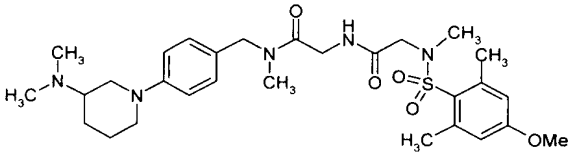


$C_{26}H_{40}N_6O_5S$ (548.70)

[M+H]+ = 549

HPLC (Método 5): Tempo de retenção = 1.39 min

Exemplo 541

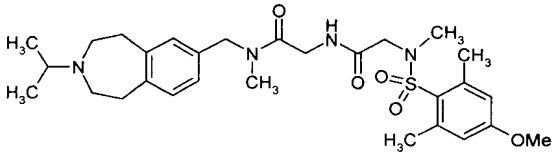


$C_{29}H_{43}N_5O_5S$ x HCl (610.21)

[M+H]+ = 574

HPLC (Método 7): Tempo de retenção = 1.88 min

Exemplo 542

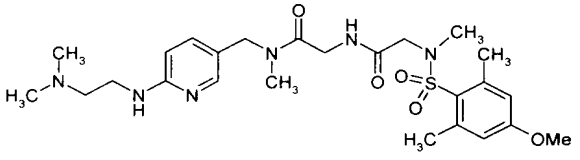


$C_{29}H_{42}N_4O_5S$ x $C_2HF_3O_2$ (672.76)

[M+H]+ = 559

HPLC (Método 5): Tempo de retenção = 1.55 min

Exemplo 543

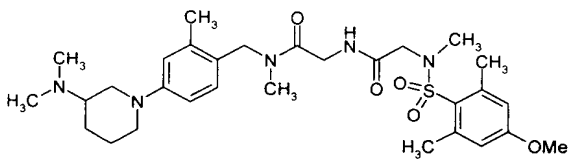


$C_{25}H_{38}N_6O_5S$ x 2HCl (607.59)

[M+H]+ = 535

HPLC (Método 5): Tempo de retenção = 1.39 min

Exemplo 544

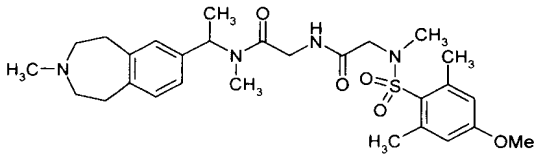


$C_{30}H_{45}N_5O_5S$ x $C_2HF_3O_2$ (701.80)

[M+H]+ = 588

HPLC (Método 5): Tempo de retenção = 1.55 min

Exemplo 545

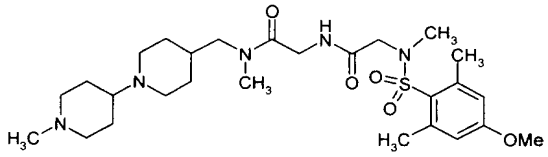


$C_{28}H_{40}N_4O_5S$ x HCl (581.17)

[M+H]+ = 545

HPLC (Método 4): Tempo de retenção = 3.3 min

Exemplo 546

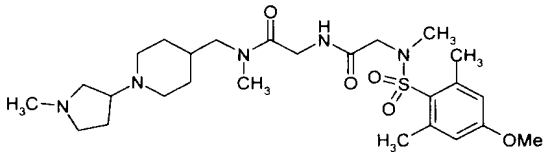


$C_{27}H_{45}N_5O_5S$ x 2HCl (624.66)

[M+H]+ = 552

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,01, Valor Rf = 0,25

Exemplo 547

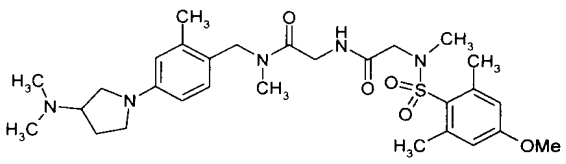


$C_{26}H_{43}N_5O_5S$ x HCl (574.18)

[M+H]+ = 538

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,01, Valor Rf = 0,10

Exemplo 548

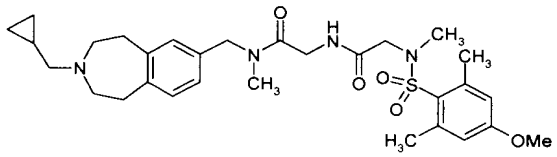


$C_{29}H_{43}N_5O_5S$ x HCl (610.21)

[M+H]+ = 574

DC: Gel de sílica, diclorometano/metanol 9:1, Valor Rf = 0,25

Exemplo 549

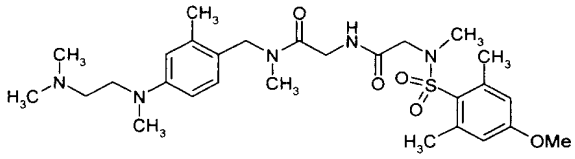


$C_{31}H_{44}N_4O_5S$ x HCl (621.23)

[M+H]+ = 585

HPLC (Método 12): Tempo de retenção = 3.0 min

Exemplo 550

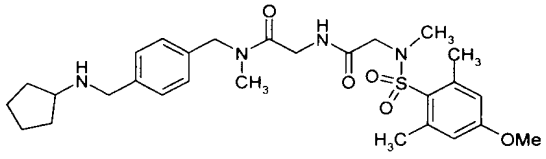


$C_{28}H_{43}N_5O_5S$ x HCl (598.20)

[M+H]+ = 562

DC: Gel de sílica, diclorometano/metanol 9:1, Valor Rf = 0,14

Exemplo 551

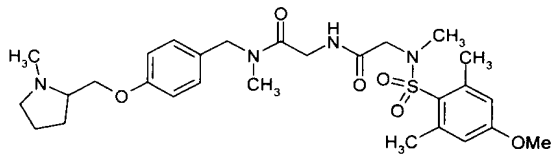


$C_{29}H_{42}N_4O_5S$ x HCl (595.19)

[M+H]+ = 559

DC: gel de sílica, diclorometano/metanol/amoníaco 9:1:0,1, Valor Rf = 0,32

Exemplo 552

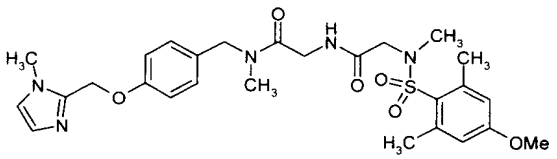


$C_{28}H_{40}N_4O_6S$ (560.71)

[M+H]+ = 561

HPLC (Método 9): Tempo de retenção = 1.66 min

Exemplo 553

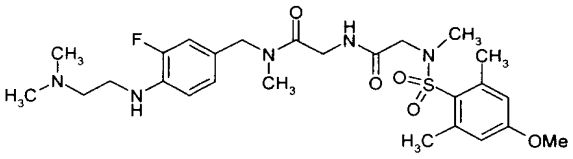


$C_{27}H_{35}N_5O_6S$ (557.66)

[M+H]+ = 558

HPLC (Método 9): Tempo de retenção = 1.64 min

Exemplo 554

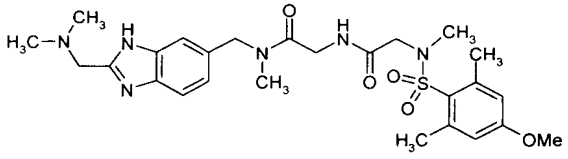


$C_{26}H_{38}FN_5O_5S$ (551.68)

[M+H]+ = 552

HPLC (Método 6): Tempo de retenção = 2.30 min

Exemplo 555

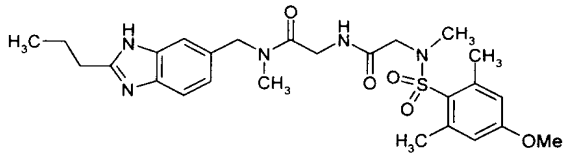


$C_{26}H_{36}N_6O_5S$ (544.67)

[M+H]+ = 545

HPLC (Método 6): Tempo de retenção = 1.48 min

Exemplo 556

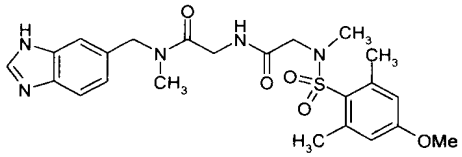


$C_{26}H_{35}N_5O_5S$ (529.65)

[M+H]+ = 530

HPLC (Método 9): Tempo de retenção = 1,61 min

Exemplo 557

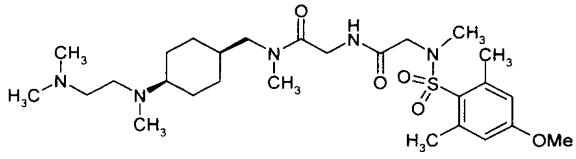


$C_{23}H_{29}N_5O_5S$ (487.57)

[M+H]+ = 488

HPLC (Método 9): Tempo de retenção = 1,53 min

Exemplo 558

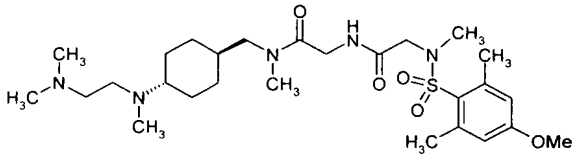


$C_{27}H_{47}N_5O_5S$ x 2HCl (626.68)

[M+H]+ = 554

HPLC (Método 7): Tempo de retenção = 1,61 min

Exemplo 559

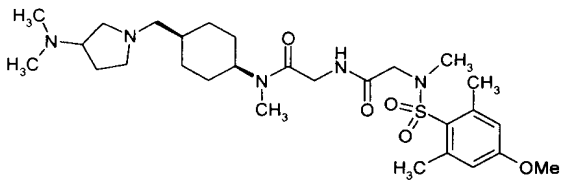


$C_{27}H_{47}N_5O_5S$ x 2HCl (626.68)

[M+H]+ = 554

HPLC (Método 7): Tempo de retenção = 1,61 min

Exemplo 560

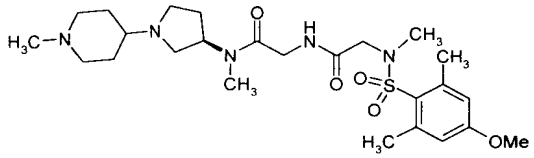


$C_{28}H_{47}N_5O_5S$ x CH_2O_2 (611.80)

[M+H]+ = 566

HPLC (Método 9): Tempo de retenção = 1.33 min

Exemplo 561

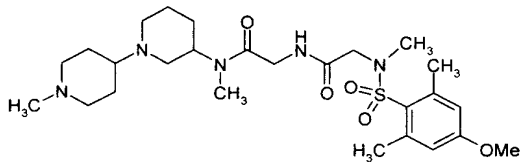


$C_{25}H_{41}N_5O_5S$ x 2HCl (596.61)

[M+H]+ = 524

HPLC (Método 12): Tempo de retenção = 2.3 min

Exemplo 562

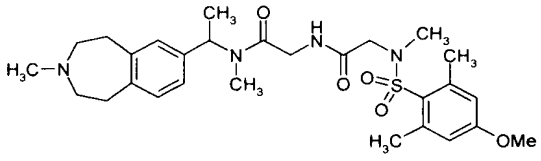


$C_{26}H_{43}N_5O_5S$ x 2HCl (610.64)

[M+H]+ = 538

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,2, Valor Rf = 0,53

Exemplo 563

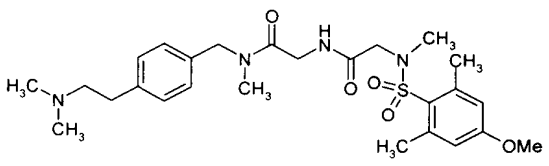


$C_{29}H_{42}N_4O_5S$ x HCl (595.19)

[M+H]+ = 559

HPLC (Método 12): Tempo de retenção = 2,8 min

Exemplo 564

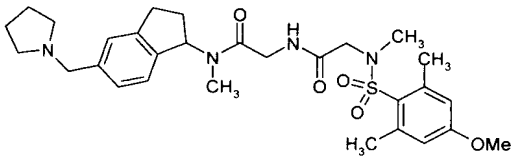


$C_{26}H_{38}N_4O_5S \times C_2HF_3O_2$ (632.69)

[M+H]+ = 519

HPLC (Método 9): Tempo de retenção = 1,61 min

Exemplo 565

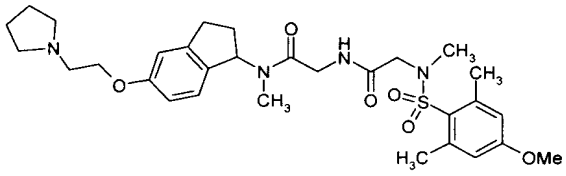


$C_{29}H_{40}N_4O_5S$ (556.72)

[M+H]+ = 557

HPLC (Método 9): Tempo de retenção = 1.69 min

Exemplo 566

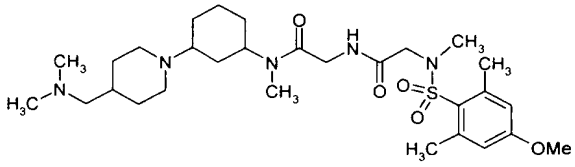


$C_{30}H_{42}N_4O_6S$ (586.74)

[M+H]+ = 587

HPLC (Método 9): Tempo de retenção = 1.74 min

Exemplo 603

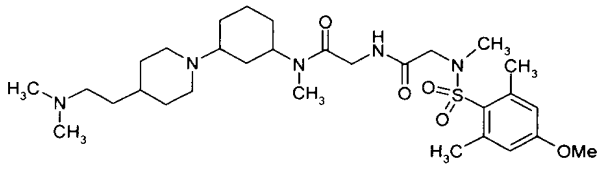


$C_{29}H_{49}N_5O_5S \times 2HCl$ (652.72)

[M+H]+ = 580

HPLC (Método 10): Tempo de retenção = 1.11 min

Exemplo 604

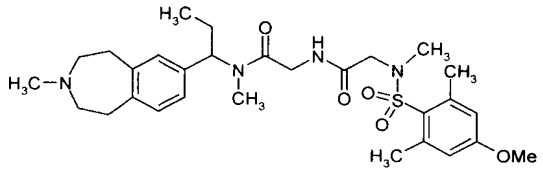


$C_{30}H_{51}N_5O_5S$ x 2HCl (666.74)

[M+H]+ = 594

HPLC (Método 10): Tempo de retenção = 1.11 min

Exemplo 605

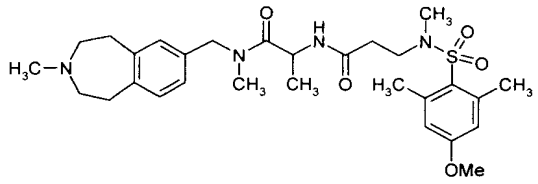


$C_{29}H_{42}N_4O_5S$ x HCl (595.19)

[M+H]+ = 559

HPLC (Método 12): Tempo de retenção = 3.1 min

Exemplo 606

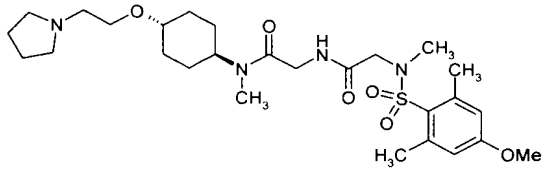


$C_{29}H_{42}N_4O_5S$ x HCl (595.19)

[M+H]+ = 559

DC: gel de sílica, diclorometano/metanol/amoníaco 8:2:0,01, Valor Rf = 0,68

Exemplo 631

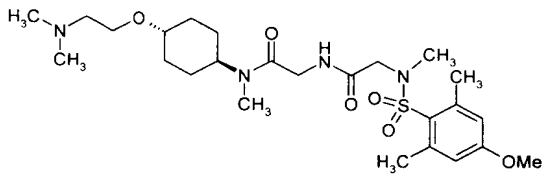


$C_{27}H_{44}N_4O_6S$ x HCl (589.19)

[M+H]+ = 553

HPLC (Método 5): Tempo de retenção = 1,35 min

Exemplo 632

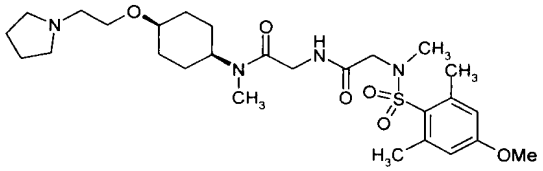


$C_{25}H_{42}N_4O_6S$ x HCl (563.15)

[M+H]+ = 527

HPLC (Método 5): Tempo de retenção = 1,38 min

Exemplo 633

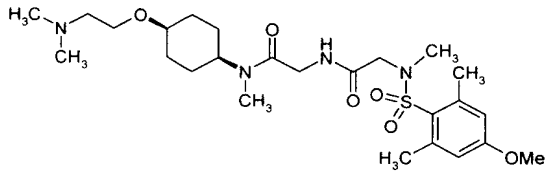


$C_{27}H_{44}N_4O_6S$ x HCl (589.19)

[M+H]+ = 553

HPLC (Método 5): Tempo de retenção = 1,35 min

Exemplo 634



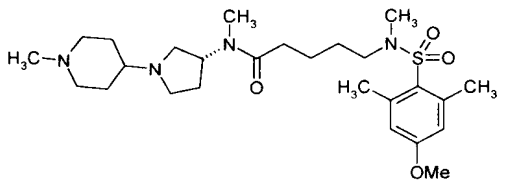
$C_{25}H_{42}N_4O_6S$ x HCl (563.15)

[M+H]+ = 527

HPLC (Método 5): Tempo de retenção = 1,32 min

Die folgenden Verbindungen wurden analog zu Exemplo 130 hergestellt:

Exemplo 567

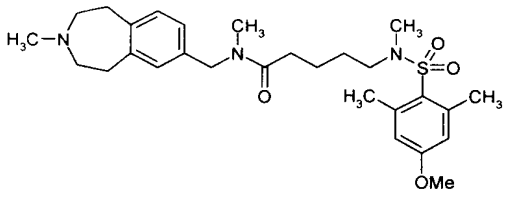


$C_{26}H_{44}N_4O_4S$ x $2C_2HF_3O_2$ (736.76)

[M+H]+ = 509

HPLC (Método 6): Tempo de retenção = 1,36 min

Exemplo 568



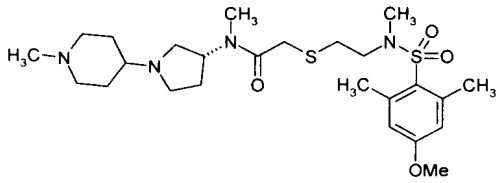
$C_{28}H_{41}N_3O_4S \times C_2HF_3O_2$ (629.73)

[M+H]+ = 516

HPLC (Método 6): Tempo de retenção = 1,77 min

Die folgenden Verbindungen wurden analog zu Exemplo 136 hergestellt:

Exemplo 569

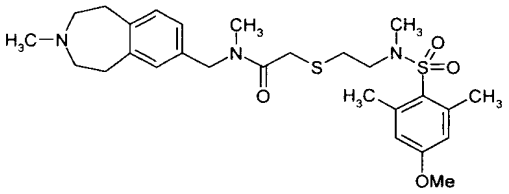


$C_{25}H_{42}N_4O_4S_2 \times C_2HF_3O_2$ (640.78)

[M+H]+ = 527

HPLC (Método 6): Tempo de retenção = 1,35 min

Exemplo 570



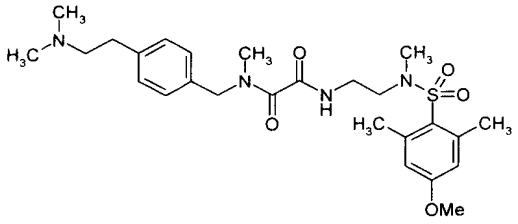
$C_{27}H_{39}N_3O_4S_2$ (533.75)

[M+H]+ = 534

HPLC (Método 6): Tempo de retenção = 1,74 min

Os seguintes compostos foram preparados de maneira análoga ao exemplo 138:

Exemplo 571

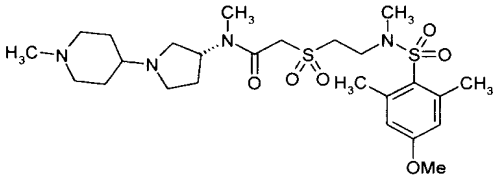


$C_{26}H_{38}N_4O_5S$ x CH_2O_2 (564.70)

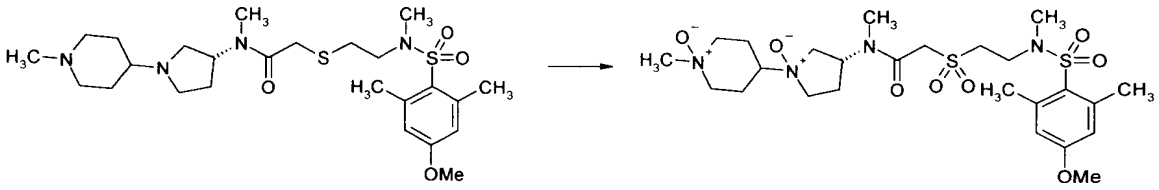
[M+H]+ = 519

HPLC (Método 6): Tempo de retenção = 2,33 min

Exemplo 572



572a)

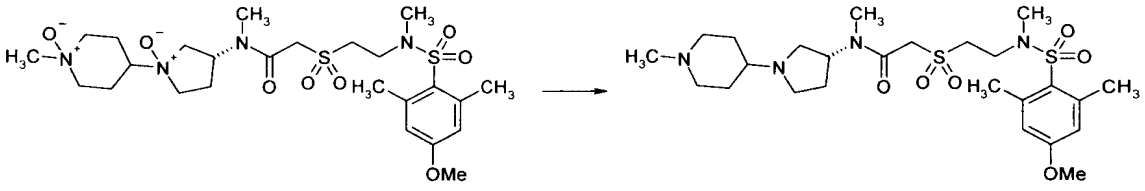


Uma mistura de 88,0 g (0,167 mmol) de 569, 0,15 g (0,61 mmol) de ácido cloroperbenzóico a 70% (Fluka) e 3 ml de diclorometano é agitada à temperatura ambiente por 30 minutos e a seguir, concentrada no vácuo à secura. O resíduo é dissolvido em metanol e filtrado através de membrana. Em seguida, o produto é obtido do filtrado por meio de HPLC preparatória.

$C_{25}H_{42}N_4O_8S_2$ (590.76)

[M+H]+ = 591

572b)



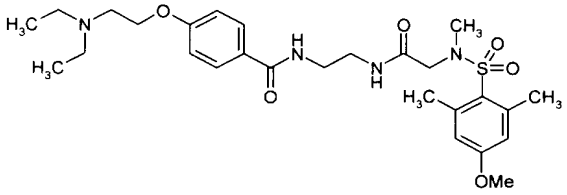
Uma mistura de 90,0 mg (0,15 mmol) do produto de 572a, 20,0 mg de níquel de Raney e 10 ml de tetrahidrofurano é agitada no autoclave por uma hora à temperatura ambiente. Em seguida, o catalisador é filtrado e o filtrado é concentrado no vácuo à secura. O produto obtido dessa maneira é purificado por meio de HPLC preparatória.

$C_{25}H_{42}N_4O_6S_2$ x CH_2O_2 (604.78)

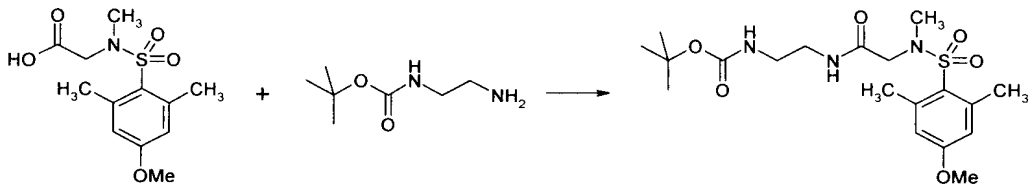
[M+H]+ = 559

HPLC (método 6): tempo de retenção = 1,33 min.

Exemplo 573



573a)

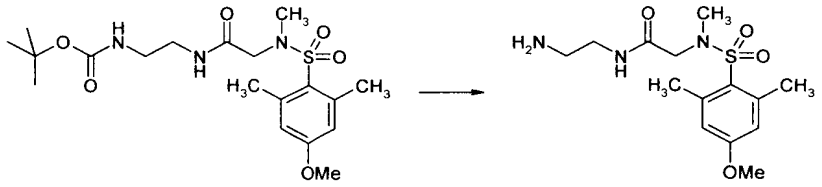


573a é preparado de maneira análoga a 1f a partir de 2,16 g (7,50 mmols) do produto de 121b, 1,20 g (7,50 mmols) de N-boc-etilenodiamina (Fluka), 3,14 ml (22,50 mmols) de trietilamina e 2,41 g (7,50 mmols) de TBTU em 28 ml de tetrahidrofurano e 4 ml de dimetilformamida.

$C_{19}H_{31}N_3O_6S$ (429.53)

DC: gel de sílica, diclorometano/etanol 19:1: valor Rf = 0,35.

573b)

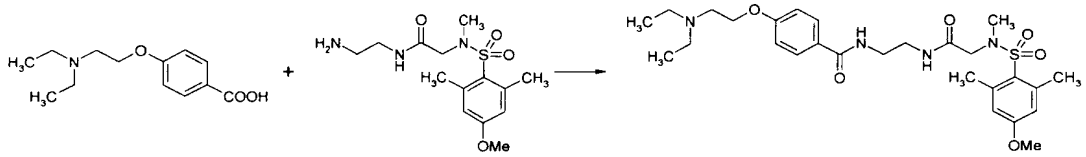


573b é preparado de maneira análoga a 28d a partir de 2,70 g (6,29 mmols) do produto de 573a e 7 ml de TFA em 50 mo de diclorometano.

$C_{14}H_{23}N_3O_4S$ (329,42)

DC: gel de sílica, diclorometano/etanol 9:1: valor Rf = 0,15.

573c)



O exemplo 573 é preparado de maneira análoga a 1f a partir de

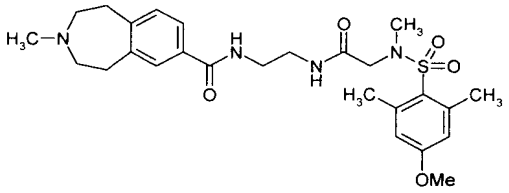
0,119 g (0,50 mmol) de ácido 4-(2-dietilaminoetoxi)-benzóico (J. Med. Chem. 14, 1971, 836-842), 0,165 g (0,50 mmol) do produto de 573b, 0,21 ml (1,50 mmol) de trietilamina e 0,16 g (0,50 mmol) de TBTU em 7 ml de tetrahidrofurano e 1 ml de dimetilformamida.

$C_{27}H_{40}N_4O_6S$ x HCl (585,16)

HPLC (método 5): tempo de retenção = 1,44 min.

Os seguintes compostos foram preparados de maneira análoga ao exemplo 573:

Exemplo 574

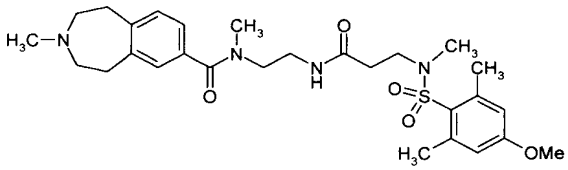


$C_{26}H_{36}N_4O_5S$ x HCl (553.11)

[M+H]+ = 517

HPLC (método 5): tempo de retenção = 1.40 min.

Exemplo 607

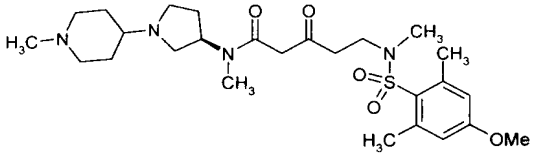


$C_{28}H_{40}N_4O_5S$ x HCl (581.17)

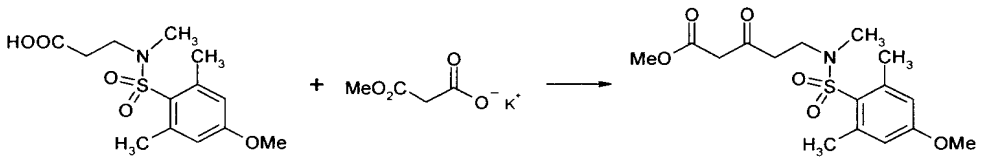
[M+H]+ = 545

HPLC (método 12): tempo de retenção = 3,51 min.

Exemplo 635



635a)



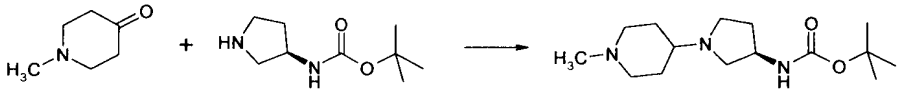
Uma mistura de 0,78 g (4,98 mmols) de sal de potássio de malonato de monometila (Fluka), 0,52 g (5,47 mmols) de cloreto de magnésio e 30 ml de tetrahidrofurano é agitada a 50°C por quatro horas. Uma segunda mistura de 1,00 g (3,32 mmols) do produto de 22c, 0,65 g (3,98 mmols) de CDI e 20 ml de tetrahidrofurano é inicialmente agitada à temperatura ambiente por uma hora e, em seguida, acrescentada à primeira mistura. Deixa-se agitar à temperatura ambiente durante a noite e em seguida, filtra-se o precipitado formado. O filtrado é concentrado no vácuo à secura. O produto obtido dessa maneira é triturado com água, filtrado e seco na estufa de secagem a vácuo a 45°C.

$C_{16}H_{23}NO_6S$ (357.42)

[M+H]+ = 358

HPLC (método 9): tempo de retenção = 2,19 min.

635b)

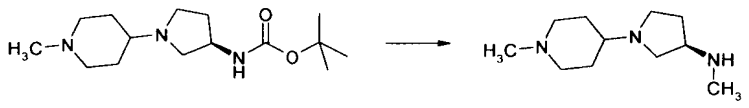


635b é preparado de maneira análoga a 60a a partir de 0,47 ml (4,07 mmols) de 1-metil-4-piperidona (Fluka), 0,76 g (4,07 mmols) de (R)-3-(boc-amino)-pirrolidina (Fluka), 1,72 g (8,13 mmols) de triacetoxiborohidreto de sódio e 0,23 ml (4,07 mmols) de ácido acético em 10 ml de diclorometano.

$C_{15}H_{29}N_3O_2$ (283,41)

[M+H]+ = 284.

635c)

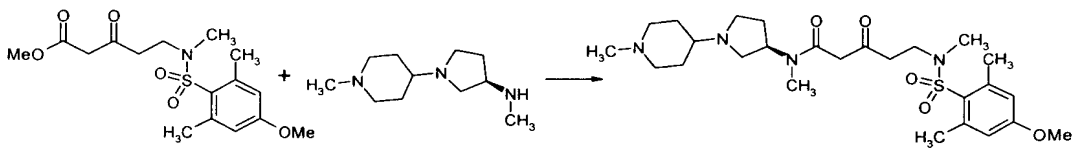


635c é preparado de maneira análoga a 38f a partir de 0,90 g (3,18 mmols) do produto de 635b e 5,0 ml (10,00 mmols) de hidreto de litioalumínio (2M em tetrahidrofurano) em 15 ml de tetrahidrofurano.

$C_{11}H_{23}N_3$ (197.32)

[M+H]+ = 198.

635d)



Uma mistura de 0,56 g (1,58 mmol) do produto de 635a, 0,54 g (2,73 mmols) do produto de 635c e 5 ml de tolueno é aquecida a 120°C por 24 horas. Em seguida, a mistura de reação é concentrada no vácuo à secura. O produto bruto obtido dessa maneira é purificado por meio de HPLC preparatória.

$C_{26}H_{42}N_4O_5S$ (522.70)

$[M+H]^+ = 523$

HPLC (método 9): tempo de retenção = 1,33 min.

Os seguintes exemplos descrevem formas de dosagem farmacêuticas, que contêm um composto desejado da fórmula geral I como substância ativa:

Exemplo I

Ampola seca com 75 mg de substância ativa por 10 ml

Composição:

substância ativa	75,0 mg
manitol	500 mg
água para fins injetáveis ad	10,0 ml

Preparação:

A substância ativa e manitol são dissolvidos em água. Após envasar, é liofilizado. A dissolução para formar a solução pronta para o uso é efetuada com água para fins de injeção.

Exemplo II

Comprimido com 50 mg de substância ativa

Composição:

(1) substância ativa	50,0 mg
(2) lactose	98,0 mg
(3) amido de milho	50,0 mg
(4) polivinilpirrolidona	15,0 mg

(5) estearato de magnésio	2,0 mg
	215,0 mg

Preparação:

(1), (2) e (3) são misturados e granulados com uma solução aquosa de (4). (5) é misturado ao granulado seco. Dessa mistura, são prensados comprimidos, biplanos com faceta bilateral e entalhe parcial monolateral.

Diâmetro dos comprimidos: 9 mm.

Exemplo III

Comprimido com 350 mg de substância ativa

Composição:

(1) substância ativa	350,0 mg
(2) lactose	136,0 mg
(3) amido de milho	80,0 mg
(4) polivinilpirrolidona	30,0 mg
(5) estearato de magnésio	4,0 mg
	600,0 mg

Preparação:

(1), (2) e (3) são misturados e granulados com uma solução aquosa de (4). (5) é misturado ao granulado. Dessa mistura, são prensados comprimidos, biplanos com faceta bilateral e entalhe parcial monolateral.

Diâmetro dos comprimidos: 12 mm.

Exemplo IV

Cápsulas com 50 mg de substância ativa

Composição:

(1) substância ativa	50,0 mg
(2) amido de milho seco	58,0 mg
(3) lactose pulverizada	50,0 mg
(4) estearato de magnésio	2,0 mg
	160,0 mg

Preparação:

(1) é triturado com (3). Essa trituração é acrescentada à mistura

de (2) e (4) sob intensa mistura.

Essa mistura em pó é envasada em uma máquina de envasar cápsulas em cápsulas de gelatina dura de duas peças do tamanho 3.

Exemplo V

Cápsulas com 350 mg de substância ativa

Composição:

(1) substância ativa	350,0 mg
(2) amido de milho seco	46,0 mg
(3) lactose pulverizada	30,0 mg
(4) estearato de magnésio	4,0 mg
	430,0 mg

Preparação:

(1) é triturado com (3). Essa trituração é acrescentada à mistura de (2) e (4) sob intensa mistura.

Essa mistura em pó é envasada em uma máquina de envasar cápsulas em cápsulas de gelatina dura de duas peças do tamanho 0.

Exemplo VI

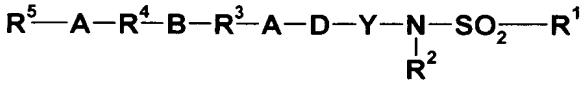
Supositórios com 100 mg de substância ativa

1 supositório contém:

substância ativa	100,0 mg
polietilenoglicol (M.G. 1500)	600,0 mg
polietilenoglicol (M.G. 6000)	460,0 mg
monoestearato de polietilenossorbitano	840,0 mg
	2000,0 mg

REIVINDICAÇÕES

1. Compostos, caracterizados pelo fato de que são da fórmula geral **I**



, (**I**)

na qual

A representa uma ligação, C_{1-4}-alquileno ou $-CH_2-C(O)-$,

B representa uma ligação, C_{1-3}-alquileno, -O- ou –C(O)-,

D representa um grupo das fórmulas gerais **II**



,

Y representa um grupo C_{1-6}-alquileno eventualmente substituído pelo radical $\mathbf{R^2}$, em que um grupo metileno pode ser adicionalmente substituído por $\mathbf{Y^1}$ e

$\mathbf{Y^1}$ representa –O-, -S-, -S(O)-, $-N(\mathbf{R^2})-$, $-N(\mathbf{R^2})-C(O)-$, $-C(O)-N(\mathbf{R^2})-$, -C(O)-, -CH(arila)-, C_{3-6}-cicloalquileno ou $-S(O)_2-$,

$\mathbf{R^1}$ C_{3-7}-cicloalquila ou aril-, heteroaril- ou aril-C_{1-3}-alquila, que em cada caso podem ser substituídos por um, dois, três ou quatro radicais $\mathbf{R^{1.1}}$, em que os radicais $\mathbf{R^{1.1}}$ podem ser iguais ou diferentes e

$\mathbf{R^{1.1}}$ representa H, F, Cl, Br, I, C_{1-3}-alquila, F_3C-, HO-, C_{1-3}-alquila-O- ou C_{1-3}-alquil-O-C_{2-4}-alquileno-O-,

$\mathbf{R^2}$ H ou C_{1-3}-alquila, em que cada grupo metileno pode ser substituído com até dois e cada grupo metila com até três átomos de flúor ou também $H_3C-C(O)-$,

$\mathbf{R^3}$ a) C_{1-6}-alquileno,

b) um grupo C_{3-6}-cicloalquileno substituído uma, duas ou três vezes por $\mathbf{R^{3.1}}$

c) um grupo C_{5-7}-cicloalquenileno substituído uma ou duas vezes por $\mathbf{R^{3.1}}$, que é condensado com um anel fenila através da ligação insaturada,

d) $-N(\mathbf{R^2})$,

e) um grupo arileno substituído uma ou duas vezes por $\mathbf{R^{3.1}}$,

f) um grupo heteroarileno substituído uma ou duas vezes por

$R^{3.1}$,

g) um anel heterocíclico saturado com 4 a 7 membros substituído uma ou duas vezes por $R^{3.1}$,

h) um anel heterocíclico insaturado com 4 a 7 membros substituído uma ou duas vezes por $R^{3.1}$, que é condensado com um ou dois anéis fenila através das ligações insaturadas, ou

i) um aza-heterobiciclo saturado com 8 a 10 membros substituído uma ou duas vezes por $R^{3.1}$,

em que os radicais $R^{3.1}$ em cada caso podem ser iguais ou diferentes e

$R^{3.1}$ representa H, F, Cl, Br, I, C_{1-3}-alquila-, HO-, C_{1-3}-alquila-O- ou C_{1-3}-alquil-O-C_{2-4}-alquileno-O- ou

R^3 também representa –O-, quando **B** não representa o grupo –O-,

R^4 a) –O-,

b) –C(O)O-,

c) –C(O)NR^2-,

d) –NR^2-,

e) –NR^2-NR^2-,

f) C_{3-7}-cicloalquileno,

g) C_{1-6}-alquileno,

h) um grupo arileno substituído uma ou duas vezes por $R^{4.1}$,

i) um grupo heteroarileno substituído uma ou duas vezes por $R^{4.1}$,

j) um anel heterocíclico saturado com 4 a 7 membros substituído uma ou duas vezes por $R^{4.1}$,

k) um diaza-heterobiciclo saturado com 8 a 10 membros substituído uma ou duas vezes por $R^{4.1}$,

l) um anel heterocíclico insaturado com 5 a 7 membros substituído uma ou duas vezes por $R^{4.1}$, que é condensado com um ou dois anéis fenila através de ligações insaturadas ou

m) um diaza-spirociclo saturado com 9 a 11 membros,

em que os radicais $R^{4.1}$ em cada caso podem ser iguais ou diferentes e

$R^{4.1}$ representa H, F, Cl, Br, I, C_{1-3}-alquila-, HO-, C_{1-3}-alquila-O- ou C_{1-3}-

alquila-O-C_{2-4}-alquileno-O-,

$\mathbf{R^5}$ H, HO-, C_{1-8}-alquila, um grupo C_{3-7}-cicloalquila eventualmente substituído por C_{1-3}-alquila, H_2N, C_{1-4}-alquila-NH, (C_{3-6}-cicloalquil)-NH, (C_{1-4}-alquil)$_2$N, (C_{1-4}-alquil)(C_{3-6}-cicloalquil)N, (ciclopropilmetil)(metil)N, H_2N-C(O), um grupo fenila substituído uma ou duas vezes por $\mathbf{R^{5.1}}$, um grupo heteroarila substituído uma ou duas vezes por $\mathbf{R^{5.1}}$ ou um anel heterocíclico saturado com 4 a 7 membros substituído uma ou duas vezes por $\mathbf{R^{5.1}}$, em que os radicais $\mathbf{R^{5.1}}$ em cada caso podem ser iguais ou diferentes e

$\mathbf{R^{5.1}}$ representa H, F, Cl, Br, I, C_{1-3}-alquila-, HO-, C_{1-3}-alquila-O-, (C_{1-3}-alquila)$_2$N ou C_{1-3}-alquil-O-C_{2-4}-alquileno-O-,

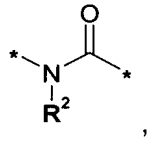
seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos.

2. Compostos da fórmula geral **I** de acordo com a reivindicação 1, caracterizados pelo fato de que

A representa uma ligação, C_{1-4}-alquileno ou $-CH_2$-C(O)-,

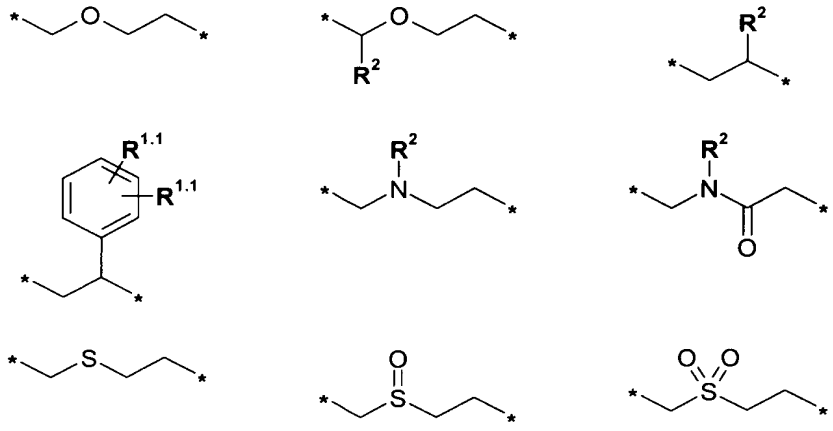
B representa uma ligação, C_{1-2}-alquileno, -O- ou –C(O)-,

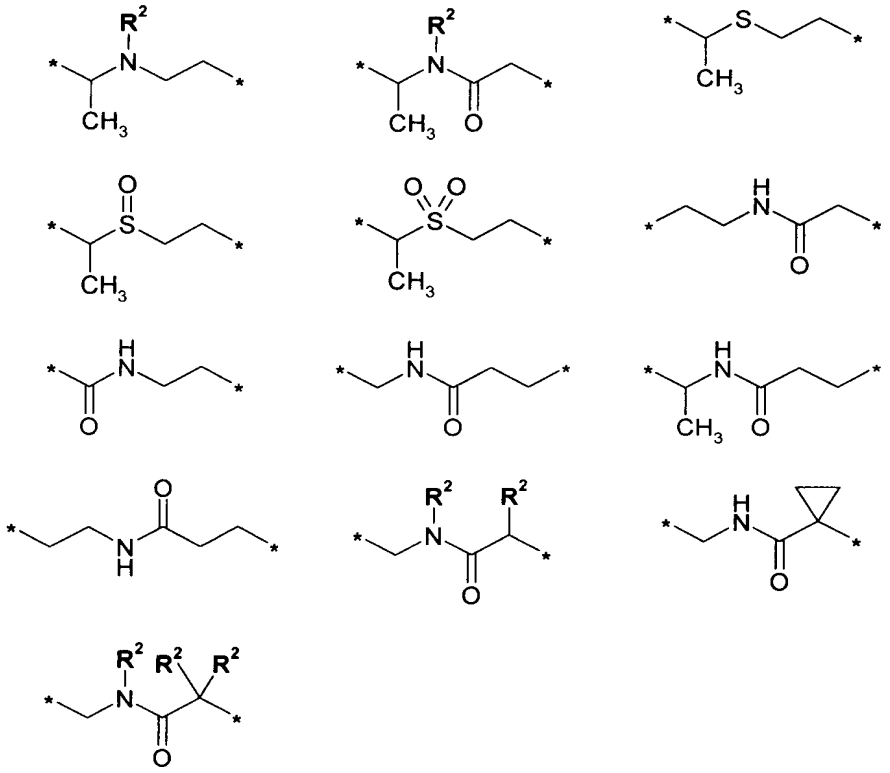
D representa um grupo da fórmula geral **II**



,

Y representa C_{1-4}-alquileno ou um grupo selecionado de



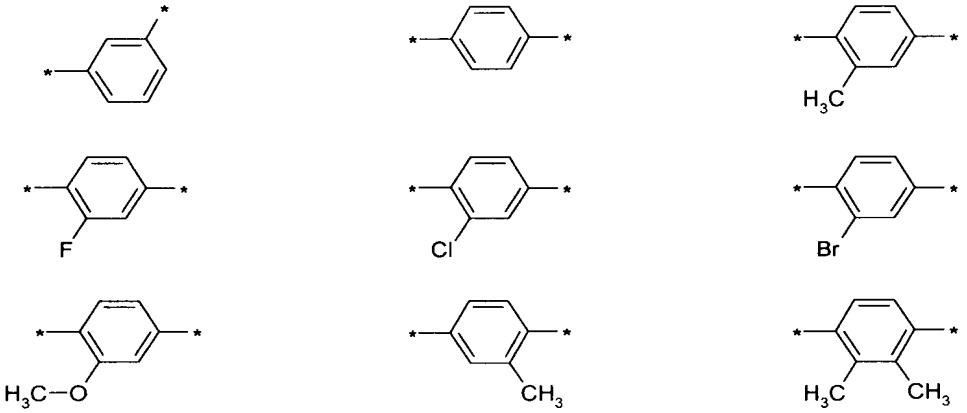


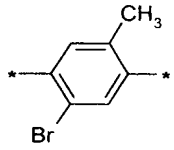
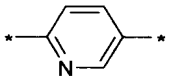
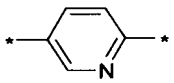
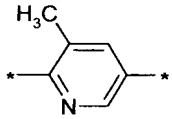
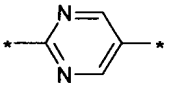
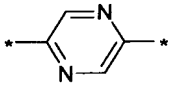
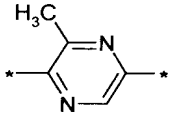
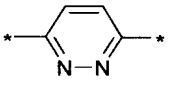
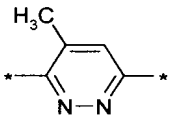
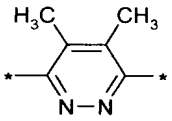
R¹ representa arila ou heteroarila, que podem ser substituídos em cada caso por um, dois, três ou quatro radicais **R^1.1**, em que os radicais **R^1.1** podem ser iguais ou diferentes e

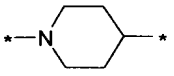
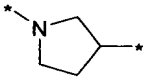
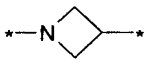
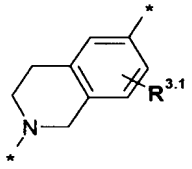
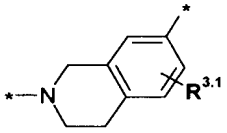
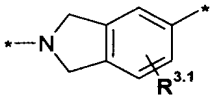
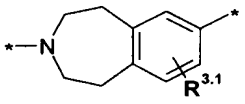
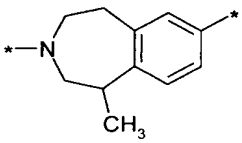
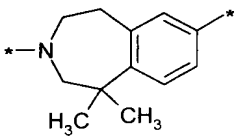
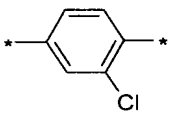
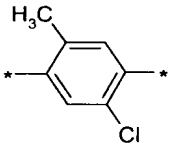
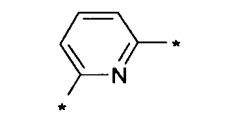
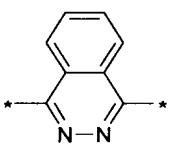
R^1.1 representa H, F, Cl, Br, I, C_{1-3}-alquila, F_3C-, HO-, C_{1-3}-alquila-O- ou C_{1-3}-alquil-O-C_{2-4}-alquileno-O-,

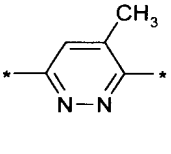
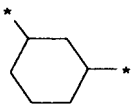
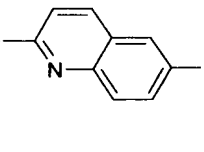
R² representa H, H_3C, H_5C_2, isopropila, F_3C-CH_2, F_2CH-CH_2 ou FH_2C-H_2C,

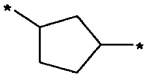
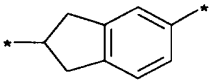
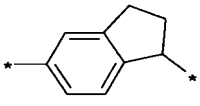
R³ representa C_{1-4}-alquileno, -N(**R²**) ou um grupo selecionado de

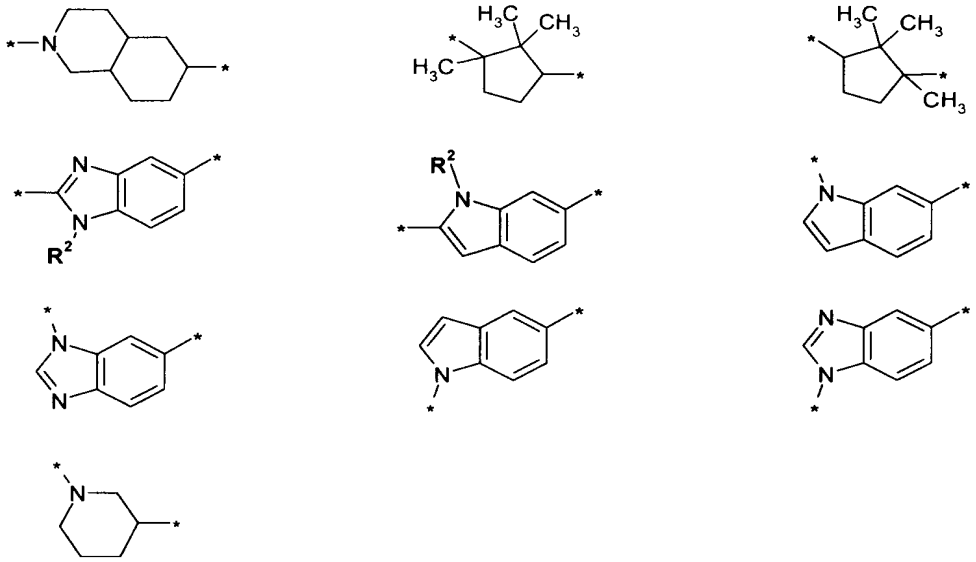


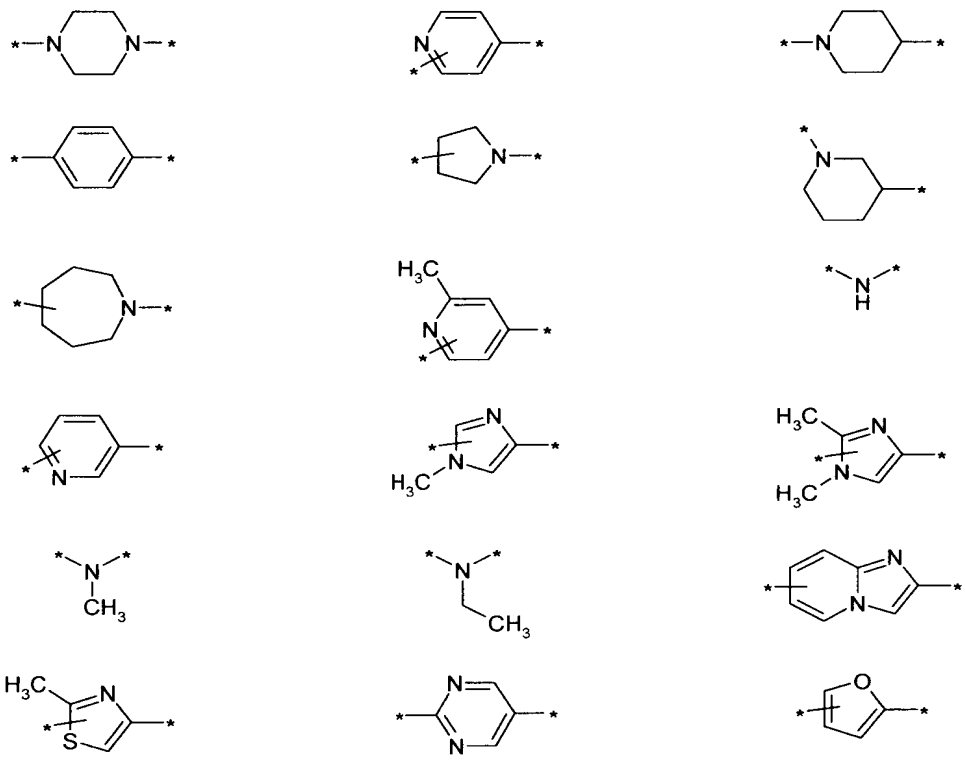


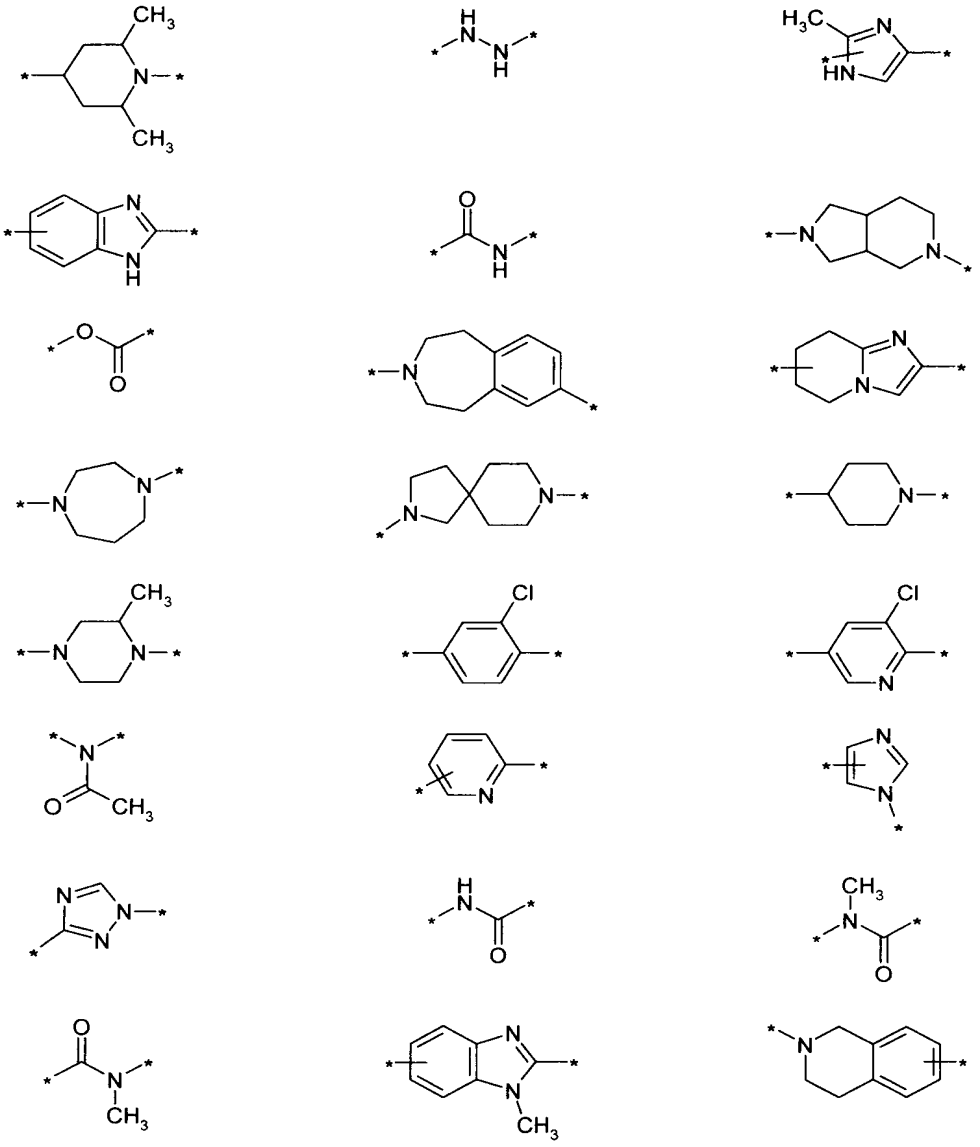
nas quais

$R^{3.1}$ representa H, F, Cl, Br, I, C_{1-3}-alquila-, HO-, C_{1-3}-alquila-O- ou C_{1-3}-alquil-O-C_{2-4}-alquileno-O- ou

R^3 também representa –O-, quando **B** não representa o grupo –O-,

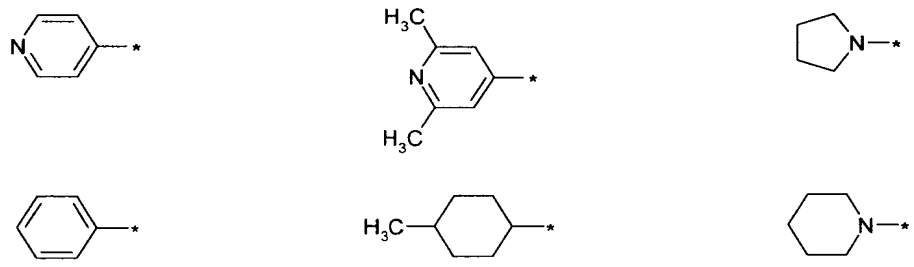
R^4 representa C_{1-4}-alquileno, C_{3-7}-cicloalquileno, -O- ou um grupo selecionado de

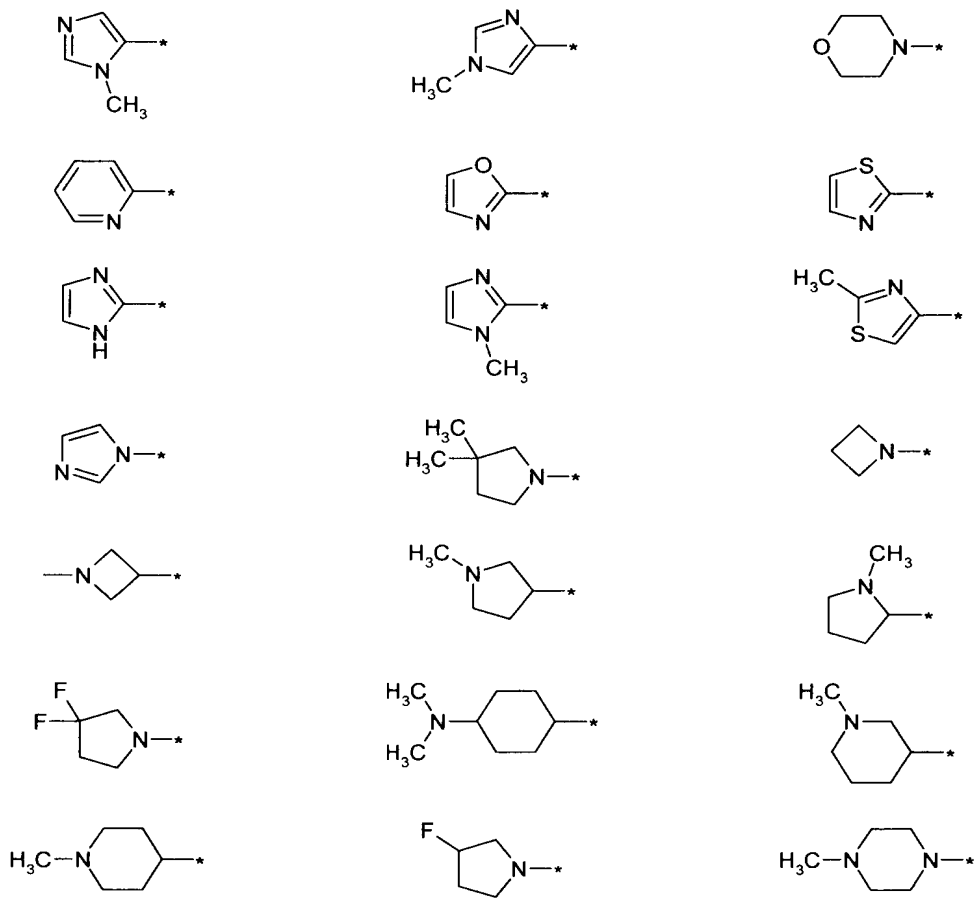




R^5 representa H, C_{1-8}-alquila, grupo C_{3-7}-cicloalquila, HO, (C_{1-3}-alquila)-O, (C_{1-4}-alquila)-NH, (C_{3-6}-cicloalquila)-NH, (C_{1-4}-alquila)$_2$N, (C_{1-4}-alquila)(C_{3-6}-cicloalquila)N, (ciclopropilmetil)(metila)N, H_2N-C(O) ou

R^5 representa um grupo selecionado de





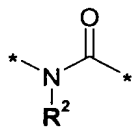
seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos.

3. Compostos da fórmula geral **I** de acordo com a reivindicação 1, caracterizados pelo fato de que

A representa uma ligação, C_{1-3}-alquileno ou $-CH_2-C(O)-$,

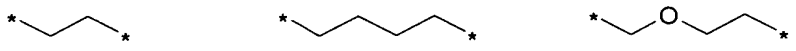
B representa uma ligação, C_{1-2}-alquileno, -O- ou $-C(O)-$,

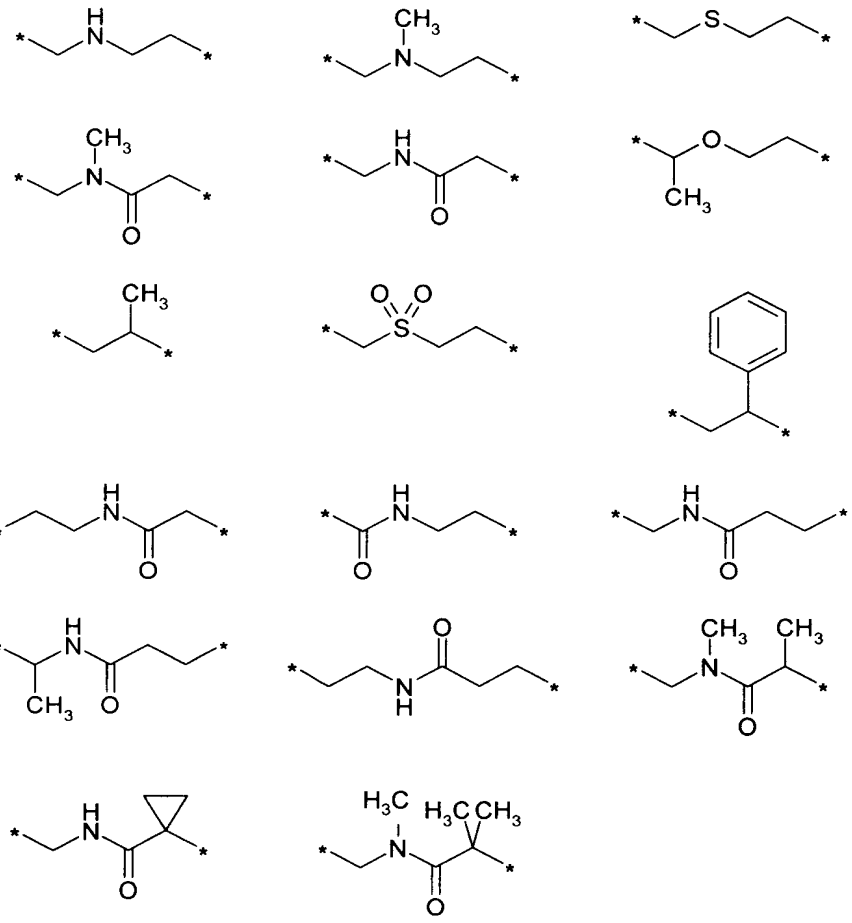
D representa um grupo da fórmula geral **II**



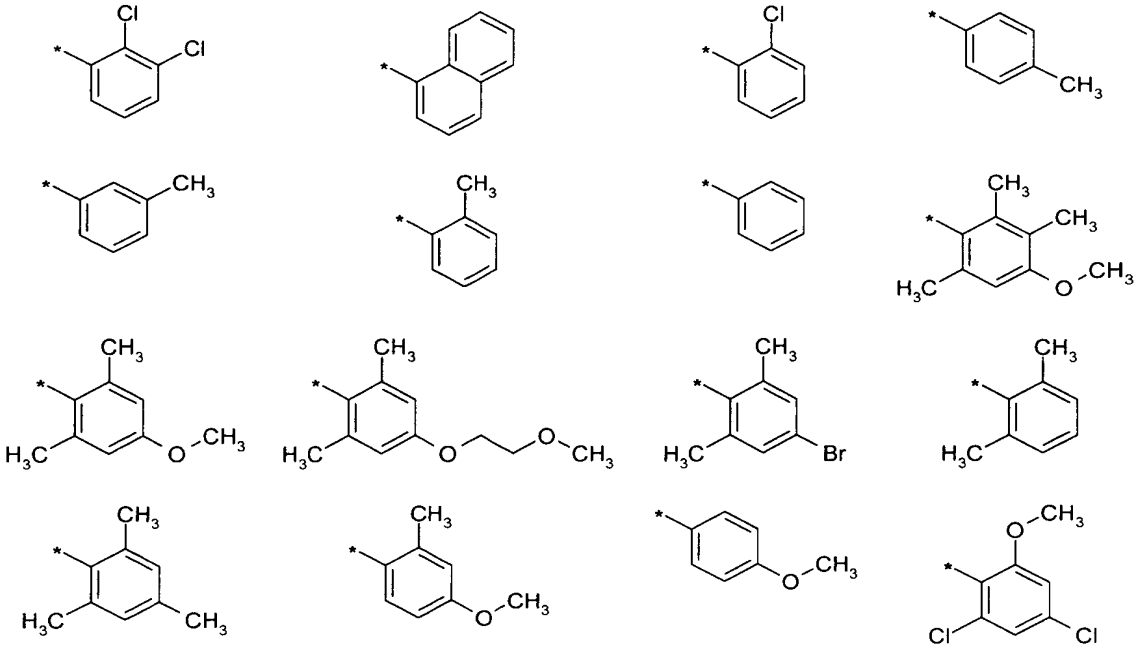
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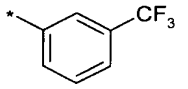
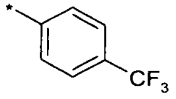
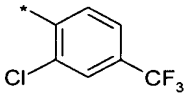
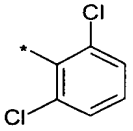
Y representa um grupo selecionado de





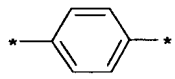
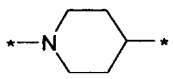
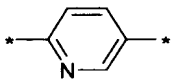
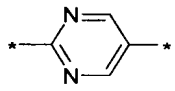
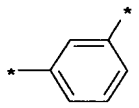
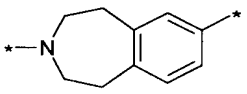
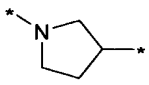
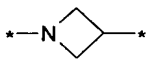
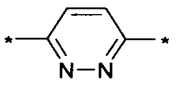
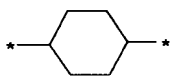
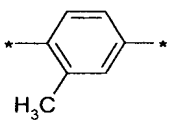
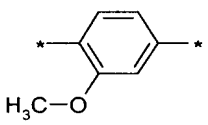
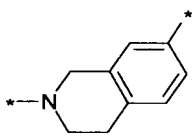
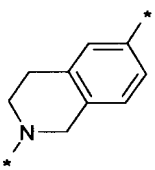
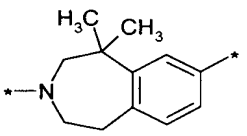
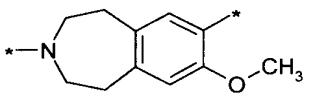
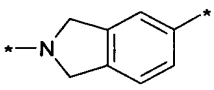
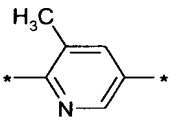
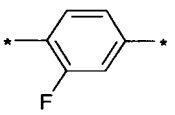
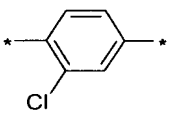
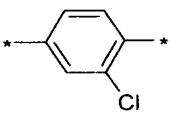
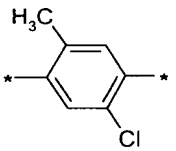
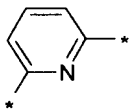
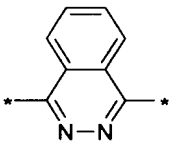
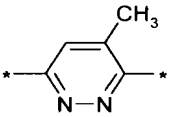
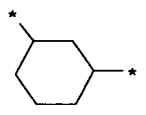
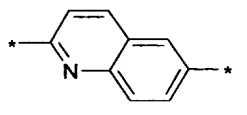
R[1] representa um grupo selecionado de

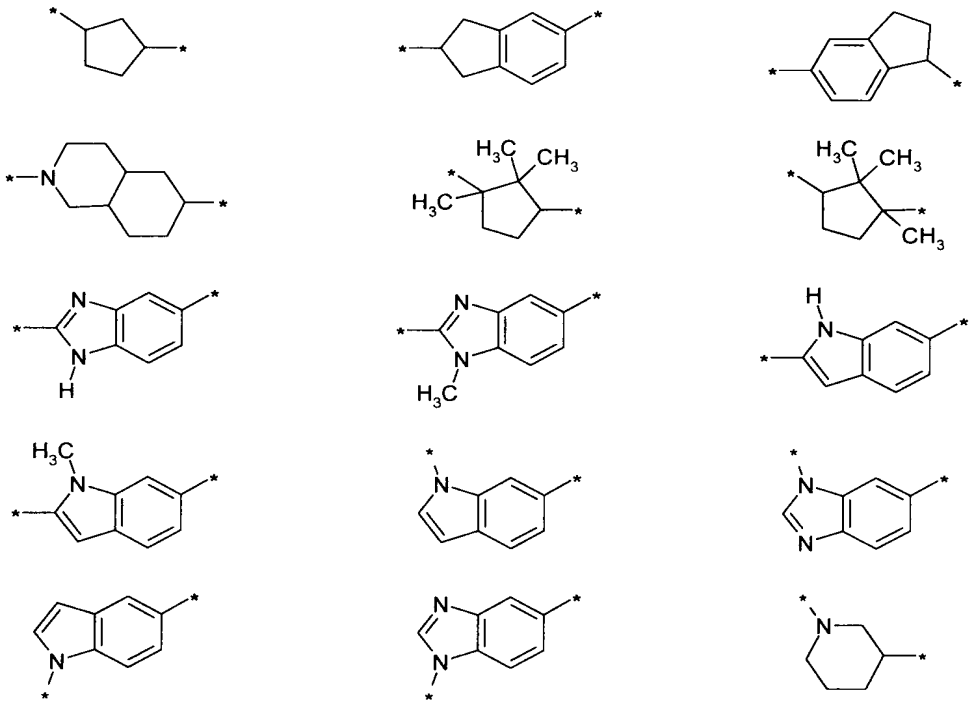


R² representa H, H_3C-, H_5C_2- ou FH_2C-H_2C-,

R³ representa C_{1-4}-alquileno, -NH-, -$N(CH_3)$- ou um grupo selecionado de

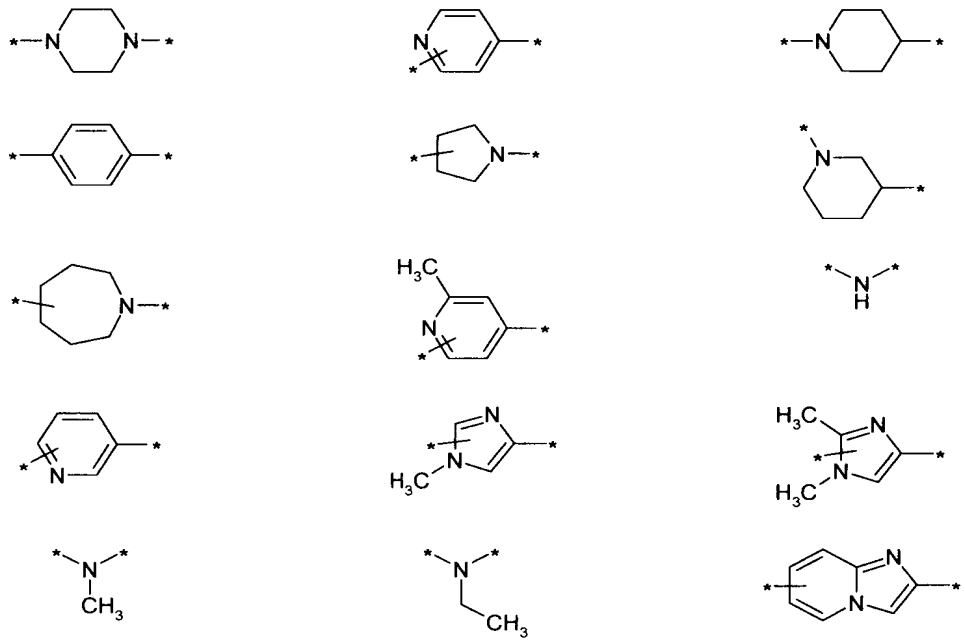




























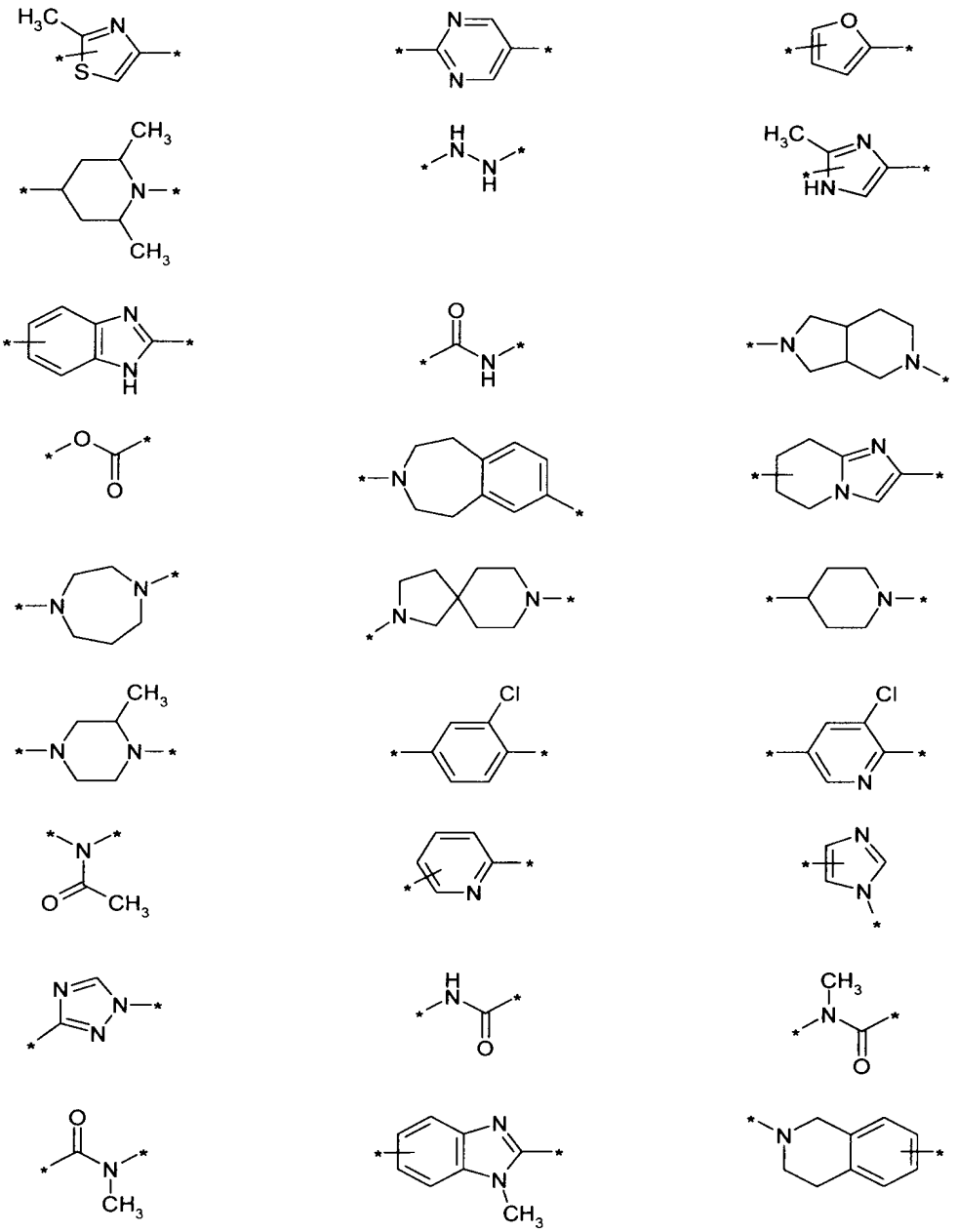


ou

R^3 também representa –O-, quando **B** não representa o grupo –O-,

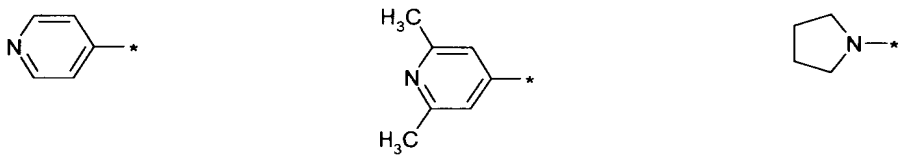
R^4 representa C_{1-4}-alquileno, C_{3-7}-cicloalquileno, -O- ou um grupo selecionado de

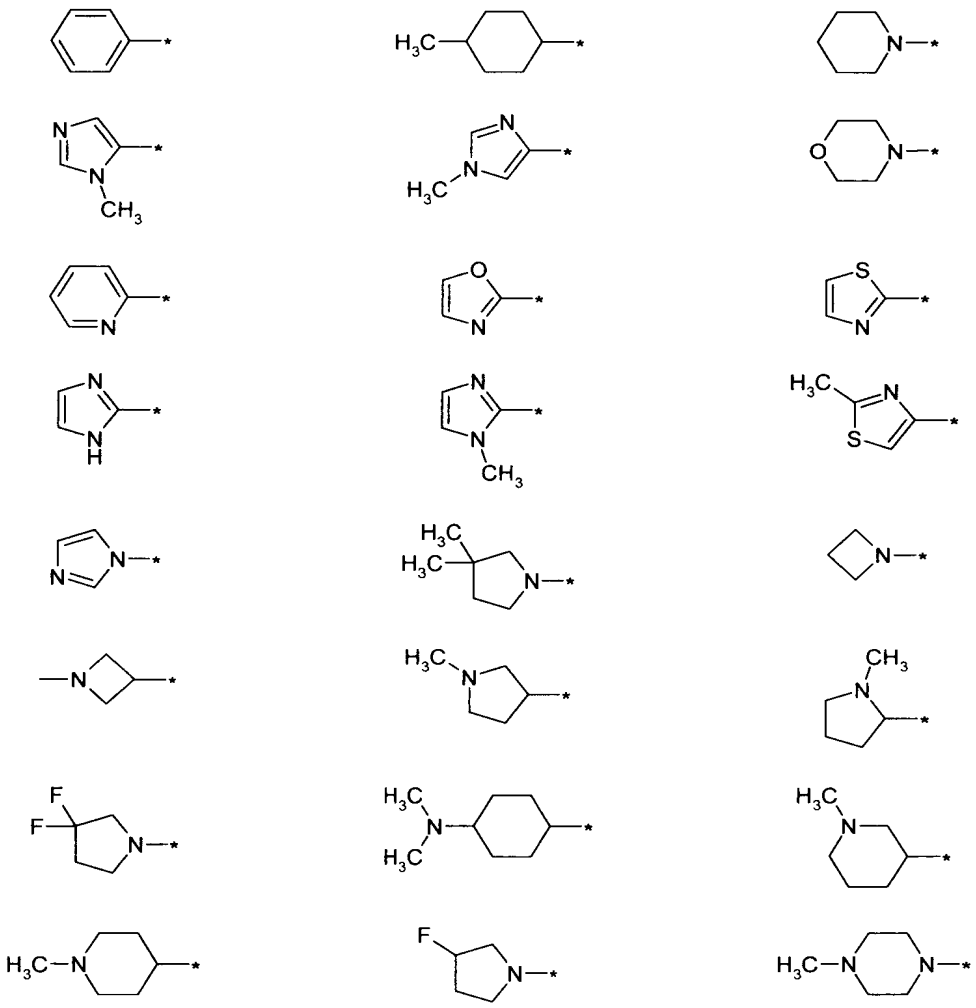




R^5 representa H, HO-, C_{1-5}-alquila, C_{3-5}-cicloalquila, H_2N-, (C_{1-2}-alquila)-NH-, (C_{3-6}-cicloalquila)-NH-, (C_{1-2}-alquila)$_2$N-, (C_{1-4}-alquil)(C_{3-6}-cicloalquila)N-, (ciclopropilmetil)(metil)N-, H_2N-C(O)- ou

R^5 representa um grupo selecionado de



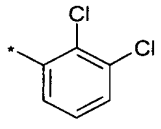


seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos.

4. Compostos da fórmula geral **I** de acordo com a reivindicação 1, caracterizados pelo fato de que

A, **B**, **D**, **Y**, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$ e $\mathbf{R^5}$ são definidos tal como na reivindicação 1, e

$\mathbf{R^1}$ representa o grupo

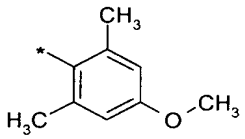


seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos.

5. Compostos da fórmula geral **I** de acordo com a reivindicação 1, caracterizados pelo fato de que

A, **B**, **D**, **Y**, R^2, R^3, R^4 e R^5 são definidos tal como na reivindicação 1, e

R^1 representa o grupo

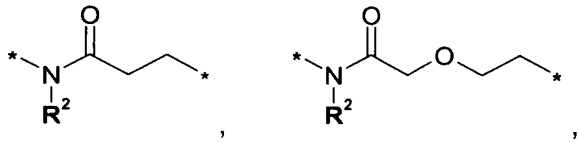


seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos.

6. Compostos da fórmula geral **I** de acordo com a reivindicação 1, caracterizados pelo fato de que

A, **B**, R^1, R^3, R^4 e R^5 são definidos tal como na reivindicação 1, e

-D-Y- juntos representam um grupo selecionado de

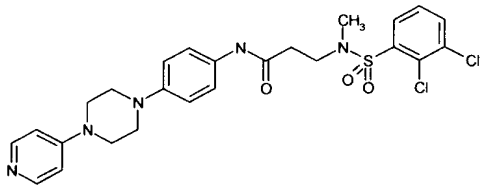


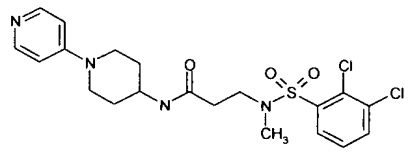
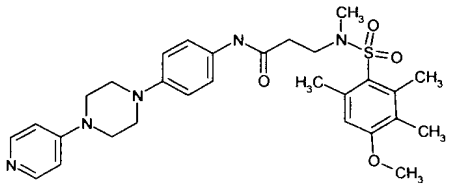
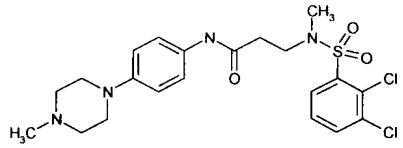
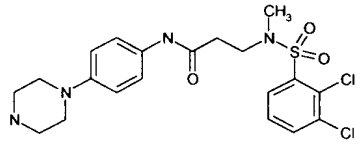
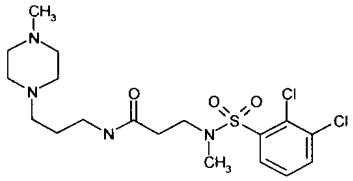
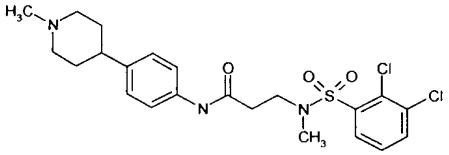
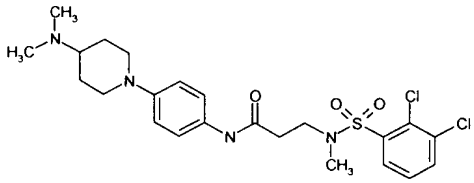
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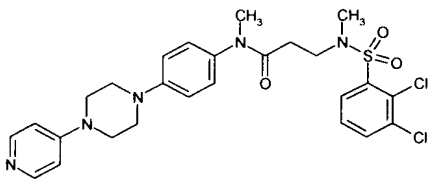
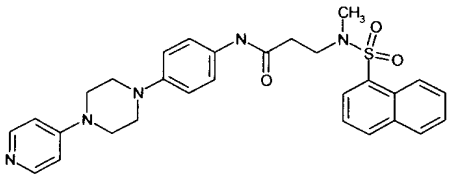
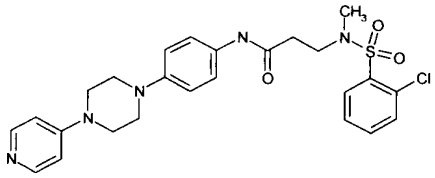
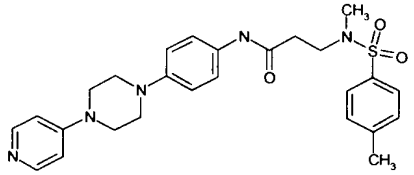
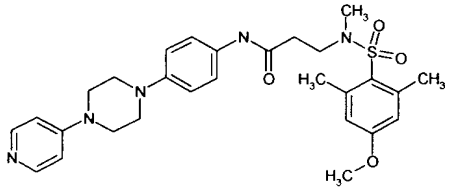
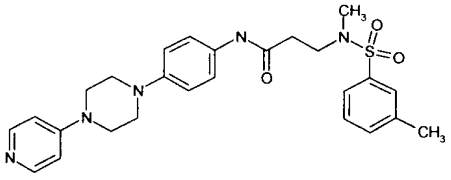
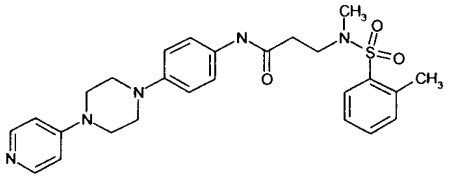
R^2 representa H ou C_{1-3}-alquila,

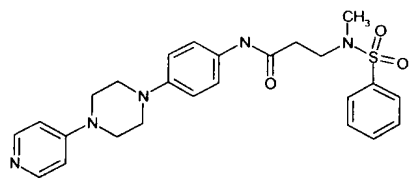
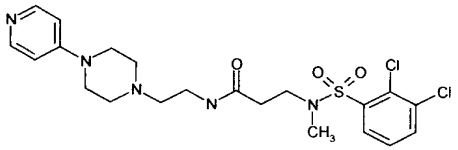
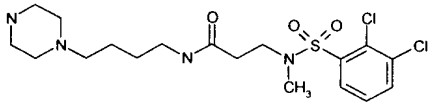
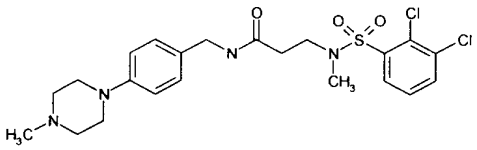
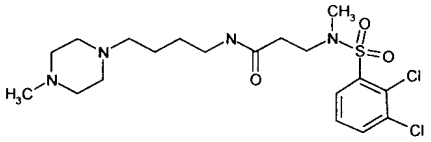
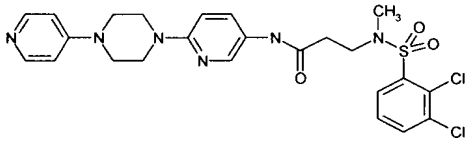
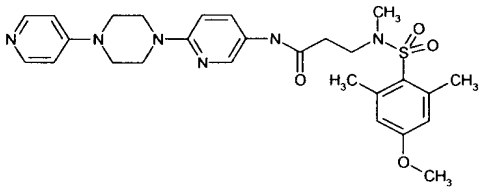
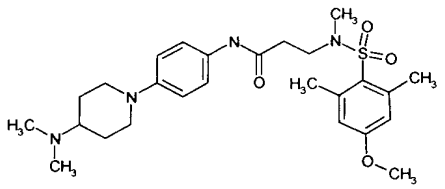
seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos.

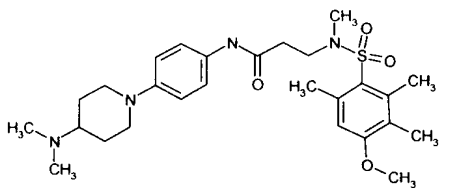
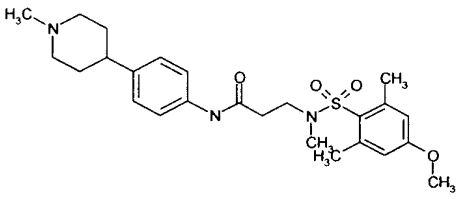
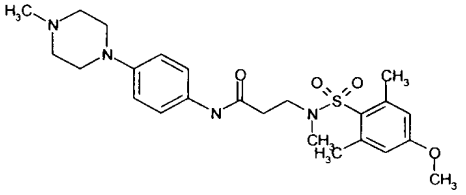
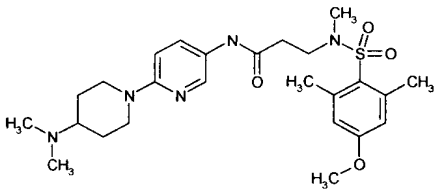
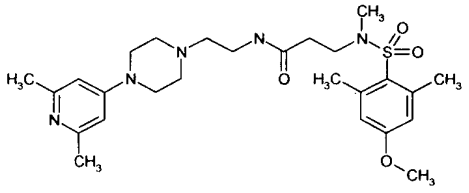
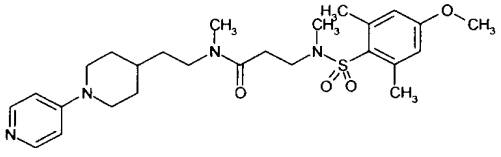
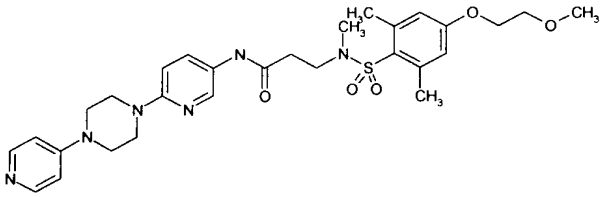
7. Compostos da fórmula geral **I** de acordo com a reivindicação 1, caracterizados pelo fato de que são

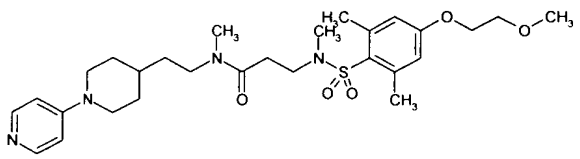
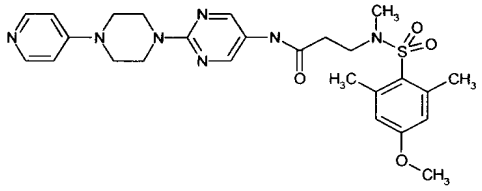
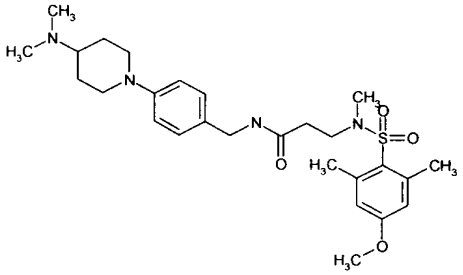
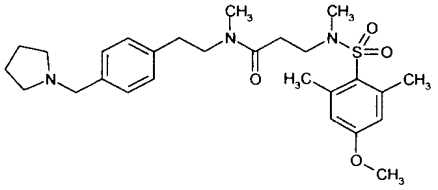
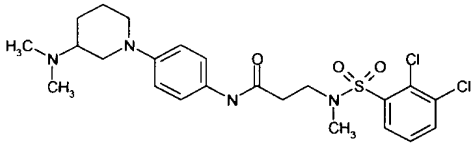
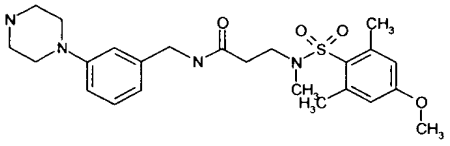
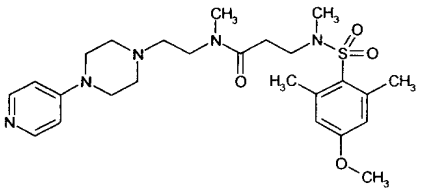
Exemplo	Estrutura
(1)	

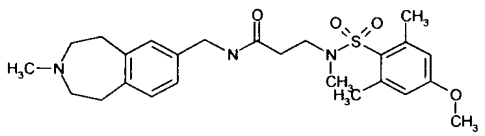
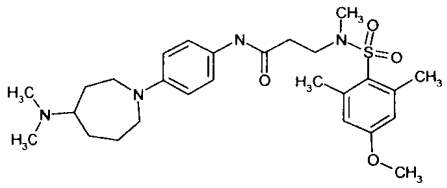
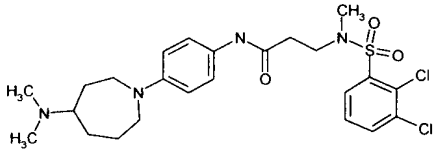
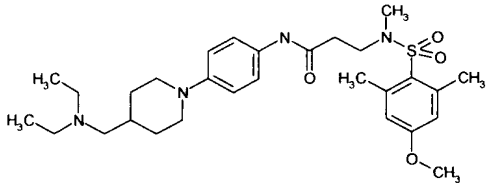
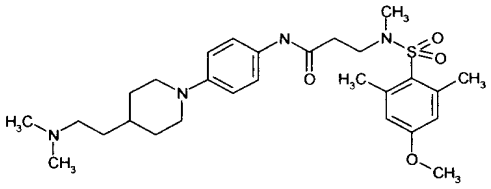
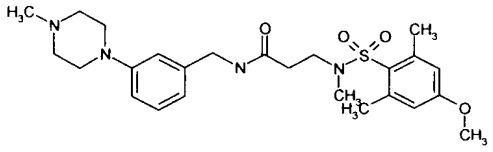
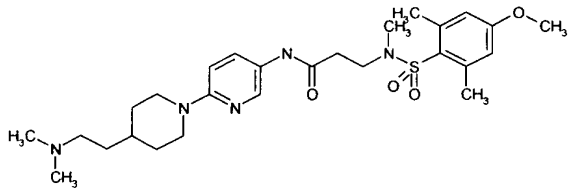
Exemplo	Estrutura
(2)	
(3)	
(4)	
(5)	
(6)	
(7)	
(8)	

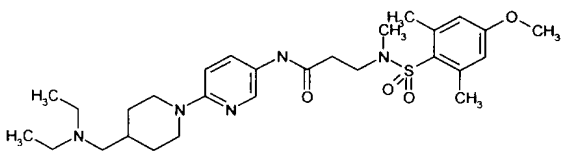
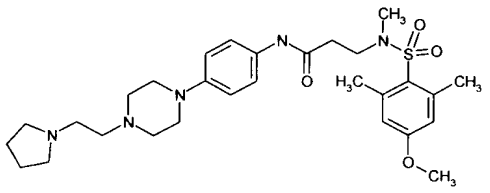
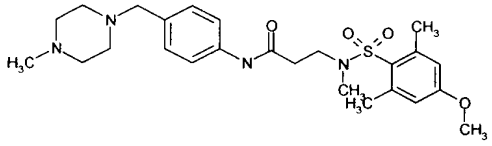
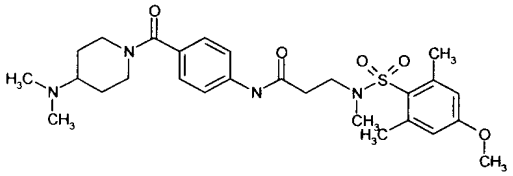
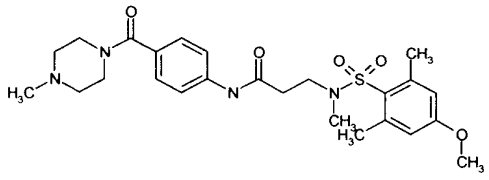
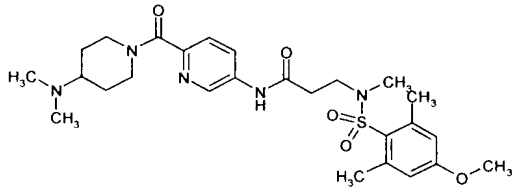
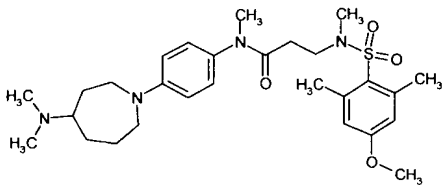
Exemplo	Estrutura
(9)	
(10)	
(11)	
(12)	
(13)	
(14)	
(15)	

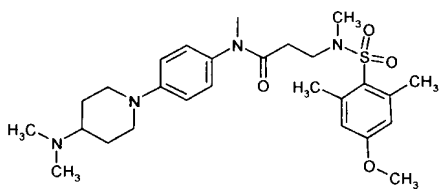
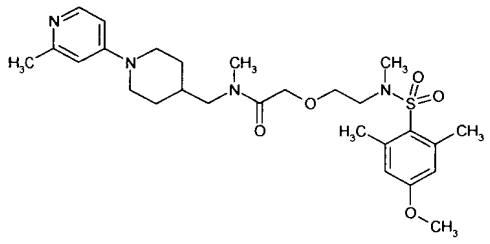
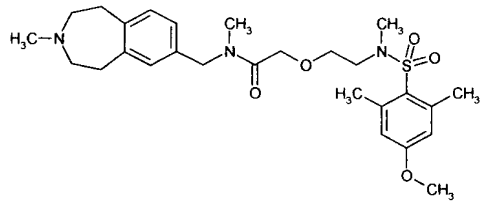
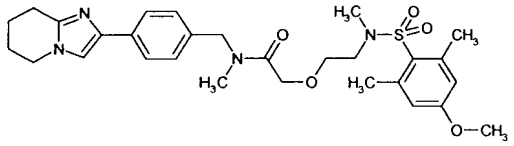
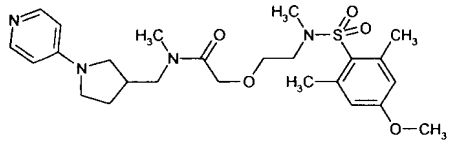
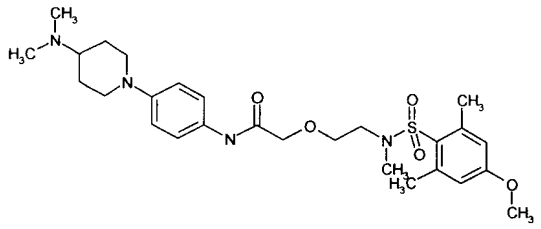
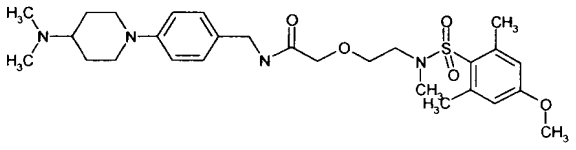
Exemplo	Estrutura
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(17)	
(18)	
(19)	
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(21)	
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(23)	

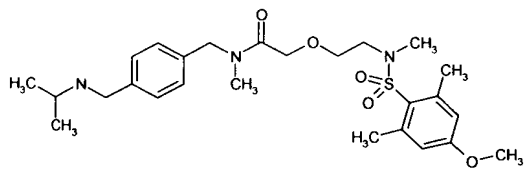
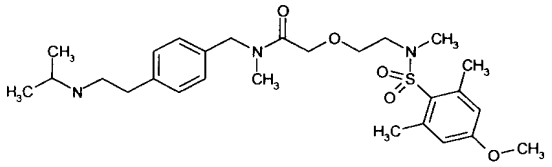
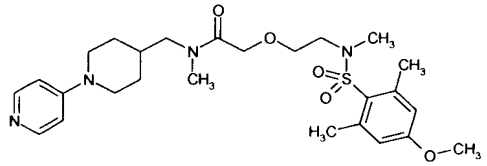
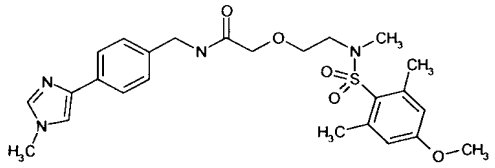
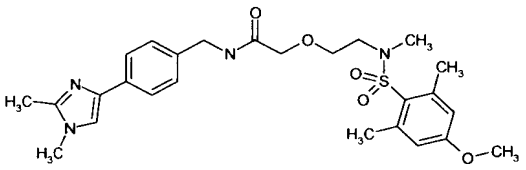
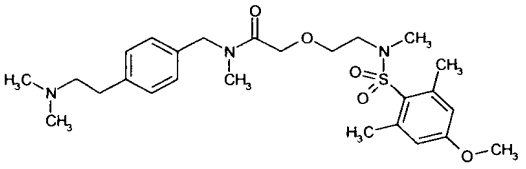
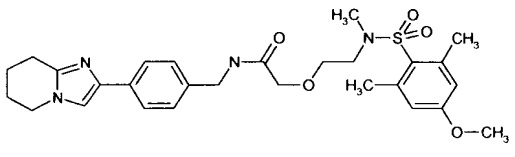
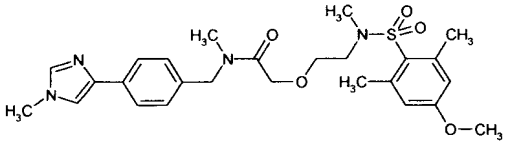
Exemplo	Estrutura
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(25)	
(26)	
(27)	
(28)	
(29)	
(30)	

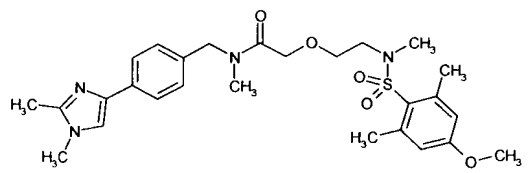
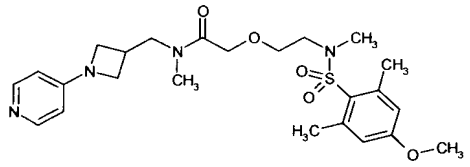
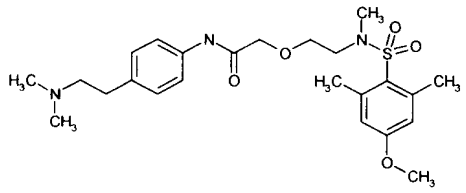
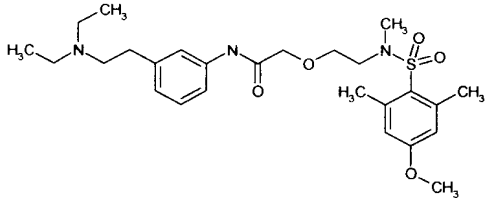
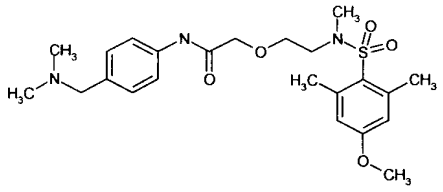
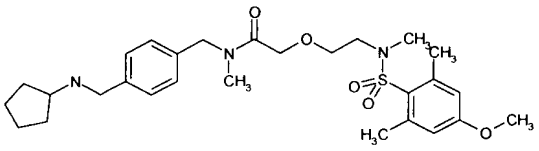
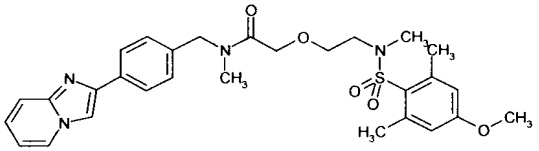
Exemplo	Estrutura
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(32)	
(33)	
(34)	
(35)	
(36)	
(37)	

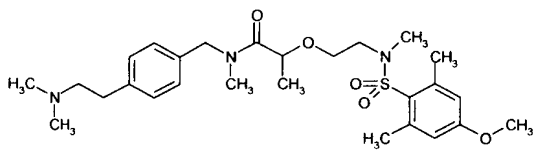
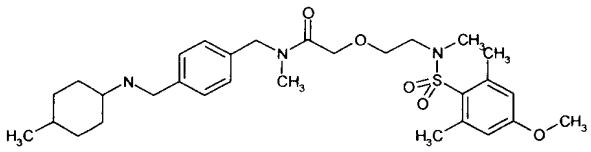
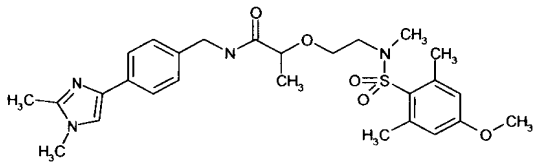
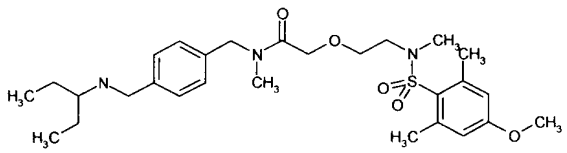
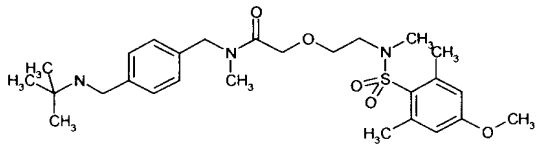
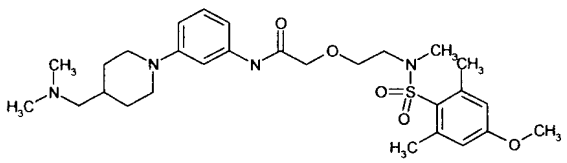
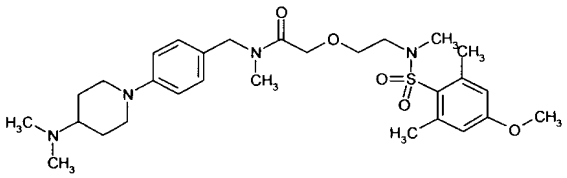
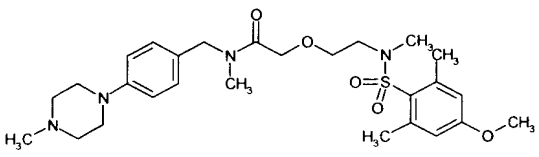
Exemplo	Estrutura
(38)	
(39)	
(40)	
(41)	
(42)	
(43)	
(44)	

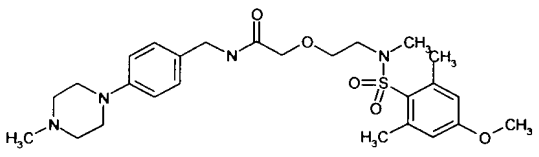
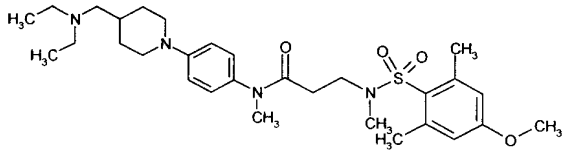
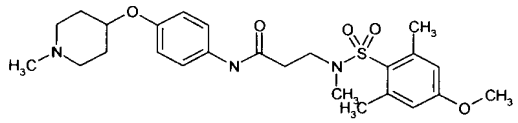
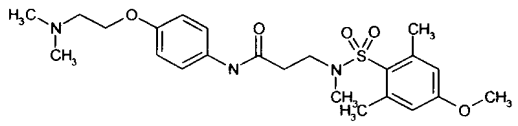
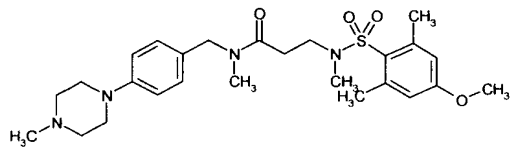
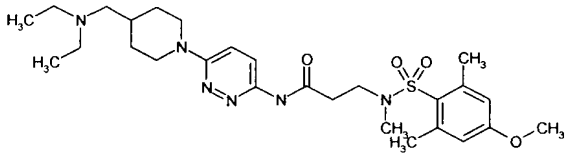
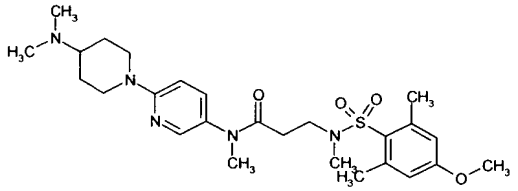
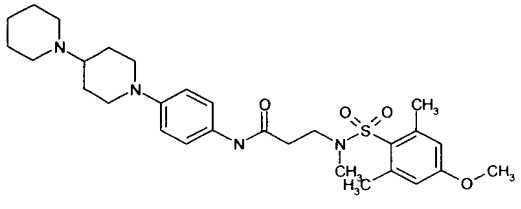
Exemplo	Estrutura
(45)	
(46)	
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(48)	
(49)	
(50)	
(51)	

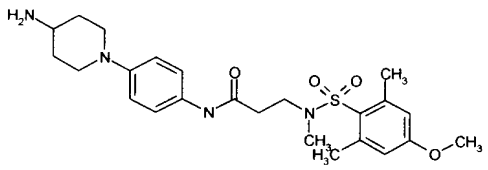
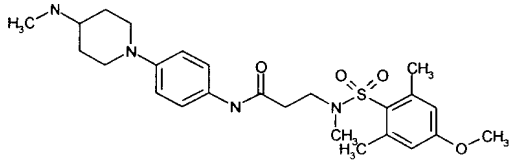
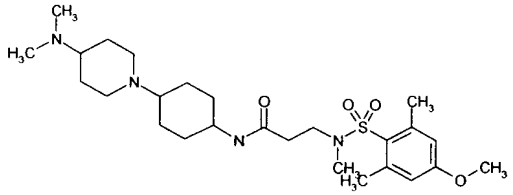
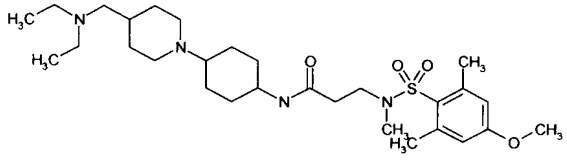
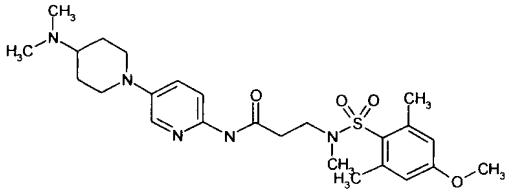
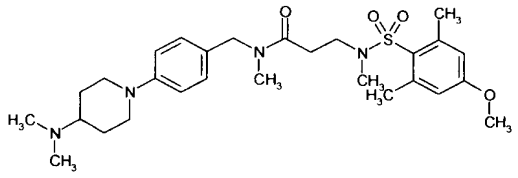
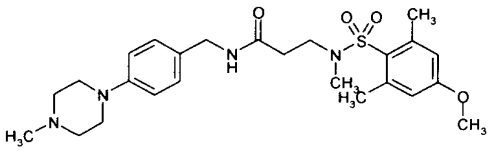
Exemplo	Estrutura
(52)	
(53)	
(54)	
(55)	
(56)	
(57)	
(58)	

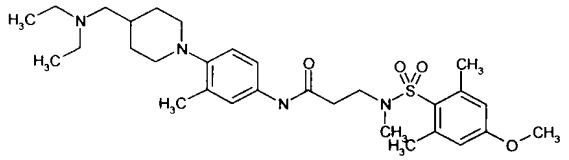
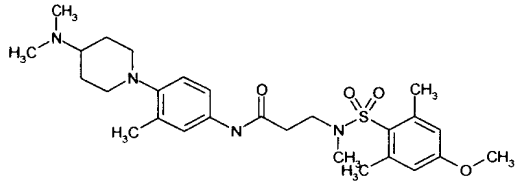
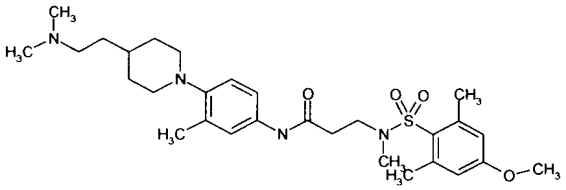
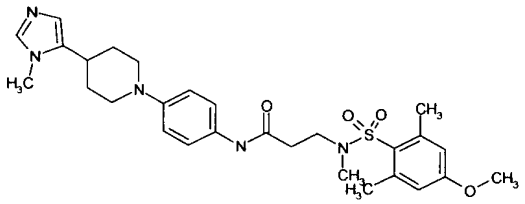
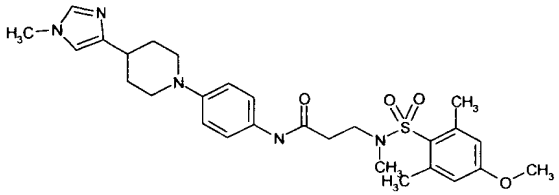
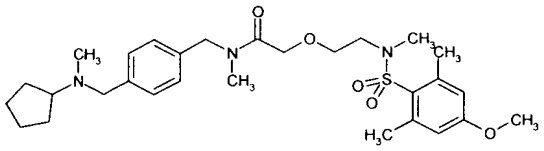
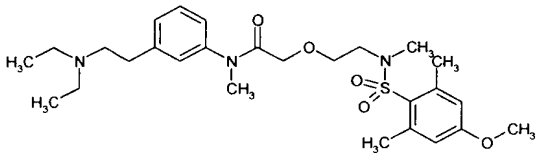
Exemplo	Estrutura
(59)	
(60)	
(61)	
(62)	
(63)	
(64)	
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(66)	

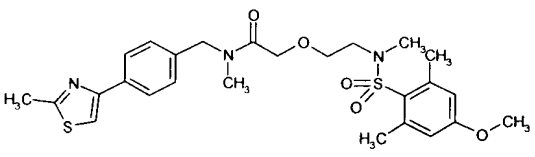
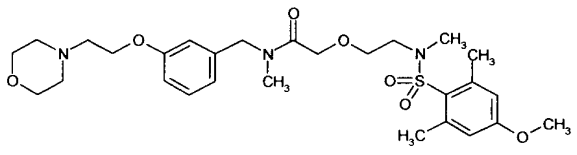
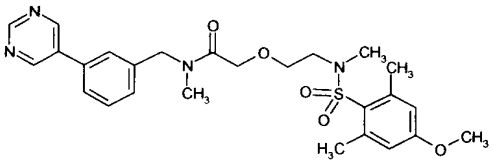
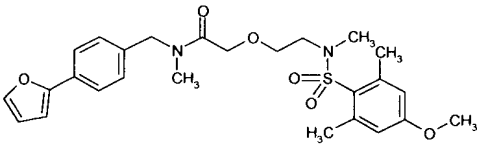
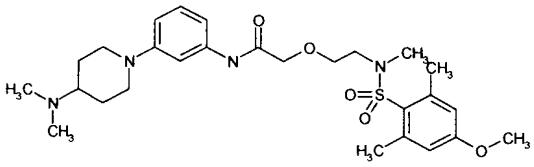
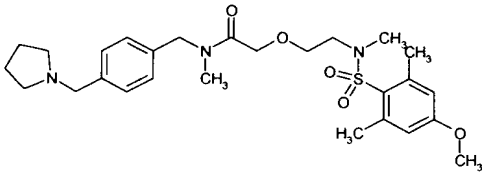
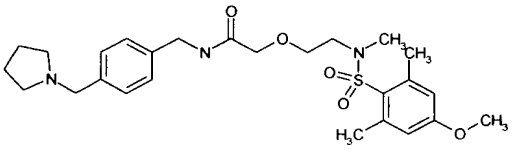
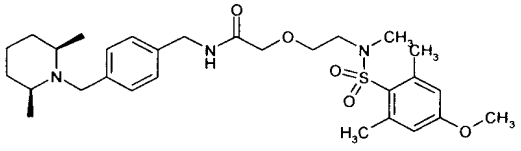
Exemplo	Estrutura
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(68)	
(69)	
(70)	
(71)	
(72)	
(73)	

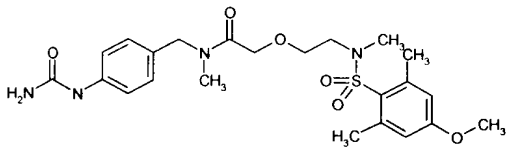
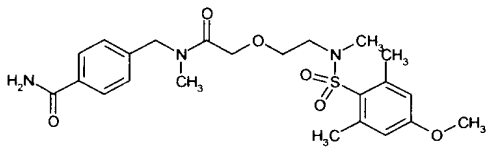
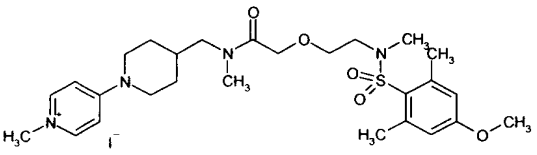
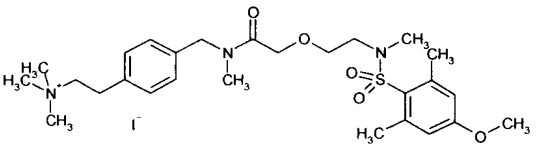
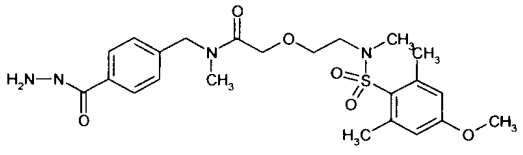
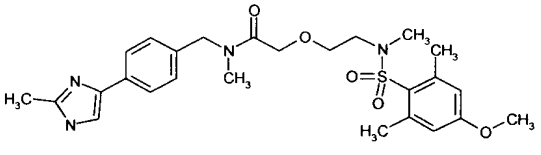
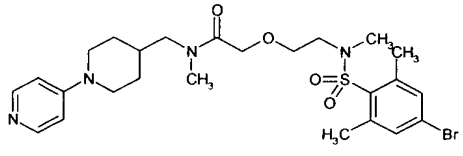
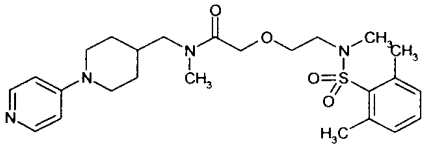
Exemplo	Estrutura
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(75)	
(76)	
(77)	
(78)	
(79)	
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(81)	

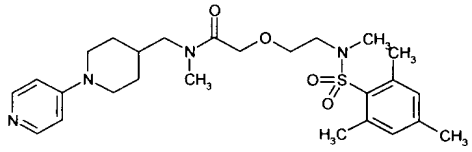
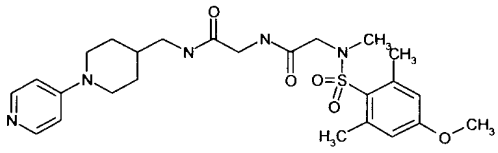
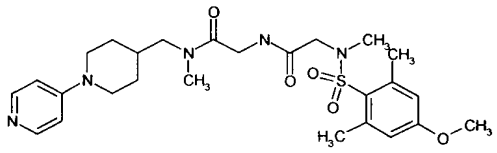
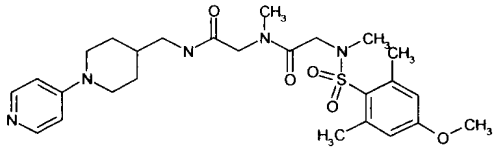
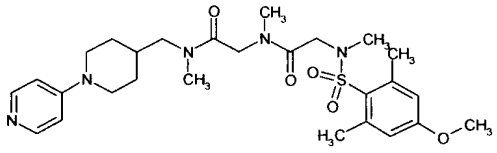
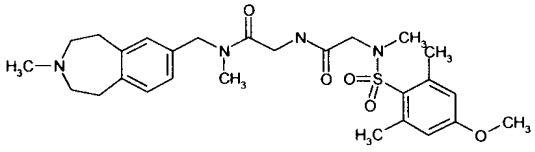
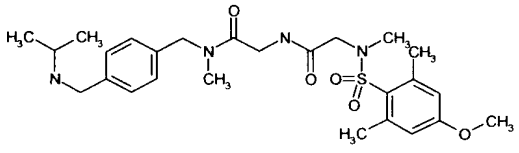
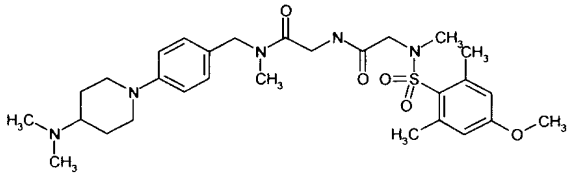
Exemplo	Estrutura
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(83)	
(84)	
(85)	
(86)	
(87)	
(88)	
(89)	

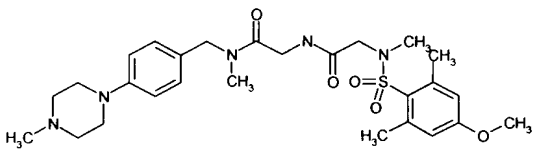
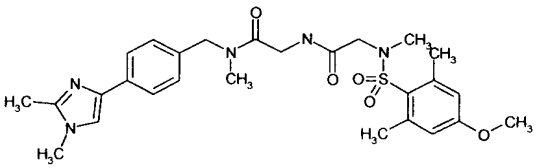
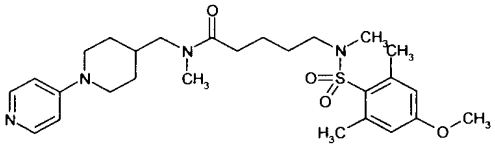
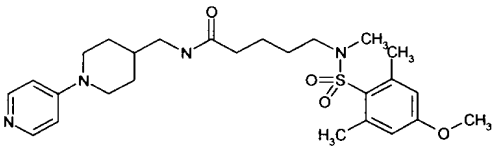
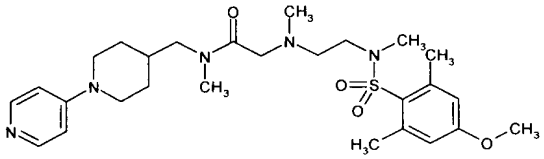
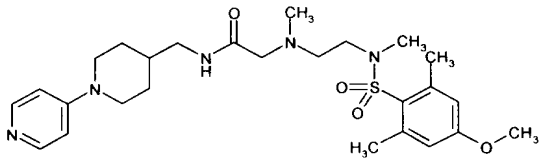
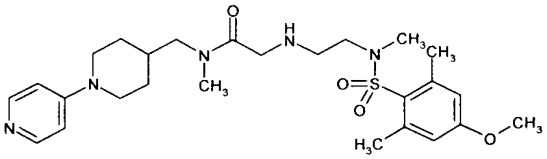
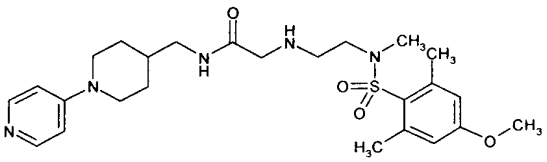
Exemplo	Estrutura
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(91)	
(92)	
(93)	
(94)	
(95)	
(96)	

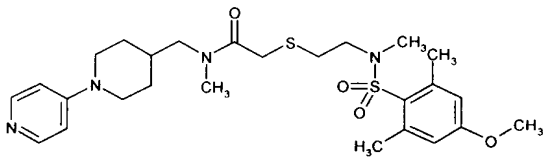
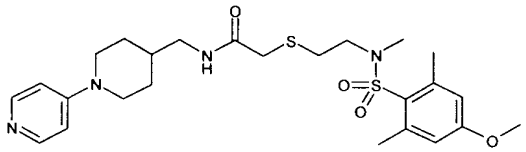
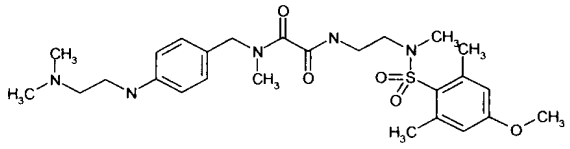
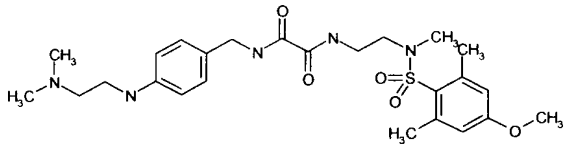
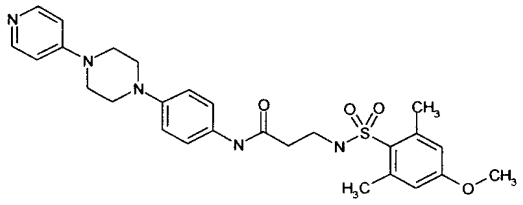
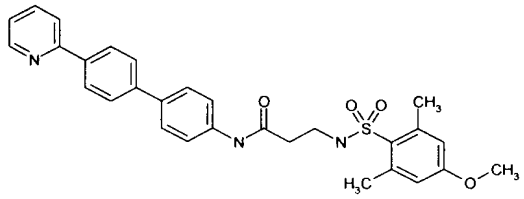
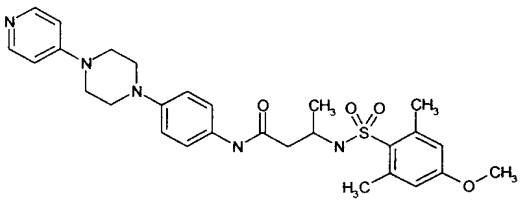
Exemplo	Estrutura
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(98)	
(99)	
(100)	
(101)	
(102)	
(103)	

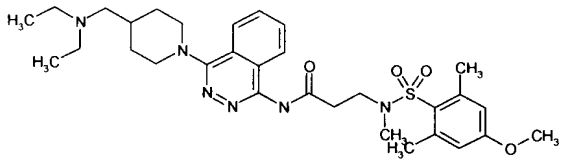
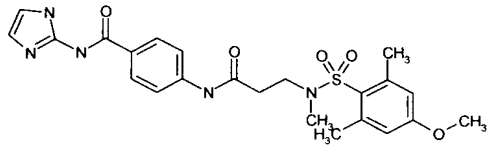
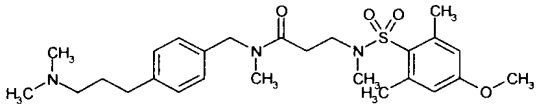
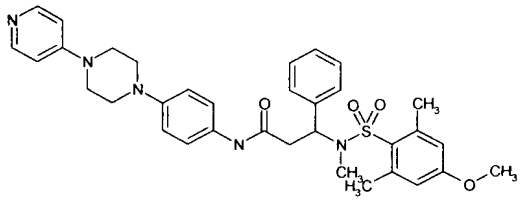
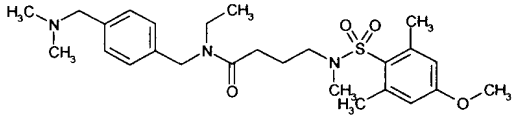
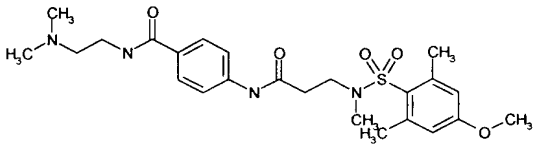
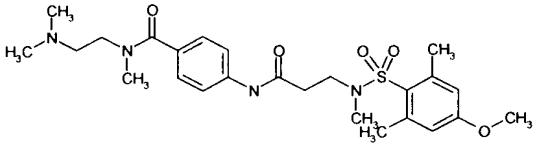
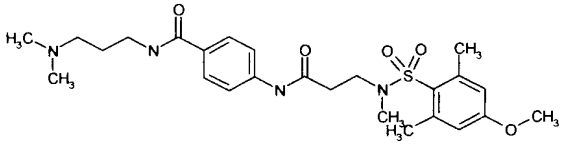
Exemplo	Estrutura
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(105)	
(106)	
(107)	
(108)	
(109)	
(110)	
(111)	

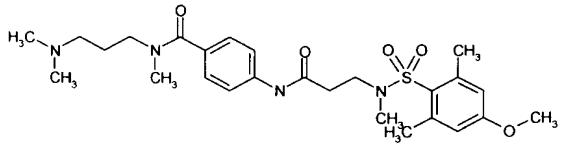
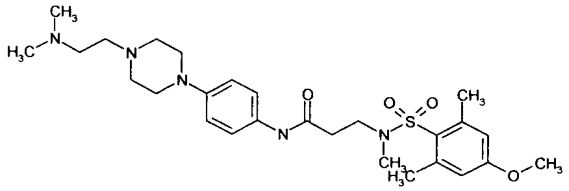
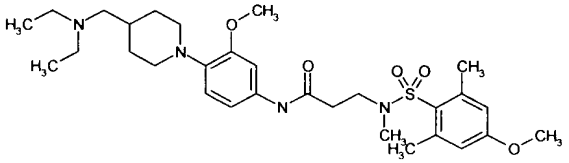
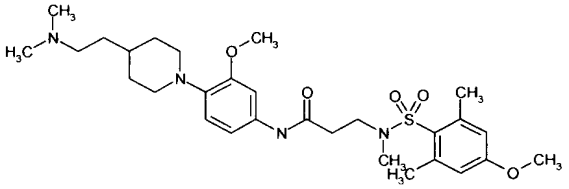
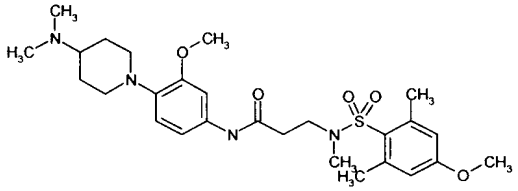
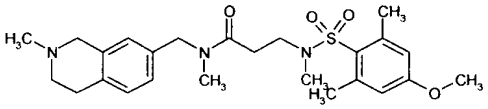
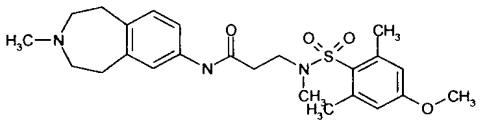
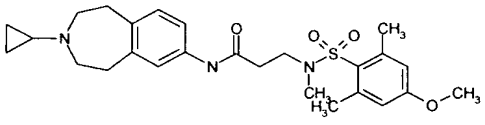
Exemplo	Estrutura
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(113)	
(114)	
(115)	
(116)	
(117)	
(118)	
(119)	

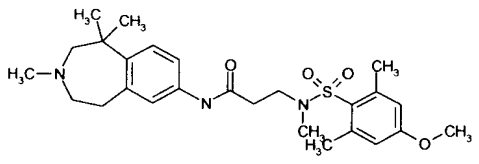
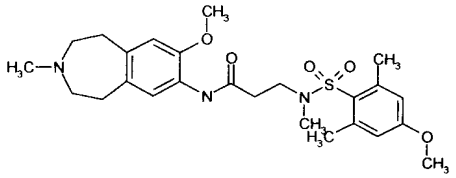
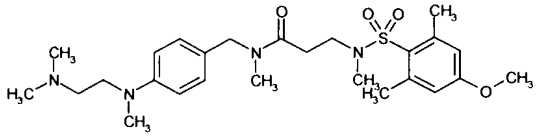
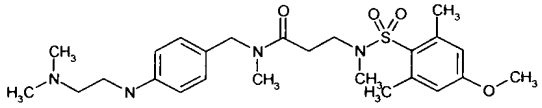
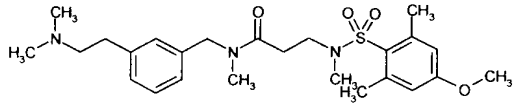
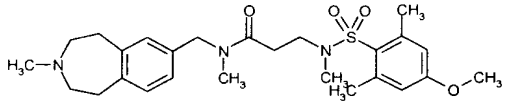
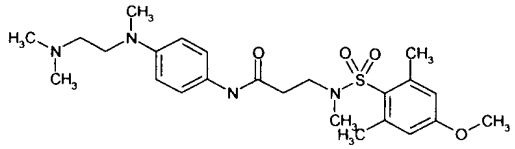
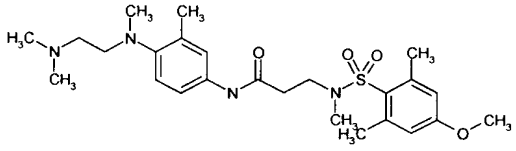
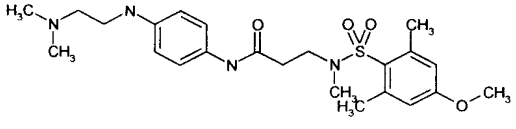
Exemplo	Estrutura
(120)	
(121)	
(122)	
(123)	
(124)	
(125)	
(126)	
(127)	

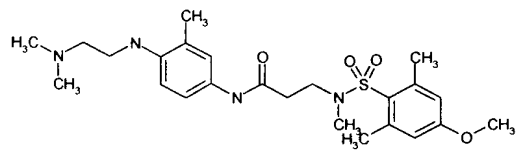
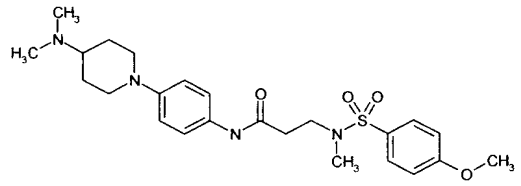
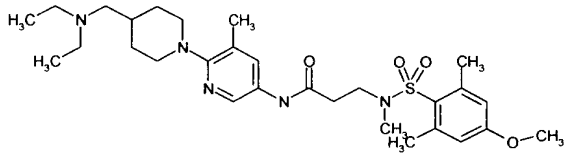
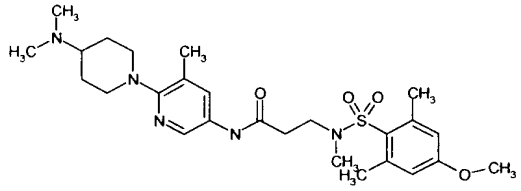
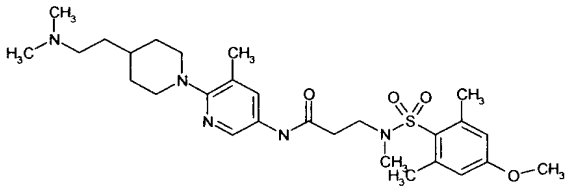
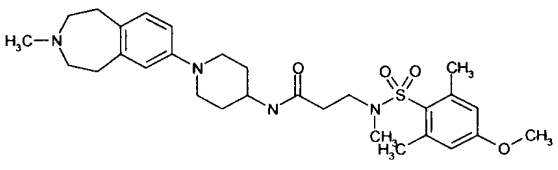
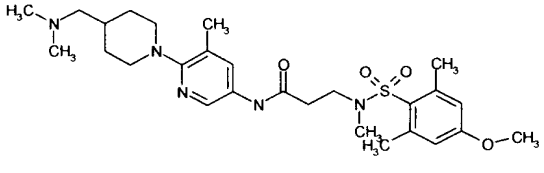
Exemplo	Estrutura
(128)	
(129)	
(130)	
(131)	
(132)	
(133)	
(134)	
(135)	

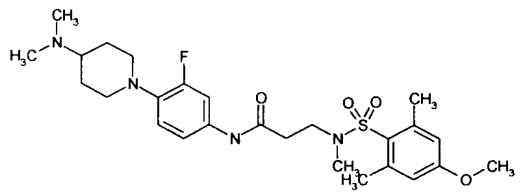
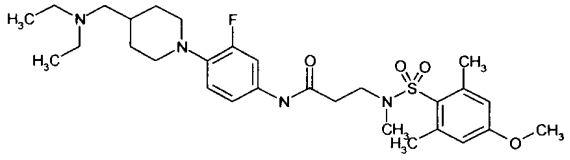
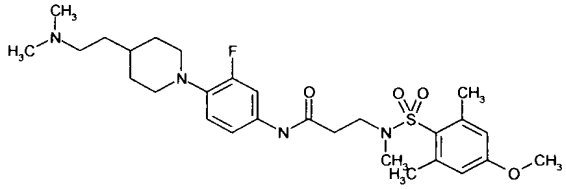
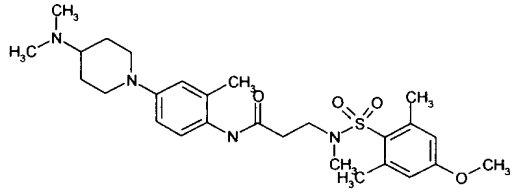
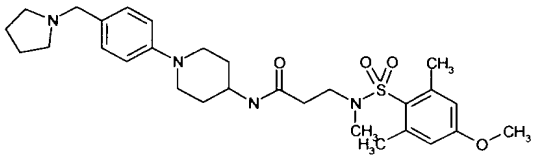
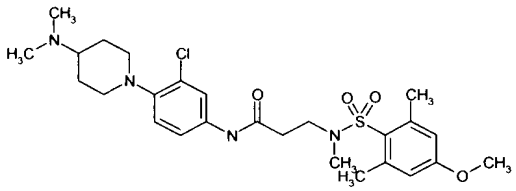
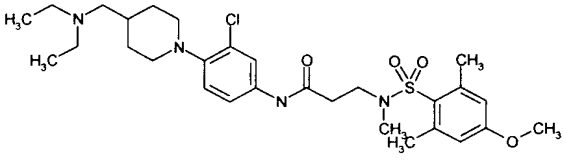
Exemplo	Estrutura
(136)	
(137)	
(138)	
(139)	
(140)	
(141)	
(142)	

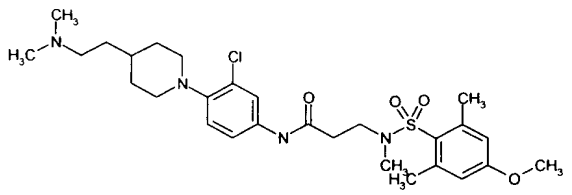
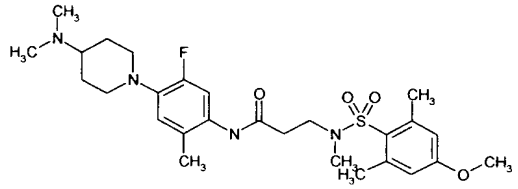
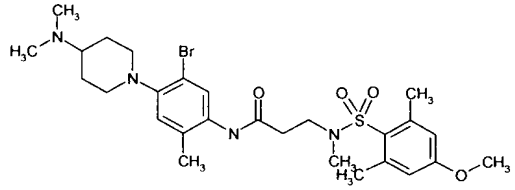
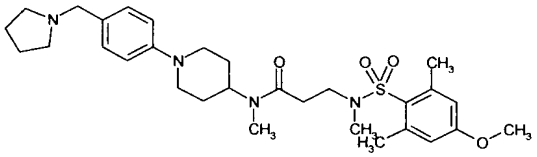
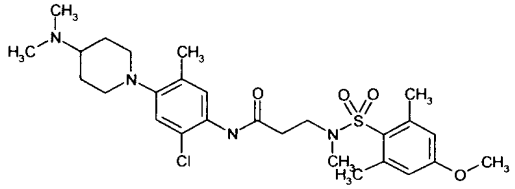
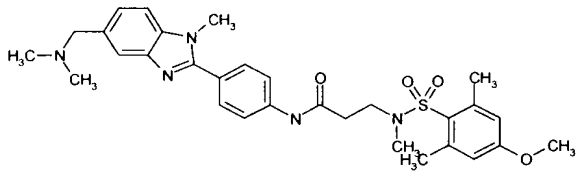
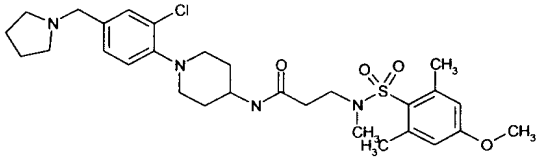
Exemplo	Estrutura
(143)	
(144)	
(145)	
(146)	
(147)	
(148)	
(149)	
(150)	

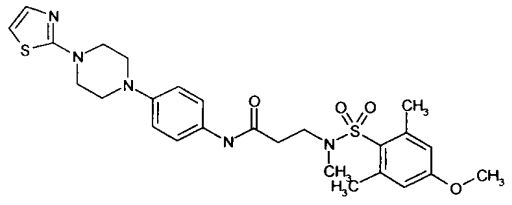
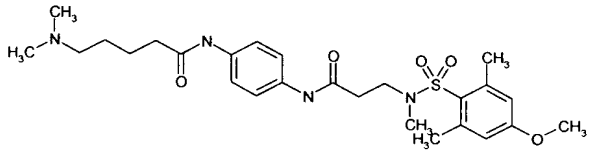
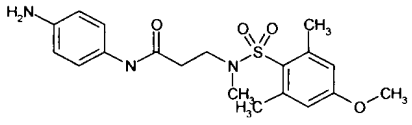
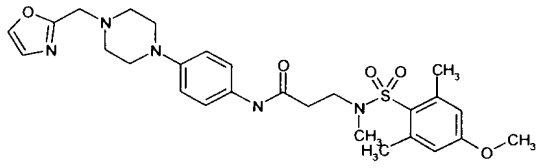
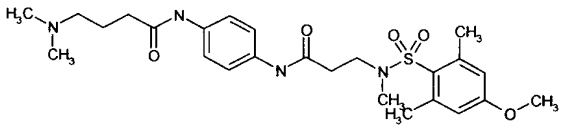
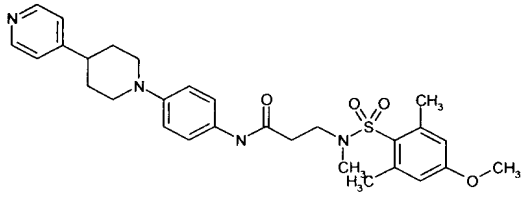
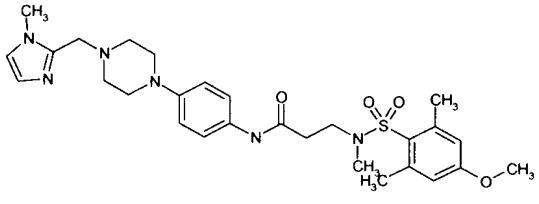
Exemplo	Estrutura
(151)	
(152)	
(153)	
(154)	
(155)	
(156)	
(157)	
(158)	

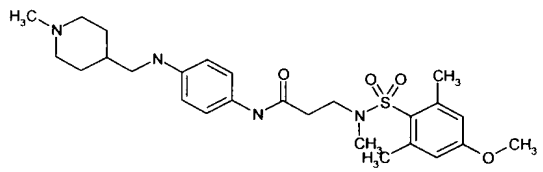
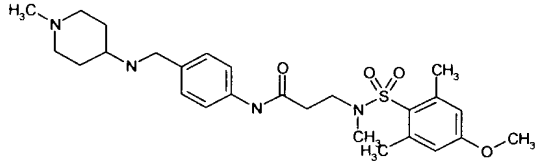
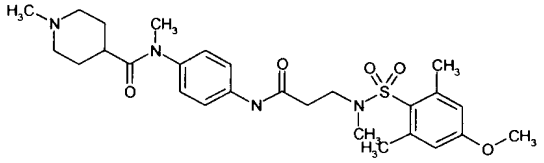
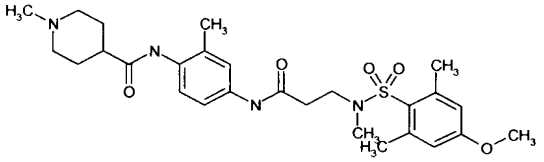
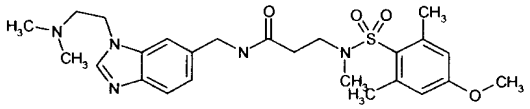
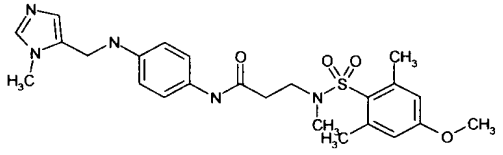
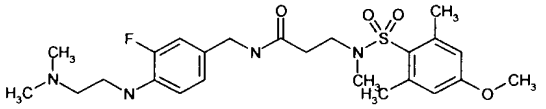
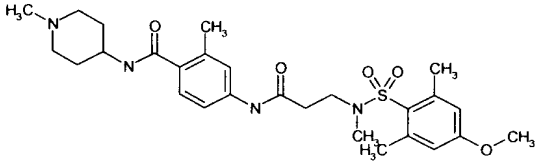
Exemplo	Estrutura
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(160)	
(161)	
(162)	
(163)	
(164)	
(165)	
(166)	
(167)	

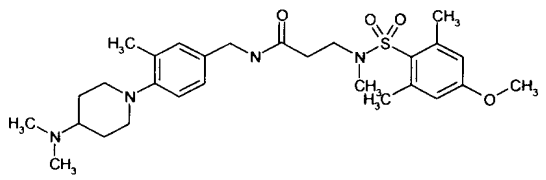
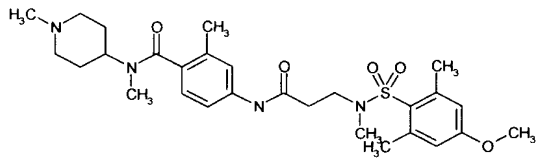
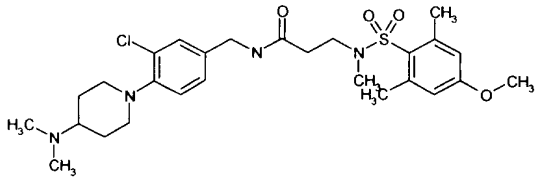
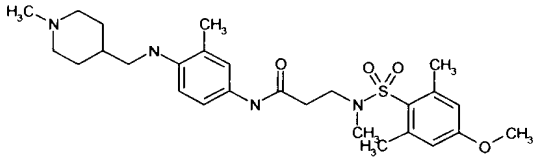
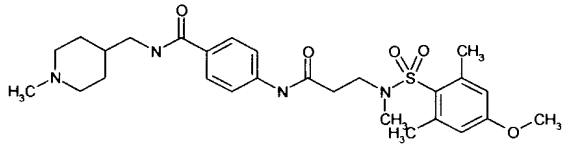
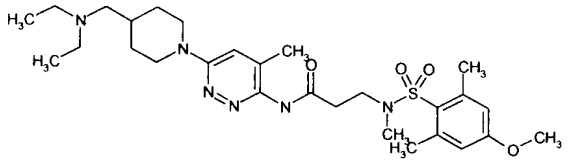
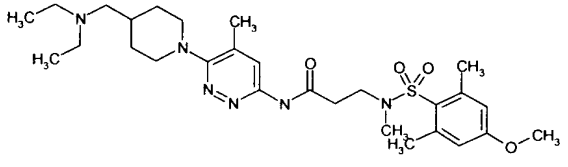
Exemplo	Estrutura
(168)	
(169)	
(170)	
(171)	
(172)	
(173)	
(174)	

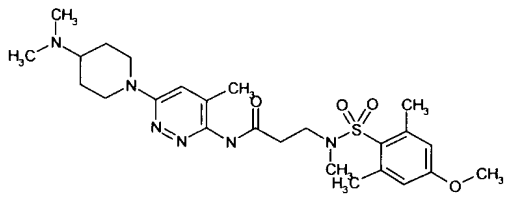
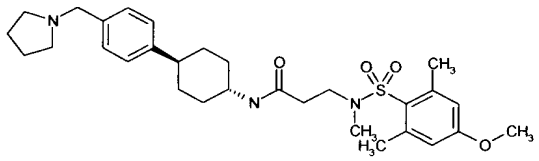
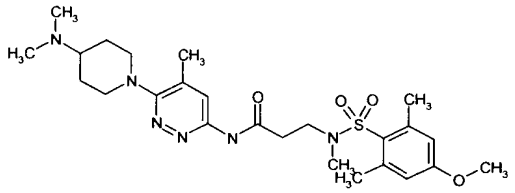
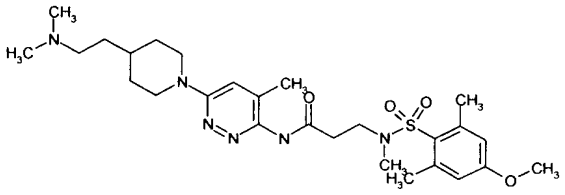
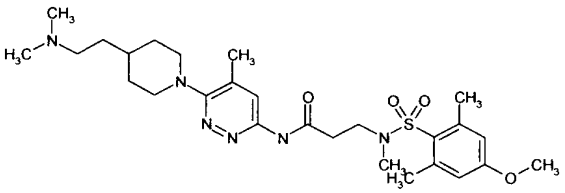
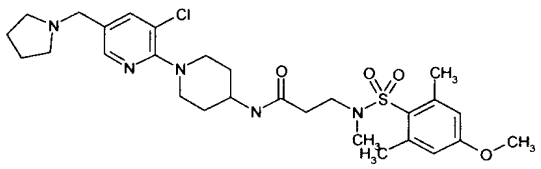
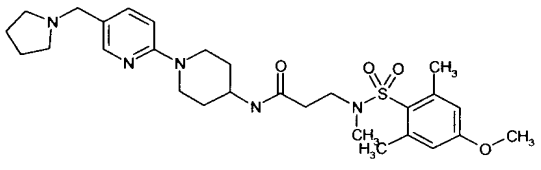
Exemplo	Estrutura
(175)	
(176)	
(177)	
(178)	
(179)	
(180)	
(181)	

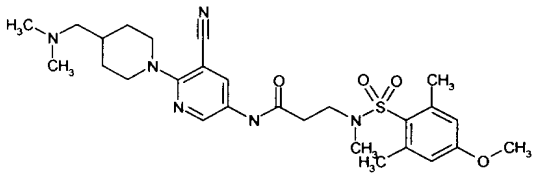
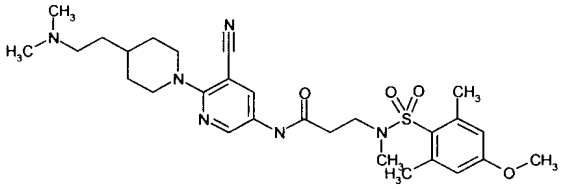
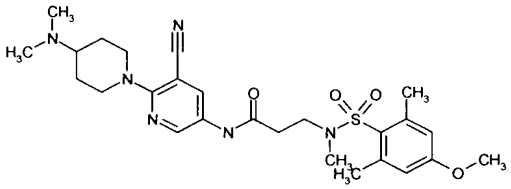
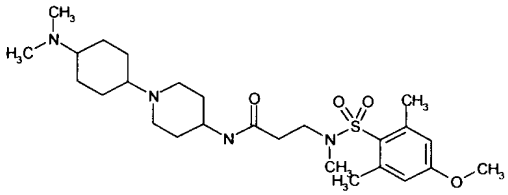
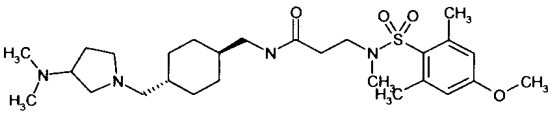
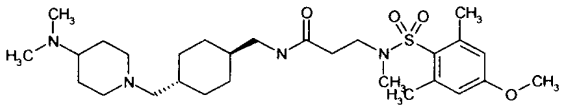
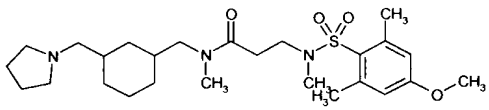
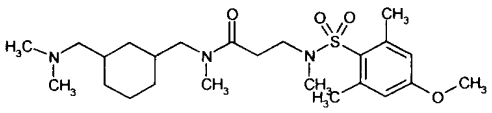
Exemplo	Estrutura
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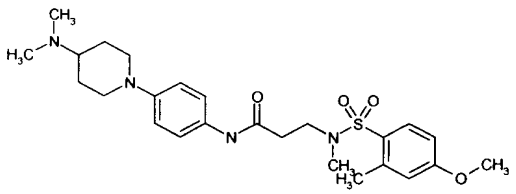
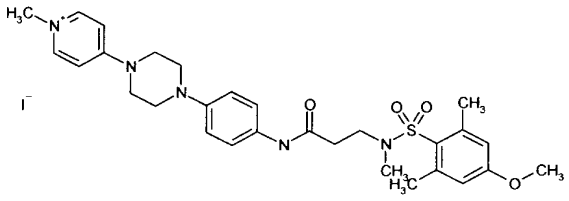
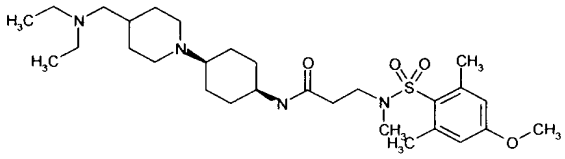
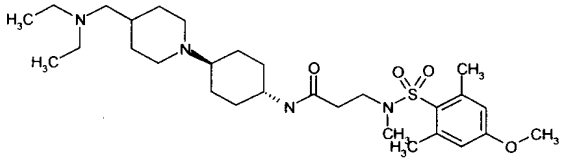
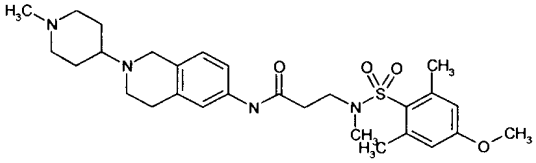
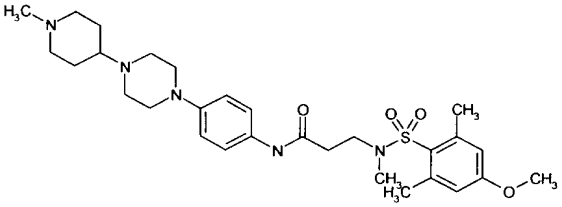
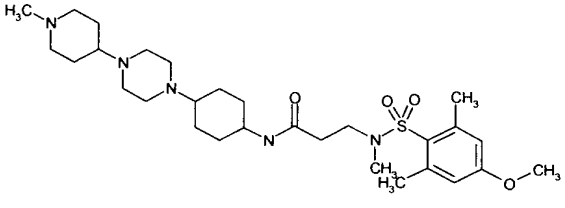
Exemplo	Estrutura
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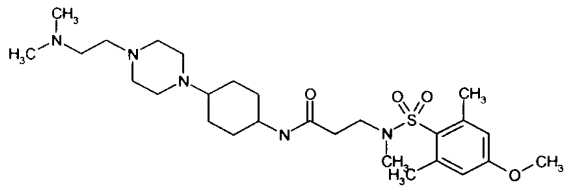
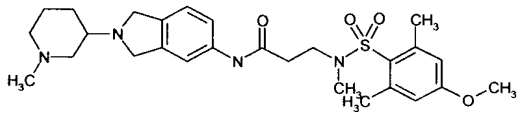
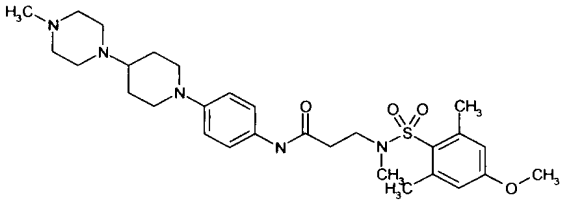
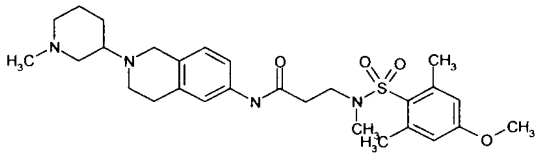
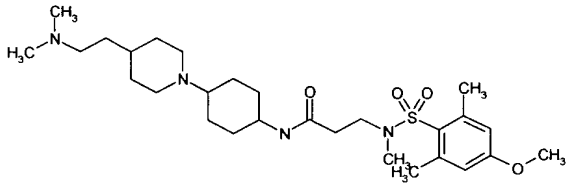
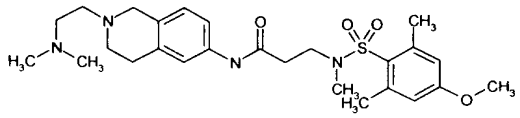
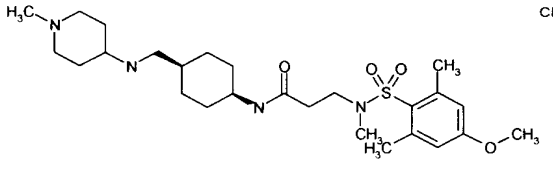
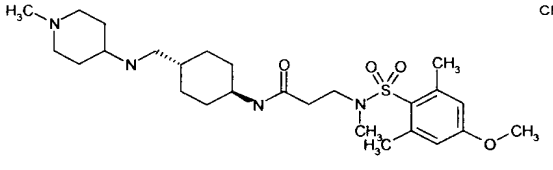
Exemplo	Estrutura
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(200)	
(201)	
(202)	
(203)	

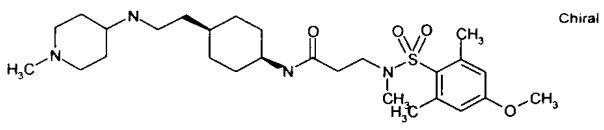
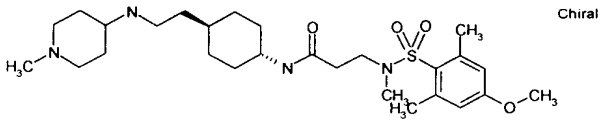
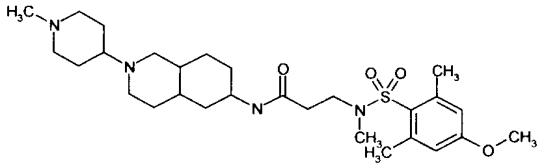
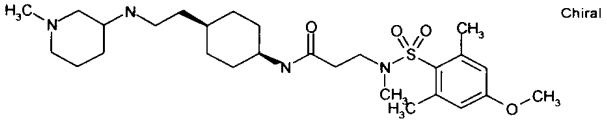
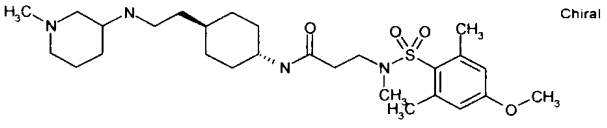
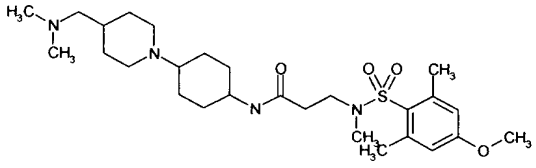
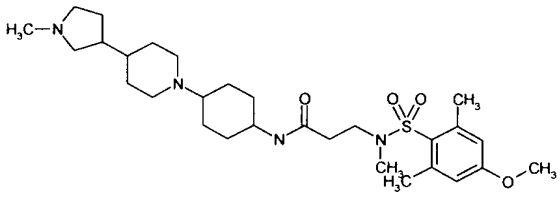
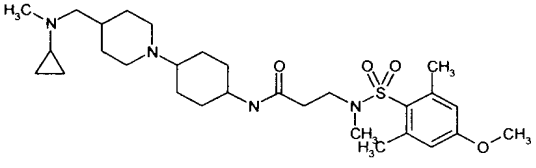
Exemplo	Estrutura
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(210)	

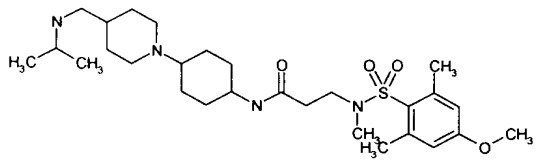
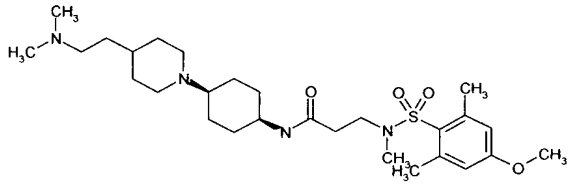
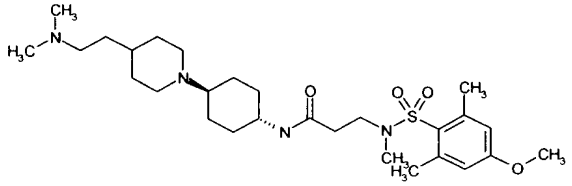
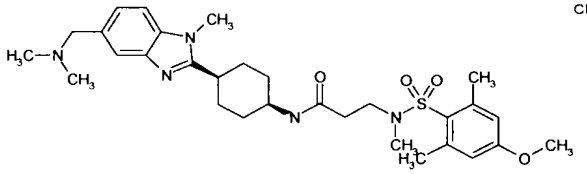
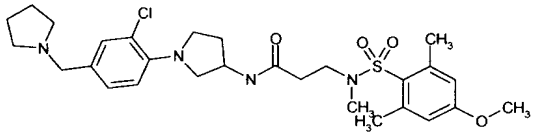
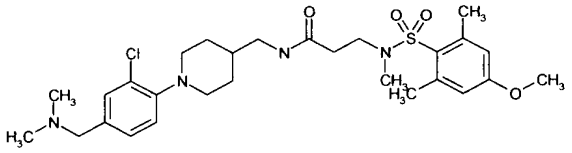
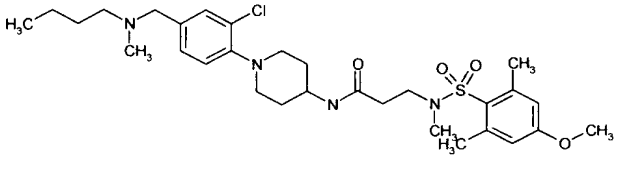
Exemplo	Estrutura
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(214)	
(215)	
(216)	
(217)	

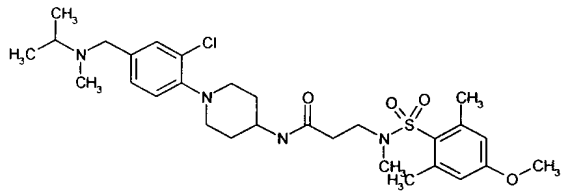
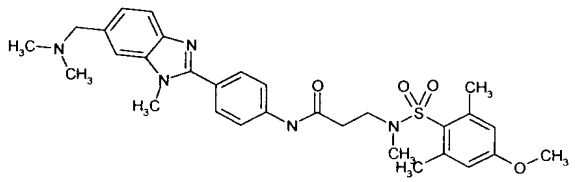
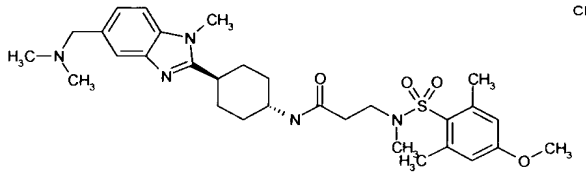
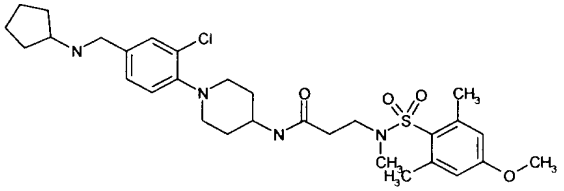
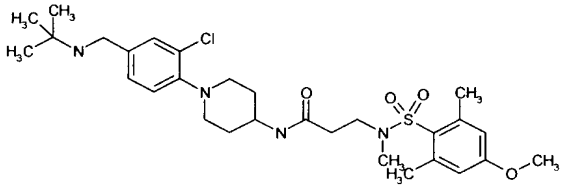
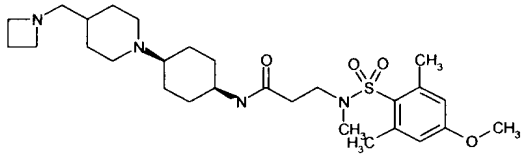
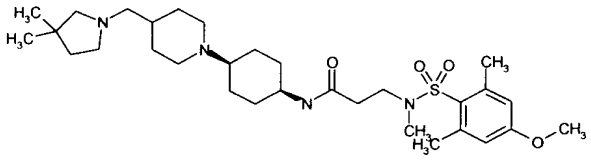
Exemplo	Estrutura
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(225)	

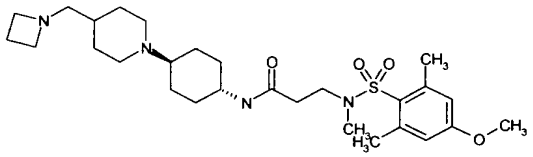
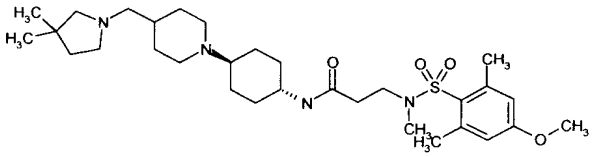
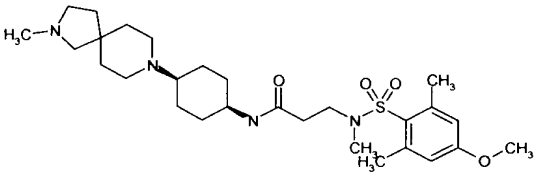
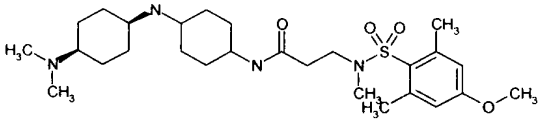
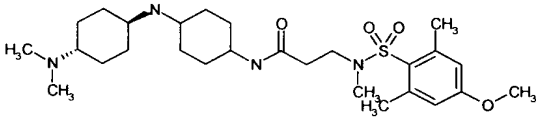
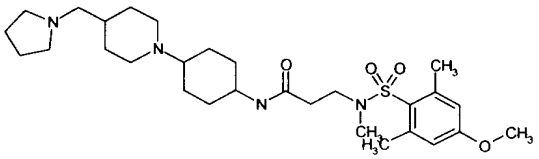
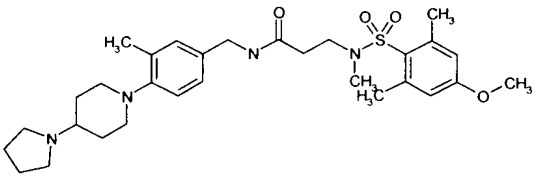
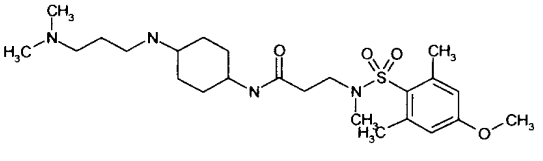
Exemplo	Estrutura
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(229)	
(230)	
(231)	
(232)	

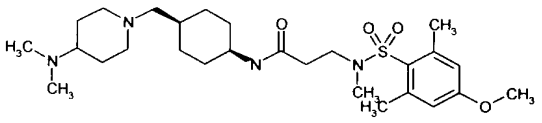
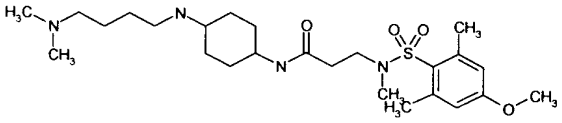
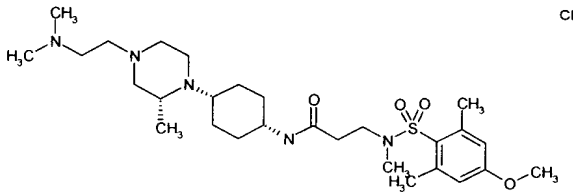
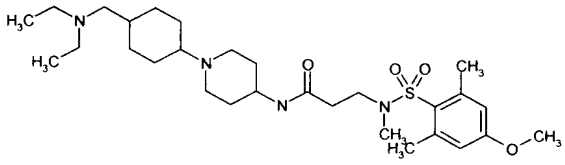
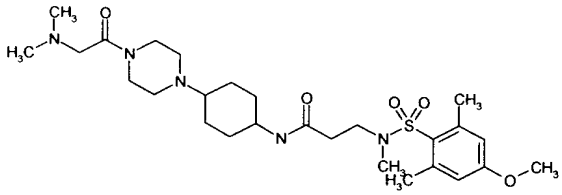
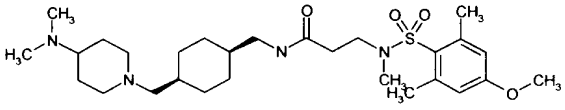
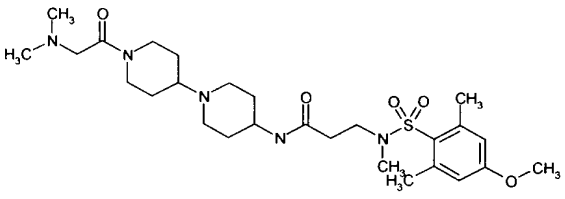
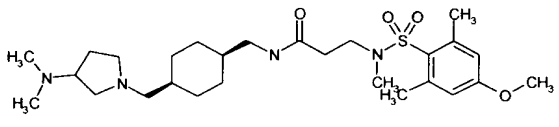
Exemplo	Estrutura
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(234)	
(235)	
(236)	
(237)	
(238)	
(239)	Chiral 
(240)	Chiral 

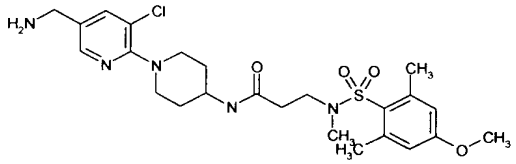
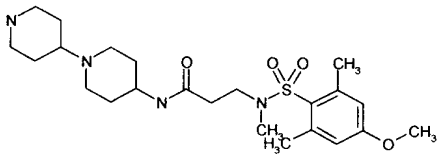
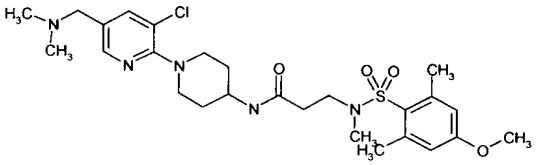
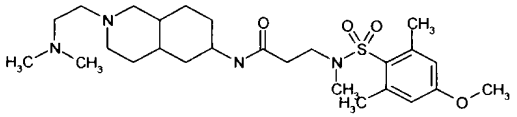
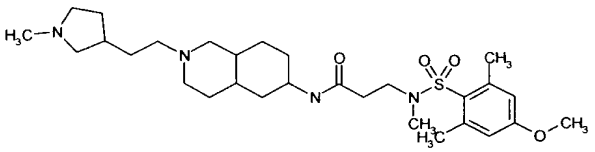
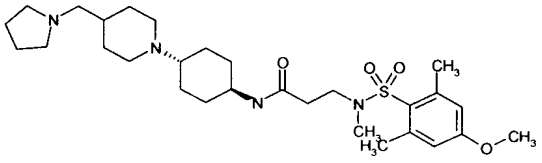
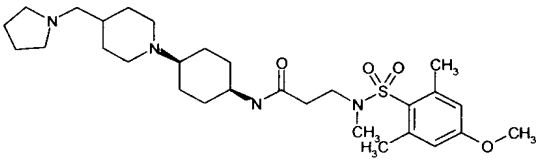
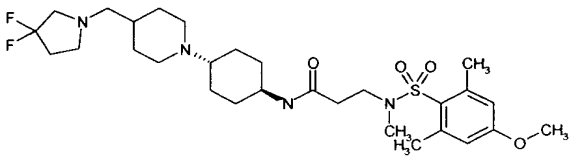
Exemplo	Estrutura
(241)	 Chiral
(242)	 Chiral
(243)	
(244)	 Chiral
(245)	 Chiral
(246)	
(247)	
(248)	

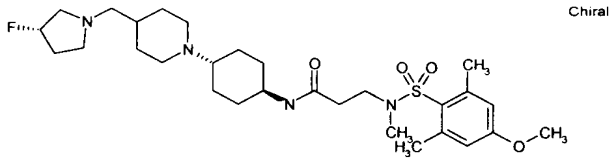
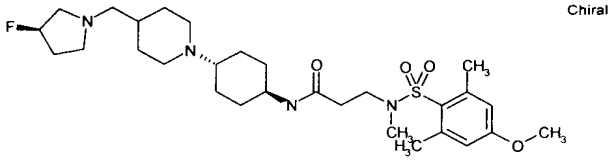
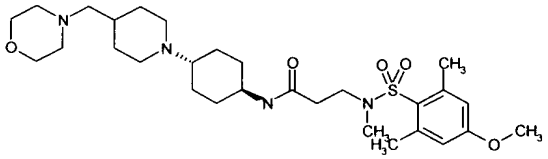
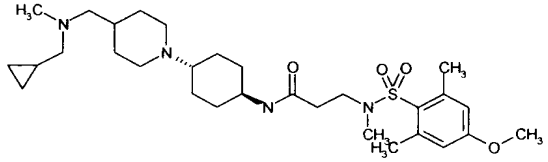
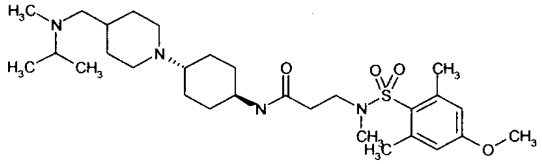
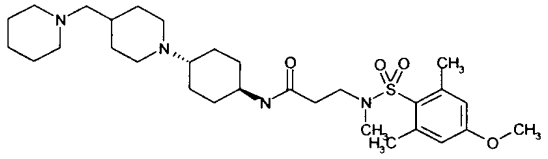
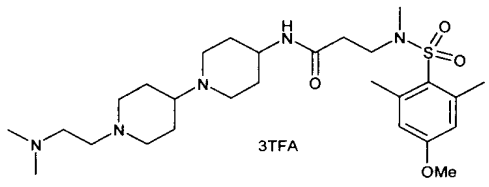
Exemplo	Estrutura
(249)	
(250)	
(251)	
(252)	Chiral 
(253)	
(254)	
(255)	

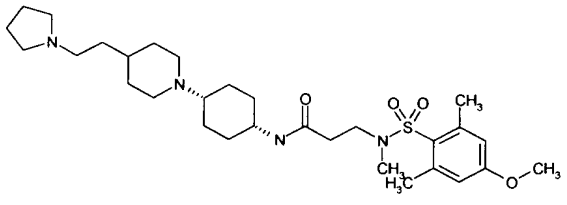
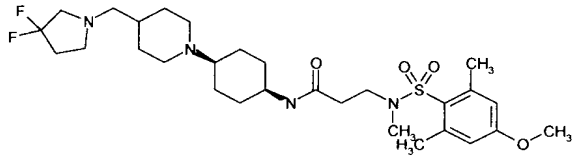
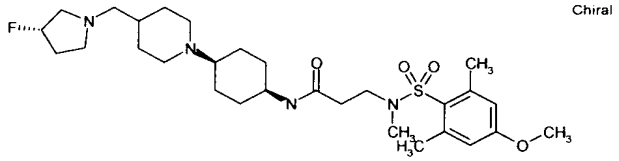
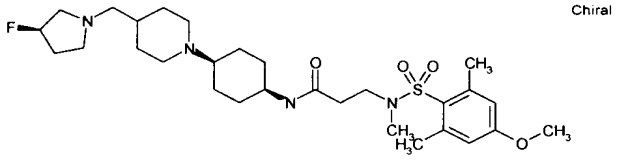
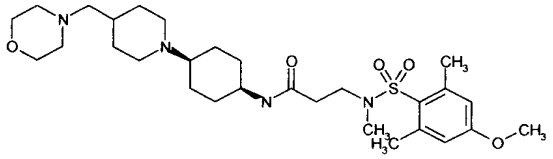
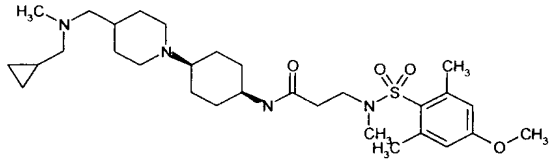
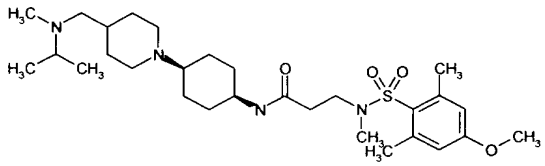
Exemplo	Estrutura
(256)	
(257)	
(258)	Chiral 
(259)	
(260)	
(261)	
(262)	

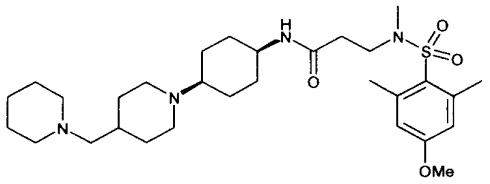
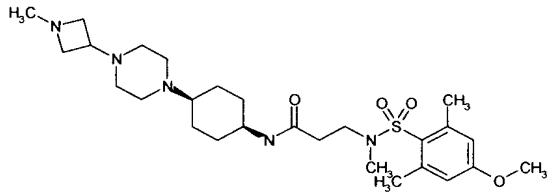
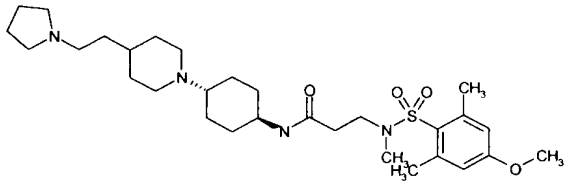
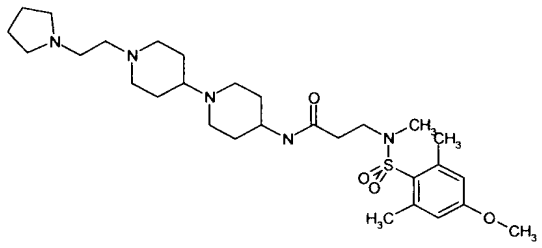
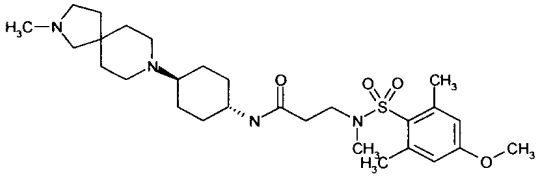
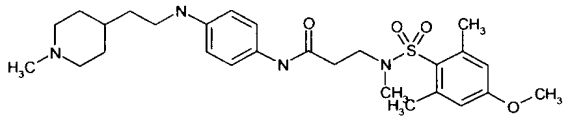
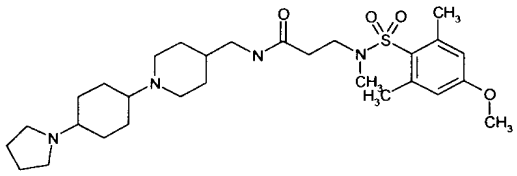
Exemplo	Estrutura
(263)	
(264)	
(265)	
(266)	
(267)	
(268)	
(269)	
(270)	

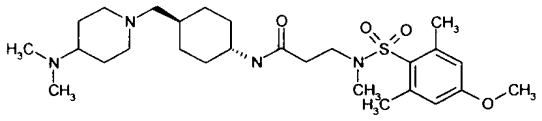
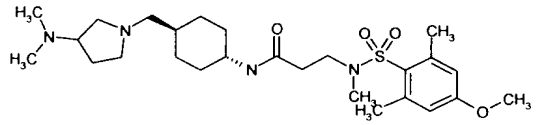
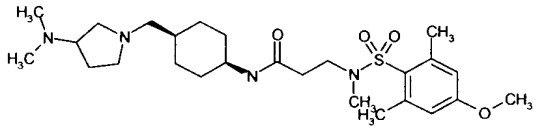
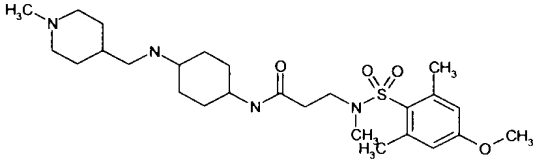
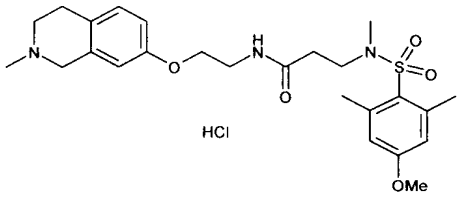
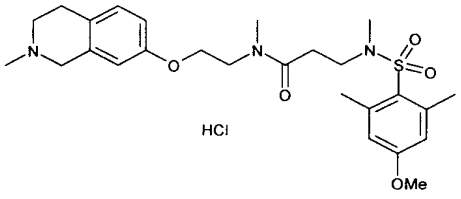
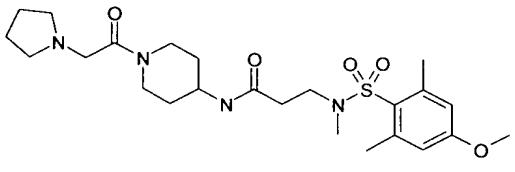
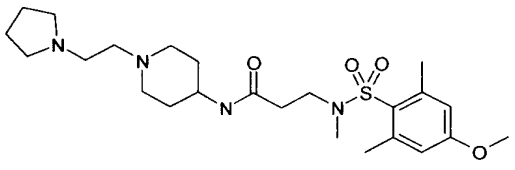
Exemplo	Estrutura
(271)	
(272)	
(273)	 Chiral
(274)	
(275)	
(276)	
(277)	
(278)	

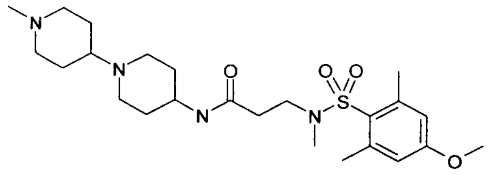
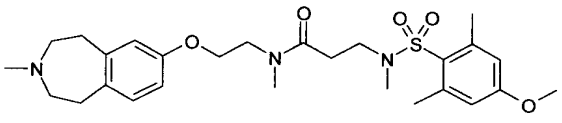
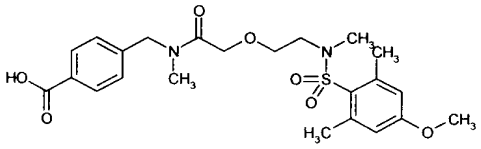
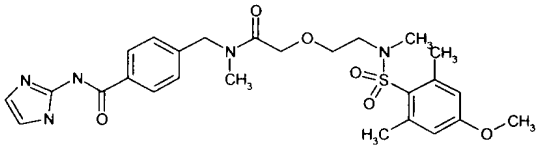
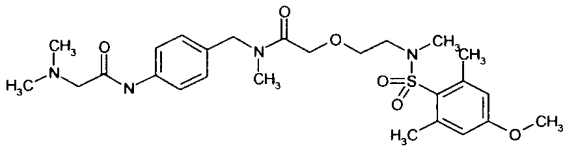
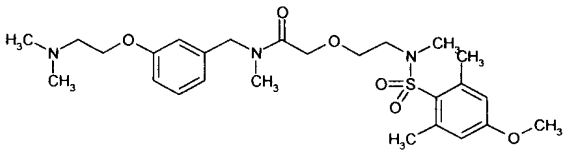
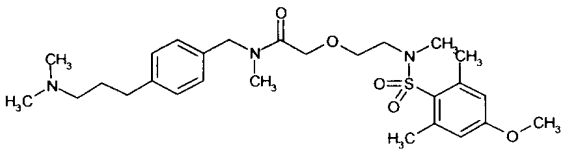
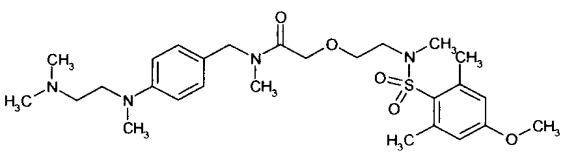
Exemplo	Estrutura
(279)	
(280)	
(281)	
(282)	
(283)	
(284)	
(285)	
(286)	

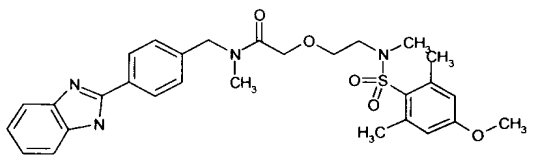
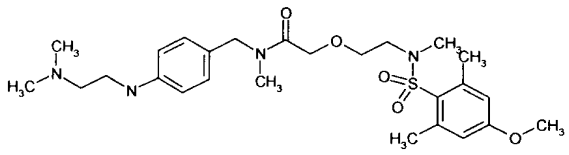
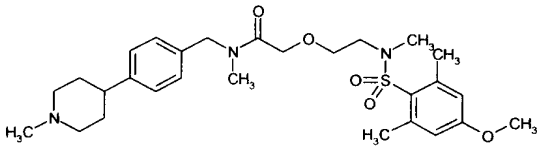
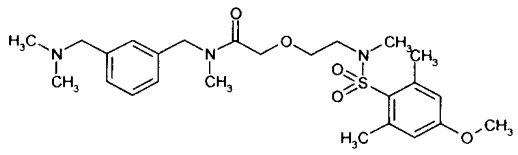
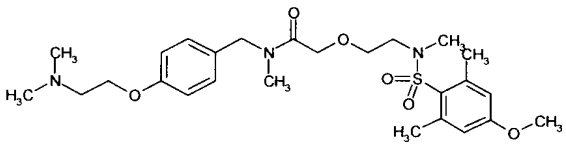
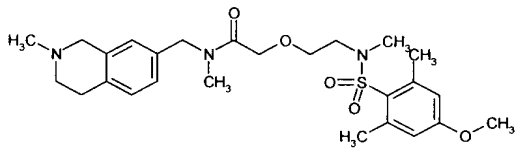
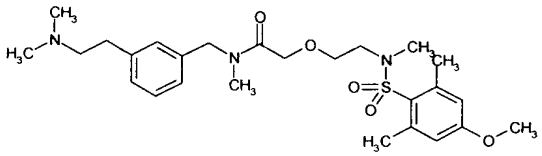
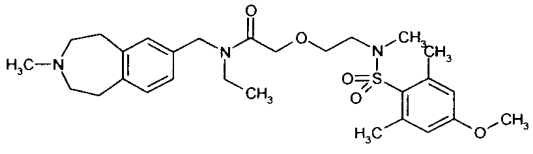
Exemplo	Estrutura
(287)	 Chiral
(288)	 Chiral
(289)	
(290)	
(291)	
(292)	
(293)	 3TFA

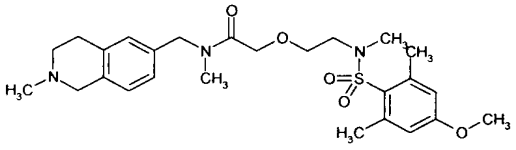
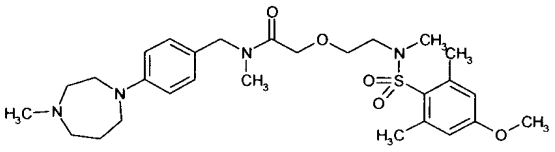
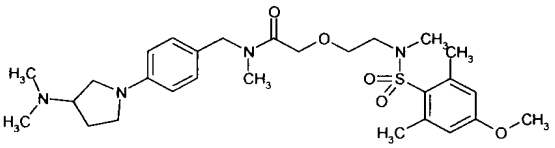
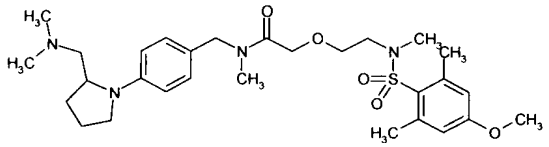
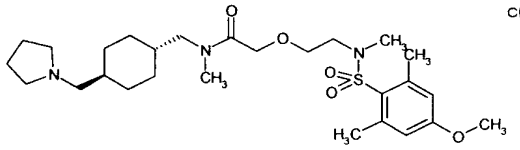
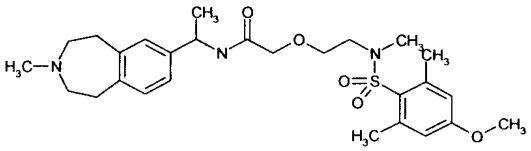
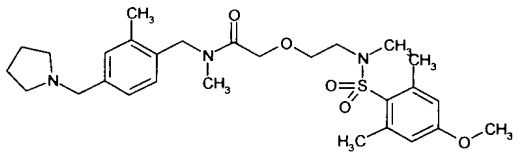
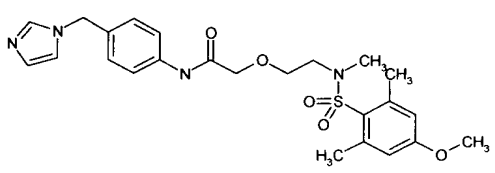
Exemplo	Estrutura
(294)	
(295)	
(296)	 Chiral
(297)	 Chiral
(298)	
(299)	
(300)	

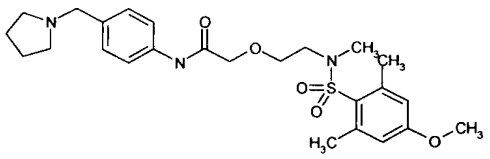
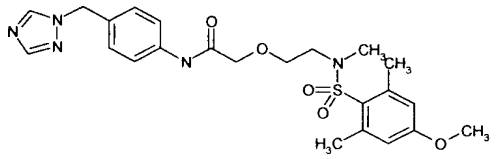
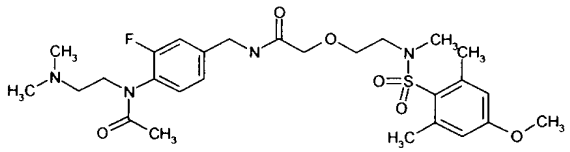
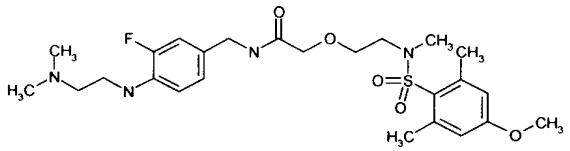
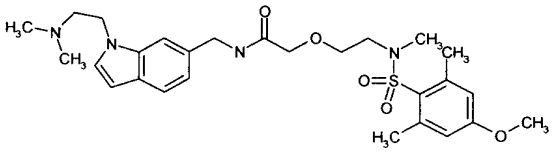
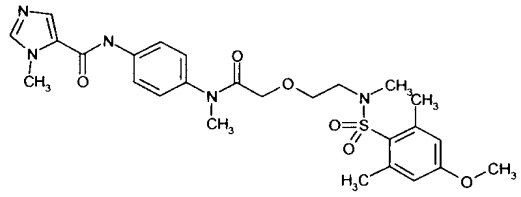
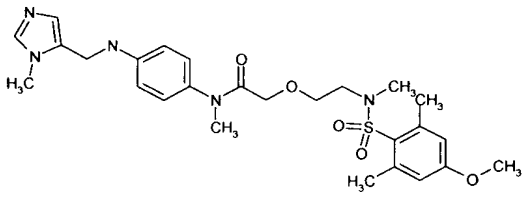
Exemplo	Estrutura
(301)	
(302)	
(303)	
(304)	
(305)	
(306)	
(307)	

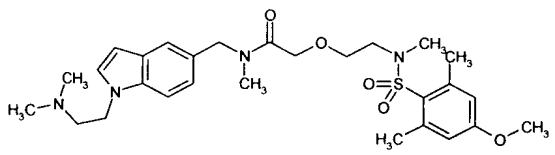
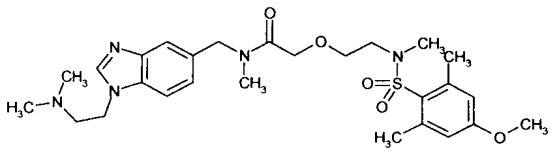
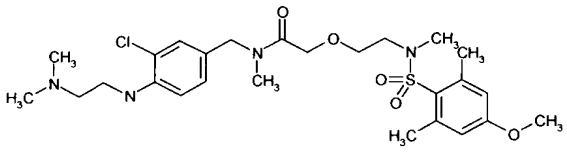
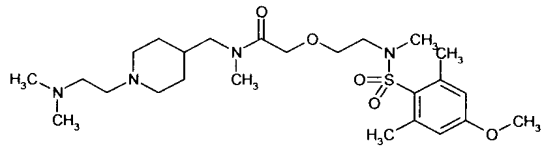
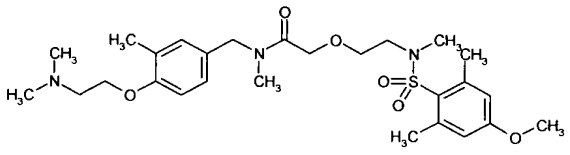
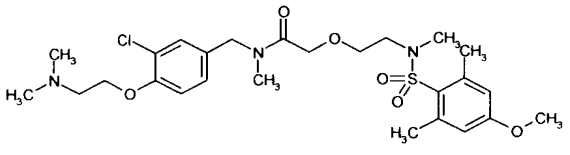
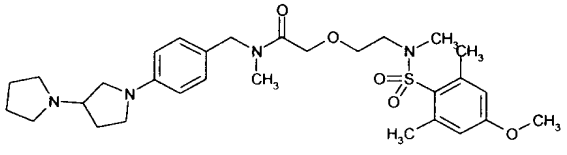
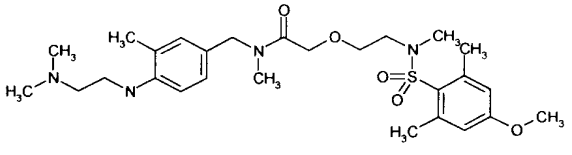
Exemplo	Estrutura
(308)	
(309)	
(310)	
(311)	
(312)	
(313)	
(314)	
(315)	

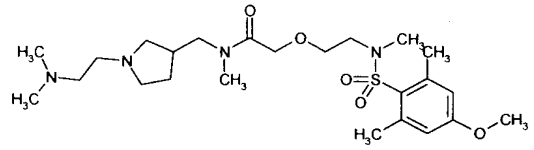
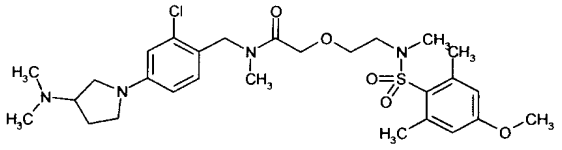
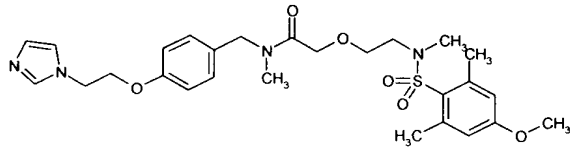
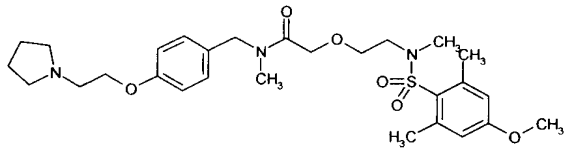
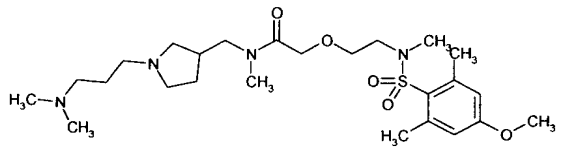
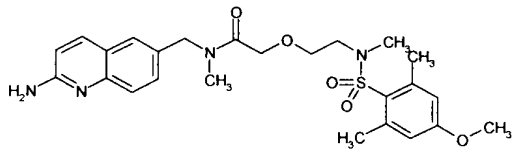
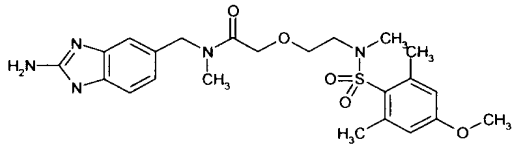
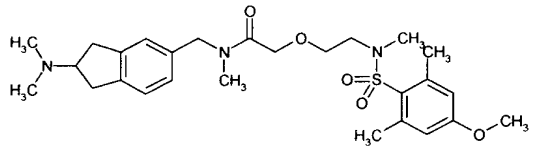
Exemplo	Estrutura
(316)	
(317)	
(318)	
(319)	
(320)	
(321)	
(322)	
(323)	

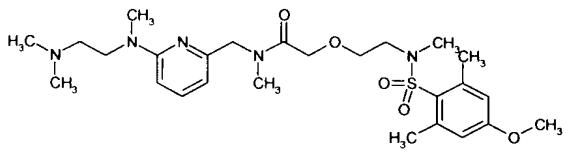
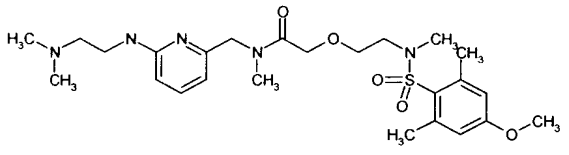
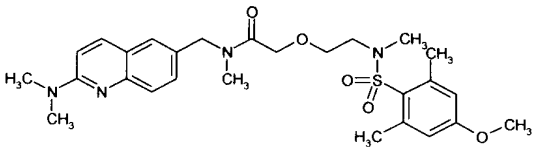
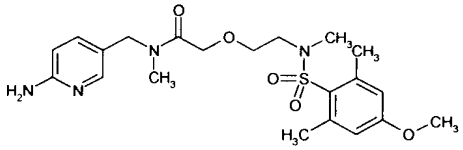
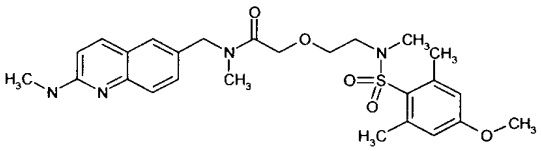
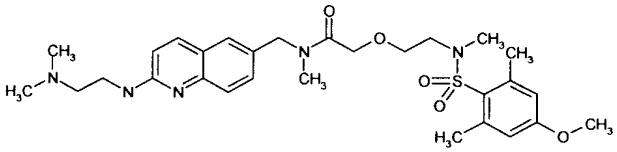
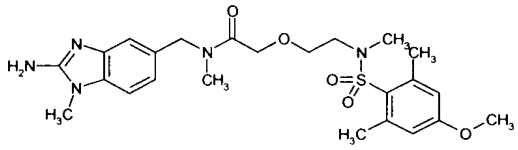
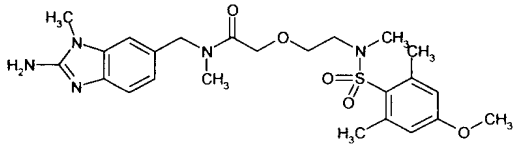
Exemplo	Estrutura
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(325)	
(326)	
(327)	
(328)	
(329)	
(330)	
(331)	

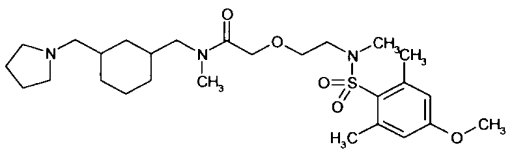
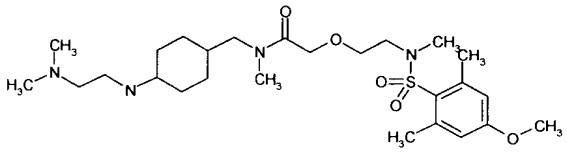
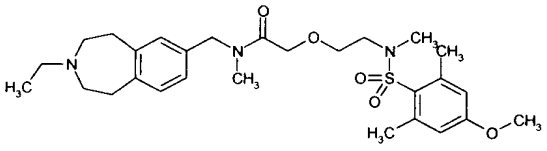
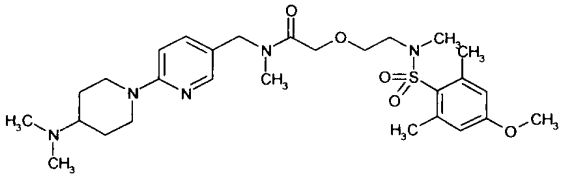
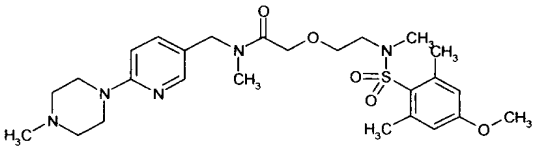
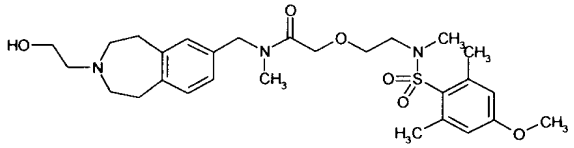
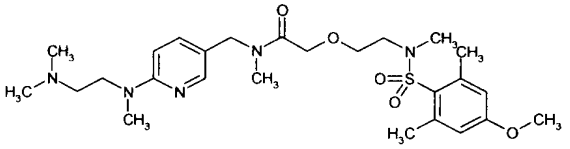
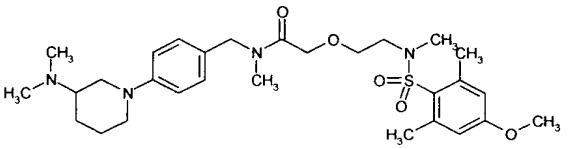
Exemplo	Estrutura
(332)	
(333)	
(334)	
(335)	
(336)	 Chiral
(337)	
(338)	
(339)	

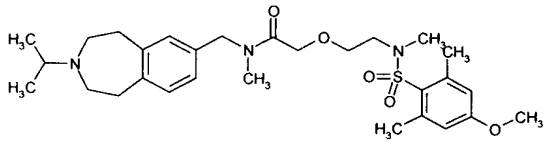
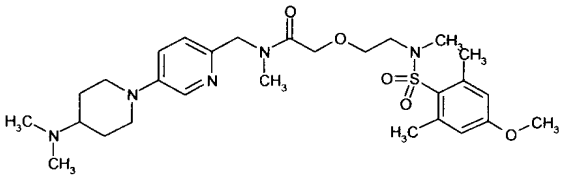
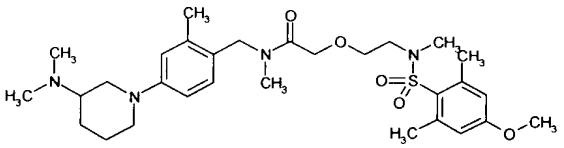
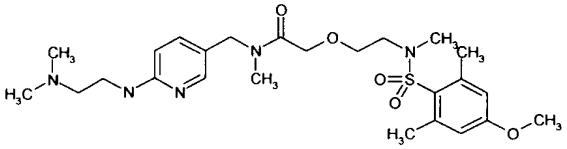
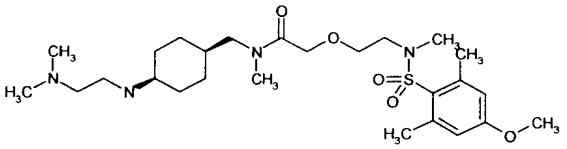
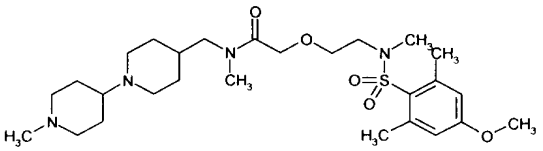
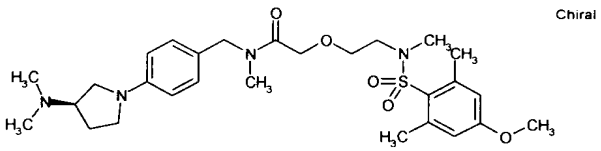
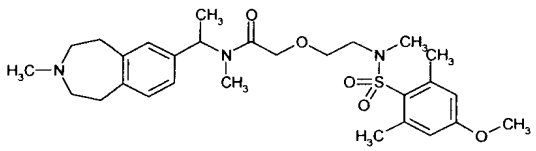
Exemplo	Estrutura
(340)	
(341)	
(342)	
(343)	
(344)	
(345)	
(346)	

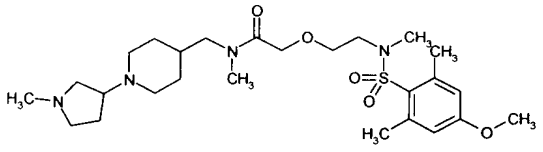
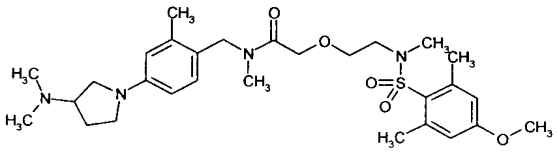
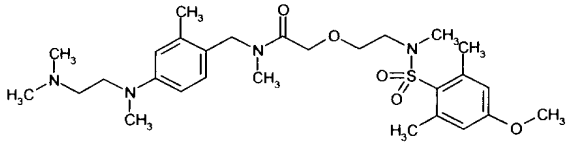
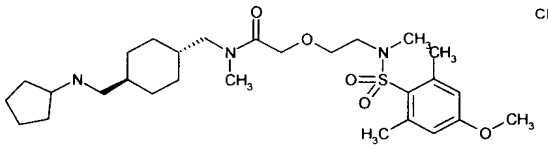
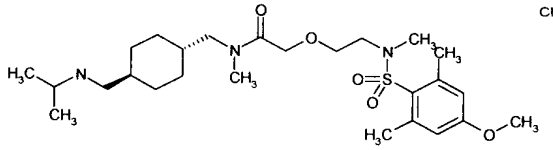
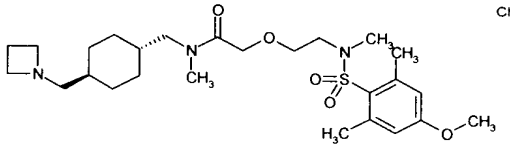
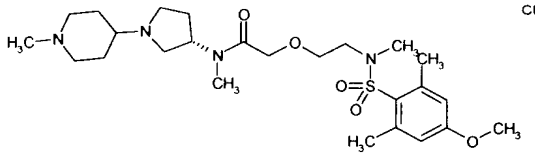
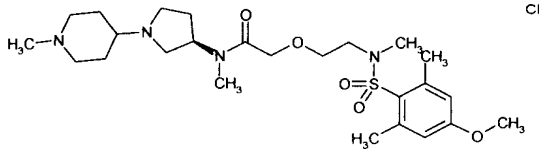
Exemplo	Estrutura
(347)	
(348)	
(349)	
(350)	
(351)	
(352)	
(353)	
(354)	

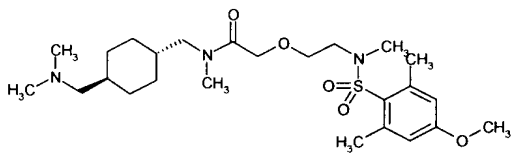
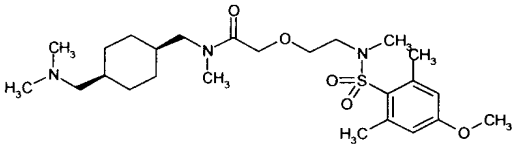
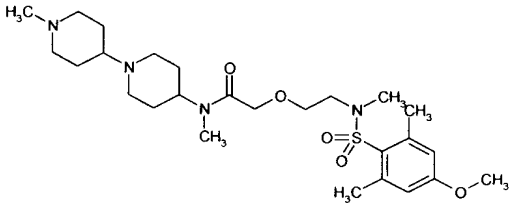
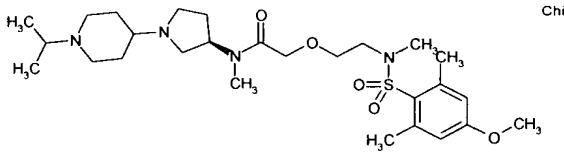
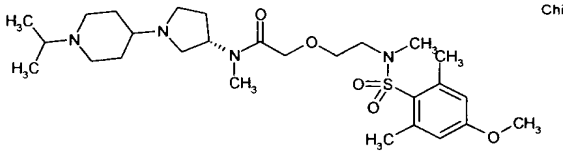
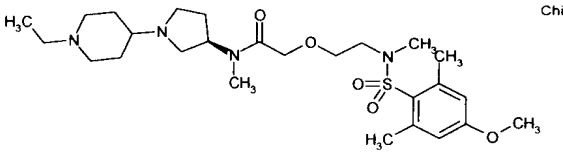
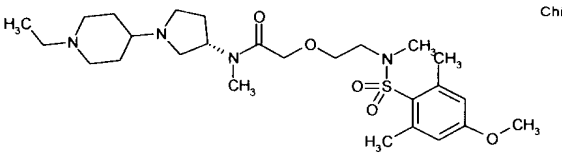
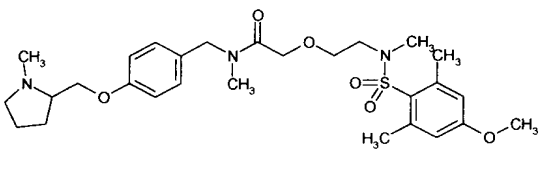
Exemplo	Estrutura
(355)	
(356)	
(357)	
(358)	
(359)	
(360)	
(361)	
(362)	

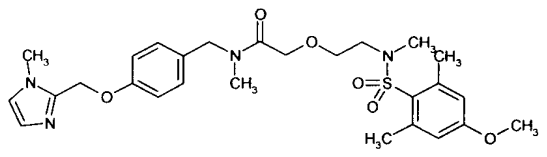
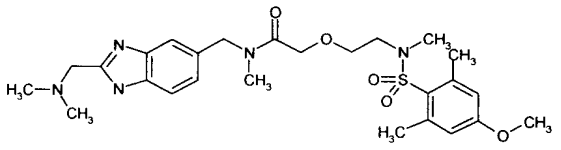
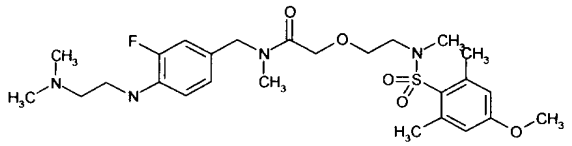
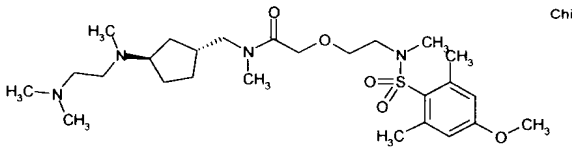
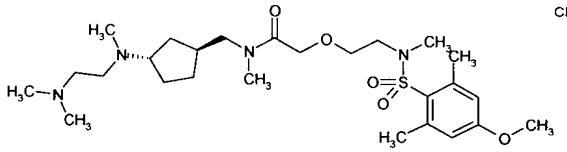
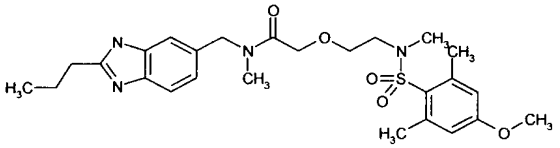
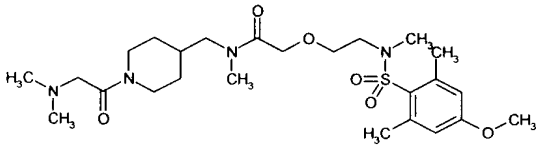
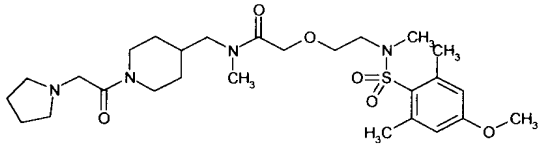
Exemplo	Estrutura
(363)	
(364)	
(365)	
(366)	
(367)	
(368)	
(369)	
(370)	

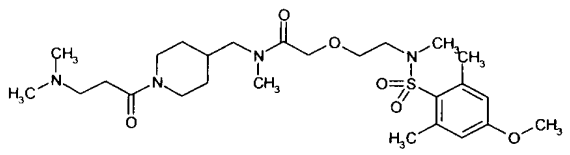
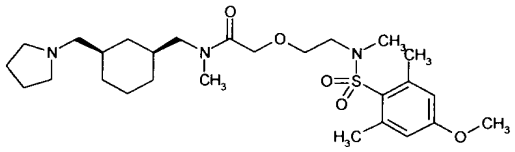
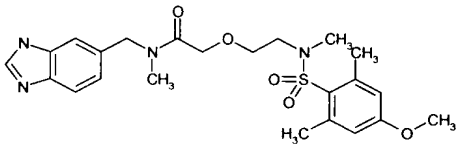
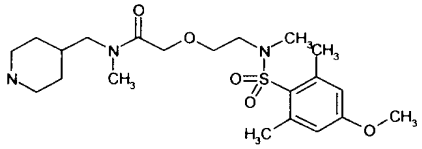
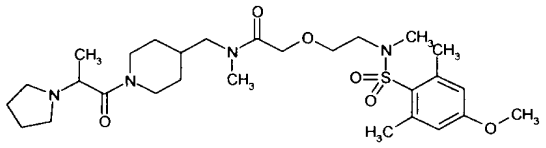
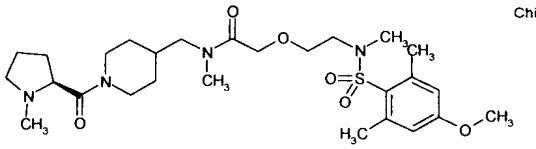
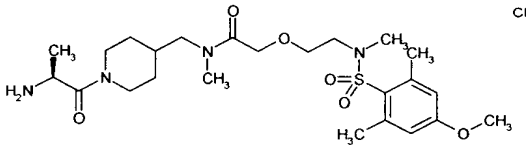
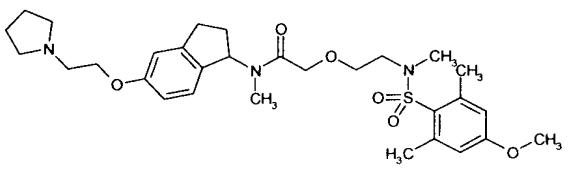
Exemplo	Estrutura
(371)	
(372)	
(373)	
(374)	
(375)	
(376)	
(377)	
(378)	

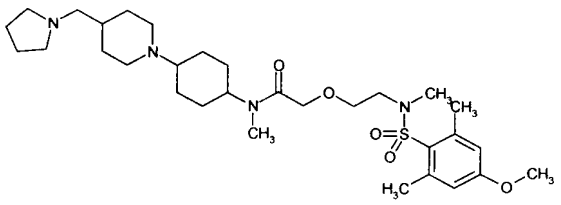
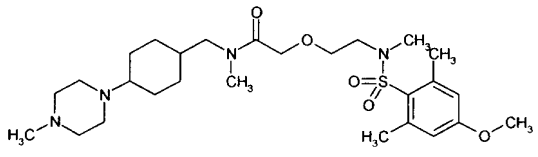
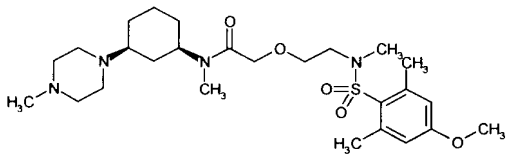
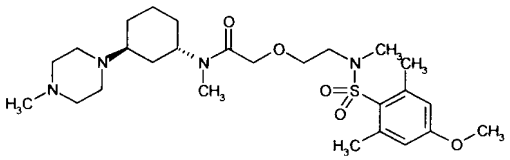
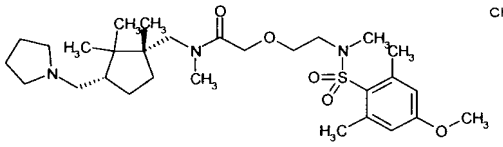
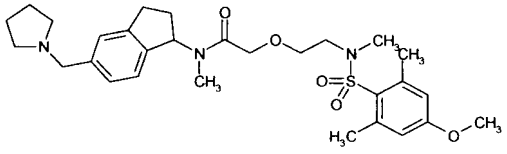
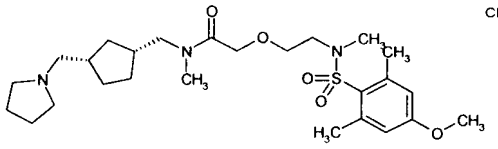
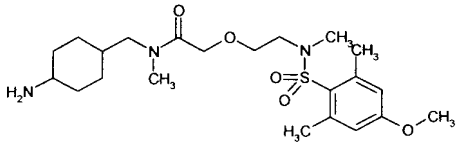
Exemplo	Estrutura
(379)	
(380)	
(381)	
(382)	
(383)	
(384)	
(385)	Chiral 
(386)	

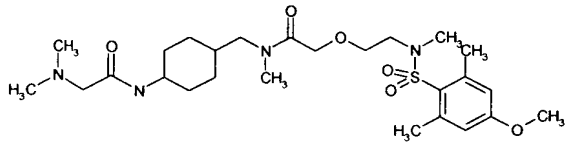
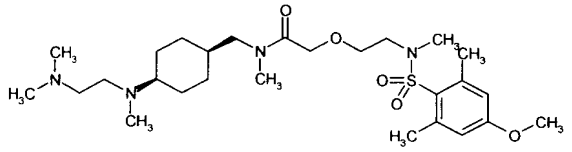
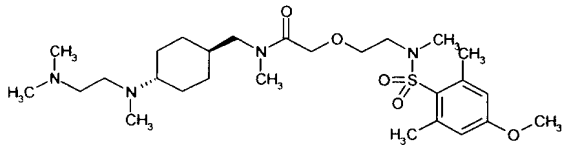
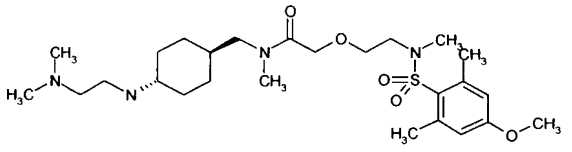
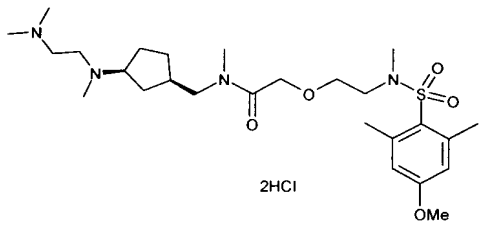
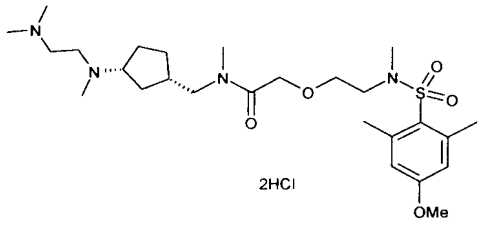
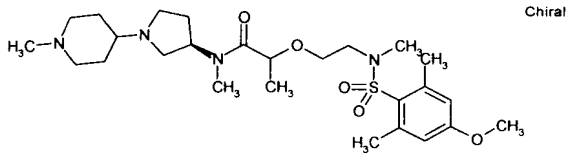
Exemplo	Estrutura
(387)	
(388)	
(389)	
(390)	Chiral 
(391)	Chiral 
(392)	Chiral 
(393)	Chiral 
(394)	Chiral 

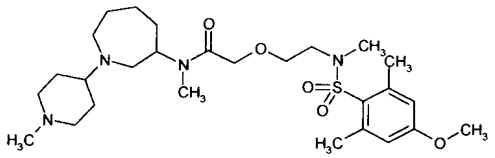
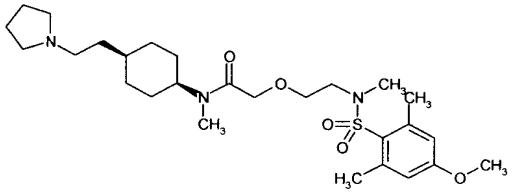
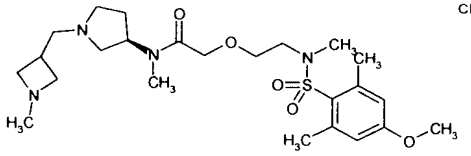
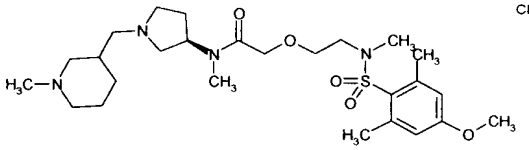
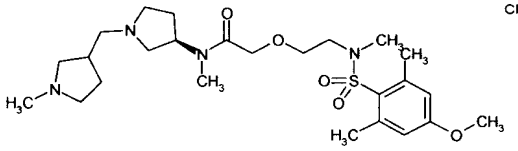
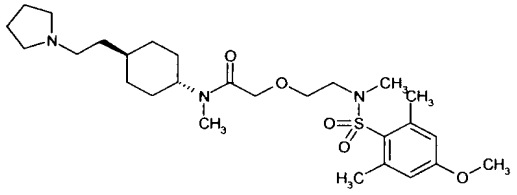
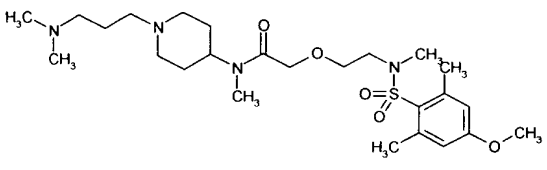
Exemplo	Estrutura
(395)	
(396)	
(397)	
(398)	Chiral 
(399)	Chiral 
(400)	Chiral 
(401)	Chiral 
(402)	

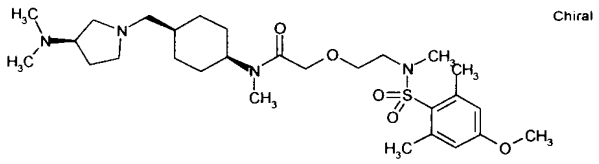
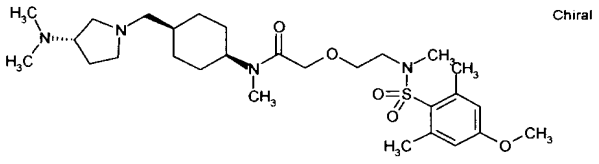
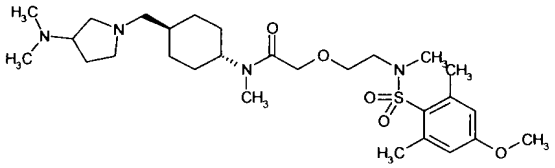
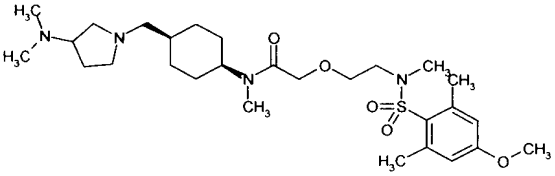
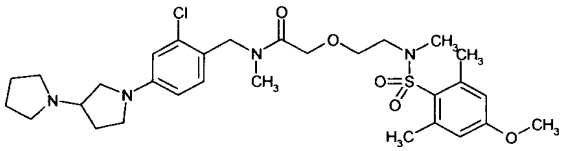
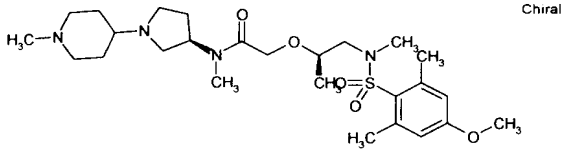
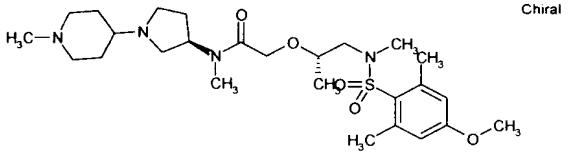
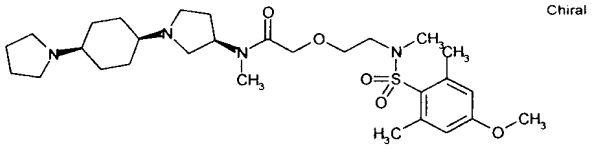
Exemplo	Estrutura
(403)	
(404)	
(405)	
(406)	 Chiral
(407)	 Chiral
(408)	
(409)	
(410)	

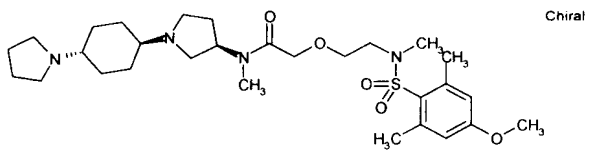
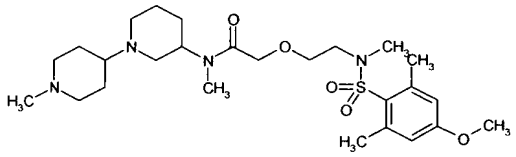
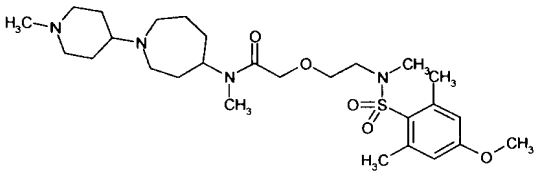
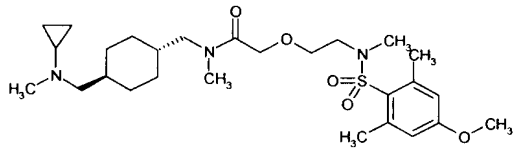
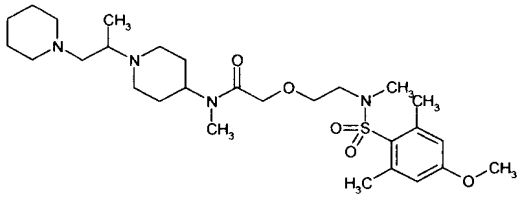
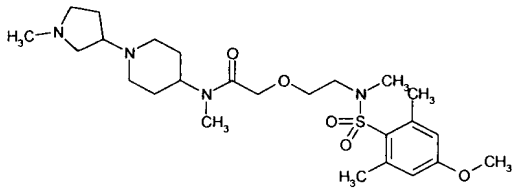
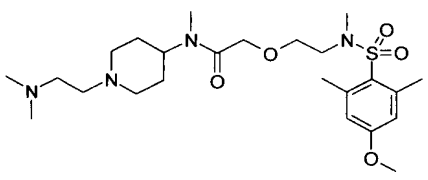
Exemplo	Estrutura
(411)	
(412)	
(413)	
(414)	
(415)	
(416)	Chiral 
(417)	Chiral 
(418)	

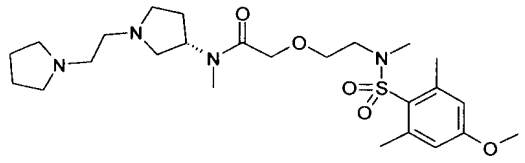
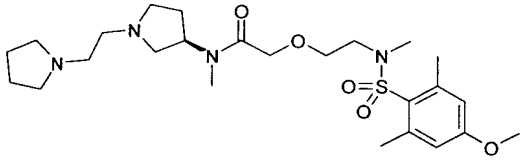
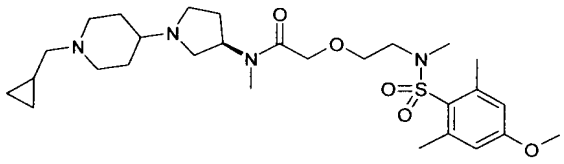
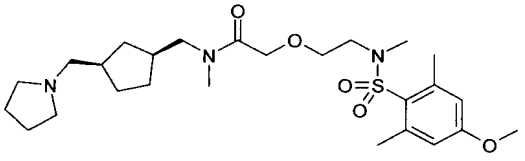
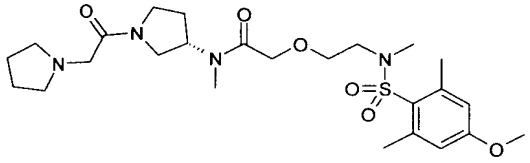
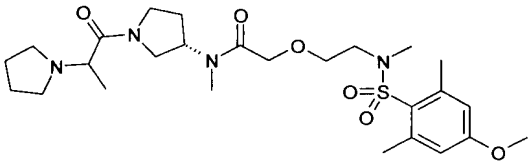
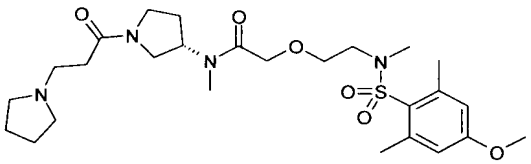
Exemplo	Estrutura
(419)	
(420)	
(421)	
(422)	
(423)	 Chiral
(424)	
(425)	 Chiral
(426)	

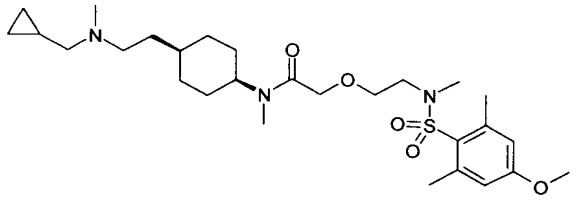
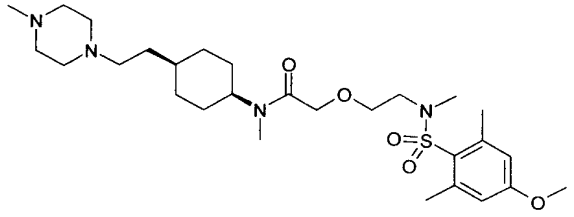
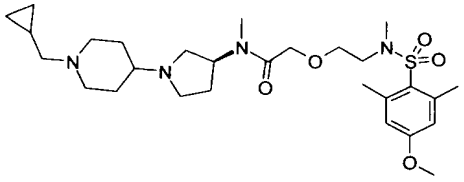
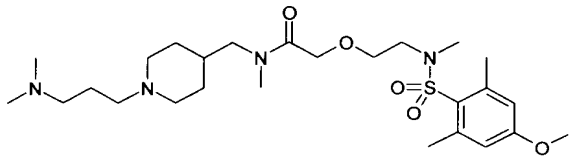
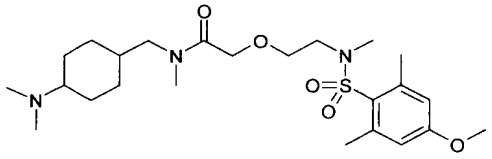
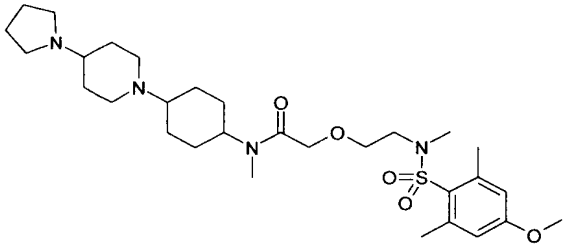
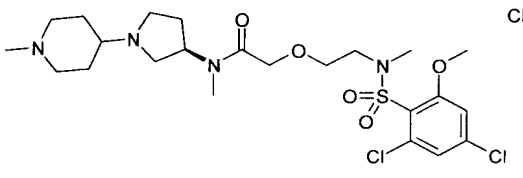
Exemplo	Estrutura
(427)	
(428)	
(429)	
(430)	
(431)	
(432)	
(433)	

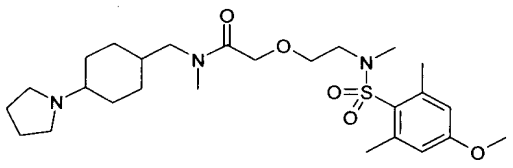
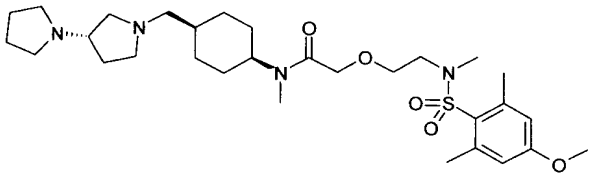
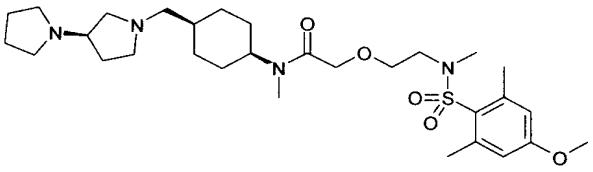
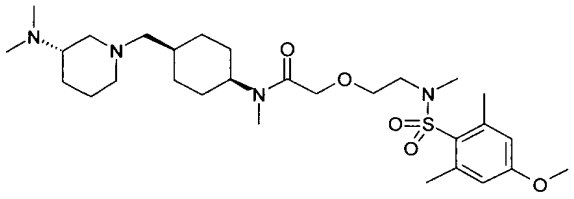
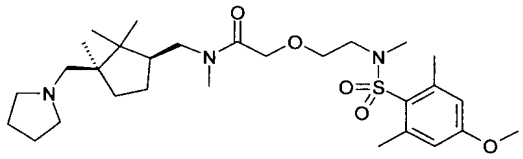
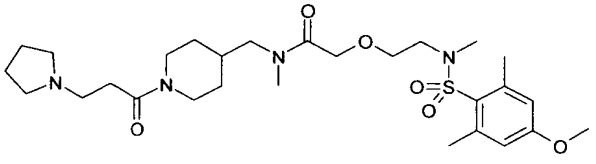
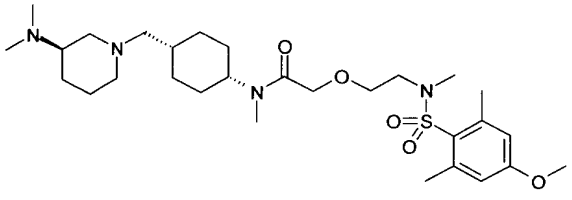
Exemplo	Estrutura
(434)	
(435)	
(436)	Chiral 
(437)	Chiral 
(438)	Chiral 
(439)	
(440)	

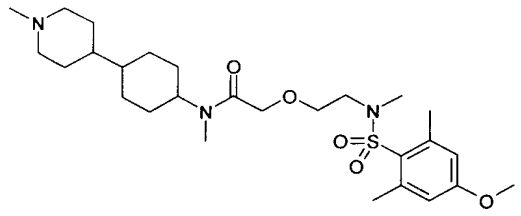
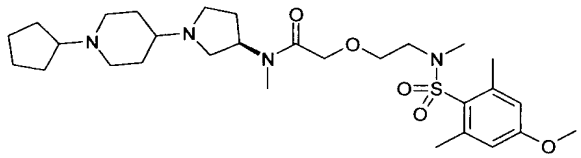
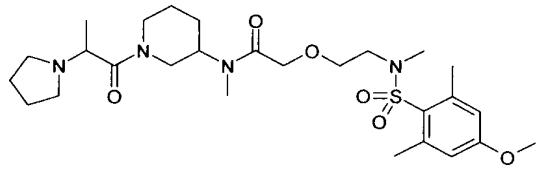
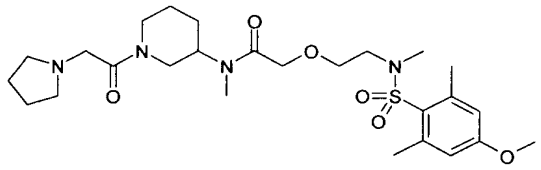
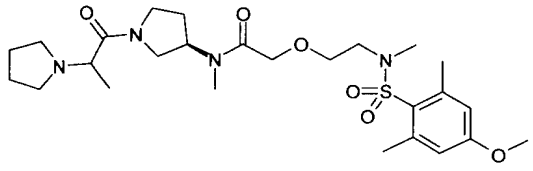
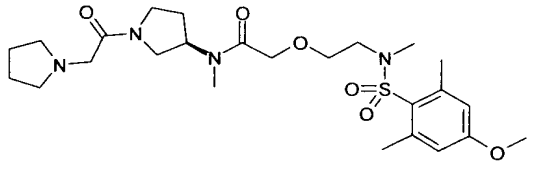
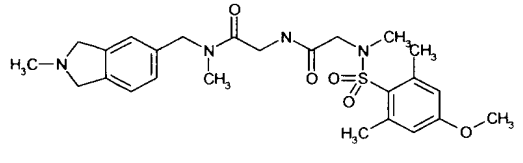
Exemplo	Estrutura
(441)	 Chiral
(442)	 Chiral
(443)	
(444)	
(445)	
(446)	 Chiral
(447)	 Chiral
(448)	 Chiral

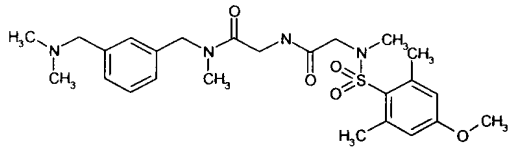
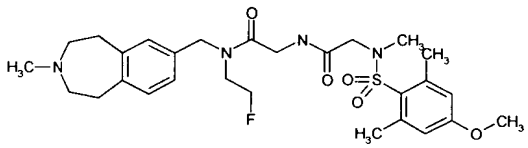
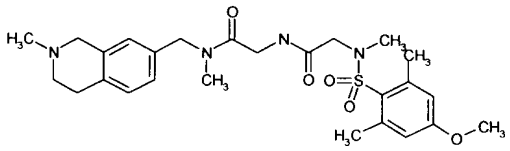
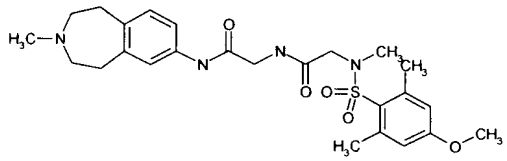
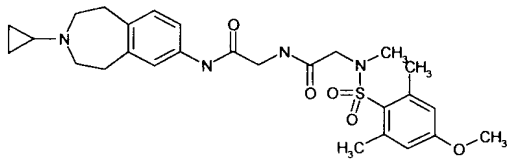
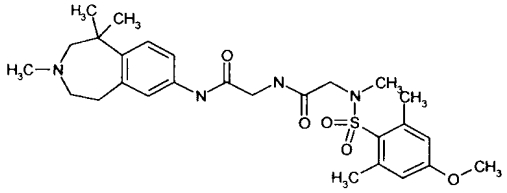
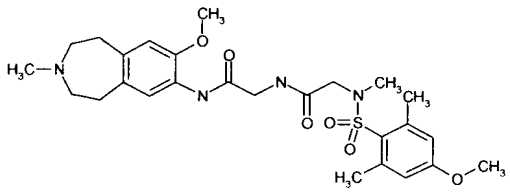
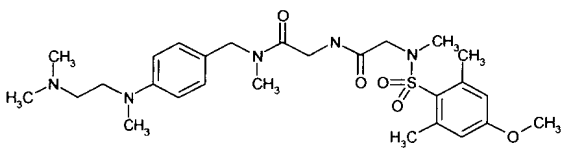
Exemplo	Estrutura
(449)	 Chiral
(450)	
(451)	
(452)	
(453)	
(454)	
(455)	

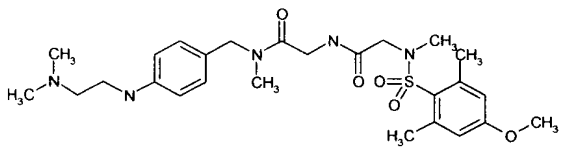
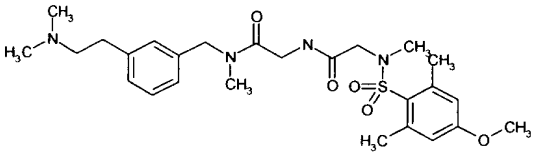
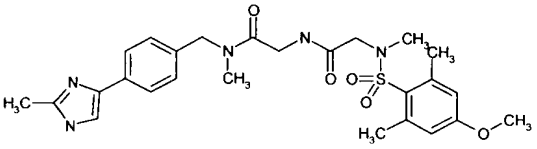
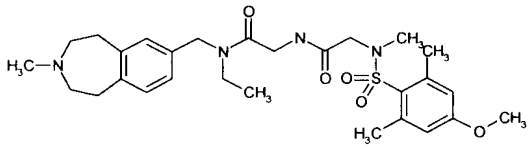
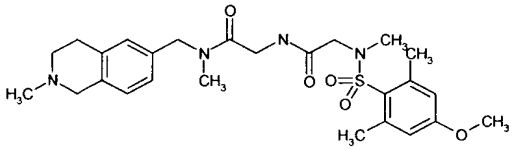
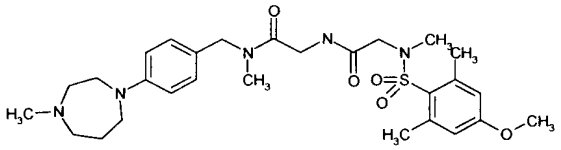
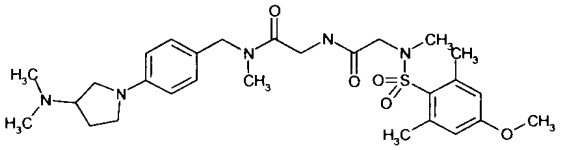
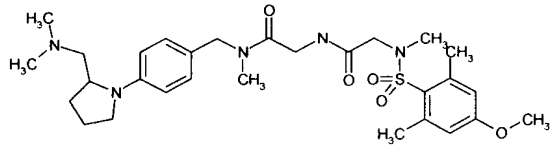
Exemplo	Estrutura
(456)	
(457)	
(458)	Chiral 
(459)	
(460)	
(461)	
(462)	

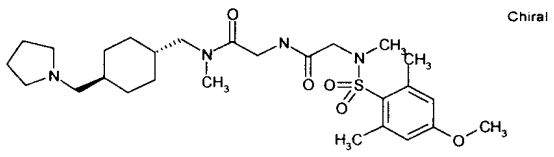
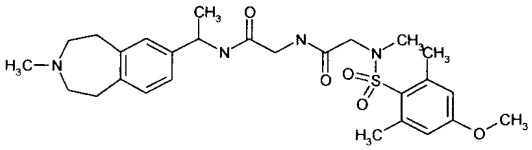
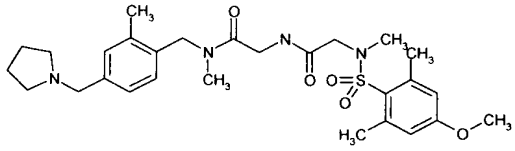
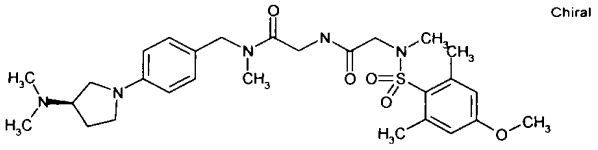
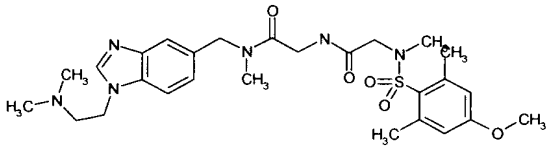
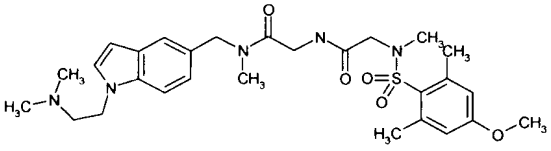
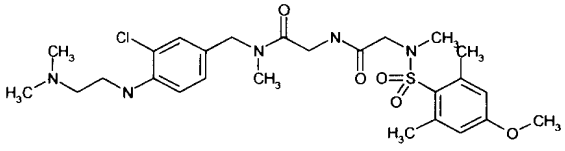
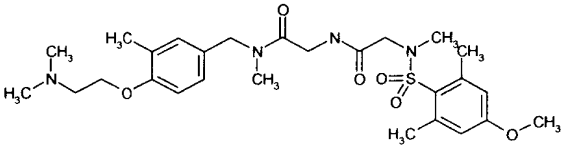
Exemplo	Estrutura
(463)	
(464)	
(465)	
(466)	
(467)	
(468)	
(469)	 Chiral

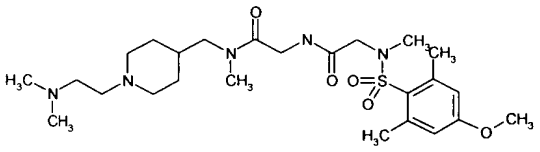
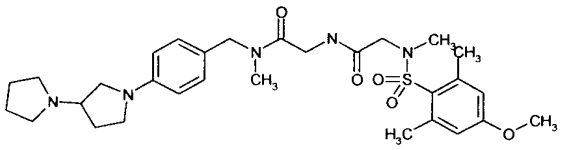
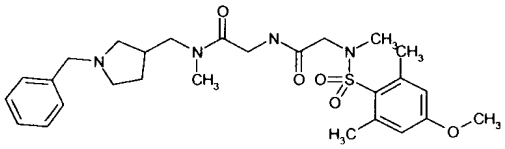
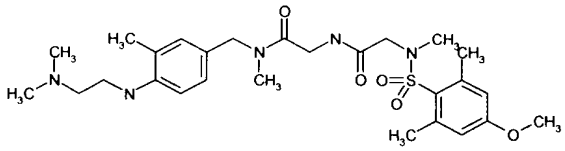
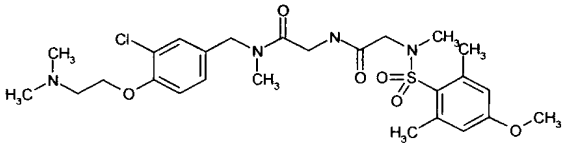
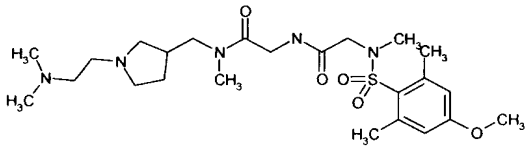
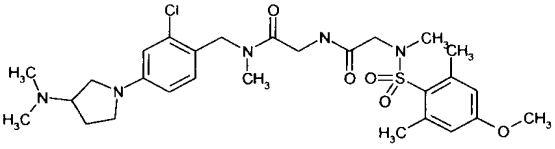
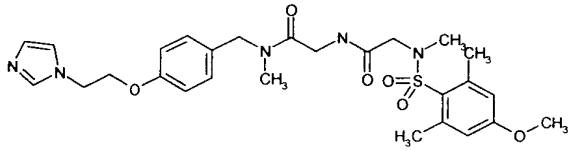
Exemplo	Estrutura
(470)	
(471)	
(472)	
(473)	
(474)	
(475)	
(476)	Chiral 

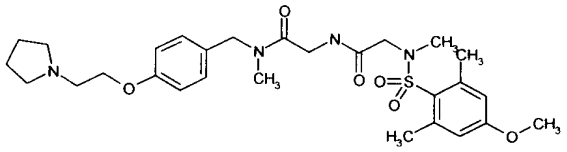
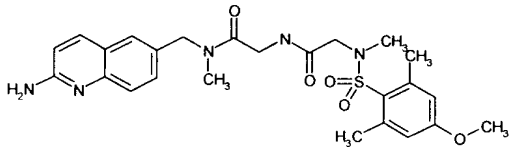
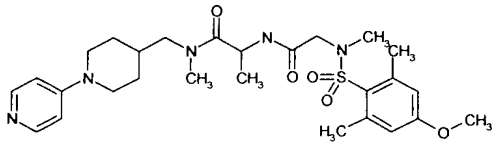
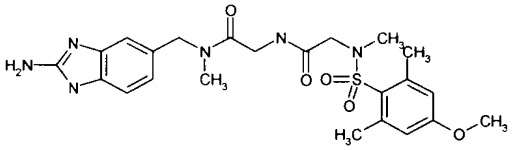
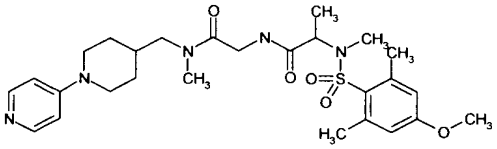
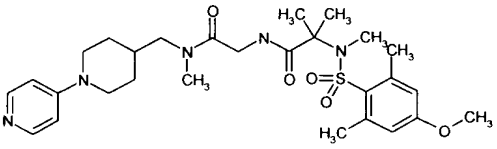
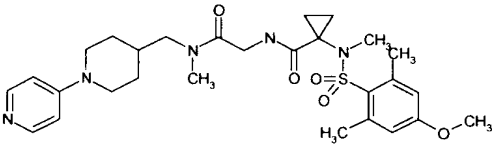
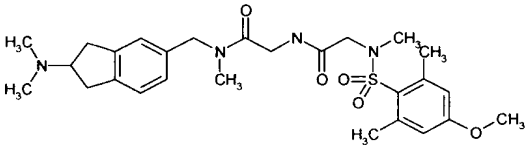
Exemplo	Estrutura
(477)	
(478)	Chiral 
(479)	
(480)	
(481)	Chiral 
(482)	Chiral 
(483)	

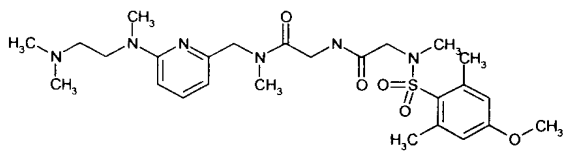
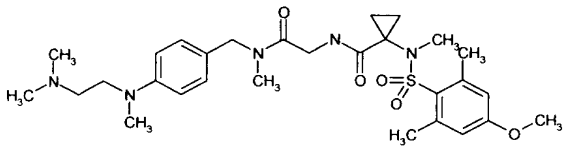
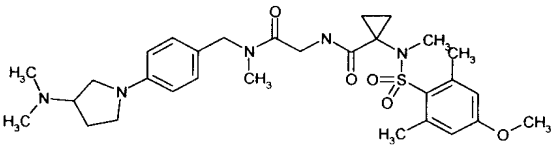
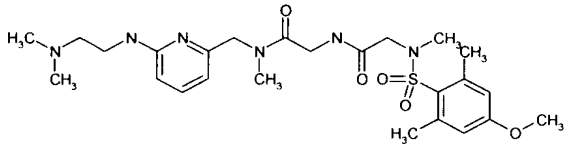
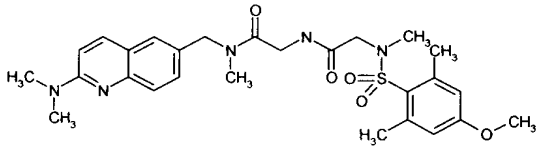
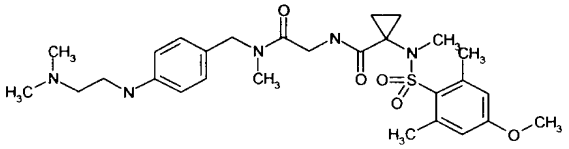
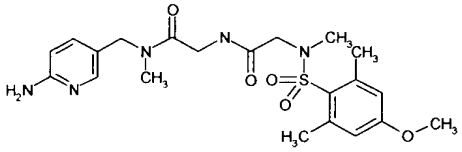
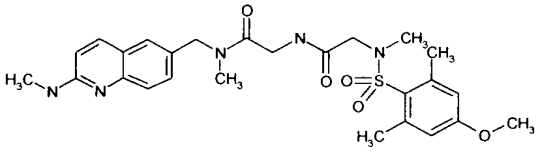
Exemplo	Estrutura
(484)	
(485)	
(486)	
(487)	
(488)	
(489)	
(490)	
(491)	

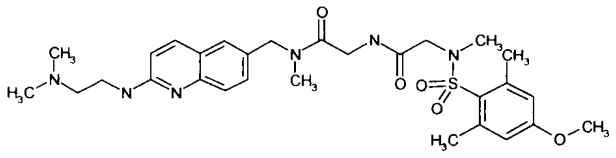
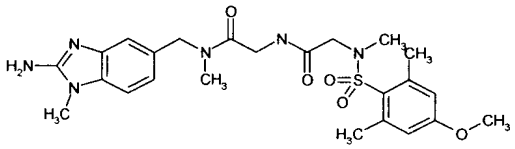
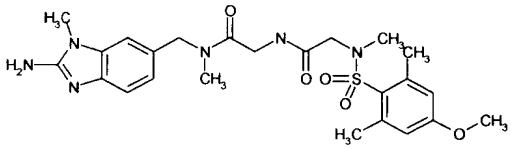
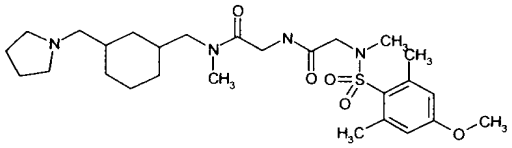
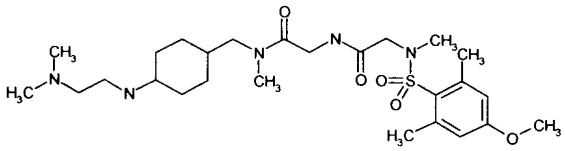
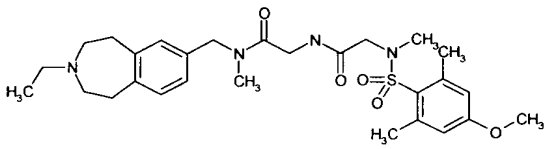
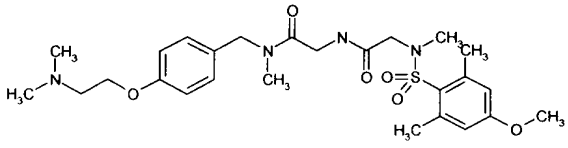
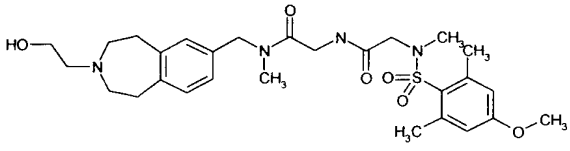
Exemplo	Estrutura
(492)	
(493)	
(494)	
(495)	
(496)	
(497)	
(498)	
(499)	

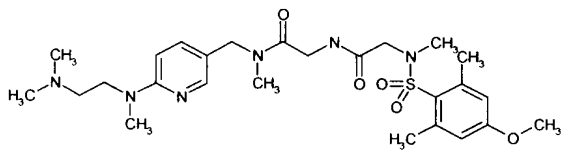
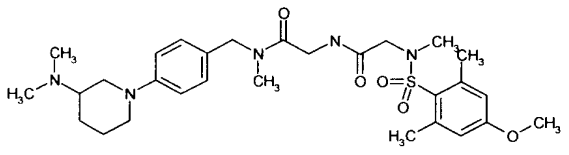
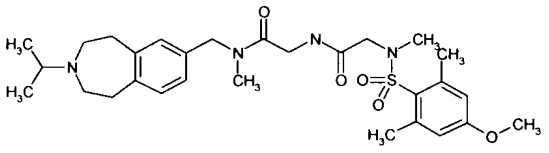
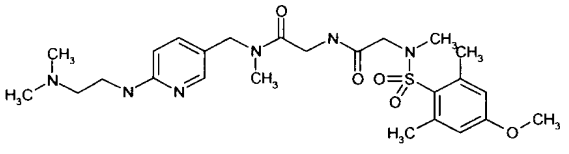
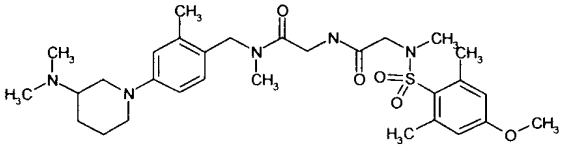
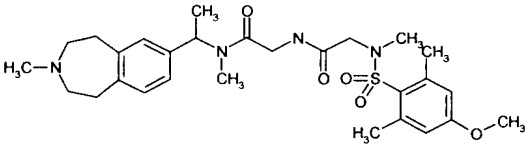
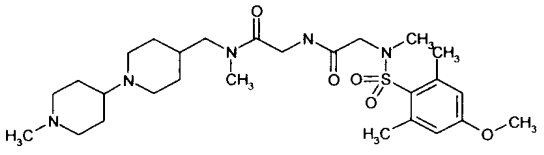
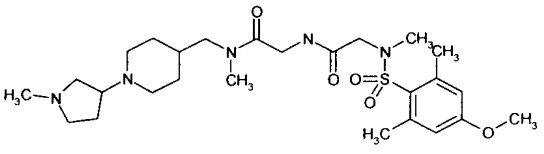
Exemplo	Estrutura
(500)	 Chiral
(501)	
(502)	
(503)	 Chiral
(504)	
(505)	
(506)	
(507)	

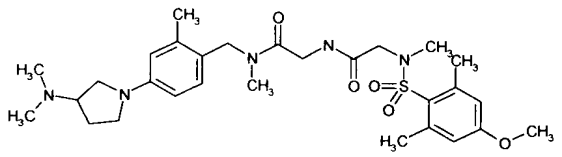
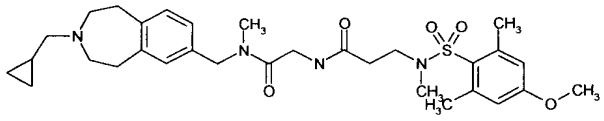
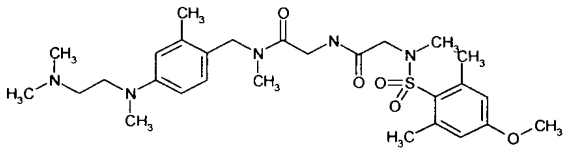
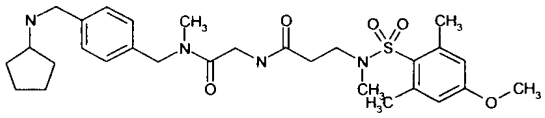
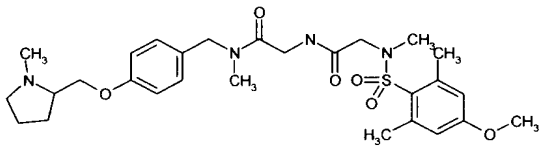
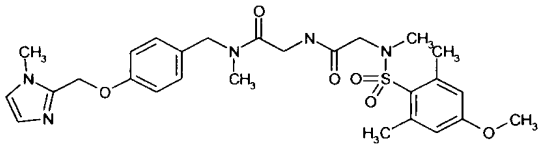
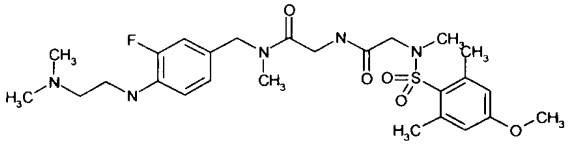
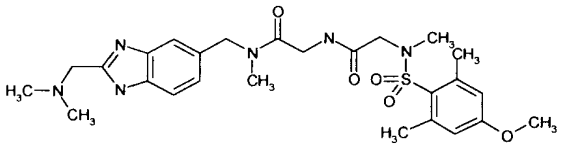
Exemplo	Estrutura
(508)	
(509)	
(510)	
(511)	
(512)	
(513)	
(514)	
(515)	

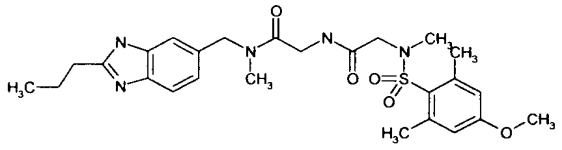
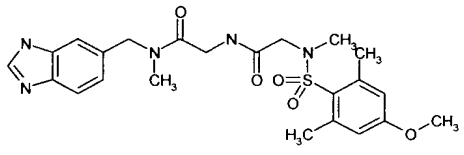
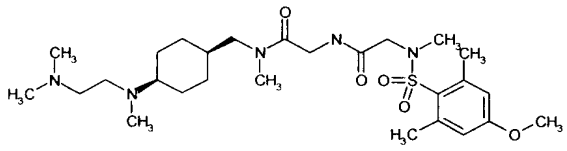
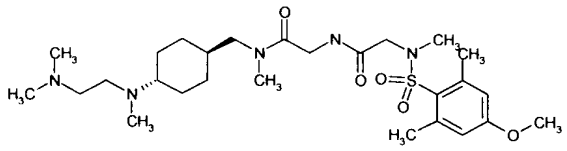
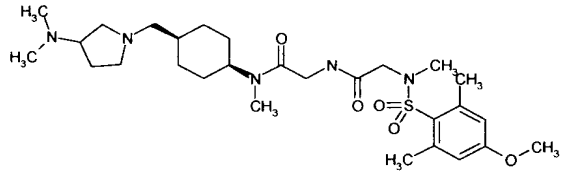
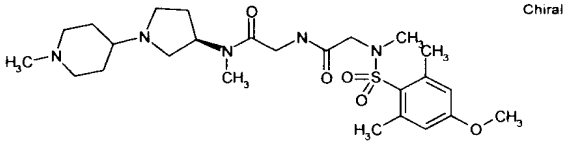
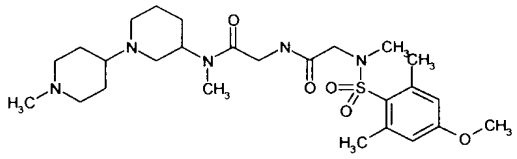
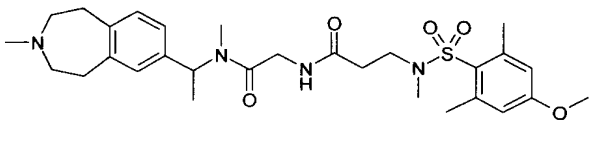
Exemplo	Estrutura
(516)	
(517)	
(518)	
(519)	
(520)	
(521)	
(522)	
(523)	

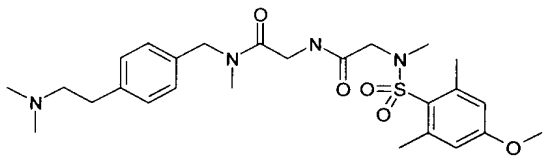
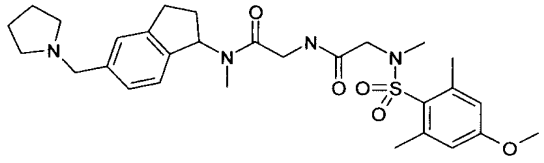
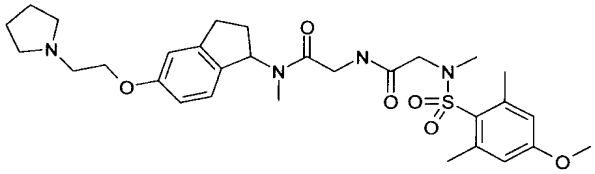
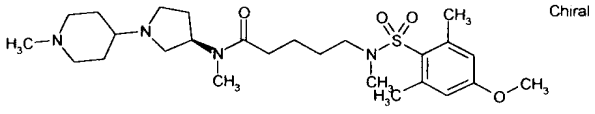
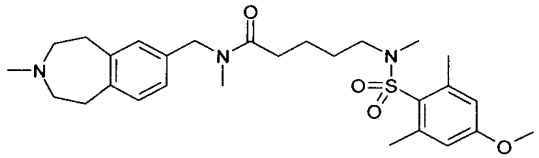
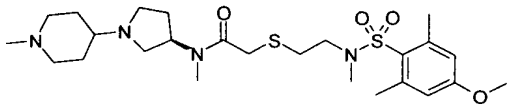
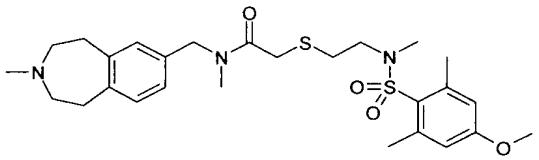
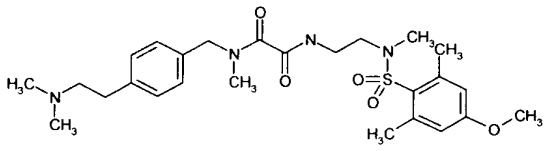
Exemplo	Estrutura
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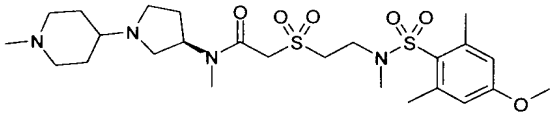
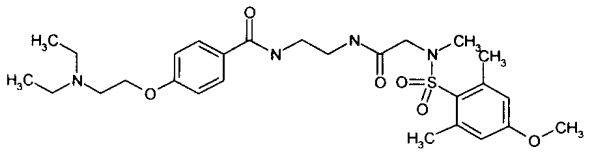
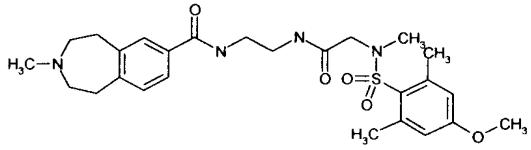
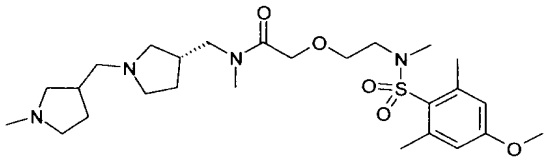
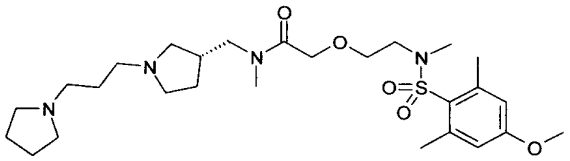
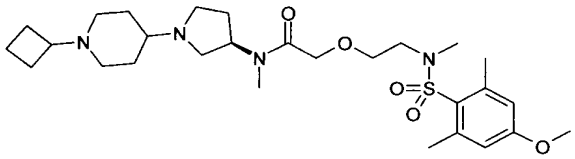
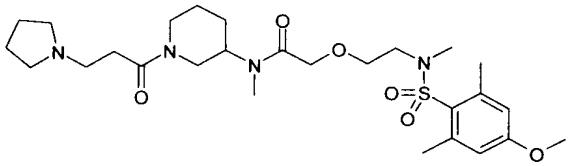
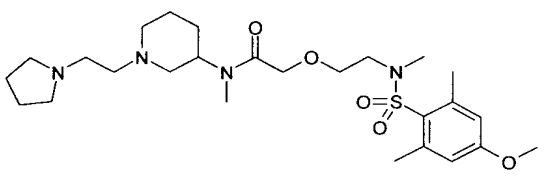
Exemplo	Estrutura
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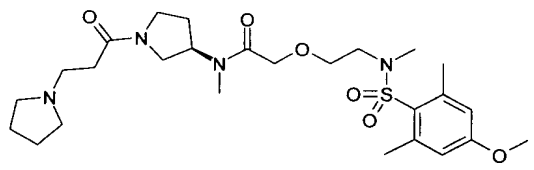
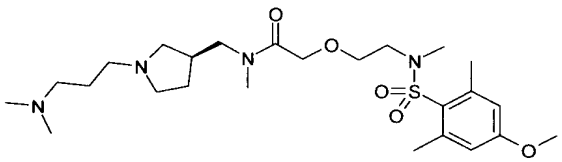
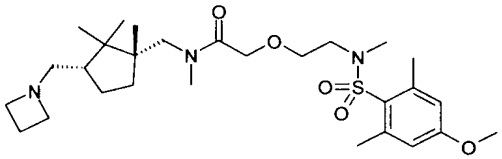
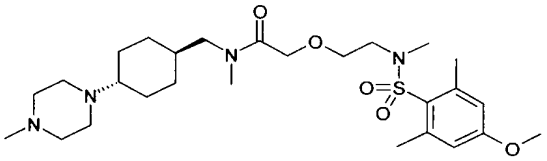
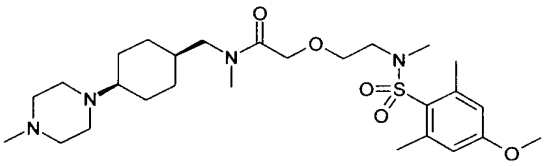
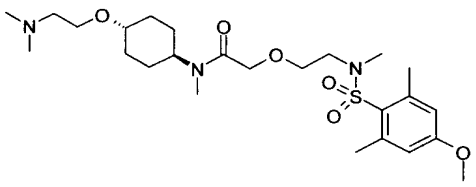
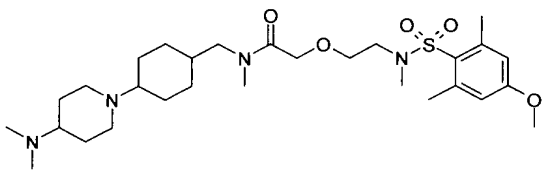
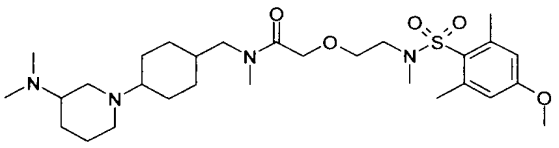
Exemplo	Estrutura
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(547)	

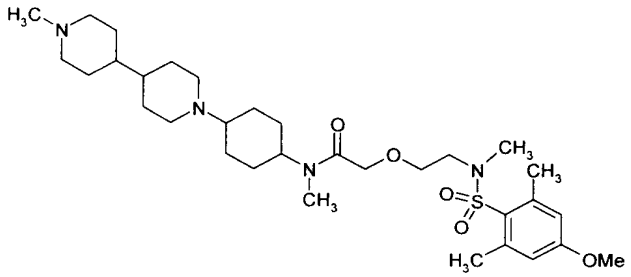
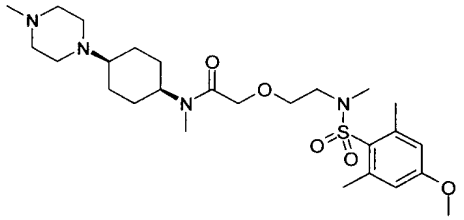
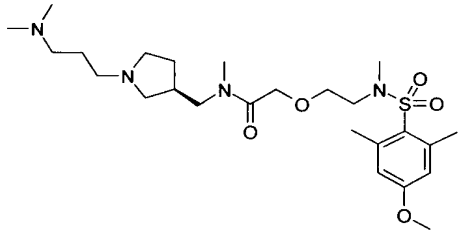
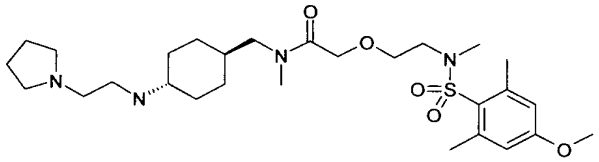
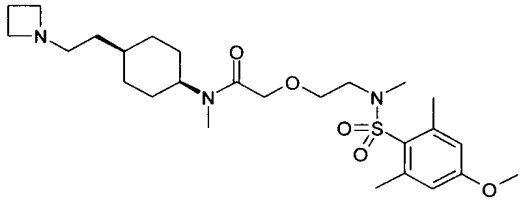
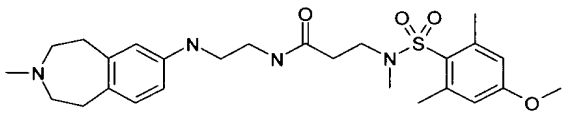
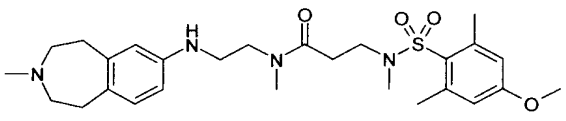
Exemplo	Estrutura
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(550)	
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(555)	

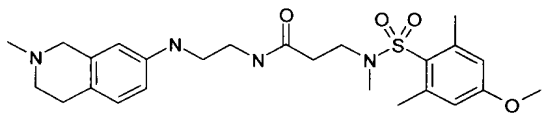
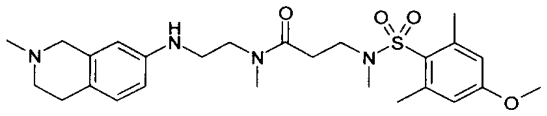
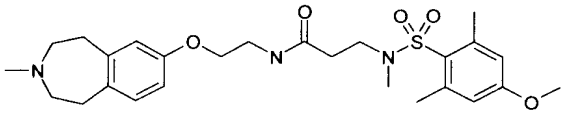
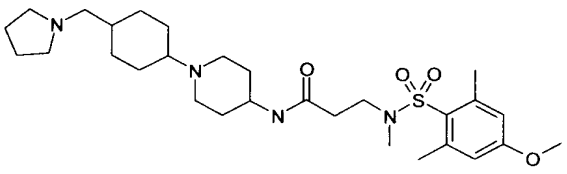
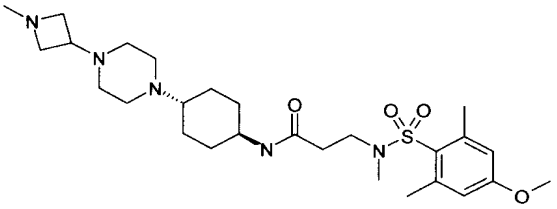
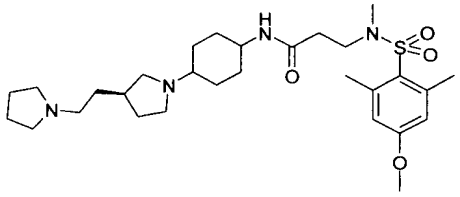
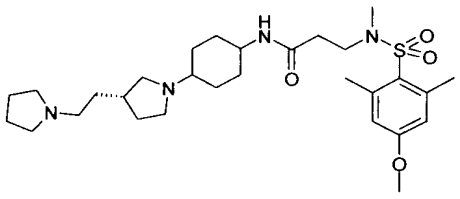
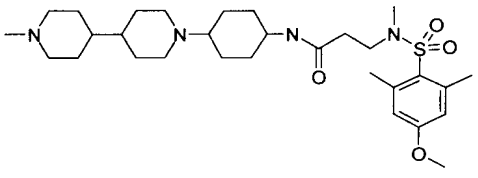
Exemplo	Estrutura
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(557)	
(558)	
(559)	
(560)	
(561)	 Chiral
(562)	
(563)	

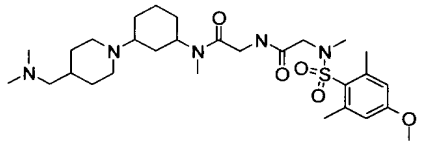
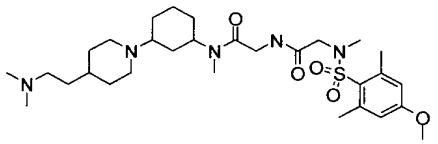
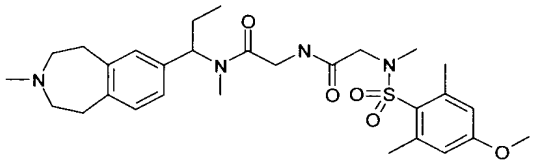
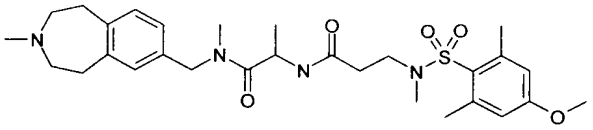
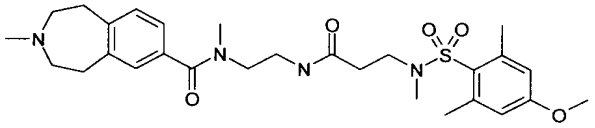
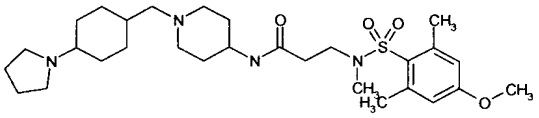
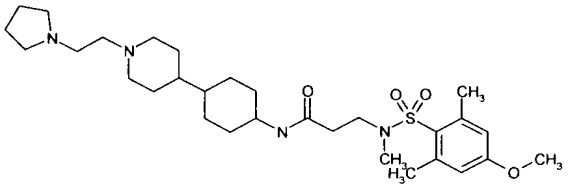
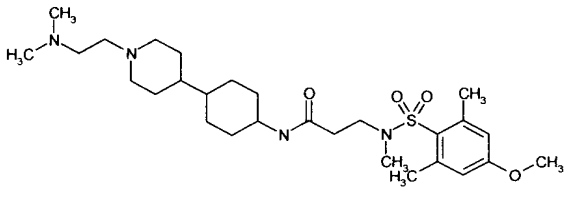
Exemplo	Estrutura
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(565)	
(566)	
(567)	 Chiral
(568)	
(569)	
(570)	
(571)	

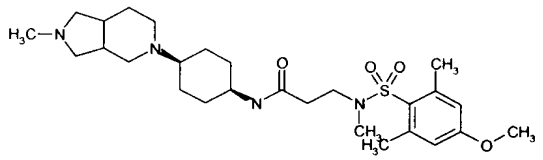
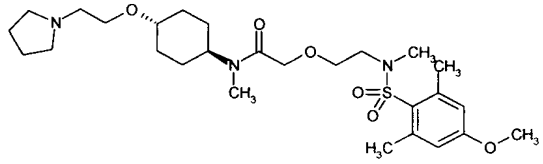
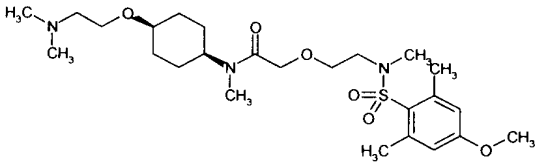
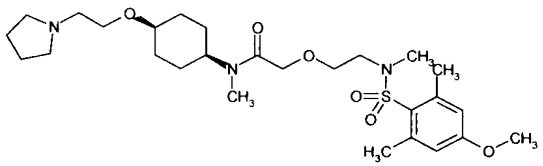
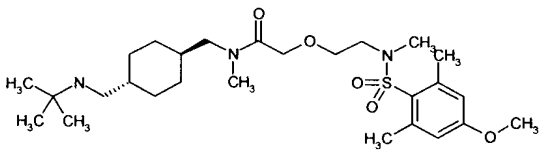
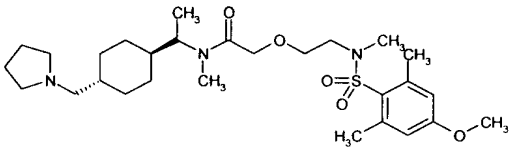
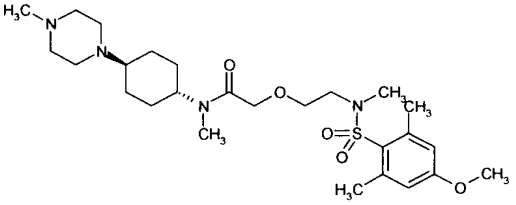
Exemplo	Estrutura
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(574)	
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(579)	

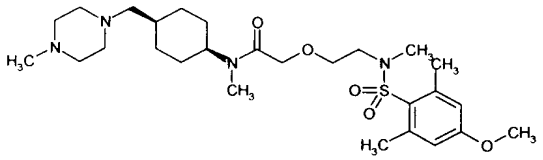
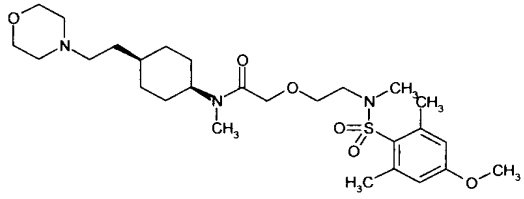
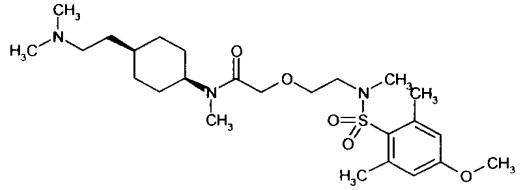
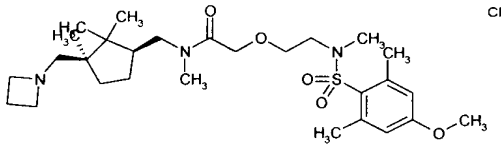
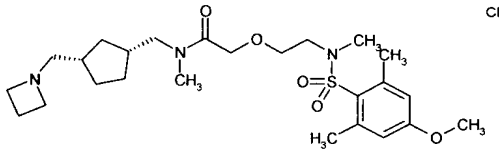
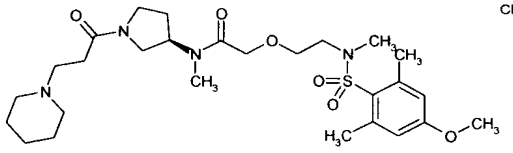
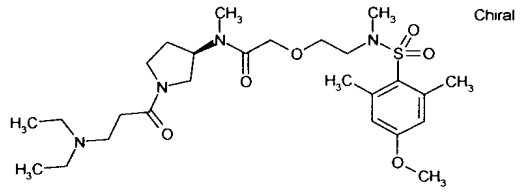
Exemplo	Estrutura
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(581)	
(582)	
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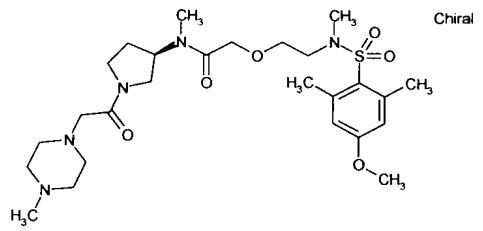
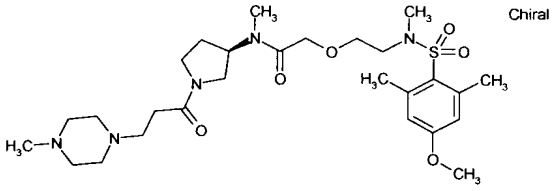
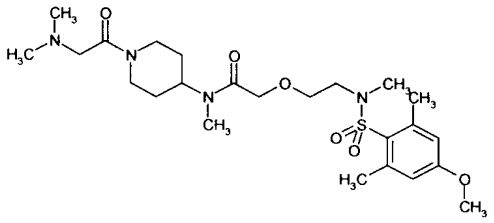
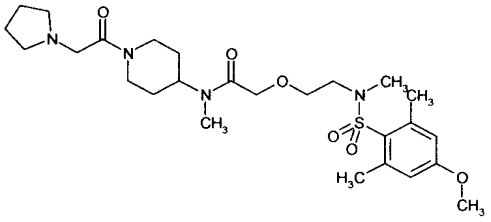
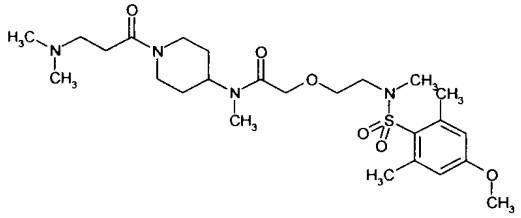
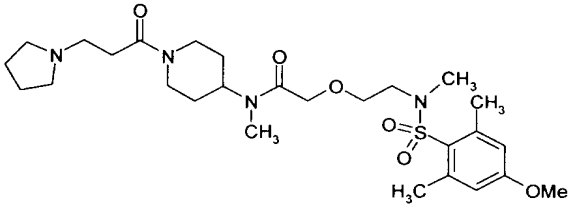
Exemplo	Estrutura
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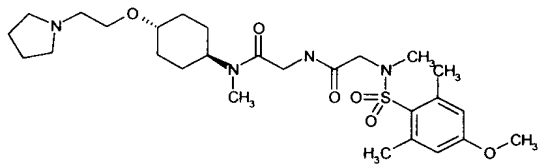
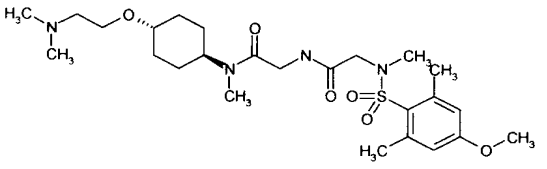
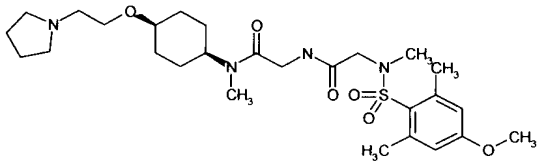
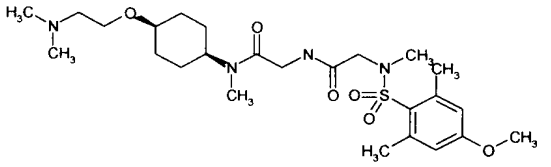
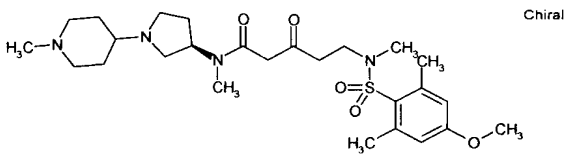
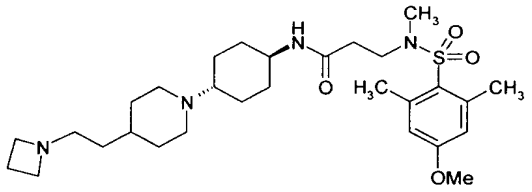
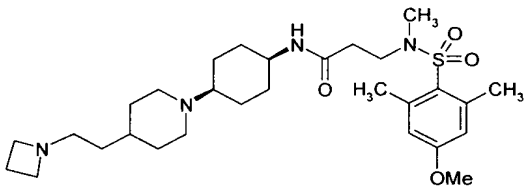
Exemplo	Estrutura
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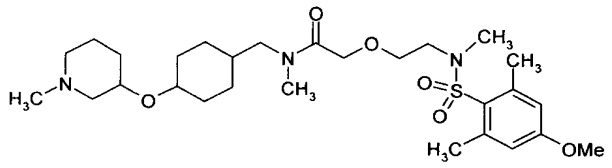
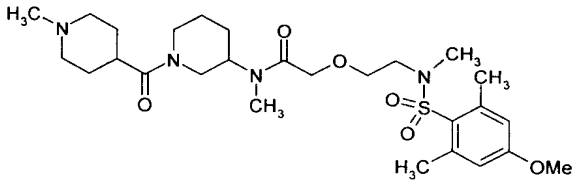
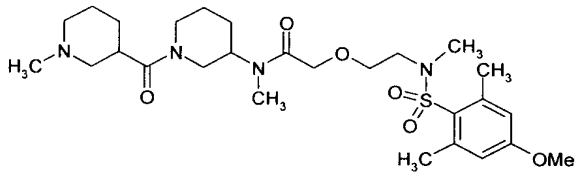
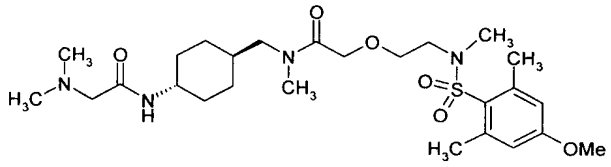
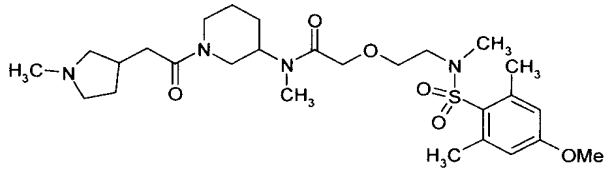
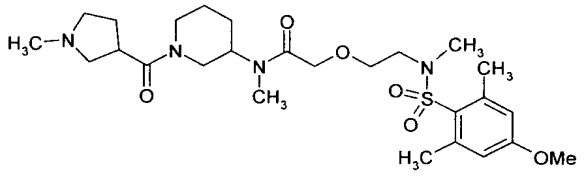
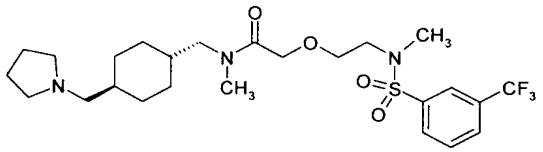
Exemplo	Estrutura
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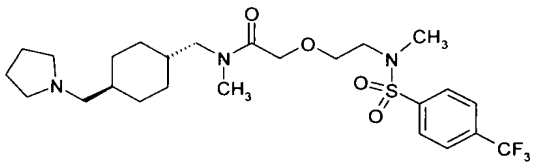
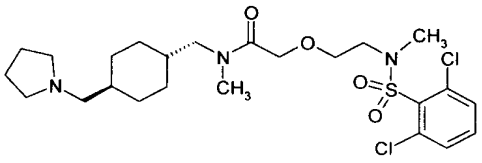
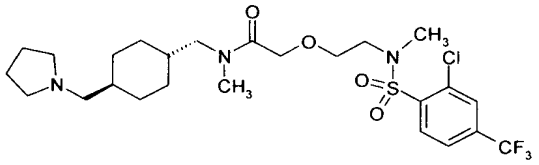
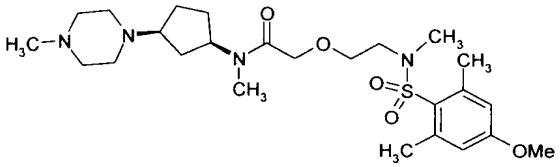
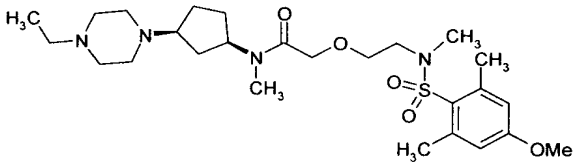
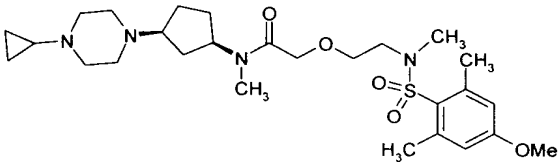
Exemplo	Estrutura
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Exemplo	Estrutura
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(620)	
(621)	Chiral 
(622)	Chiral 
(623)	Chiral 
(624)	Chiral 

Exemplo	Estrutura
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Exemplo	Estrutura
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(635)	 Chiral
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Exemplo	Estrutura
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Exemplo	Estrutura
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seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos.

8. Sais fisiologicamente toleráveis dos compostos como definidos em qualquer uma das reivindicações 1 a 7, caracterizados pelo fato de que são com ácidos ou bases inorgânicos ou orgânicos.

9. Medicamento, caracterizado pelo fato de que contém um composto como definido em qualquer uma das reivindicações 1 a 7, ou um

sal fisiologicamente tolerável como definido na reivindicação 8, além de eventualmente um ou mais veículos e/ou diluentes inertes.

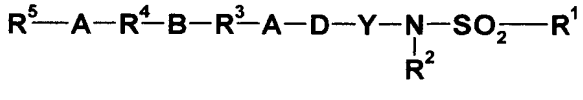
10. Uso de um composto como definido em qualquer uma das reivindicações 1 a 8, caracterizado pelo fato de que é para a produção de um medicamento para o tratamento agudo e profilático de dores agudas, dores abdominais, dores neuropáticas, dores inflamatórias/causadas pelo receptor da dor, dores tumorais e doenças de dor de cabeça.

11. Processo para a produção de um medicamento como definido na reivindicação 9, caracterizado pelo fato de que um composto como definido em qualquer uma das reivindicações 1 a 8, é incorporado em um ou mais veículos e/ou diluentes inertes por processo não químico.

RESUMO

Patente de Invenção: **ARILSULFONAMIDAS COM EFEITO ANALGÉSICO".**

A presente invenção refere-se a compostos da fórmula geral (I),



, (I)

na qual A, B, D, Y, R^1, R^2, R^3, R^4 e R^5 são definidos tal como na reivindicação 1, seus enantiômeros, seus diastereômeros, suas misturas e seus sais, especialmente seus sais fisiologicamente toleráveis com ácidos ou bases orgânicos ou inorgânicos, os quais apresentam valiosas propriedades, sua preparação, os medicamentos contendo os compostos farmacologicamente eficazes, sua produção e seu uso.