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(57) Resumo: DERIVADOS DE QUINAZOLINA TENDO ATIVIDADE INIBITÓRIA DE TIROSINA CINASE E COMPOSIÇÃO FARMACÊUTICA CONTENDO-OS. A presente invenção refere-se a um composto que inibe tanto a tirosina cinase do receptor EGF quanto a tirosina cinase HER2. Composto representado pela fórmula geral (I): Fórmula química 1 (I) em que Rx é um grupo representado pela fórmula: Fórmula químca 2 em que R1 é um átomo de hidrogênio, alquila opcionalmente substituida, etc.; Z é -O-, -N(R10)-, etc.; R10 é um átomo de hidrogênio, alquila, etc.; R2 é um átomo de hidrogênio, alquila opcionalmente substituida, etc.; R18 é um átomo de hidrogênio, alquila opcionalmente substituida, etc.; R19 é alquila opcionalmente substituida, etc.; W1 e um grupo contendo nitrogênio não aromático opcionalmente substituído; R17 é um átomo de hidrogênio, alquila opcionalmente substituida, etc.; R3 e R4 são independentemente um átomo de hidrogênio, alquila opcionalmente substituída, etc.; X é -O-, -S-, ou -N(R12)-, etc.; R12 é um átomo de hidrogênio, alquila, etc.; e A é fenila opcionalmente tendo um substituinte, etc., seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

Relatório Descritivo da Patente de Invenção para **"DERIVADOS DE QUINAZOLINA TENDO ATIVIDADE INIBITÓRIA DE TIROSINA CINASE E COMPOSIÇÃO FARMACÊUTICA QUE OS COMPREENDE"**.

Campo Técnico

[001] A presente invenção refere-se a um composto que inibe tanto a tirosina cinase receptora de EGF quanto a tirosina cinase HER2, e a uma composição farmacêutica contendo o mesmo como ingrediente ativo.

Antecedentes da Técnica

[002] Tirosina cinase é uma enzima que fosforila resíduos tirosina em proteínas de substratos, e sabe-se que desempenha um papel importante no sistema de transdução de sinal intracelular no que se refere à diferenciação e proliferação celular. Duas tirosina cinases receptoras, o receptor de EGF (doravante EGFR) e HER2 (também chamada ErbB2 ou Neu) estão consideravelmente envolvidos no desenvolvimento de câncer, e suas atividades são aumentadas em vários cânceres humanos (Literatura Não-Patentiada 1, Literatura Não-Patentiada 2 e Literatura Não-Patentiada 3). Também se sabe que essas cinases são expressas de forma aberrante em cânceres de cérebro, pulmão, estômago, intestino, pâncreas, cabeça e pescoço, esôfago, bexiga, rim, próstata, ovário, mama, útero, e glândula tireóide (Literatura Não-patentiada 4 e Literatura Patentiada 1). Portanto, acredita-se que um inibidor dessas cinases seja útila como fármaco anticâncer que pode ser eficaz em muitos tipos de cânceres e tem pouco efeito colateral. Como inibidor de tirosina cinases, são conhecidos os compostos descritos na Literatura Patentiada 2, Literatura Patentiada 3, Literatura Patentiada 4, Literatura Patentiada 5, Literatura Patentiada 6, Literatura Patentiada 7.

[003] Além disso, sabe-se que a transformação celular devido ao

EGFR é acelerada pela coexpressão adicional de HER2 (Literatura Não-patentiada 5). Ademais, a expressão concomitante de EGFR e HER2 é relatada como um marcador de pobre prognóstico na mama, cavidade oral e cânceres de pulmão (Literatura Não-patentiada 6). Como uma fármaco que inibe tanto o EGFR quanto o HER2, são conhecidos os compostos descritos na Literatura Patentiada 8.

[004] Um agente anticâncer tendo um substituinte tipo oxima na posição 4 de um derivado de quinazolina está descrito na Literatura Patentiada 9 e Literatura Patentiada 10.

Literatura Patentiada 1 - Pedido de Patente Japonesa Aberto à Inspeção Pública (JP-A) N° 5-208911

Literatura Patentiada 2 - WO 92/20642

Literatura Patentiada 3 - EPA N° 92305703.8

Literatura Patentiada 4 - EPA N° 0566266

Literatura Patentiada 5 - EPA N° 0602851

Literatura Patentiada 6 - EPA N° 0520722

Literatura Patentiada 7 - WO 98/02434

Literatura Patentiada 8 - WO 02/066445

Literatura Patentiada 9 - WO 2004/0691545

Literatura Patentiada 10 - WO 2004/105765

Literatura Não-patentiada 1 - Cancer Res., 1991, vol.51, pp. 4430-4435

Literatura Não-patentiada 2 - Cancer Res., 1992, vol.52, pp. 3636-3641

Literatura Não-patentiada 3 - Cancer Chemother. Pharmacol., 1993, vol.32, pp. 1-19

Literatura Não-patentiada 4 - Expart. Opin. Invest. Drugs, 1994, vol.3, No.6, pp. 577-595

Literatura Não-patentiada 5 - Cell, 1987, vol.58, pp. 287-292

Literatura Não-patentiada 6 - Clin. Cancer Res., 1999, vol.5, pp. 4164-4174

Descrição da Invenção

Problemas a serem resolvidos pela invenção

[005] Em comparação com um inibidor seletivo de EGFR ou HER2, espera-se que um inibidor dual para EGFR e HER2 seja mais eficaz, pois este último inibidor apresenta efeito mais forte em uma maior faixa de doenças por efeito sinergístico de inibição dual. Portanto, deseja-se um composto que iniba tanto o EGFR quanto o HER2.

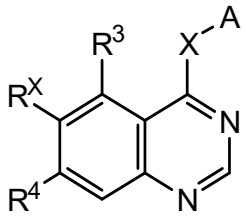
Meios para resolver os problemas

[006] Na situação acima, os presentes inventores estudaram intensamente e, como resultado, descobriram que um derivado de quinazolina tendo um certo substituinte na posição 6 tem excelente atividade inibitória dual em um receptor de EGF e HER2.

[007] Isto é, a presente invenção refere-se a:

(1) um composto representado pela fórmula geral (I):

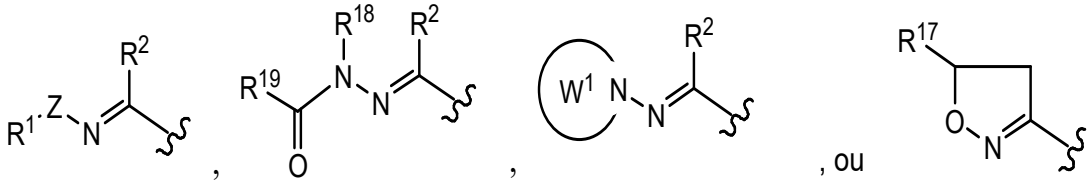
Fórmula química 1



(I)

onde R^X é um grupo representado pela fórmula:

Fórmula química 2



onde

R^1 é um átomo de hidrogênio, alquila opcionalmente substituída, alquenila opcionalmente substituída, arila opcionalmente substituída, ou um grupo heterocíclico contendo nitrogênio não-aromático opcionalmente substituído;

Z é -O-, -N(R^{10})-, ou alquileno que pode ser interposto com -

O- ou -N(R^{11})-; onde R^{10} e R^{11} são independentemente um átomo de hidrogênio, alquila, acila, alquiloxicarbonila, alqueniloxicarbonila, ou aralquiloxicarbonila;

R^2 é um átomo de hidrogênio, alquila opcionalmente substituída, alquenila opcionalmente substituída, alquinila opcionalmente substituída, cicloalquila opcionalmente substituída, arila opcionalmente substituída, ou heteroarila opcionalmente substituída;

R^{19} é alquila opcionalmente substituída, arila opcionalmente substituída, heteroarila opcionalmente substituída, ou um grupo heterocíclico não aromático opcionalmente substituído;

R^{18} é um átomo de hidrogênio, alquila opcionalmente substituída, alquenila opcionalmente substituída, ou alquinila opcionalmente substituída;

W^1 é um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído ou heteroarila opcionalmente substituída;

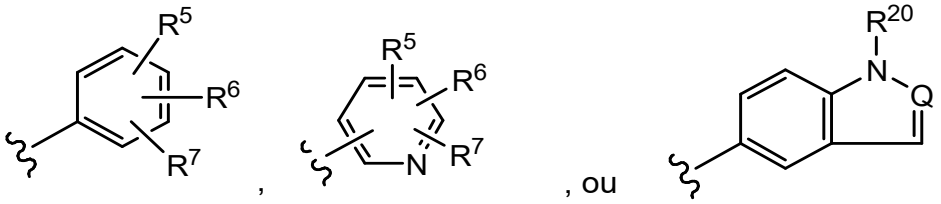
R^{17} é um átomo de hidrogênio, alquila opcionalmente substituída, alquenila opcionalmente substituída, ou um grupo heterocíclico contendo nitrogênio não-aromático opcionalmente substituído;

R^3 e R^4 são independentemente um átomo de hidrogênio, alquila opcionalmente substituída, alquenila opcionalmente substituída, alquinila opcionalmente substituída, alquilóxi opcionalmente substituído, alquenilóxi opcionalmente substituído, halogênio, hidróxi, mercapto, ou amina opcionalmente substituída,;

X é -O-, -S-, -N(R^{12})-, ou alquileno que pode ser interposto com -O-, -S-, ou -N(R^{13})-; onde R^{12} e R^{13} são independentemente um átomo de hidrogênio, alquila, acila, alquiloxicarbonila, alqueniloxicarbonila, ou aralquiloxicarbonila; e

[008] A é um grupo representado pela fórmula:

Fórmula química 3



onde

R^5 é um átomo de hidrogênio, halogênio, alquilóxi opcionalmente substituído, alquenilóxi opcionalmente substituído, alquinilóxi opcionalmente substituído, ou um grupo representado pela fórmula: -Y-R^8 onde Y é -O-, -S-, -SO_2-, ou alquileno que pode ser interposto com -O-, -S-, ou -N(R^9)-, R^8 é arila opcionalmente substituída ou heteroarila opcionalmente substituída; R^9 é um átomo de hidrogênio, alquila, acila, alquiloxicarbonila, alqueniloxicarbonila, ou aralquiloxicarbonila;

R^6 e R^7 são independentemente um átomo de hidrogênio, alquila opcionalmente substituída, alquenila opcionalmente substituída, alquinila opcionalmente substituída, alquilóxi opcionalmente substituído, alquenilóxi opcionalmente substituído, alquinilóxi opcionalmente substituído, halogênio, hidróxi, mercapto, ciano, ou amina opcionalmente substituída;

R^{20} é alquila opcionalmente substituída, alquenila opcionalmente substituída, alquinila opcionalmente substituída, ou um grupo representado pela fórmula:

Fórmula química 4



onde

R^5, R^6 e R^7 são como definidos acima;

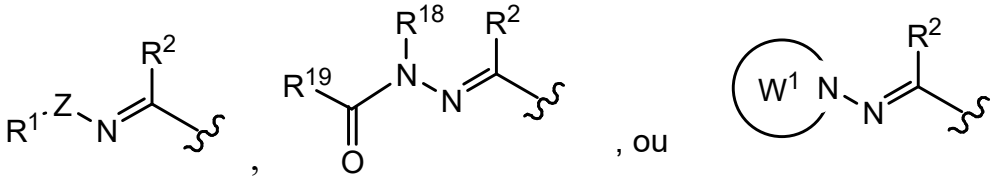
Q é N ou CH_2,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[009] Mais particularmente, a presente invenção refere-se aos itens (2) a (20) a seguir.

(2) O composto de acordo com o item (1), onde R^X é um grupo representado pela fórmula:

Fórmula química 5



onde

R^1, R^2, R^{18}, R^{19}, Z, eW^1 são como definidos no item (1),

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(3) O composto de acordo com o item (1) ou (2), onde R^1 é alquila opcionalmente substituída com um substituinte selecionado do grupo A de substituintes que consiste em hidróxi, heteroarila, carbóxi, amina opcionalmente substituída, um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído, aminocarbonila opcionalmente substituída, e carbonila heterocíclico contendo nitrogênio não aromático opcionalmente substituído, ou um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído com um substituinte selecionado do grupo B de substituintes que consiste em alquiloxicarbonila, aminocarbonila opcionalmente substituída, oxo, amino, carbóxi, ciano, cianoalquila, hidroxialquila, alquilcarbonilamino, alquilsulfonilamino, e aminocarbonilalquila,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(4) O composto de acordo com qualquer um dos itens (1) a (3), onde R^1 é alquila substituída com amina opcionalmente substituída com um substituinte selecionado do grupo C de substituintes que consiste em alquila, alquenila, alquinila, arila opcionalmente substituída,

aralquila, alquilóxi, hidroxialquila, hidroxialquiloxialquila, haloalquila, aminoalquila opcionalmente substituída com 1 ou 2 alquilas, alquilsulfonila, alquilsulfonilalquila, alquilcarbonila opcionalmente substituída com halogênio ou alquilóxi, alquiloxicarbonila, cicloalquila opcionalmente substituída, carboxialquila, aminocarbonilalquila opcionalmente substituída, aminocarboniloxialquila opcionalmente substituída, alquiloxialquila, alquiltioalquila, alquilcarbonilaminoalquila, alquilsulfonilaminoalquila, alquilsulfonila(alquila)aminoalquila, alquiloxicarbonilalquila, alquiltio(hidroxi)alquila, cicloalquilalquila, cianoalquila, aminoalquilcarbonila opcionalmente substituída, heteroarila opcionalmente substituída, heteroarilalquila, hidroxialquiloxialquila, um grupo heterocíclico não aromático opcionalmente substituído, e alquila heterocíclica não aromática opcionalmente substituída,

alquila substituída com um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído com um substituinte selecionado do grupo D de substituintes que consiste em halogênio; arila; hidróxi; oxo; aminocarbonila opcionalmente substituída; alquiloxicarbonila; alquila opcionalmente substituída com um substituinte selecionado do grupo H de substituintes que consiste em aminocarbonila opcionalmente substituída, ciano, alquilóxi, alquilsulfonilamino, amino, carbóxi, alquiloxicarbonila, and hidróxi; alquilaminocarbonila; carbóxi; ciano; alquilsulfonila; alquilcarbonila; alquenilcarbonila; alquilsulfonilalquilcarbonila; alquiloxialquilcarbonila; alquilcarbonilamino; aminocarbonilóxi; um grupo heterocíclico contendo nitrogênio não aromático; e carbonila heterocíclico não aromático, ou

um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído com um substituinte selecionado do grupo B de substituintes,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(5) O composto de acordo com qualquer um dos itens (1) a

(4), onde Z é -O-, seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(6) O composto de acordo com o item (1) ou (2), onde R^{19} é alquila opcionalmente substituída com um substituinte selecionado do grupo A de substituintes;

arila opcionalmente substituída com um substituinte selecionado do grupo I de substituintes que consiste em alquiloxicarbonila, aminocarbonila opcionalmente substituída, ciano, cianoalquila, hidroxialquila, e aminocarbonilalquila, ou

heteroarila opcionalmente substituída com um substituinte selecionado do grupo I de substituintes;

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(7) O composto de acordo com qualquer um dos itens (1), (2), e (6), onde R^{19} é alquila substituída com amina opcionalmente substituída com um substituinte selecionado do grupo C de substituintes; ou

alquila substituída com um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído com um substituinte selecionado do grupo D de substituintes;

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(8) O composto de acordo com o item (1) ou (2), onde W^1 é um grupo representado por um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído com um substituinte selecionado do grupo J de substituintes que consiste em alquila, cianoalquila, hidroxialquila, aminocarbonilalquila, alquilóxi, alquiloxicarbonila, aminocarbonila opcionalmente substituída, e ciano; ou

um grupo representado por heteroarila opcionalmente substituída com um substituinte selecionado do grupo J de substituintes;

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(9) O composto de acordo com qualquer um dos itens (1) a (8), onde R^2 é um átomo de hidrogênio, C1-C6 alquila opcionalmente substituída com halogênio, C2-C6 alquenila, C2-C6 alquinila, halogênio, ou fenila, seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

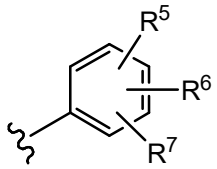
(10) O composto de acordo com qualquer um dos itens (1) a (9), onde R^2 é C2-C4 alquinila,
seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(11) O composto de acordo com qualquer um dos itens (1) a (10), onde um de R^3 e R^4 é um átomo de hidrogênio, e o outro é um átomo de hidrogênio, alquilóxi opcionalmente substituído ou alquenilóxi opcionalmente substituído,
seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(12) O composto de acordo com qualquer um dos itens (1) a (11), onde X é -NH-,
seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(13) O composto de acordo com qualquer um dos itens (1) a (12), onde A é um grupo representado pela fórmula:

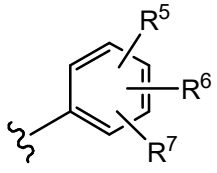
Fórmula química 6



onde R^5 é um átomo de hidrogênio ou halogênio; R^6 é halogênio ou alquinila; e R^7 é um átomo de hidrogênio,
seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(14) O composto de acordo com qualquer um dos itens (1) a (12), onde A é um grupo representado pela fórmula:

Fórmula química 7



onde R^5 é alquilóxi opcionalmente substituído com um substituinte selecionado do grupo E de substituintes que consiste em carbóxi, alcoxioxicarbonila, cicloalquila, e aminocarbonila opcionalmente substituída;

alquenilóxi opcionalmente substituído com um substituinte selecionado do grupo E de substituintes; ou

alquinilóxi opcionalmente substituído com um substituinte selecionado do grupo E de substituintes;

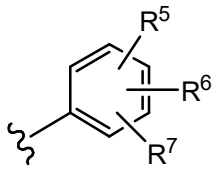
R^6 é alquinila opcionalmente substituída, alquilóxi opcionalmente substituído, ou halogênio; e

R^7 é um átomo de hidrogênio,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(15) O composto de acordo com qualquer um dos itens (1) a (12), onde A é um grupo representado pela fórmula:

Fórmula química 8



onde

R^5 é um grupo representado pela fórmula: -Y-R^8 onde Y é alquileno que pode ser interposto com -O-;

R^8 é fenila opcionalmente substituída com um substituinte selecionado do grupo F de substituintes que consiste em halogênio, carbóxi, alquila, haloalquila, hidroxialquila, alquilóxi, alquiloxicarbonila, e amina opcionalmente substituída; piridila opcionalmente substituída com um substituinte selecionado do grupo F de substituintes;

furila opcionalmente substituída com um substituinte selecionado do grupo F de substituintes;

tienila opcionalmente substituída com um substituinte selecionado do grupo F de substituintes;

tiazolila opcionalmente substituída com um substituinte selecionado do grupo F de substituintes; ou

oxazolila opcionalmente substituída com um substituinte selecionado do grupo F de substituintes;

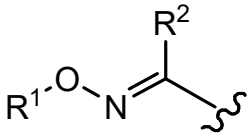
R^6 é alquinila opcionalmente substituída, alquilóxi opcionalmente substituído, ou halogênio; e

R^7 é um átomo de hidrogênio,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(16) O composto de acordo com o item (1), onde R^X é um grupo representado pela fórmula:

Fórmula química 9



onde

R^1 é alquila substituída com amina opcionalmente substituída com alquila, hidroxialquila, alquilcarbonilaminoalquila ou um heterociclo não aromático;

alquila substituída com um heterociclo contendo nitrogênio não aromático opcionalmente substituído com alquila, hidroxialquila ou alquilcarbonilamino; ou

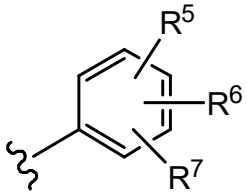
um grupo heterocíclico contendo nitrogênio não aromático substituído com hidroxialquila; e R^2 é C2-C4 alquinila;

R^3 e R^4 são ambos um átomo de hidrogênio;

X é -NH-; e

[010] A é um grupo representado pela fórmula:

Fórmula química 10



onde

R^5 é um grupo representado pela fórmula: -Y-R^8 onde Y é C1-C3 alquileno que pode ser interposto com -O-;

R^8 é fenila opcionalmente substituída com halogênio, ou piridila opcionalmente substituída com halogênio;

R^6 é halogênio; e

R^7 é um átomo de hidrogênio,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(17) Uma composição farmacêutica contendo o composto definido em qualquer um dos itens (1) a (16) como ingrediente ativo.

(18) Uma composição farmacêutica útila para o tratamento de câncer contendo o composto definido em qualquer um dos itens (1) a (16) como ingrediente ativo.

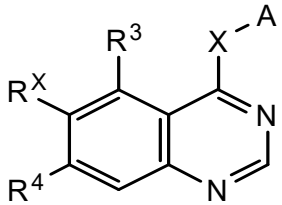
(19) Um método para prevenir e/ou tratar um câncer, compreendendo administrar o composto de acordo com qualquer um dos itens (1) a (16), seus sal farmaceuticamente aceitável ou um solvato do mesmo.

(20) Uso do composto de acordo com qualquer um dos itens (1) a (16), seu solvato farmaceuticamente aceitável ou um sal para produzir uma composição para prevenir e/ou tratar um câncer.

[011] Além disso, a presente invenção inclui as seguintes invenções como outro aspecto.

(I) Um composto representado pela fórmula geral (I):

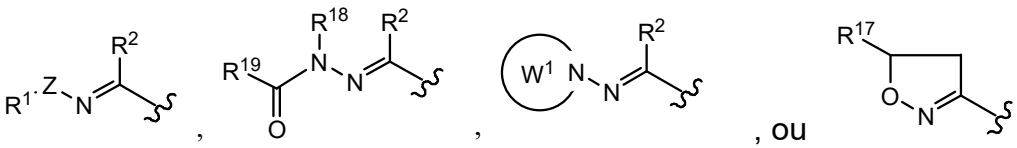
Fórmula química 11



(I)

onde R^X é um grupo representado pela fórmula:

Fórmula química 12



onde

R^1 é um átomo de hidrogênio, alquila opcionalmente substituída, alquenila opcionalmente substituída, ou um grupo heterocíclico contendo nitrogênio não-aromático opcionalmente substituído;

Z é -O- ou -N(R^{10})-, ou alquileno que pode ser interposto com -O- ou -N(R^{11})-; R^{10} e R^{11} são independentemente um átomo de hidrogênio, alquila, acila, alquiloxicarbonila, alqueniloxicarbonila, ou aralquiloxicarbonila;

R^2 é um átomo de hidrogênio, alquila opcionalmente substituída, alquenila opcionalmente substituída, alquinila opcionalmente substituída, arila opcionalmente substituída, ou heteroarila opcionalmente substituída;

R^{19} é alquila opcionalmente substituída, arila opcionalmente substituída, heteroarila opcionalmente substituída, ou um grupo heterocíclico não aromático opcionalmente substituído;

R^{18} é um átomo de hidrogênio, alquila opcionalmente substituída, alquenila opcionalmente substituída, ou alquilnila opcionalmente substituída;

W^1 é um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído ou heteroarila opcionalmente substituída;

R^{17} é um grupo hidrogênio, alquila opcionalmente substituída, alquenila opcionalmente substituída, ou um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído;

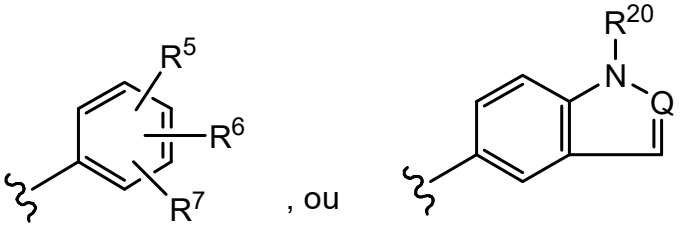
R^3 e R^4 são independentemente um átomo de hidrogênio,

alquila opcionalmente substituída, alquenila opcionalmente substituída, alquinila opcionalmente substituída, alquilóxi opcionalmente substituído, alquenilóxi opcionalmente substituído, halogênio, hidróxi, mercapto, ou amina opcionalmente substituída;

X é -O-, -S-, -N(R^{12})-, ou alquileno que pode ser interposto com -O-, -S-, ou -N(R^{13})-; onde R^{12} e R^{13} são independentemente um átomo de hidrogênio, alquila, acila, alquiloxicarbonila, alqueniloxicarbonila, ou aralquiloxicarbonila; e

[012] A é um grupo representado pela fórmula:

Fórmula química 13



onde

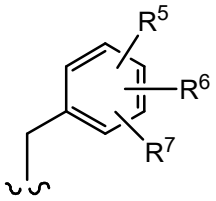
R^5 é um átomo de hidrogênio, halogênio, alquilóxi opcionalmente substituído, alquenilóxi opcionalmente substituído, alquinilóxi opcionalmente substituído, ou um grupo representado pela fórmula: -Y-R^8 onde Y é -O-, -S-, ou alquileno que pode ser interposto com -N(R^9)-; R^8 é arila opcionalmente substituída, ou heteroarila opcionalmente substituída; R^9 é um átomo de hidrogênio, alquila, acila, alquiloxicarbonila, alqueniloxicarbonila, ou aralquiloxicarbonila;

R^6 e R^7 são independentemente um átomo de hidrogênio, alquila opcionalmente substituída, alquenila opcionalmente substituída, alquinila opcionalmente substituída, alquilóxi opcionalmente substituído, alquenilóxi opcionalmente substituído, alquinilóxi opcionalmente substituído, halogênio, hidróxi, mercapto, ou amina opcionalmente substituída;

R^{20} é alquila opcionalmente substituída, alquenila opcionalmente substituída, alquinila opcionalmente substituída, ou um

grupo representado pela fórmula:

Fórmula química 14



onde

R^5, R^6 e R^7 são como definidos acima;

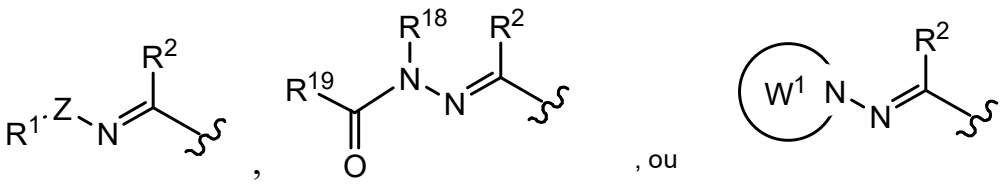
Q é N ou CH_2,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[013] Mais particularmente, a presente invenção refere-se aos itens (II) a (XV) a seguir.

(II) Um composto de acordo com o item (I), onde R^X é um grupo representado pela fórmula:

Fórmula química 15



onde

R^1, R^2, R^{18}, R^{19}, Z, e W^1 são como definidos no item (I),

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(III) O composto de acordo com o item (I) ou (II), onde R^1 é alquila opcionalmente substituída com um substituinte selecionado do grupo A' de substituintes que consiste em hidróxi, amina opcionalmente substituída, um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído, aminocarbonila opcionalmente substituída, e carbonila heterocíclico contendo nitrogênio não aromático opcionalmente substituído, ou

um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído com um substituinte selecionado do grupo B'

de substituintes que consiste em alquiloxicarbonila, aminocarbonila opcionalmente substituída, ciano, cianoalquila, hidroxialquila, e aminocarbonilalquila,
seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(IV) O composto de acordo com qualquer um dos itens (I) a (III), onde R^1 é alquila opcionalmente substituída com amino substituído com um substituinte selecionado do grupo C' de substituintes que consiste em alquila, alquinila, alquilsulfonilalquila, hidroxialquila, alquilcarbonila opcionalmente substituída com halogênio, alquiloxicarbonila, cicloalquila, opcionalmente substituída com aminocarbonilalquila, aminocarboniloxialquila opcionalmente substituída, alquiloxialquila, cicloalquilalquila, cianoalquila, e aminoalquilcarbonila opcionalmente substituída, ou

alquila substituída com um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído com um substituinte selecionado de um grupo D' de substituintes que consiste em hidróxi; oxo; aminocarbonila opcionalmente substituída; alquiloxicarbonila; alquila opcionalmente substituída com um substituinte selecionado do grupo H' de substituintes que consiste em aminocarbonila opcionalmente substituída, ciano, alquilóxi, e hidróxi; alquilaminocarbonila; ciano; alquilsulfonila; alquilcarbonila; alquenilcarbonila; alquilsulfonilalquilcarbonila; alquiloxialquilcarbonila; alquilcarbonilamino; e carbonila heterocíclico não aromático,
seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(V) O composto de acordo com o item (I) ou (II), onde R^{19} é alquila opcionalmente substituída com um substituinte selecionado do grupo A' de substituintes, arila opcionalmente substituída com um substituinte selecionado do grupo I' de substituintes que consiste em alquiloxicarbonila, aminocarbonila opcionalmente substituída, ciano, cianoalquila, hidroxialquila, e aminocarbonilalquila, ou

heteroarila substituída com um substituinte selecionado do grupo I' de substituintes,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(VI) O composto de acordo com qualquer um dos itens (I), (II) e (V), onde R^{19} é alquila substituída com amina opcionalmente substituída com um substituinte selecionado do grupo C' de substituintes, ou

alquila substituída com um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído com um substituinte selecionado do grupo D' de substituintes,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(VII) O composto de acordo com o item (I) ou (II), onde W^1 é um grupo representado por um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído com um substituinte selecionado do grupo J' de substituintes que consiste em alquila, cianoalquila, hidroxialquila, aminocarbonilalquila, alquilóxi, alquiloxicarbonila, aminocarbonila opcionalmente substituída, e ciano, ou

um grupo representado por heteroarila opcionalmente substituída com um substituinte selecionado do grupo J' de substituintes,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(VIII) O composto de acordo com qualquer um dos itens (I) a (VII), onde R^2 é um átomo de hidrogênio, C1-C6 alquila opcionalmente substituída com halogênio, C2-C6 alquenila, C2-C6 alquinila, halogênio, ou fenila,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(IX) O composto de acordo com qualquer um dos itens (I) a (VIII), onde um de R^3 e R^4 são um átomo de hidrogênio, e o outro é um átomo de hidrogênio, alquilóxi opcionalmente substituído ou alquenilóxi

opcionalmente substituído,

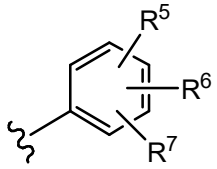
seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(X) O composto de acordo com qualquer um dos itens (I) a (IX), onde X é -NH-,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(XI) O composto de acordo com qualquer um dos itens (I) a (IX), onde A é um grupo representado pela fórmula:

Fórmula química 16



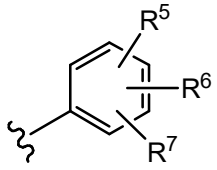
onde

R^5 é um átomo de hidrogênio ou halogênio; R^6 é halogênio ou alquinila; e R^7 é um hidrogênio,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(XII) O composto de acordo com qualquer um dos itens (I) a (IX), onde A é um grupo representado pela fórmula:

Fórmula química 17



onde

R^5 é alquilóxi opcionalmente substituído com um substituinte selecionado do grupo E' de substituintes que consiste em carbóxi, alquiloxicarbonila, cicloalquila, e aminocarbonila opcionalmente substituída,

alquenilóxi opcionalmente substituído com um substituinte selecionado do grupo E' de substituintes, ou

alquinilóxi opcionalmente substituído com um substituinte selecionado do grupo E' de substituintes;

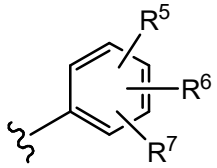
R^6 é alquinila opcionalmente substituída, alquilóxi opcionalmente substituído, ou halogênio; e

R^7 é um átomo de hidrogênio,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(XIII) O composto de acordo com qualquer um dos itens (I) a (IX), onde A é um grupo representado pela fórmula:

Fórmula química 18



onde

R^5 é um grupo representado pela fórmula: -Y-R^8 onde Y é alquileno que pode ser interposto com -O-;

R^8 é fenila opcionalmente substituída com um substituinte selecionado do grupo F' de substituintes que consiste em halogênio, carbóxi, alquila, haloalquila, hidroxialquila, alquilóxi, alquiloxicarbonila, e amina opcionalmente substituída;

piridila opcionalmente substituída com um substituinte selecionado do grupo F' de substituintes;

furila opcionalmente substituída com um substituinte selecionado de um grupo F' de substituintes;

tienila opcionalmente substituída com um substituinte selecionado de um grupo F' de substituintes;

tiazolila opcionalmente substituída com um substituinte selecionado de um grupo F' de substituintes; ou

oxazolila opcionalmente substituída com um substituinte selecionado de um grupo F' de substituintes;

R^6 é alquinila opcionalmente substituída, alquilóxi opcionalmente substituído, ou halogênio; e

R^7 é um átomo de hidrogênio,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(XIV) Uma composição farmacêutica contendo o composto definido em qualquer um dos itens (I) a (XIII) como ingrediente ativo.

(XV) Uma composição farmacêutica útila para o tratamento de câncer contendo o composto definido em qualquer um dos itens (I) a (XIII) como um ingrediente ativo.

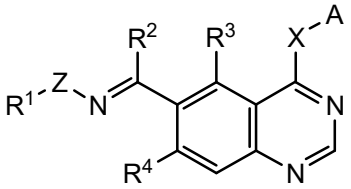
(XVI) Um método para prevenir e/ou tratar um câncer, compreendendo administrar o composto definido em qualquer um dos itens (I) a (XIII), seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(XVII) Uso do composto definido em qualquer um dos itens (I) a (XIII), seu sal farmaceuticamente aceitável, ou um solvato do mesmo para produzir uma composição para prevenir e/ou um câncer.

[014] Ainda um outro aspecto da presente invenção inclui as seguintes invenções.

(i) um composto representado pela fórmula geral (I'):

Fórmula química 19



(I')

onde

R^1 é um átomo de hidrogênio, alquila opcionalmente substituída, alquenila opcionalmente substituída, ou um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído;

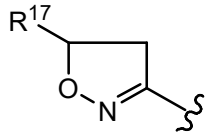
Z é -O- ou -N(R^{10})-, ou alquileno que pode ser interposto com -O- ou -N(R^{11})-; R^{10} e R^{11} são independentemente um átomo de hidrogênio, alquila, acila, alquiloxicarbonila, alqueniloxicarbonila, ou aralquiloxicarbonila;

R^2 é um átomo de hidrogênio, alquila opcionalmente

substituída, alquenila, alquinila, arila opcionalmente substituída, ou heteroarila opcionalmente substituída, ou

um grupo representado por -C(R^2) = N-Z-R^1 é um grupo representado pela fórmula:

Fórmula química 20



onde

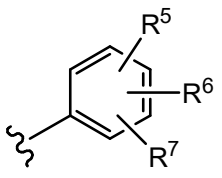
R^{17} é um átomo de hidrogênio, alquila opcionalmente substituída, alquenila opcionalmente substituída, ou um grupo heterocíclico contendo nitrogênio não-aromático opcionalmente substituído;

R^3 e R^4 são independentemente um átomo de hidrogênio, alquila opcionalmente substituída, alquenila opcionalmente substituída, alquinila opcionalmente substituída, alquilóxi opcionalmente substituído, alquenilóxi opcionalmente substituído, halogênio, hidróxi, mercapto ou amina opcionalmente substituída;

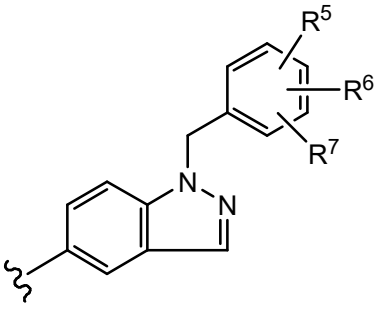
X é -O-, -S-, ou -N(R^{12})-, ou alquileno que pode ser interposto com -O-, -S-, ou -N(R^{13})-; onde R^{12} e R^{13} são independentemente um átomo de hidrogênio, alquila, acila, alquiloxicarbonila, alqueniloxicarbonila, ou aralquiloxicarbonila; e

[015] A é um grupo representado pela fórmula:

Fórmula química 21



, ou



onde

R^5 é um átomo de hidrogênio, halogênio, alquilóxi opcionalmente substituído, alquenilóxi opcionalmente substituído, alquinilóxi opcionalmente substituído, ou um grupo representado pela fórmula: -Y-R^8 onde Y é -O-, -S-, ou alquileno que pode ser interposto com -N(R^9)-; R^8 é arila opcionalmente substituída, ou heteroarila opcionalmente substituída; R^9 é um átomo de hidrogênio, alquila, acila, alquiloxicarbonila, alqueniloxicarbonila, ou aralquiloxicarbonila;

R^6 e R^7 são independentemente um átomo de hidrogênio, alquila opcionalmente substituída, alquenila opcionalmente substituída, alquinila opcionalmente substituída, alquilóxi opcionalmente substituído, alquenilóxi opcionalmente substituído, alquinilóxi opcionalmente substituído, halogênio, hidróxi, mercapto, ou amina opcionalmente substituída,
seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(ii) O composto de acordo com o item (i), onde R^1 é alquila opcionalmente substituída com um substituinte selecionado do grupo A'' de substituintes que consiste em amina opcionalmente substituída, e um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído, ou

um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído com um substituinte selecionado do grupo B'' de substituintes que consiste em alquiloxicarbonila, aminocarbonila opcionalmente substituída, e ciano,
seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(iii) O composto de acordo com o item (i) ou (ii), onde R^1 é alquila substituída com amina opcionalmente substituída com um substituinte selecionado do grupo C'' de substituintes que consiste em alquila, alquilsulfonilalquila, alquilcarbonila opcionalmente substituído com halogênio, alquiloxicarbonila, cicloalquila, aminocarbonilalquila opcionalmente substituída, aminocarboniloxialquila opcionalmente substituída, alquiloxialquila, e aminoalquilcarbonila opcionalmente substituído, ou

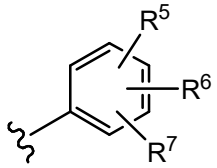
alquila substituída com um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído com um substituinte selecionado do grupo D" de substituintes que consiste em oxo, aminocarbonila opcionalmente substituída, alquiloxicarbonila, alquila opcionalmente substituída com ciano ou alquilóxi, ciano, alquilsulfonila, alquilcarbonila, alquenilcarbonila, e alquilsulfonilalquilcarbonila,
seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(iv) O composto de acordo com qualquer um dos itens (i) a (iii), onde um de R^3 e R^4 é um átomo de hidrogênio, e o outro é um átomo de hidrogênio, alquilóxi opcionalmente substituído ou alquenilóxi opcionalmente substituído,
seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(v) O composto de acordo com qualquer um dos itens (i) a (iv), onde X é -NH-,
seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(vi) O composto de acordo com qualquer um dos itens (i) a (v), onde A é um grupo representado pela fórmula:

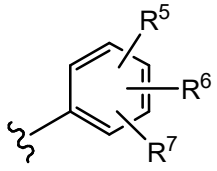
Fórmula química 22



onde R^5 é um átomo de hidrogênio ou halogênio; R^6 é halogênio ou alquinila; e R^7 é um átomo de hidrogênio,
seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(vii) O composto de acordo com qualquer um dos itens (i) a (vi), onde A é um grupo representado pela fórmula:

Fórmula química 23



onde

R^5 é alquilóxi opcionalmente substituído com um substituinte selecionado do grupo E'' de substituintes que consiste em carbóxi, alquiloxicarbonila, e aminocarbonila opcionalmente substituída,

alquenilóxi opcionalmente substituído com um substituinte selecionado de um grupo E'' de substituintes, ou

alquinilóxi opcionalmente substituído com um substituinte selecionado de um grupo E'' de substituintes;

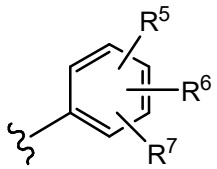
R^6 é alquinila opcionalmente substituída, alquilóxi opcionalmente substituído, ou halogênio; e

R^7 é um átomo de hidrogênio,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(viii) O composto de acordo com qualquer um dos itens (i) a (vii), onde A é um grupo representado pela fórmula:

Fórmula química 24



onde

R^5 é um grupo representado pela fórmula: -Y-R^8 onde Y é alquileno que pode ser interposto com -O-;

R^8 é fenila opcionalmente substituída com um substituinte selecionado do grupo F'' de substituintes que consiste em halogênio, carbóxi, alquila, haloalquila, hidroxialquila, alquilóxi, alquiloxicarbonila, e amina opcionalmente substituída;

piridila opcionalmente substituída com um substituinte selecionado de um grupo F'' de substituintes;

furila opcionalmente substituída com um substituinte selecionado de um grupo F'' de substituintes;

tienila opcionalmente substituída com um substituinte

selecionado de um grupo F'' de substituintes;

tiazolila opcionalmente substituída com um substituinte selecionado de um grupo F'' de substituintes; ou

oxazolila opcionalmente substituída com um substituinte selecionado de um grupo F'' de substituintes;

R^6 é alquinila opcionalmente substituída, alquilóxi opcionalmente substituído, ou halogênio; e

R' é um átomo de hidrogênio,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(ix) Uma composição farmacêutica contendo o composto definido em qualquer um dos itens (i) a (viii) como ingrediente ativo.

(x) Uma composição farmacêutica útila para o tratamento de câncer contendo o composto definido em qualquer um dos itens (i) a (viii) como um ingrediente ativo.

(xi) Um método para prevenir e/ou tratar um câncer, compreendendo administrar o composto definido em qualquer um dos itens (i) a (viii), seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

(xii) Uso do composto definido em qualquer um dos itens (i) a (viii), seu sal farmaceuticamente aceitável, ou um solvato do mesmo para produzir uma composição para prevenir e/ou tratar um câncer.

[016] Conforme usado neste relatório, "halogênio" significa flúor, cloro, bromo ou iodo. Flúor, cloro e bromo são preferidos.

[017] Conforme usado neste relatório, "alquila" que é usado isolado ou está em combinação com outro termo inclui um grupo hidrocarboneto monovalente de cadeia reta ou ramificada tendo 1 a 10 átomos de carbono. Exemplos incluem metila, etila, n-propila, isopropila, n-butila, isobutila, sec-butila, tert-butila, n-pentila, isopentila, neo-pentila, n-hexila, isohexila, n-heptila, n-octila, n-nonanila, e n-decanila. Exemplos preferidos incluem C1-C10 alquila. Outros exemplos

preferidos incluem C1-C6 alquila. Exemplos mais preferidos incluem C1-C4 alquila.

[018] Conforme usado neste relatório, o termo "haloalquila" que é usado isolado ou está em combinação com outro termo inclui "alquila" que é substituído com "halogênio" nas posições 1 a 8, de preferência nas posições 1 a 5. Exemplos incluem trifluormetila, triclorometila, difluoretila, trifluoretila, dicloroetila, e tricloroetila. Exemplos preferidos incluem C1-C6 alquila que é substituído com "halogênio" nas posições 1 a 5.. Particularmente, C1-C3 alquila substituída com "halogênio" nas posições 1 a 3 é preferido. Exemplos mais preferidos incluem trifluormetila.

[019] Conforme usado neste relatório, "alquilsulfonila" inclui metilsulfonila, etilsulfonila, e propilsulfonila. Exemplos preferidos incluem C1-C6 alquilsulfonila. Particularmente, C1-C3 alquilsulfonila é preferido.

[020] Conforme usado neste relatório, exemplos de "alquilsulfonilalquila" incluem metilsulfonilmetila, metilsulfoniletila, metilsulfonilpropila, metilsulfonilbutila, e metilsulfonilpropila. Exemplos preferidos incluem C1- C6 alquilsulfonila C1-C6 alquila. Particularmente, C1-C3 alquilsulfonila C1-C4 alquila é preferida.

[021] Conforme usado neste relatório, exemplos de "alquilóxi" incluem metilóxi, etilóxi, n-propilóxi, isopropilóxi, n-butilóxi, isobutilóxi, sec-butilóxi, ter-butilóxi, n-pentilóxi, n-hexilóxi, n-heptilóxi, n-octilóxi, n-nonanilóxi, e n-decanilóxi. Exemplos preferidos incluem C1-C6 alquilóxi. Particularmente, C1-C3 alquilóxi é preferido.

[022] Conforme usado neste relatório, exemplos de "alquiloxialquila" incluem metiloximetila, metiloxietila, metiloxipropila, etiloximetila, etiloxietila, e etiloxipropila. Exemplos preferidos incluem C1-C6 alquilóxi C1-C6 alquila. Particularmente, C1-C3 alquilóxi C1-C4 alquila é preferida.

[023] Conforme usado neste relatório, exemplos de "alquiloxicarbonila" incluem metiloxicarbonila, etiloxicarbonila, n-propiloxicarbonila, isopropiloxicarbonila, n-butiloxicarbonila, t-butiloxicarbonila, e n-pentiloxicarbonila. Exemplos preferidos incluem C1-C6 alquiloxicarbonila. Particularmente, C1-C3 alquiloxicarbonila é preferido.

[024] Conforme usado neste relatório, exemplos de "alquilcarbonila" incluem metilcarbonila, etilcarbonila, n-propilcarbonila, isopropilcarbonila, n-butilcarbonila, t-butilcarbonila, e n-pentilcarbonila. Exemplos preferidos incluem C1-C6 alquilcarbonila. Particularmente, C1-C3 alquilcarbonila é preferido.

[025] Conforme usado neste relatório, exemplos de "haloalquilóxi" incluem trifluormetilóxi, triclorometilóxi, difluoretilóxi, trifluoretilóxi, dicloroetilóxi, e tricloroetilóxi. Exemplos preferidos incluem halo C1-C6 alquilóxi. Particularmente, halo C1-C3 alquilóxi é preferido. Exemplos mais preferidos incluem trifluormetilóxi.

[026] Conforme usado neste relatório, exemplos de "aminocarbonilalquila" incluem aminocarbonilmetila, aminocarboniletila, aminocarbonilpropila, e aminocarbonilbutila. Exemplos preferidos incluem aminocarbonila C1-C6 alquila. Particularmente, aminocarbonila C1-C3 alquila é preferido.

[027] Conforme usado neste relatório, exemplos de "aminocarbonilalquilóxi" incluem aminocarbonilmetilóxi, aminocarboniletilóxi, aminocarbonilpropilóxi, e aminocarbonilbutilóxi. Exemplos preferidos incluem aminocarbonila C1-C6 alquilóxi. Particularmente, aminocarbonila C1-C3 alquilóxi é preferido.

[028] Conforme usado neste relatório, exemplos de "hidroxialquila" incluem hidroximetila, hidroxietila, hidroxipropila, e hidroxibutila. Exemplos preferidos incluem hidroxi C1-C6 alquila. Particularmente, hidróxi C1-C3 alquila é preferido.

[029] Conforme usado neste relatório, exemplos de "alquiltio" incluem metiltio, etiltio, propiltio, e butiltio. Exemplos preferidos incluem C1-C6 alquiltio. Particularmente, C1-C3 alquiltio é preferido.

[030] Conforme usado neste relatório, o "alquileno" que é usado isolado ou em combinação com outro termo inclui um grupo hidrocarboneto divalente de cadeia reta ou ramificada tendo 1 a 4 átomos de carbono. Exemplos incluem metileno, etileno, propileno, e butileno. Exemplos preferidos incluem C1-C3 alquileno. Particularmente, C1-C2 alquileno é preferido.

[031] O "alquileno que pode ser interposto com -O- ou -N(R^{11})-" em Z inclui -CH_2-O-, -O-CH_2-, -CH_2-N(R^{11})-, -N(R^{11})-CH_2-, -$(CH_2)_2$-O-, -O-$(CH_2)_2$-, -$(CH_2)_2$-N(R^{11})-, e -N(R^{11})-$(CH_2)_2$-. Particularmente, -O-CH_2-, -N(R^{11})-CH_2-, -O-$(CH_2)_2$-, e -N(R^{11})-$(CH_2)_2$- são preferidos.

[032] O "alquileno que pode ser interposto com -O-, -S-, ou -N(R^{12})-" em X inclui -CH_2-O-, -O-CH_2-, -CH_2-S-, -S-CH_2-, -CH_2-N(R^{12})-, -N(R^{12})-CH_2-, -$(CH_2)_2$-O-, -O-$(CH_2)_2$-, -$(CH_2)_2$-S-, -S-$(CH_2)_2$-, -$(CH_2)_2$-N(R^{12})-, e -N(R^{12})-$(CH_2)_2$-.

[033] O "alquileno que pode ser interposto com -O-, -S-, ou -N(R^9)-" em Y inclui -CH_2-O-, -O-CH_2-, -CH_2-S-, -S-CH_2-, -CH_2-N(R^9)-, -N(R^9)-CH_2-, -$(CH_2)_2$-O-, -O$(CH_2)_2$-, -$(CH_2)_2$-S-, -S-$(CH_2)_2$-, -$(CH_2)_2$-N(R^9)-, -N(R^9)-$(CH_2)_2$-, e -O-CH(CH_3)-.

[034] Conforme usado neste relatório, "cicloalquila" que é usada isolada ou em combinação com outro termo inclui cicloalquila tendo 3 a 8 átomos de carbono. Exemplos incluem ciclopropila, ciclobutila, ciclopentila, ciclohexila, cicloheptila, e ciclooctila. Exemplos preferidos incluem C5-C6 cicloalquila.

[035] Conforme usado neste relatório, "alquenila" inclui um hidrocarboneto monovalente de cadeia reta ou ramificada tendo 2 a 8 átomos de carbono e tendo 1 ou 2 ou mais ligações duplas. A alquenila pode ter uma ligação tripla em uma cadeia. Exemplos incluem vinila,

alila, 1-propenila, 2-propenila, e vários isômeros butenílicos. Exemplos preferidos incluem C2-C6 alquenila. Outros exemplos preferidos incluem C2-C4 alquenila.

[036] Conforme usado neste relatório, exemplos de "alquenilóxi" incluem vinilóxi, alilóxi, 1-propenilóxi, 2-propenilóxi, e vários butenilóxis. Exemplos preferidos incluem C2-C6 alquenilóxi. Particularmente, C2-C4 alquenilóxi é preferido.

[037] Conforme usado neste relatório, exemplos de "alqueniloxicarbonila" incluem viniloxicarbonila, aliloxicarbonila, 1-propeniloxicarbonila, 2-propeniloxicarbonila, e várias buteniloxicarbonilas. Exemplos preferidos incluem C2-C6 alqueniloxicarbonila. Particularmente, C2-C4 alqueniloxicarbonila é preferida.

[038] Conforme usado neste relatório, "alquinila" inclui um grupo hidrocarboneto monovalente de cadeia reta ou ramificada tendo 2 a 8 átomos de carbono e tendo 1 ou 2 ou mais ligações triplas. Exemplos incluem etinila, 1-propinila, 2-propinila, 1-butinila, 2-butinila, 3-butinila, 1-pentinila, 2-pentinila, e vários isômeros pentinílicos. Exemplos preferidos incluem C2-C6 alquinila. Outros exemplos preferidos incluem C2-C4 alquinila.

[039] Conforme usado neste relatório, exemplos de "alquinilóxi" incluem etinilóxi, propinilóxi, butinilóxi, e pentinilóxi. Exemplos preferidos incluem C2-C6 alquinilóxi. Particularmente, C2-C4 alquinilóxi é preferido.

[040] Conforme usado neste relatório, "arila" que é usada isolada ou em combinação com outro termo inclui um hidrocarboneto aromático cíclico fundido ou monocíclico. Exemplos incluem fenila, 1-naftila, 2-naftila, e antrila. Fenila, 1-naftila, e 2-naftila são preferidos. Particularmente, fenila é preferido.

[041] Conforme usado neste relatório, "aralquila" inclui "alquila" substituído com um ou duas ou mais "arila", e estas podem ser

substituídos em todas as posições possíveis. Exemplos incluem benzila, feniletila (por exemplo, 2-feniletila, etc.), fenilpropila (por exemplo, 3-fenilpropila, etc.), naftilmetila (por exemplo, 1-naftilmetila, 2-naftilmetila, etc.), e antrilmetila (por exemplo, 9-antrilmetila, etc.). Exemplos preferidos incluem benzila, e feniletila.

[042] Conforme usado neste relatório, exemplos de "aralquilóxi" incluem benzilóxi, feniletilóxi (por exemplo 2-feniletilóxi, etc.), fenilpropilóxi (por exemplo 3-fenilpropilóxi, etc.), naftilmetilóxi (por exemplo 1-naftilmetila, 2-naftilmetilóxi, etc.), antrilmetilóxi (por exemplo 9-antrilmetilóxi, etc.). Exemplos preferidos incluem benzilóxi, e feniletilóxi.

[043] Conforme usado neste relatório, exemplos de "aralquiloxicarbonila" incluem benziloxicarbonila, feniletiloxicarbonila (por exemplo 2-feniletiloxicarbonila, etc.), fenilpropiloxicarbonila (por exemplo 3-fenilpropiloxicarbonila, etc.), naftilmetiloxicarbonila (por exemplo 1-naftilmetila, 2-naftilmetiloxicarbonila, etc.), antrilmetiloxicarbonila (por exemplo 9-antrilmetiloxicarbonila, etc.). Exemplos preferidos incluem benziloxicarbonila, e feniletiloxicarbonila.

[044] Conforme usado neste relatório, o termo "grupo heterocíclico não aromático" que é usado isolado ou em combinação com outro termo inclui um anel não aromático de 5 a 7 membros contendo um ou mais de um átomo de oxigênio, um átomo de enxofre ou um átomo de nitrogênio arbitrariamente selecionados em um anel, e um grupo derivado de um anel no qual um ou mais outros "grupos heterocíclicos não aromáticos" ou "heteroarilas" estão fundidos. Exemplos incluem pirrolidinila (por exemplo 1-pirrolidinila, 2-pirolidinila), pirrolinila (por exemplo 3-pirrolinila), imidazolidinila (por exemplo 2-imidazolidinila), imidazolinila (por exemplo imidazolinila), pirazolidinila (por exemplo 1-pirazolidinila, 2-pirazolidinila), pirazolinila (por exemplo pirazolinila), piperidila (por exemplo piperidino, 2-piperidila), piperazinila (por

exemplo 1-piperazinila, 2-piperazinila), indolinila (por exemplo 1-indolinila), isoindolinila (por exemplo isoindolinila), morfolinila (por exemplo morfolino, 2-morfolinila, 3-morfolinila), tetrahidrofuranila, dihidropiranila, tetrahidropiranila, dioxolanila, tetrahidrotienila, dihidrotiopiranila, tetrahidrotiofuranila, decahidroisoquinolinila, azepinila, oxepinila, dihidrooxepinila, tetrahidrooxepinila, oxepanila, 4, 5, 6, 7-tetrahidrotieno[3, 2]piridila, 2-oxa-5-aza-biciclo[2.2.1]hepta-5-ila, e hexahidropirazila[2.1-b][1, 3]ozadin-8-ila.

[045] Como o "grupo heterocíclico não aromático" em R^{19}, pirrodilinila (por exemplo 1-pirrodilinila, 2-pirrolidinila), piperidila (por exemplo piperidino, 2-piperidila), piperazinila (por exemplo 1-piperazinila), morfolinila (por exemplo morfolino, 3-morfolinila), e tetrahidrofuranila são preferidas.

[046] Conforme usado neste relatório, o termo "grupo heterocíclico contendo nitrogênio não aromático" que é usado isolado, ou em combinação com outro termo inclui um anel não aromático de 4 a 7 membros contendo pelo menos um átomo de nitrogênio em um anel e, ainda opcionalmente, contendo um ou mais átomos arbitrariamente selecionados de um átomo de oxigênio e um átomo de enxofre em um anel, ou um grupo derivado de um anel no qual dois ou mais deles estão fundidos. Exemplos incluem azetidinila (por exemplo 1-azetidinila, 2-azetidinila, 3-azetidinila), pirrolidinila (por exemplo 1-pirrolidinila, 2-pirrolidinila, 3-pirrolidinila), pirrolinila (por exemplo 3-pirrolinila), imidazolidinila (por exemplo 2-imidazolidinila), imidazolinila (por exemplo imidazolinila), pirazolidinila (por exemplo 1-pirazolidinila, 2-pirazolidinila), pirazolinila (por exemplo pirazolinila), piperidila (por exemplo piperidino, 2-piperidila, 3-piperidila, 4-piperidila), piperazinila (por exemplo 1-piperazinila, 2-piperazinila), indolinila (por exemplo 1-indolinila), isoindolinila (por exemplo isoindolinila), morfolinila (por exemplo morfolino, 2-morfolinila, 3-morfolinila), 1, 4-tiazinila (por

exemplo 1, 4-tiazin-1-ila, 1, 4-tiazin-2-ila), tiomorfolinila (por exemplo 1-tiomorfolinila, 2-tiomorfolinila), decahidroisoquinolila (por exemplo 2-decahidroisoquinolila), azepinila (por exemplo 1-azepinila), diazepinila, 4, 5, 6, 7-tetrahidrotieno[3, 2]piridila, 2-oxa-5-aza-biciclo[2.2.1]hept-5-ila, e hexahidropirazila[2.1-b][1, 3]oxazin-8-ila.

[047] Como o "grupo heterocíclico contendo nitrogênio não aromático" em R^1 e R^{17}, azetidinila (por exemplo 1-azetidinila, 2-azetidinila, 3-azetidinila), pirrolidinila (por exemplo 1-pirrolidinila, 2-pirrolidinila, 3-pirrolidinila), e piperidila (por exemplo piperidino, 2-piperidila, 3-piperidila, 4-piperidila) são preferidas.

[048] Como o "grupo heterocíclico contendo nitrogênio não aromático" em W^1, azetidinila (por exemplo 1-azetidinila, 2-azetidinila, 3-azetidinila), pirrolidinila (por exemplo 1-pirrolidinila, 2-pirrolidinila, 3-pirrolidinila), piperidila (por exemplo piperidino, 2-piperidila, 3-piperidila, 4-piperidila), piperazinila (por exemplo 1-piperazinila), e morfolinila (por exemplo morfolino, 3-morfolinila) são preferidas.

[049] Como o "grupo heterocíclico contendo nitrogênio não aromático" no grupo A de substituintes, pirrolidinila (por exemplo 1-pirrolidinila, 2-pirrolidinila, 3-pirrolidinila), piperidila (por exemplo piperidino, 2-piperidila, 3-piperidila, 4-piperidila), piperazinila (por exemplo 1-piperazinila, 2-piperazinila), morfolinila (por exemplo morfolino, 2-morfolinila, 3-morfolinila), tiomorfolinila (por exemplo 1-tiomorfolinila, 2-tiomorfolinila), decahidroisoquinolila (por exemplo 2-decahidroisoquinolila), azepinila (por exemplo 1-azepinila), diazepinila, 4, 5, 6, 7-tetrahidrotieno[3, 2]piridila, 2-oxa-5-aza-biciclo[2.2.1]hept-5-ila, e hexahidropirazila[2.1-b][1, 3]oxazin-8-ila são preferidos.

[050] Conforme usado neste relatório, "heteroarila" que é usado isolado, ou em combinação com outro termo inclui um grupo aromático de 5 a 6 membros contendo um ou mais de um átomo de oxigênio, um átomo de enxofre e um átomo de nitrogênio arbitrariamente selecionado

em um anel. Este pode ser fundido com a "cicloalquila", a "arila", o "grupo heterocíclico não aromático", ou outro heteroarila em todas as posições possíveis. Quando heteroarila é qualquer um de um monociclo e um ciclo fundido, ele pode se ligar em todas as posições possíveis. Exemplos incluem pirrolila (por exemplo 1-pirrolila, 2-pirrolila, 3-pirrolila), furila (por exemplo 2-furila, 3-furila), tienila (por exemplo 2-tienila, 3-tienila), imidazolila (por exemplo 2-imidazolila, 4-imidazolila), pirazolila (por exemplo 1-pirazolila, 3-pirazolila), isotiazolila (por exemplo 3-isotiazolila), isooxazolila (por exemplo 3-isooxazolila), oxazolila (por exemplo 2-oxazolila), tiazolila (por exemplo 2-tiazolila, 5-tiazolila), piridila (por exemplo 2-piridila, 3-piridila, 4-piridila), pirazinila (por exemplo 2-pirazinila), pirimidinila (por exemplo 2-pirimidinila, 4-pirimidinila), piridazinila (por exemplo 3-piridazinila), triazolila, tetrazolila (por exemplo 1H-tetrazolila), oxadiazolila (por exemplo 1, 3, 4-oxadiazolila), tiadiazolila (por exemplo 1, 3, 4-tiadiazolila), indolidinila (por exemplo 2-indolidinila, 6-indolidinila), isoindolila (por exemplo 2-isoindolila), indolila (por exemplo 1-indolila, 2-indolila, 3-indolila), indazolila (por exemplo 3-indazolila), purinila (por exemplo 8-purinila), quinolizinila (por exemplo 2-quinolizinila), isoquinolila (por exemplo 3-isoquinolila), quinolila (por exemplo 2-quinolila, 5-quinolila), ftalazinila (por exemplo 1-ftalazinila), naftiridinila (por exemplo 2-naftiridinila), quinolanila (por exemplo 2-quinolanila), quinazolinila (por exemplo 2-quinazolinila), cinolinila (por exemplo 3-cinolinila), pteridinila (por exemplo 2-pteridinila), carbazolila (por exemplo 2-carbazolila, 4-carbazolila), fenantridinila (por exemplo 2-fenantridinila, 3-fenantridinila), acridinila (por exemplo 1-acridinila, 2-acridinila), dibenzofuranila (por exemplo 1-dibenzofuranila, 2-dibenzofuranila), benzoimidazolila (por exemplo 2-benzoimidazolila), benzoisooxazolila (por exemplo 3-benzoisooxazolila), benzooxazolila (por exemplo 2-benzooxazolila), benzooxadiazolila (por exemplo 4-benzooxadiazolila),

benzoisotiazolila (por exemplo 3-benzoisotiazolila), benzotiazolila (por exemplo 2-benzotiazolila), benzofurila (por exemplo 3-benzofurila), benzotienila (por exemplo 2-benzotienila), 4, 5-dihidronafto[1, 2-d]tiazolila, 4H-cromeno[4, 3-d]tiazolila, 4H-tiocromeno[4, 3-d]tiazolila, 4, 5-dihidrotiazolo[5, 4-c]quinolila, 8H-indeno[1, 2-d]tiazolila, e 5, 6-dihidro-4H-3-tia-1-aza-benzo[e]azulenila.

[051] Como "heteroarila" em R^2, piridila, furila, tienila, tiazolila, oxazolila, tiadiazolila, oxadiazolila, e triazolila são preferidos. Outros exemplos preferidos incluem piridila, furila, tienila, tiazolila.

[052] Como "heteroarila" em R^8, piridila, furila, tienila, tiazolila, oxazolila, tiadiazolila, oxadiazolila, e triazolila são preferidos. Outros exemplos preferidos incluem piridila, furila, tienila, e tiazolila.

[053] Como "heteroarila" em R^{19}, piridila, furila, e tienila são preferidas.

[054] Como "heteroarila" em W^1, pirrolila, imidazolila, pirazolila, triazolila, e tetrazolila são preferidas.

[055] Conforme usado neste relatório, "heteroarilalquila" inclui "alquila" em que uma ou duas ou mais de "heteroarila" são substituídos em uma posição arbitrária do mesmo, e estes podem ser substituídos em todas as posições possíveis. Exemplos incluem tienilmetila (por exemplo 2-tienilmetila), tieniletila (por exemplo 2-(tiofen-2-ila)etila), furilmetila (por exemplo 2-furilmetila), furiletila (por exemplo 2-(furan-2-ila)etila), pirrolilmetila (por exemplo 2-pirrolilmetila), pirroliletila (por exemplo 2-(pirrol-2-ila)etila), imidazolilmetila (por exemplo 2-imidazolilmetila, 4-imidazolilmetila), imidazoliletila (por exemplo 2-(imidazol-2-ila)etila), pirazolilmetila (por exemplo 3-pirazolilmetila), pirazoliletila (por exemplo 2-(pirazol-3-ila)etila), tiazolilmetila (por exemplo 2-tiazolilmetila), tiazoliletila (por exemplo 2-(tiazol-2-ila)etila), isotiazolilmetila (por exemplo 3-isotiazolilmetila), isooxazolilmetila (por exemplo 3-isooxazolilmetila), oxazolilmetila (por exemplo 2-

oxazolilmetila), oxazoliletila (por exemplo 2-(oxazol-2-ila)etila), piridilmetila (por exemplo 2-piridilmetila, 3-piridilmetila, 4-piridiilmetila), e piridiletila (por exemplo 2-piridiletila).

[056] Conforme usado neste relatório, o termo "acila" que é usado isolado, ou em combinação com outro termo inclui alquilcarbonila em que uma parte alquila é o "alquila", haloalquilcarbonila em que uma parte haloalquila é a "haloalquila", alquenilcarbonila em que uma parte alquenila é o "alquenila", aralquilcarbonila em que uma parte aralquila é o "aralquila", e arilcarbonila em que uma parte arila é o "arila". Exemplos incluem acetila, propionila, butiroila, trifluormetilcarbonila, vinilcarbonila, fenilacetila, e benzoila. A "alquila", o "alquenila" e o "arila" podem ser substituídos com cada substituinte descrito abaixo.

[057] Como "acila" em R^{10} e R^{11}, acetila, benzoila, e fenilacetila são preferidas.

[058] Como "acila" em R^{12} e R^{13}, acetila, benzoila, e fenilacetila são preferidas.

[059] Como "acila" em R^{9}, acetila, benzoila, e fenilacetila são preferidas.

[060] Conforme usado neste relatório, exemplos de "aciloxi" incluem acetiloxi, propioniloxi, e benzoiloxi.

[061] Conforme usado neste relatório, um termo "amina opcionalmente substituída" que é usado isolado, ou em combinação com outro termo inclui amina opcionalmente substituída com o "alquila" opcionalmente substituído com um substituinte selecionado do grupo A de substituintes, "haloalquila", "alquenila", "alquinila", "alquilsulfonila", "alquilsulfonilalquila", "alquiloxicarbonila", "aminocarboniloxialquila", "alquiloxi", "alquiloxialquila" opcionalmente substituído com um substituinte selecionado do grupo A de substituintes, "cicloalquila" opcionalmente substituído com um substituinte selecionado do grupo A de substituintes, "arila" opcionalmente substituído com um substituinte

selecionado do grupo G de substituintes que consiste em alquila, alquenila, e aralquila, "aralquila", "heteroarila", "heteroarilalquila", "acila", "aminocarbonilalquila" opcionalmente substituído com um substituinte selecionado do grupo G de substituintes, "aminoalquil-carbonila" opcionalmente substituído com um substituinte selecionado do grupo G de substituintes, "alqueniloxicarbonila" em que uma parte alquenilóxi é "alquenilóxi", e "aralquiloxicarbonila" em que uma parte aralquilóxi é "aralquilóxi" em uma ou duas posições. Exemplos incluem amino, metilamino, dimetilamino, etilmetilamino, dietilamino, etilmetila-mino, diisopropilamino, benzilamino, acetilamino, trifluormetilcarbonila, benzoilamino, metiloxicarbonilamino, etiloxicarbonilamino, n-propiloxicarbonilamino, isopropiloxicarbonilamino, n-butilóxi, isobutiloxi-carbonilamino, sec-butiloxicarbonilamino, terc-butiloxicarbonilamino, aliloxicarbonilamino, benziloxicarbonilamino, ciclopentilamino, e ciclohexilamino.

[062] Como um substituinte do "amina opcionalmente substituída" em R^3 e R^4, alquila, acila, e outros são preferidos.

[063] Como um substituinte do "amina opcionalmente substituída" em R^6 e R^7, alquila e outros são preferidos.

[064] Como um substituinte da "amina opcionalmente substituída" e do "aminocarbonila opcionalmente substituída" em um grupo de substituintes A, alquila, alquenila, alquinila, arila opcionalmente substituída com um substituinte selecionado do grupo I de substituintes, aralquila, alquilóxi, hidroxialquila, hidroxialquiloxialquila, haloalquila, aminoalquila opcionalmente substituída com 1 ou 2 alquila(s), alquilsulfonila, alquilsulfonilalquila, alquilcarbonila opcionalmente substituído com halogênio ou alquilóxi, alquiloxicarbonila, cicloalquila opcionalmente substituída com um substituinte selecionado do grupo I de substituintes, carboxialquila, aminocarbonilalquila opcionalmente substituída com um substituinte selecionado do grupo G de

substituintes, aminocarboniloxialquila opcionalmente substituída com um substituinte selecionado do grupo G de substituintes, alquiloxialquila, alquiltioalquila, alquilcarbonilaminoalquila, alquilsulfonilaminoalquila, alquilsulfonila(alquila)aminoalquila, alquiloxicarbonilalquila, alquiltio(hidroxi)alquila, cicloalquilalquila, cianoalquila, aminoalquilcarbonila opcionalmente substituído com um substituinte selecionado do grupo G de substituintes, heteroarila opcionalmente substituída com um substituinte selecionado do grupo G de substituintes, heteroarilalquila, hidroxialquiloxialquila, um grupo heterocíclico não aromático opcionalmente substituído com um substituinte selecionado do grupo I de substituintes, e um alquila heterocíclico não aromático opcionalmente substituído com um substituinte selecionado do grupo I de substituintes.

[065] Aqui, como um substituinte na "aminocarbonila opcionalmente substituída", alquila, alquenila, aralquila, e outros são preferidos. Particularmente, alquila é preferido.

[066] Como um substituinte na "aminocarbonila opcionalmente substituída" em um grupo B de substituintes, alquila, alquenila, aralquila, e outros são preferidos.

[067] Como um substituinte na "aminocarbonila opcionalmente substituída" em um grupo D de substituintes, alquila, alquenila, aralquila, e outros são preferidos.

[068] Como um substituinte no "aminocarbonila opcionalmente substituída" em um grupo E de substituintes, alquila, alquenila, aralquila, e outros são preferidos.

[069] Como um substituinte no "aminocarbonila opcionalmente substituída" em um grupo H de substituintes, alquila, alquenila, aralquila, e outros são preferidos.

[070] Aqui, como um substituinte no "aminocarbonilalquila opcionalmente substituída", alquila, alquenila aralquila, e outros são

preferidos. Particularmente, alquila é preferida.

[071] Como um substituinte no "aminocarbonilalquila opcionalmente substituída" em um grupo C de substituintes, alquilalquenila, aralquila, e outros são preferidos.

[072] Aqui, como um substituinte no "aminocarboniloxialquila opcionalmente substituída", alquila, alquenila, aralquila, e outros são preferidos. Particularmente, alquila é preferido.

[073] Como um substituinte no "aminocarboniloxialquila opcionalmente substituída" em um grupo C de substituintes, alquila, alquenila, aralquila, e outros são preferidos.

[074] Aqui, como um substituinte na "aminoalquilcarbonila opcionalmente substituído", alquila, alquenila, aralquila, e outros são preferidos. Particularmente, alquila é preferido.

[075] Como um substituinte na "aminoalquilcarbonila opcionalmente substituído" em um grupo C de substituintes, alquila, alquenila, aralquila, e outros são preferidos.

[076] Aqui, o termo "ureído opcionalmente substituído" inclui ureído opcionalmente substituído com "alquila", "cicloalquila", "arila", "aralquila", "heteroarila", "heteroarilalquila", "acila", cianoalquila, ou alquiloxialquila em uma ou duas ou mais posições.

[077] Aqui, o termo "guanidino opcionalmente substituído" inclui guanidino opcionalmente substituído com "alquila", "cicloalquila", "arila", "aralquila", "heteroarila", "heteroarilalquila", "acila", ciano, cianoalquila, ou alquiloxialquila em uma ou duas ou mais posições.

[078] Aqui, exemplos de um substituinte em "alquila opcionalmente substituída" incluem amina opcionalmente substituída, um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído, carbonila heterocíclico contendo nitrogênio não aromático opcionalmente substituído, alquila, alquilóxi, ciano, alquilsulfonila, cicloalquila, alquenila, heteroarila, heteroarilóxi, hidróxi,

mercapto, alquiltio, halogênio, nitro, carbóxi, alquiloxicarbonila, hidroxialquila, haloalquila, haloalquilóxi, alquilcarbonilóxi, carbamoilóxi, aminocarbonila opcionalmente substituída, aminocarbonilalquilóxi, acila, acilóxi, arilóxi, aralquila, aralquilóxi, guanidino opcionalmente substituído, um grupo azo, e ureído opcionalmente substituído. Estes podem ser substituídos com um ou mais substituintes em todas as posições possíveis.

[079] Como um substituinte na "alquila opcionalmente substituída" em R^1, R^{17} e R^{19}, um substituinte selecionado do grupo A de substituintes, alquilóxi, ciano, halogênio, heteroarila, e outros são preferidos. Particularmente, amina opcionalmente substituída com um substituinte selecionado do grupo C de substituintes, e um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído com um substituinte selecionado do grupo D de substituintes são preferidos.

[080] Como um substituinte da "alquila opcionalmente substituída" em R^2, um substituinte selecionado do grupo A de substituintes, alquilóxi, alquilcarbonila, e halogênio são preferidos. Particularmente, hidróxi, alquilóxi, e halogênio são preferidos.

[081] Como um substituinte da "alquila opcionalmente substituída" em R^3 e R^4, alquilóxi, alquiloxicarbonila, aminocarbonila, ciano, e outros são preferidos.

[082] Como um substituinte da "alquila opcionalmente substituída" em R^6 e R^7, alquilóxi, alquiloxicarbonila, aminocarbonila, ciano, hidróxi, e outros são preferidos.

[083] Como um substituinte da "alquila opcionalmente substituída" em R^{18}, hidróxi, alquilóxi, halogênio, ciano, e outros são preferidos.

[084] Como um substituinte da "alquila opcionalmente substituída" em R^{20}, hidróxi, alquilóxi, halogênio, ciano, e outros são preferidos.

[085] Aqui, exemplos de um substituinte em "alquenila

opcionalmente substituída" e em "alquinila opcionalmente substituída" incluem amina opcionalmente substituída, um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído, cicloalquila, hidróxi, alquilóxi, mercapto, alquiltio, halogênio, nitro, ciano, carbóxi, alquiloxicarbonila, haloalquila, haloalquilóxi, aminocarbonila opcionalmente substituída, acila, acilóxi, arila, arilóxi, aralquila, aralquilóxi, alquilsulfonila, guanidino, um grupo azo, ureído opcionalmente substituído, e outros. Estes podem ser substituídos com um ou mais substituintes em todas as posições possíveis.

[086] Como um substituinte do "alquenila opcionalmente substituída" em R^1 e R^{17}, um substituinte selecionado do grupo A de substituintes é preferido. Em particular, amina opcionalmente substituída com um substituinte selecionado do grupo C de substituintes, e um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído com um substituinte selecionado do grupo D de substituintes são preferidos.

[087] Como um substituinte do "alquenila opcionalmente substituída" e do "alquinila opcionalmente substituída" em R^2, um substituinte selecionado do grupo A de substituintes, cicloalquila, alquilóxi, e halogênio são preferidos. Particularmente, hidróxi, cicloalquila, alquilóxi, e halogênio são preferidos.

[088] Como um substituinte da "alquenila opcionalmente substituída" e do "alquinila opcionalmente substituída" em R^3 e R^4, alquilóxi, alquiloxicarbonila, aminocarbonila, alquila opcionalmente substituída com ciano e outros, alquilóxi, alquiloxicarbonila, aminocarbonila, alquiloxicarbonila opcionalmente substituído com ciano e outros, e aminocarbonila opcionalmente substituída, e outros são preferidos.

[089] Como um substituinte da "alquenila opcionalmente substituída" e do "alquinila opcionalmente substituída" em R^6 e R^7, alquilóxi, alquiloxicarbonila, aminocarbonila, alquila opcionalmente

substituída com ciano e outros, alquilóxi, alquiloxicarbonila, aminocarbonila, alquiloxicarbonila opcionalmente substituído com ciano e outros, e aminocarbonila opcionalmente substituída, e outros são preferidos.

[090] Como um substituinte da "alquenila opcionalmente substituída" e da "alquinila opcionalmente substituída" em R^{18}, hidróxi, alquilóxi, halogênio, ciano, e outros são preferidos.

[091] Como um substituinte do "alquenila opcionalmente substituída" e do "alquinila opcionalmente substituída" em R^{20}, hidróxi, alquilóxi, halogênio, ciano, e outros são preferidos.

[092] Aqui, exemplos de um substituinte em "cicloalquila opcionalmente substituída" incluem alquiloxicarbonila, aminocarbonila opcionalmente substituída com um substituinte selecionado do grupo G de substituintes, ciano, alquila opcionalmente substituída com um substituinte selecionado do grupo M de substituintes que consiste em ciano, hidróxi, carbóxi, aminocarbonila, alquiloxicarbonila, e alquilóxi, alquilsulfonila, alquilsulfonilalquilcarbonila, cicloalquila, hidróxi, alquilóxi, mercapto, alquiltio, halogênio, nitro, carbóxi, haloalquila, haloalquilóxi, acila, acilóxi, arila, arilóxi (por exemplo fenilóxi), aralquila, aralquilóxi (por exemplo benzilóxi), um grupo heterocíclico contendo nitrogênio não aromático, alquilcarbonilamino, aminocarbonilóxi, amino, oxo, guanidino, um grupo azo, e ureído opcionalmente substituído.

[093] Como um substituinte do "cicloalquila opcionalmente substituída" no grupo C de substituintes, os substituintes exemplificados no grupo I de substituintes são preferidos.

[094] Aqui, exemplos de um substituinte de "alquilóxi opcionalmente substituído", "alquenilóxi opcionalmente substituído", e "alquinilóxi opcionalmente substituído" incluem cicloalquila, alquenila, hidróxi, alquilóxi, mercapto, alquiltio, halogênio, nitro, ciano, carbóxi, alquiloxicarbonila, haloalquila, haloalquilóxi, amina opcionalmente

substituída, aminocarbonila opcionalmente substituída, acila, aciloxi, um grupo heterocíclico não aromático opcionalmente substituído, ariloxi, aralquiloxi, alquilsulfonila, guanidino, um grupo azo, e ureído opcionalmente substituído. Estes podem ser substituídos em um ou mais lugares de todas as posições possíveis. Exemplos preferidos incluem halogênio.

[095] Como um substituinte do "alquiloxi opcionalmente substituído" e do "alqueniloxi opcionalmente substituído" em R^3 e R^4, alquiloxi, amina opcionalmente substituída, um grupo heterocíclico não aromático opcionalmente substituído com um substituinte selecionado do grupo D de substituintes, ciano, e outros são preferidos.

[096] Como um substituinte de "alquiloxi opcionalmente substituído", "alqueniloxi opcionalmente substituído", e "alquiniloxi opcionalmente substituído" em R^5, um substituinte selecionado do grupo E de substituintes é preferido.

[097] Como um substituinte de "alquiloxi opcionalmente substituído", "alqueniloxi opcionalmente substituído", e "alquiniloxi opcionalmente substituído" em R^6 e R^7, alquiloxi, ciano, alquiloxi-carbonila, aminocarbonila opcionalmente substituída, e outros são preferidos.

[098] Aqui, exemplos de um substituinte no "grupo heterocíclico não aromático opcionalmente substituído" incluem alquiloxicarbonila, aminocarbonila opcionalmente substituída com um substituinte selecionado do grupo G de substituintes, ciano, alquila opcionalmente substituída com um substituinte selecionado do grupo M de substituintes que consiste em ciano, hidróxi, carbóxi, aminocarbonila, alquiloxi-carbonila, e alquiloxi, alquilsulfonila, alquilsulfonilalquilcarbonila, cicloalquila, hidróxi, alquiloxi, mercapto, alquiltio, halogênio, nitro, carbóxi, haloalquila, haloalquiloxi, acila, aciloxi, arila, ariloxi (por exemplo feniloxi), aralquila, aralquiloxi (por exemplo benziloxi), um

grupo heterocíclico contendo nitrogênio não aromático, alquilcarbonilamino, aminocarbonilóxi, amino, oxo, guanidino, um grupo azo, e ureído opcionalmente substituído.

[099] Aqui, exemplos de um substituinte no "grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído" incluem alquiloxicarbonila, aminocarbonila opcionalmente substituída com um substituinte selecionado do grupo G de substituintes, ciano, alquila opcionalmente substituída com um substituinte selecionado do grupo M de substituintes que consiste em ciano, hidróxi, carbóxi, aminocarbonila, alquiloxicarbonila, e alquilóxi, alquilsulfonila, alquilsulfonilalquilcarbonila, cicloalquila, hidróxi, alquilóxi, mercapto, alquiltio, halogênio, nitro, carbóxi, haloalquila, haloalquilóxi, acila, acilóxi, arila, arilóxi (por exemplo fenilóxi), aralquila, aralquilóxi (por exemplo benzilóxi), um grupo heterocíclico contendo nitrogênio não aromático, alquilcarbonilamino, aminocarbonilóxi, amina opcionalmente substituída, oxo, guanidino, um grupo azo, e ureído opcionalmente substituído.

[0100] Como um substituinte do "grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído" em R^1 e R^{17}, alquila, alquiloxicarbonila, aminocarbonila opcionalmente substituída com um substituinte selecionado do grupo G de substituintes, ciano, oxo, amino, carboxila, hidroxialquila, cianoalquila, alquiloxialquila, alquilsulfonila, alquilcarbonila, alquenilcarbonila, alquilsulfonilalquilcarbonila, alquilcarbonilamino, alquilsulfonilamino, carboxialquila, alquiloxicarbonilalquila, e outros são preferidos. Particularmente, os substituintes exemplificados no grupo B de substituintes são preferidos.

[0101] Como um substituinte do "grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído" em W^1, alquila, alquiloxicarbonila, aminocarbonila opcionalmente substituída, ciano, hidroxialquila, cianoalquila, alquiloxialquila, alquilsulfonila, alquilcarbonila, alquenilcarbonila, alquilsulfonilalquilcarbonila, e outros são

preferidos. Particularmente, os substituintes exemplificados no grupo J de substituintes são preferidos.

[0102] Como um substituinte do "grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído" e do "carbonila heterocíclico contendo nitrogênio não aromático opcionalmente substituído" no grupo A de substituintes, um substituinte selecionado do grupo D de substituintes é preferido.

[0103] Aqui, exemplos de um substituinte em "arila opcionalmente substituída", "fenila opcionalmente substituída", "heteroarila opcionalmente substituída", "piridila opcionalmente substituída", "furila opcionalmente substituída", "tienila opcionalmente substituída", "tiazolila opcionalmente substituída", "oxazolila opcionalmente substituída", "grupo heterocíclico não aromático opcionalmente substituído", "alquila heterocíclico não aromático opcionalmente substituído", "cicloalquila opcionalmente substituída", "aralquila opcionalmente substituída", e "heteroarilalquila opcionalmente substituída" incluem alquila opcionalmente substituída (como substituinte, halogênio, hidróxi, nitro, ciano, carbóxi, alquilóxi, alquiloxicarbonila, acila, etc.), cicloalquila, alquenila, alquinila, hidróxi, alquilóxi, aralquilóxi, mercapto, alquiltio, halogênio, nitro, ciano, carbóxi, alquiloxicarbonila, ariloxicarbonila, haloalquila, haloalquilóxi, amina opcionalmente substituída, aminocarbonila opcionalmente substituída, acila, aciloxi, arila opcionalmente substituída (como substituinte, halogênio, hidróxi, nitro, ciano, carbóxi, alquilóxi, alquiloxicarbonila, acila, etc.), heteroarila opcionalmente substituída (como substituinte, halogênio, hidróxi, nitro, ciano, carbóxi, alquilóxi, alquiloxicarbonila, acila, etc.), um grupo heterocíclico não aromático opcionalmente substituído (como substituinte, halogênio, hidróxi, nitro, ciano, carbóxi, alquilóxi, alquiloxicarbonila, acila, etc.), aralquila opcionalmente substituída (como substituinte, halogênio, hidróxi, nitro, ciano, carbóxi, alquilóxi, alquiloxicarbonila, acila, etc.), alquilsulfonila,

guanidino, um grupo azo, -N = N- (fenila opcionalmente substituída), e ureído opcionalmente substituído. Estes podem substituir em uma ou mais de todas as posições possíveis.

[0104] Como um substituinte de "arila opcionalmente substituída" em R^1, substituintes exemplificados no grupo I de substituintes são preferidos.

[0105] Como um substituinte de "arila opcionalmente substituída" e "heteroarila opcionalmente substituída" em R^2, alquila opcionalmente substituída com hidróxi ou amina opcionalmente substituída, amina opcionalmente substituída, halogênio, e outros são preferidos. Particularmente, alquila opcionalmente substituída com hidróxi ou amina opcionalmente substituída é preferida.

[0106] Como um substituinte do "arila opcionalmente substituída", do "heteroarila opcionalmente substituída", e do "grupo heterocíclico não aromático opcionalmente substituído" em R^8, alquiloxicarbonila, aminocarbonila opcionalmente substituída, ciano, halogênio, alquila, alquilóxi, alquiltio, haloalquila e outros são preferidos. Particularmente, substituintes exemplificados no grupo F de substituintes são preferidos.

[0107] Como um substituinte de "arila opcionalmente substituída" e "heteroarila opcionalmente substituída" em R^{19}, alquiloxicarbonila, aminocarbonila opcionalmente substituída, ciano, cianoalquila, hidroxi-alquila, aminocarbonilalquila. e outros são preferidos. Particularmente, substituintes exemplificados no grupo I de substituintes são preferidos.

[0108] Como um substituinte de "heteroarila opcionalmente substituída" em W^1, alquila, hidróxi, alquilóxi, e outros são preferidos. Particularmente, substituintes exemplificados no grupo J de substituintes são preferidos.

[0109] Como um substituinte do "arila opcionalmente substituída", do "heteroarila opcionalmente substituída", do "grupo heterocíclico não aromático opcionalmente substituído" e do "alquila heterocíclico não

aromático opcionalmente substituído" em um grupo C de substituintes, substituintes exemplificados no grupo I de substituintes são preferidos.

[0110] Aqui, a "composição farmacêutica útila para tratar câncer e a "terapêutica para um câncer" incluem produtos terapêuticos para tumor cerebral (por exemplo glioblastoma), câncer de órgão urinário (por exemplo câncer de bexiga, câncer renal), câncer genital (câncer de próstata, câncer de ovário, câncer de útero), tumor linfóide, câncer do trato digestivo (por exemplo câncer de estômago, câncer de intestino grosso), câncer de faringe, câncer de pulmão (por exemplo câncer de glândulas pulmonares, câncer de pulmão de células pequenas, câncer de pulmão de células não-pequenas), câncer de pâncreas, câncer de mama, câncer de cabeça e pescoço, câncer de esôfago, e glândula tireóide. Em particular, a composição é de preferência usada como produto terapêutico para câncer de mama, tumor cerebral, câncer de bexiga, câncer renal, câncer de próstata, câncer de ovário, câncer de útero, câncer de pulmão, câncer de pâncreas, câncer de intestino grosso, câncer de cabeça de pescoço.

[0111] A presente invenção inclui um método para tratar ou prevenir um câncer em um mamífero no qual é necessário tratar ou prevenir um câncer, e o método compreende administrar uma quantidade terapeuticamente eficaz do composto de fórmula (I) ao mamífero. Um câncer que é de preferência tratado é selecionado de tumor cerebral (por exemplo glioblastoma), câncer de órgão urinário (por exemplo câncer de bexiga, câncer renal), câncer genital (câncer de próstata, câncer de ovário, câncer de útero), tumor linfóide, câncer do trato digestivo (por exemplo câncer de estômago), câncer de faringe, câncer de pulmão (por exemplo câncer de glândulas pulmonares, câncer de pulmão de células pequenas, câncer de pulmão de células não-pequenas), câncer de pâncreas, câncer de mama, câncer de cabeça e pescoço, câncer de esôfago, e glândula tireóide. Mais preferivelmente

são câncer de mama, tumor cerebral, câncer de bexiga, câncer renal, câncer de próstata, câncer de ovário, câncer de útero, câncer de pulmão, câncer de pâncreas, câncer de intestino grosso e câncer de cabeça de pescoço.

Efeito da Invenção

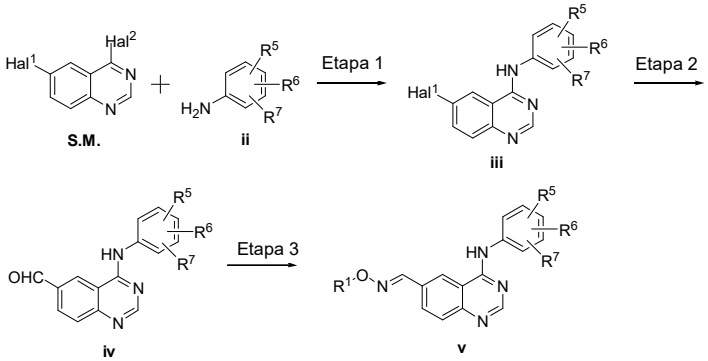
[0112] O presente composto possui a ação excelente de inibir um receptor de EGF e HER2, e é bastante seguro (possui atividade inibitória de CYP reduzida) e, portanto, é útila como medicamento, entre outras coisas, como um produto terapêutico para câncer.

Melhor modo de realizar a invenção

[0113] O presente composto (I) pode ser sintetizado por qualquer um dos métodos A a E descritos abaixo. Alternativamente, visto que um método para sintetizar um derivado de quinazolina está descrito no documento WO 96/09294, WO 98/02434 e outros, o presente composto (I) também pode ser sintetizado de acordo com este. Quando o composto tem um grupo que tem influência em cada reação, o grupo pode ser protegido com um grupo protetor adequado, e pode ser desprotegido em um estágio adequado. Além disso, quando uma matéria-prima, um reagente, um intermediário e um produto reacional em cada etapa pode formar um sal, o sal está incluído.

(Método A)

Fórmula química 25



onde Hal^1 e Hal^2 são cada independentemente halogênio; R^1, R^5, R^6, e R^7 são como definidos no item (1).

Etapa 1

[0114] A primeira etapa é a etapa de sintetizar um composto (iii) por reação de uma matéria-prima de partida (S.M.) que pode ser sintetizada de acordo com o método descrito no documento WO 96/09294 ou outros, ou que está comercialmente disponível, e um composto (ii) que pode ser sintetizado de acordo com o método descrito no documento WO 98/02434 ou outros, ou que está comercialmente disponível.

[0115] A matéria-prima de partida (S.M.) e o composto (ii) podem ser reagidos em um solvente tal como tetrahidrofurano, acetonitrila e outros a uma temperatura de 20°C até uma temperatura abaixo do refluxo térmico, de preferência a uma temperatura de 60°C até uma temperatura abaixo do refluxo térmico, para obter o composto (iii).

Etapa 2

[0116] A segunda etapa é a etapa de inserir monóxido de carbono no composto (iii) na presença de um catalisador à base de paládio para obter um composto (iv).

[0117] O composto (iii) pode ser reagido a uma temperatura de 50°C a 150°C, de preferência 70°C a 90°C sob a atmosfera de monóxido de carbono em um solvente tal como N,N-dimetilformamida, N,N-dimetilacetamida, N,N'-dimetilimidazolidinona, dimetila sulfóxido e outros, na presença de uma fonte de hidrogênio tal como formiato de sódio, hidreto de tributila estanho e outros, um catalisador à base de paládio tal como diclorobis(trifenilfosfina)paládio, tetracis(trifenilfosfina)paládio, tris(dibenzilidenoacetona)dipaládio, [1, 1'-bis(difenilfosfino)ferroceno]dicloropaládio, acetato de paládio + trifenilfosfina e outros, e uma base tal como trietilamina, di(isopropila)etilamina e outros para obter o composto (iv).

Etapa 3

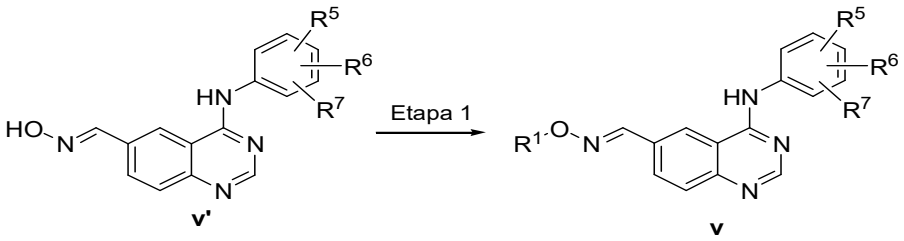
[0118] A terceira etapa é uma etapa de sintetizar um composto desejado (v) por reação do composto (iv) e um composto representado

pela fórmula: R^1-O-NH_2 onde R^1 é como definido no item (1).

[0119] A matéria-prima de partida (iv) e o composto representado pela fórmula: R^1-O-NH_2 onde R^1 é como definido no item (1) ou um sal podem ser reagidos a uma temperatura de 0°C até uma temperatura abaixo do refluxo térmico, de preferência, a uma temperatura de 20°C a 70°C, em um solvente tal como tetrahidrofurano, dioxano, metanol e outros, ou em um solvente misto dos mesmos e água, se necessário, na presença de um ácido tal como ácido clorídrico, ácido sulfúrico, ácido p-toluenossulfônico, ácido metanossulfônico, ácido fórmico, ácido acético, ácido trifluoracético e outros para obter o composto (v).

(Método B)

Fórmula química 26



onde R^1, R^5, R^6, e R^7 são como definidos no item (1).

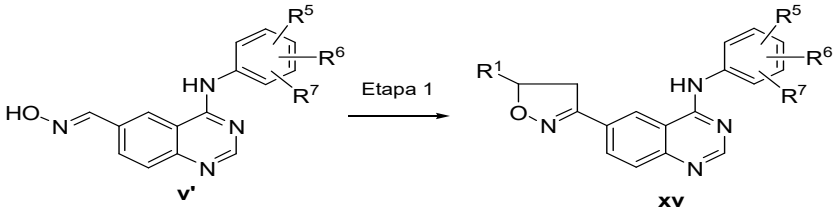
(Etapa 1)

[0120] A primeira etapa é a etapa de sintetizar um composto desejado (v) por reação de um composto (v') obtido pela reação do composto (iv) obtido no método A com hidroxilamina, e um composto representado pela fórmula: R^1-Hal^3 onde Hal^3 é halogênio; R^1 é como definido no item (1).

[0121] O composto (v') e o composto representado pela fórmula: R^1-Hal^3 onde Hal^3 é halogênio; R^1 é como definido no item (1) podem ser dissolvidos em um solvente tal como N,N-dimetilacetamida, N,N-dimetilacetamida, N,N'-dimetilimidazolidinona, dimetila sulfóxido e outros, e reagidos a uma temperatura de 50°C a 150°C, de preferência 60oC a 80°C na presença de uma base tal como carbonato de potássio, carbonato de sódio, e outras para obter o composto (v).

(Método C)

Fórmula química 27



onde R^1, R^5, R^6, e R^7 são como definidos no item (1).

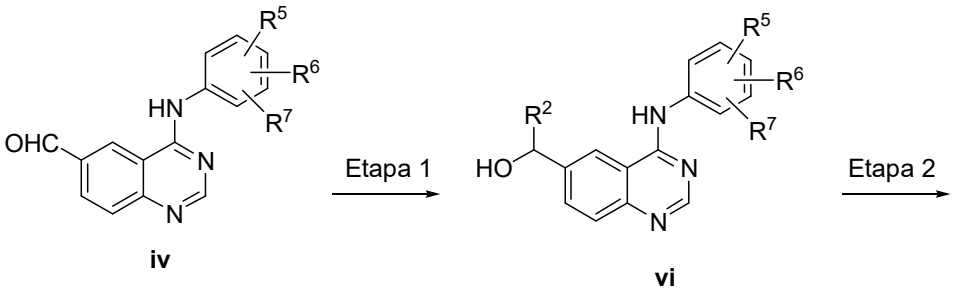
(Etapa 1)

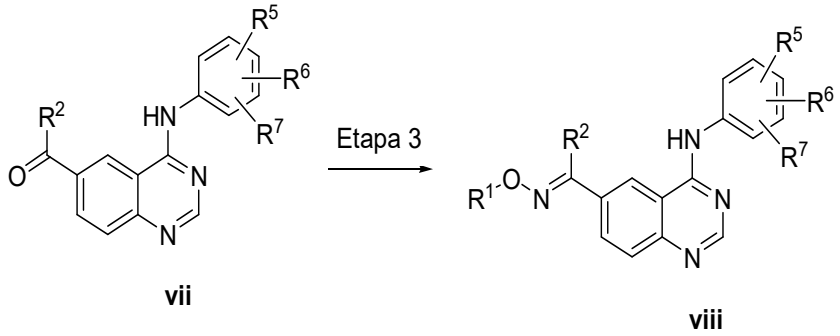
[0122] A primeira etapa é uma etapa de sintetizar um composto desejado (xv) por reação de um composto (v') obtido por reação do composto (iv) obtido no Método A com hidroxilamina, e um composto representado pela fórmula: R^1-CH=CH_2 onde R^1 é como definido no item (1).

[0123] O composto (xv) pode ser obtido por dissolução do composto (v') em um solvente tal como clorofórmio, diclorometano, 1, 2-dicloroetano e outros, e reação com um agente oxidante à base de cloro tal como N-clorosuccinimida, N-cloroftalimida e outros a uma temperatura de 20°C a 100°C, de preferência 50°C a 60°C na presença de uma quantidade catalítica de uma base tal como piridina, 4-dimetilaminopiridina e outros, e subseqüentemente, adição de um composto representado pela fórmula: R^1-CH=CH_2 onde R^1 é como definido no item (1), e uma base tal como trietilamina, di(isopropila)etilamina e outros, e reação dos mesmos a uma temperatura de 0°C a 100°C, de preferência 10°C a 30°C.

(Método D)

Fórmula química 28





onde R^1, R^2, R^5, R^6, e R^7 são como definidos no item (1)

(Etapa 1)

[0124] A primeira etapa é a etapa de reagir o composto (iv) obtido no método A com um reagente representado pela fórmula: R^2MgHal^4 ou R^2Li onde Hal^4 é halogênio; R^2 é como definido no item (1) para obter um composto (vi).

[0125] O composto (vi) pode ser obtido por reação do composto (iv) e do reagente representado pela fórmula: R^2MgHal^4 ou R^2Li onde Hal^4 é halogênio; R^2 é como definido no item (1) a uma temperatura de -100°C a 50°C, de preferência, -78°C a 10°C em um solvente tal como tetrahidrofurano, éter dietílico, tolueno, n-hexano e outros.

(Etapa 2)

[0126] A segunda etapa é a etapa de oxidar o composto (vi) para sintetizar um composto (vii).

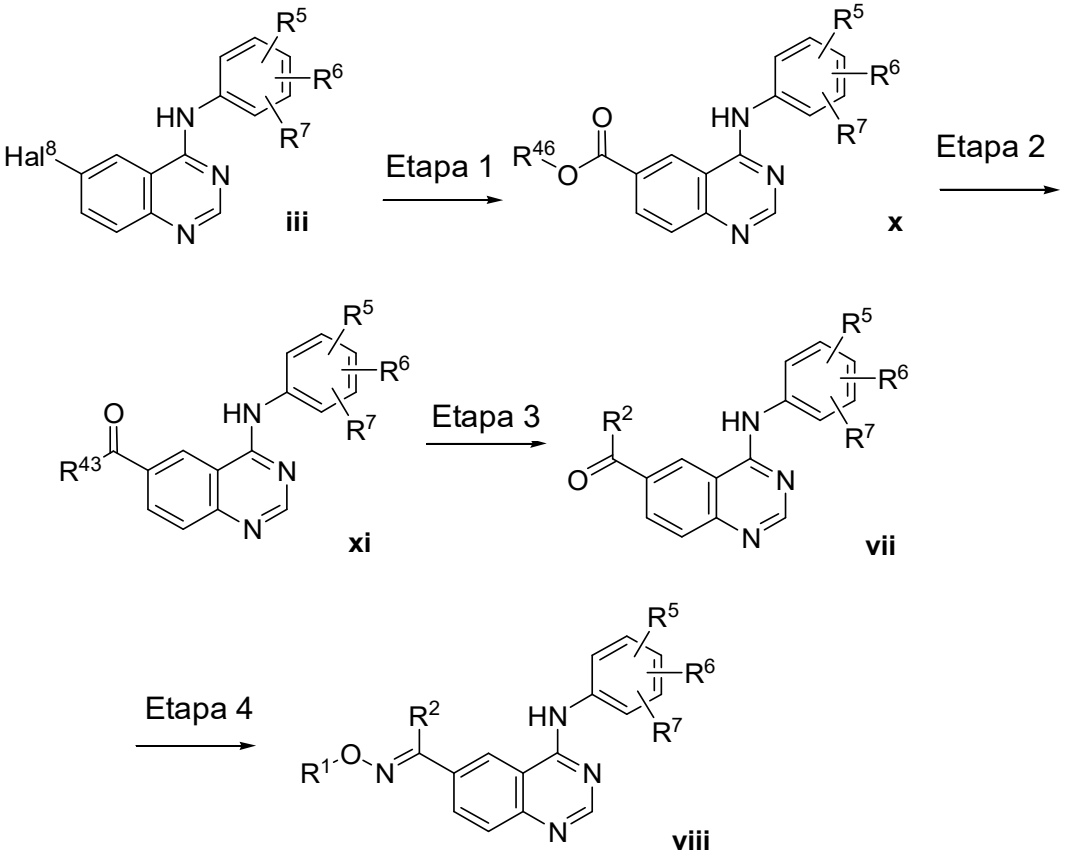
[0127] O composto (vii) pode ser obtido por oxidação do composto (vi) por um método geral de oxidação de um álcool secundário descrito em Experimental Chemistry Course, vol. 23, Fourth edition (editado por The Chemical Society of Japan) ou outros.

(Etapa 3)

[0128] De acordo com o mesmo método da terceira etapa do Método A, é possível obter um composto (viii) a partir do composto (vii).

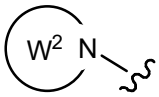
(Método E)

Fórmula química 29



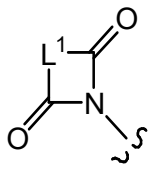
onde Hal^8 é halogênio; R^{43} é um grupo representado pela fórmula: $R^{44}(R^{45}O)N$ onde R^{44} e R^{45} são independentemente C1-C3 alquila ou um grupo representado pela fórmula:

Fórmula química 30



onde W^2 é um grupo heterocíclico contendo nitrogênio não aromático; R^{46} é C1-C3 alquila ou um grupo representado pela fórmula:

Fórmula química 31



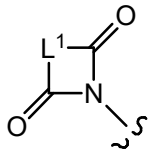
onde L^1 é C2-C3 alquileno;

R^1, R^2, R^5, R^6, e R^7 são como definidos no item (1)

(Etapa 1)

[0129] A primeira etapa é a etapa de obter um composto (x) por reação do composto (iii) obtido no A método com um álcool ou um reagente representado pela fórmula:

Fórmula química 32



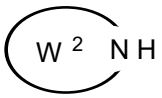
onde L^1 é C2-C3 alquileno enquanto monóxido de carbono é inserido na presença de um catalisador à base de paládio.

[0130] O composto (x) pode ser obtido por reação do composto (iii) com um álcool tal como metanol, etanol, n-propanol, isopropanol e outros, ou um reagente tal como imida de ácido N-hidroxissuccínico e outros a uma temperatura de 50°C a 150°C, de preferência, 70°C a 90°C sob uma atmosfera de monóxido de carbono em um solvente tal como N,N-dimetilformamida, N,N-dimetilacetamida, N,N'-dimetilimidazolidinona, dimetila sulfóxido e outros na presença de um catalisador à base de paládio tal como diclorobis(trifenilfosfina)paládio, tetracis(trifenilfosfina)paládio, tris(dibenzilidenoacetona)dipaládio, [1, 1'-bis(difenilfosfino)ferroceno]dicloropaládio, acetato de paládio + trifenilfosfina, acetato de paládio + 1,3-bisdifenilfosfinopropano e outros, e uma base tal como trietilamina, di(isopropila)etilamina e outras.

(Etapa 2)

[0131] A segunda etapa é uma etapa de obter um composto (xi) por reação do composto (x) com um reagente representado pela fórmula: $R^{44}(R^{45}O)NH$ onde R^{44} e R^{45} são independentemente C1-C3 alquila ou um reagente representado pela fórmula:

Fórmula química 33



onde W^2 é um grupo heterocíclico contendo nitrogênio não aromático.

[0132] O composto (xi) pode ser obtido por misturação do composto (x) com um reagente representado pela fórmula: $R^{44}(R^{45}O)NH$ onde R^{44} e R^{45} são independentemente C1-C3 alquila ou um reagente representado pela fórmula:

Fórmula química 34



onde W^2 é um grupo heterocíclico contendo nitrogênio não aromático em um solvente tal como tetrahidrofurano, N,N-dimetilformamida, clorofórmio, diclorometano e outros, e adição de um reagente tal como cloreto de metilmagnésio, brometo de metilmagnésio, cloreto de isopropilmagnésio, metila lítio e outros a uma temperatura de -100°C a 50°C, de preferência -78°C a 20°C para reagir os mesmos.

(Etapa 3)

[0133] A terceira etapa é uma etapa de reagir o composto (xi) com um reagente representado pela fórmula: R^2M onde M é Li, Na, K, ou um grupo representado pela fórmula: $MgHal^5$ onde Hal^5 é halogênio; R^2 é como definido no item (1) para obter um composto (vii).

[0134] O composto (vii) pode ser obtido por reação do composto (xi) com um reagente representado pela fórmula: R^2M onde M é Li, Na, K, ou um grupo representado pela fórmula: $MgHal^5$ onde Hal^5 é halogênio; R^2 é como definido no item (1) a uma temperatura de -100°C a 50°C, de preferência -78°C a 20°C em um solvente tal como tetrahidrofurano, éter dietílico, tolueno, n-hexano e outros.

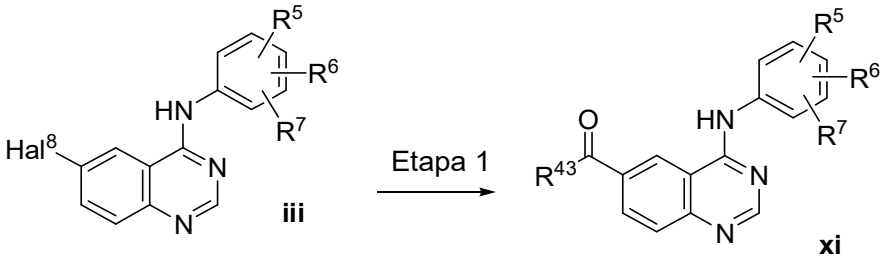
(Etapa 4)

[0135] Da mesma maneira que para a terceira etapa do Método A, um composto (viii) pode ser obtido a partir do composto (vii).

[0136] Como um método alternativo para a primeira etapa e a segunda etapa do Método E, temos o Método E' a seguir.

(Método E')

Fórmula química 35



onde Hal^8 e R^{43} são como definidos acima; R^5, R^6, e R^7 são como definidos no item (1).

(Etapa 1)

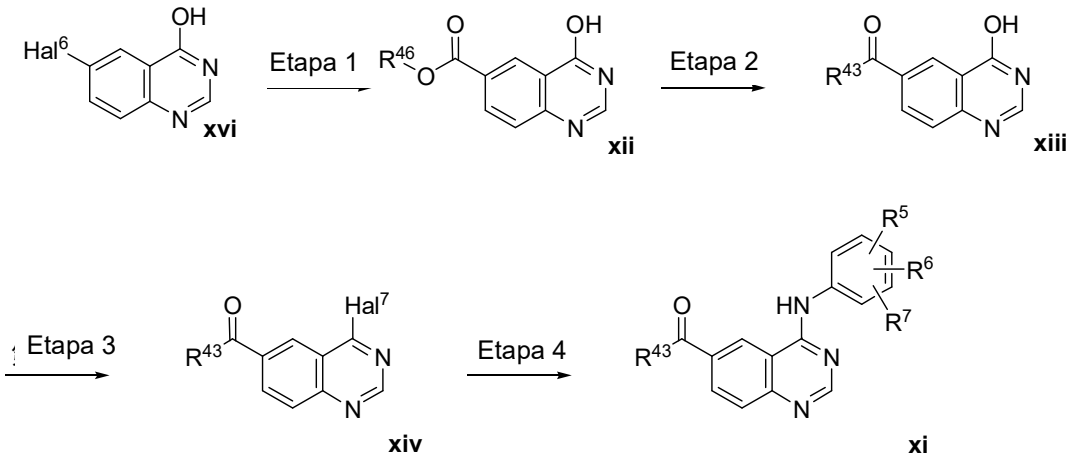
[0137] A primeira etapa é uma etapa de obter um composto (xi) por reação do composto (iii) com um reagente representado pela fórmula: $R^{43}H$ onde R^{43} é como definido acima enquanto monóxido de carbono é inserido na presença de um catalisador à base de paládio.

[0138] Por reação de um reagente representado por $R^{43}H$ onde R^{43} é como definido acima no lugar de álcool ou outros da mesma maneira que aquela da primeira etapa do Método E, o composto (xi) pode ser obtido a partir do composto (iii).

[0139] Como outro método para obter um derivado tipo amida (xi) do método E, temos o método E" a seguir.

(Método E")

Fórmula química 36



onde Hal^6 é halogênio; Hal^7 é halogênio; R^{43} e R^{46} são como definidos acima; R^5, R^6, e R^7 são como definidos no item (1).

(Etapa 1)

[0140] Da mesma maneira que para a primeira etapa do Método E, um composto (xii) pode ser obtido a partir de um composto (xvi).

(Etapa 2)

[0141] Da mesma maneira que para a segunda etapa do Método E, um composto (xiii) pode ser obtido a partir do composto (xii).

(Etapa 3)

[0142] A terceira etapa é uma etapa de converter um grupo hidroxila do composto (xiii) em halogênio para obter um composto (xiv).

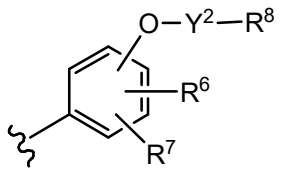
[0143] O composto (xiv) pode ser obtido por reação do composto (xiii) com um agente halogenante tal como oxicloreto de fósforo, oxibrometo de fósforo e outros a uma temperatura de 0°C a 200°C, de preferência 20°C a 150°C em um solvente tal como tolueno, tetrahidrofurano e outros na presença de uma base tal como trietilamina, diisopropiletilamina, piridina e outros.

(Etapa 4)

[0144] Da mesma maneira que para a primeira etapa do Método A, um composto (xi) pode ser obtido a partir do composto (xiv).

[0145] O presente composto (I) no qual A é um grupo representado pela fórmula:

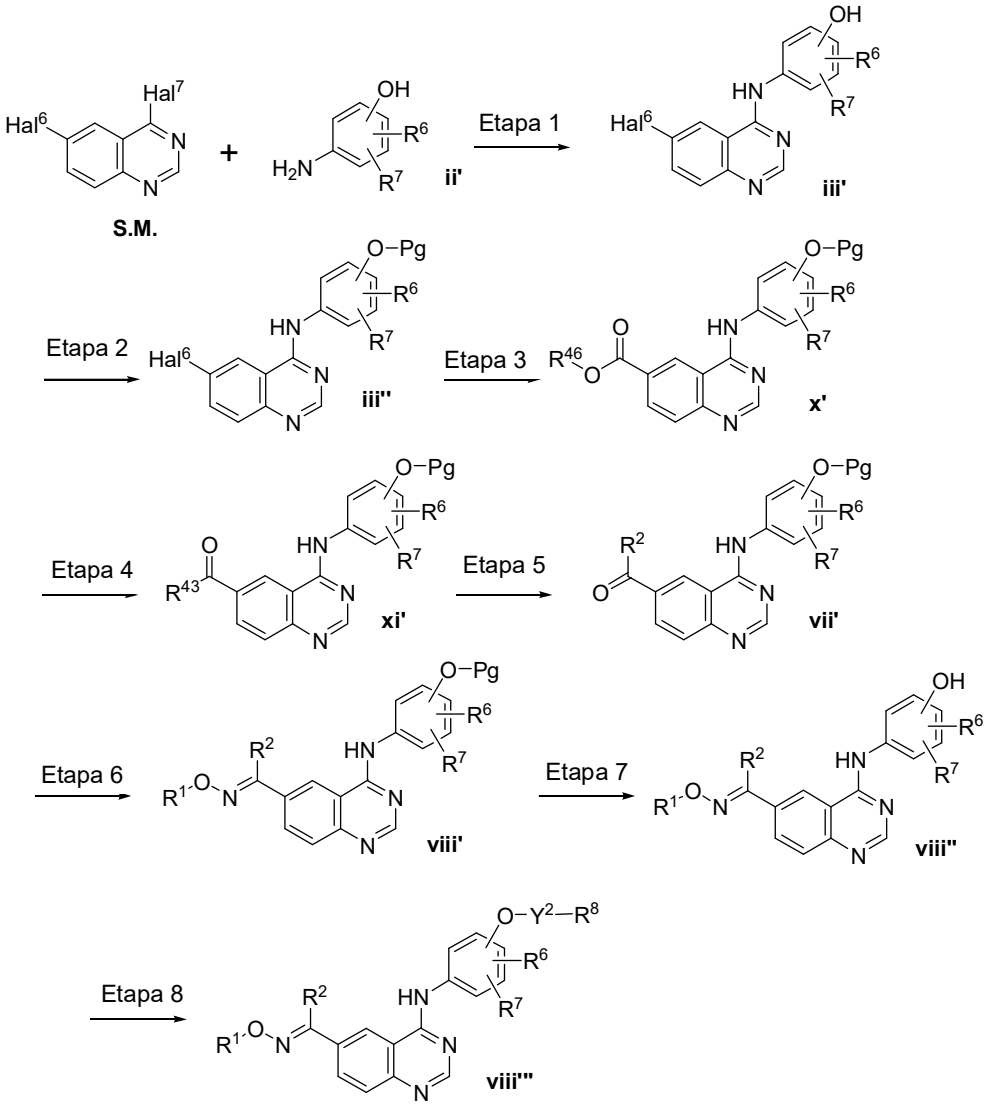
Fórmula química 37



onde Y^2 é uma ligação simples ou C1-C3 alquileno; R^6, R^7, e R^8 são como definidos no item (1) também pode ser sintetizado pelo Método F a seguir.

(Método F)

Fórmula química 38



onde Hal^6 e Hal^7 são halogênio; Y^2 é uma ligação simples ou C1-C3 alquileno; Pg é um grupo protetor adequado para um grupo hidroxila; R^1, R^2, R^6, R^7, e R^8 são como definidos no item (1); R^{43} e R^{46} são como definidos acima.

(Etapa 1)

[0146] Da mesma maneira que para a primeira etapa do Método A, um composto (iii') pode ser obtido a partir de um composto de partida (S.M.) e um composto (ii').

(Etapa 2)

[0147] A segunda etapa é uma etapa de ligar um grupo protetor a

um grupo hidroxila do composto (iii') para sintetizar um composto (iii").

[0148] Um grupo protetor adequado pode ser ligado pelo método descrito em Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons) ou outros.

(Etapa 3)

[0149] Da mesma maneira que para a primeira etapa do Método E, um composto (x') pode ser obtido a partir do composto (iii").

(Etapa 4)

[0150] Da mesma maneira que para a segunda etapa do Método E, um composto (xi') pode ser obtido a partir do composto (x').

(Etapa 5)

[0151] Da mesma maneira que para a terceira etapa do Método E, um composto (vii') pode ser obtido a partir do composto (xi').

(Etapa 6)

[0152] Da mesma maneira que para a terceira etapa do Método A, um composto (viii') pode ser obtido a partir do composto (vii').

(Etapa 7)

[0153] A sétima etapa é uma etapa de remover um grupo protetor do composto (viii') para sintetizar um composto (viii").

[0154] A desproteção pode ser efetuada na condição adequada pelo método descrito em Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons) ou outros.

(Etapa 8)

[0155] A oitava etapa é uma etapa de reagir o composto (viii") com um reagente representado pela fórmula: R^8-Y^2-Hal^8 onde Hal^8 é halogênio; Y^2 é uma ligação simples ou C1-C3 alquileno; R^8 é como definido no item (1) para obter um composto (viii"').

[0156] O composto (viii"') pode ser obtido por reação do composto (viii") com um reagente representado pela fórmula: R^8-Y^2-Hal^8 onde Hal^8 é halogênio; Y^2 é uma ligação simples ou C1-C3 alquileno; R^8 é como

definido no item (1) a uma temperatura de -20°C a 200°C, de preferência 0°C a 100°C em um solvente tal como N,N-dimetilformamida, dimetila sulfóxido, tetrahidrofurano, éter dietílico, tolueno, n-hexano e outros na presença de uma base tal como carbonato de césio, carbonato de potássio, carbonato de sódio, carbonato de lítio, bicarbonato de potássio, bicarbonato de sódio, hidróxido de potássio, hidróxido de sódio, trietilamina, piridina e outros.

[0157] Como Y^2 no Método F, C1-C3 alquileno é preferido. Particularmente, metileno é preferido.

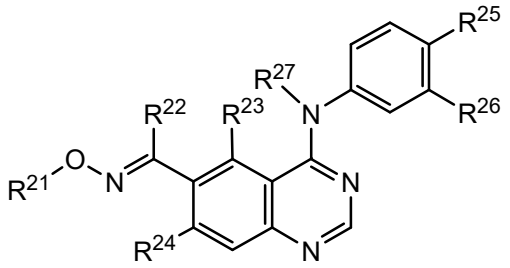
[0158] Como R^8 no Método F, fenila opcionalmente substituída com halogênio, ou piridila opcionalmente substituída com halogênio é preferido.

[0159] Um reagente tipo alcoxiamino representado pela fórmula: R^1-O-NH_2 onde R^1 é como definido no item (1) usado na terceira etapa do Método A encontra-se comercialmente disponível, ou pode ser sintetizado usando, como matéria-prima de partida, um composto tipo álcool que pode ser sintetizado de acordo com o método descrito em J. Med. Chem., 1999, 42:2007-2020, Liebigs Ann. Chem., 1988:1149-1153, Organic Letters, 2004, 6:4069-4072, Organic Letters, 2005, 7:937-939, WO 04/054514 ou outros, de acordo com o método descrito no documento WO 02/062313 ou outros.

[0160] No composto representado pela fórmula (I), os compostos representados pela fórmula (I-A) até a fórmula (I-P) a seguir são preferidos.

[0161] Um composto representado na fórmula (I-A):

Fórmula química 39



(I-A)

onde R^{21} é alquila substituída com amina opcionalmente substituída com um substituinte selecionado do grupo C de substituintes que consiste em alquila, alquenila, alquinila, arila opcionalmente substituída, aralquila, alquilóxi, hidroxialquila, hidroxialquiloxialquila, haloalquila, aminoalquila opcionalmente substituída com 1 ou 2 alquila(s), alquilsulfonila, alquilsulfonilalquila, alquilcarbonila opcionalmente substituído com halogênio ou alquilóxi, alquiloxicarbonila, cicloalquila opcionalmente substituída, carboxialquila, aminocarbonilalquila opcionalmente substituída, aminocarboniloxialquila opcionalmente substituída, alquiloxialquila, alquiltioalquila, alquilcarbonilaminoalquila, alquilsulfonilaminoalquila, alquilsulfonila(alquila)aminoalquila, alquiloxi-carbonilalquila, alquiltio(hidroxi)alquila, cicloalquilalquila, cianoalquila, aminoalquilcarbonila opcionalmente substituído, heteroarila opcional-mente substituída, heteroarilalquila, hidroxialquiloxialquila, um grupo heterocíclico não aromático opcionalmente substituído, e alquila heterocíclico não aromático opcionalmente substituído;

alquila substituída com um grupo heterocíclico contendo nitrogênio não aromático, onde o grupo heterocíclico contendo nitrogênio não aromático é selecionado de pirrolidinila, piperidila, piperazinila, morfolinila, e tiomorfolinila, opcionalmente substituído com um substituinte selecionado do grupo D de substituintes que consiste em halogênio; arila; hidróxi; oxo; aminocarbonila opcionalmente substituída; alquiloxicarbonila; alquila opcionalmente substituída com um substituinte selecionado do grupo H de substituintes que consiste em aminocarbonila opcionalmente substituída, ciano, alquilóxi, alquilsulfonilamino, amino, carbóxi, alquiloxicarbonila, e hidróxi; alquilaminocarbonila; carbóxi; ciano, alquilsulfonila; alquilcarbonila; alquenilcarbonila; alquilsulfonilalquilcarbonila; alquiloxialquilcarbonila; alquilcarbonilamino; aminocarbonilóxi; um grupo heterocíclico contendo nitrogênio não aromático; e carbonila heterocíclico não aromático; ou

um grupo heterocíclico contendo nitrogênio não aromático, onde o grupo heterocíclico contendo nitrogênio não aromático é selecionado de azetidinila, pirrolidinila, e piperidila, opcionalmente substituído com um substituinte selecionado do grupo B de substituintes que consiste em alquiloxicarbonila, aminocarbonila opcionalmente substituída, oxo, amino, carbóxi, ciano, cianoalquila, hidroxialquila, alquilcarbonilamino, alquilsulfonilamino, e aminocarbonilalquila;

R^{22} é alquila opcionalmente substituída com um substituinte selecionado do grupo K de substituintes que consiste em amina opcionalmente substituída com alquila, hidróxi, alquilóxi, e halogênio; alquenila opcionalmente substituída com um substituinte selecionado do grupo K de substituintes, alquinila opcionalmente substituída com um substituinte selecionado do grupo K de substituintes; hidróxi; halogênio; fenila; piridila; furila; tienila; ou tiazolila;

um de R^{23} e R^{24} é um átomo de hidrogênio, e o outro é um átomo de hidrogênio, alquilóxi, alquiloxialquilóxi, halogênio, ou aminoalquila opcionalmente substituída com alquila;

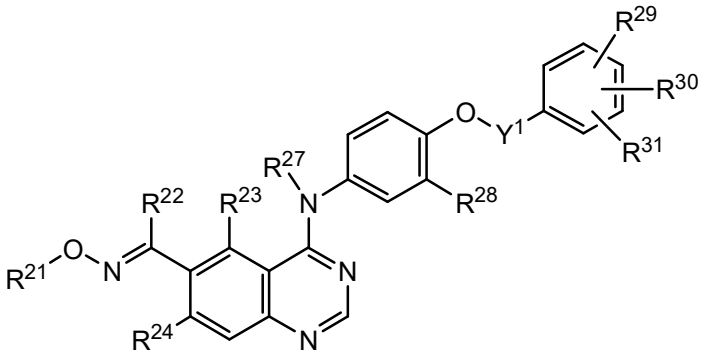
R^{27} é um átomo de hidrogênio, alquila, ou acila; e

R^{25} e R^{26} são cada um independentemente um átomo de hidrogênio, halogênio, alquinila, hidróxi, alquilóxi, alquenilóxi, alquinilóxi, ou heteroarilalquilóxi,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[0162] Um composto representado pela fórmula (I-B):

Fórmula química 40



(I-B)

onde R^{21}, R^{22}, R^{23}, R^{24} e R^{27} são como definidos acima;

Y^1 é C1-C3 alquileno;

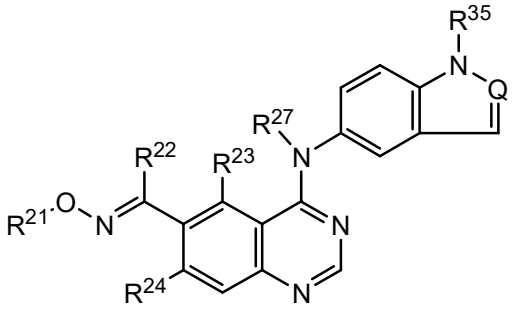
R^{28} é alquila, alquilóxi, alquinila, ou halogênio; e

R^{29}, R^{30}, e R^{31} são cada um independentemente um átomo de hidrogênio ou um substituinte selecionado do grupo F de substituintes que consiste em halogênio, carbóxi, alquila, haloalquila, hidroxialquila, alquilóxi, alquiloxicarbonila, e amina opcionalmente substituída,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[0163] Um composto representado pela fórmula (I-C):

Fórmula química 41



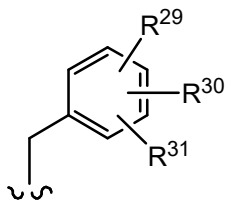
(I-C)

onde R^{21}, R^{22}, R^{23}, R^{24}, e R^{27} são como definidos acima;

R^{35} é alquila opcionalmente substituída com um substituinte selecionado do grupo L de substituintes que consiste em hidróxi, alquilóxi, halogênio, e ciano; alquenila opcionalmente substituída com um substituinte selecionado do grupo L de substituintes; alquinila opcionalmente substituída com um substituinte selecionado do grupo L de substituintes; ou

um grupo representado pela fórmula:

Fórmula química 42



onde

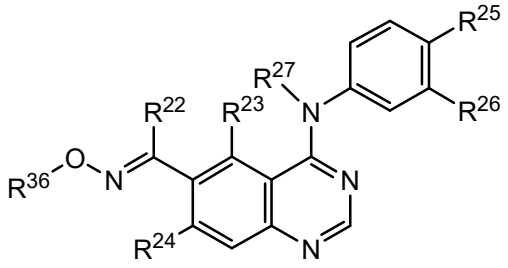
R^{29}, R^{30}, e R^{31} são como definidos acima;

Q é N ou CH_2,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[0164] Um composto representado pela fórmula (I-D):

Fórmula química 43



(I-D)

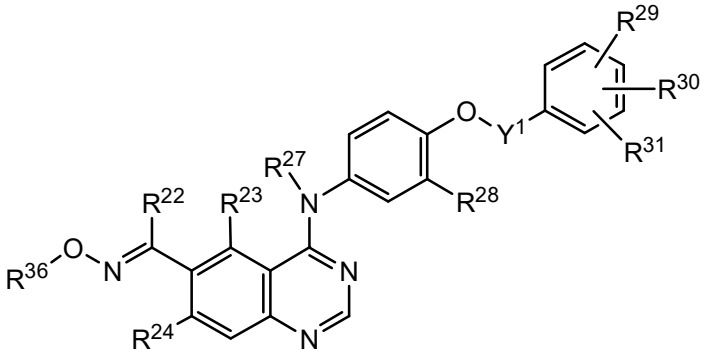
onde R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, e R^{27} são como definidos acima; e R^{36} é alquila substituída com aminocarbonila opcionalmente substituída com um substituinte selecionado do grupo C de substituintes ou

alquila substituída com carbonila heterocíclico não aromático, onde o heterociclo contendo nitrogênio não aromático é selecionado de pirrolidinila, piperidinila, piperazinila, morfolinila, e tiomorfolinila, opcionalmente substituído com um substituinte selecionado do grupo D de substituintes,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[0165] Um composto representado pela fórmula (I-E):

Fórmula química 44



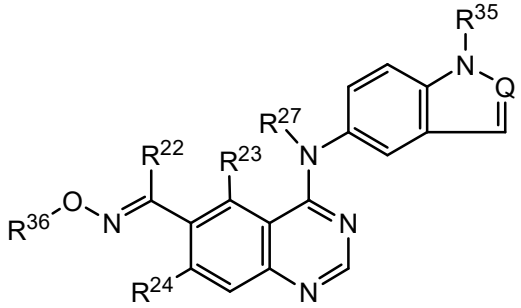
(I-E)

onde R^{21}, R^{22}, R^{23}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{36}, e Y^1 são como definidos acima,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[0166] Um composto representado pela fórmula (I-F):

Fórmula química 45

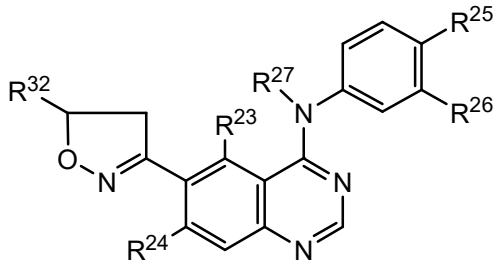


(I-F)

onde R^{22}, R^{23}, R^{24}, R^{27}, R^{36}, e Q são como definidos acima,
seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[0167] Um composto representado pela fórmula (I-G):

Fórmula química 46



(I-G)

onde

R^{23}, R^{24}, R^{25}, R^{26}, e R^{27} são como definidos acima;

R^{32} é alquila substituída com amina opcionalmente substituída com um substituinte selecionado do grupo C de substituintes,

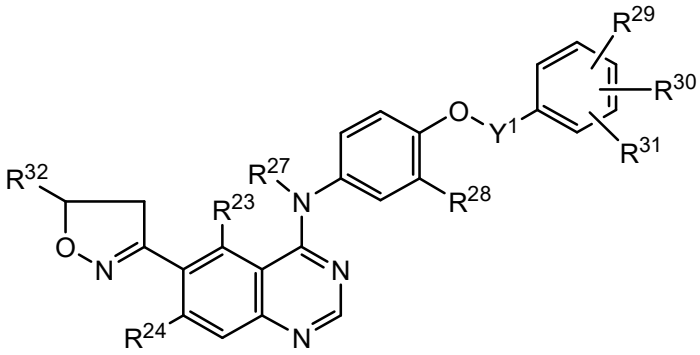
alquila substituída com um grupo heterocíclico contendo nitrogênio não aromático, onde o grupo heterocíclico contendo nitrogênio não aromático é selecionado de pirrolidinila, piperidila, piperazinila, morfolinila, e tiomorfolinila, opcionalmente substituído com um substituinte selecionado do grupo D de substituintes, ou

um grupo heterocíclico contendo nitrogênio não aromático, onde o grupo heterocíclico contendo nitrogênio não aromático é selecionado de azetidinila, pirrodilinila, e piperidila, opcionalmente substituído com um substituinte selecionado do grupo B de substituintes,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[0168] Um composto representado pela fórmula (I-H):

Fórmula química 47

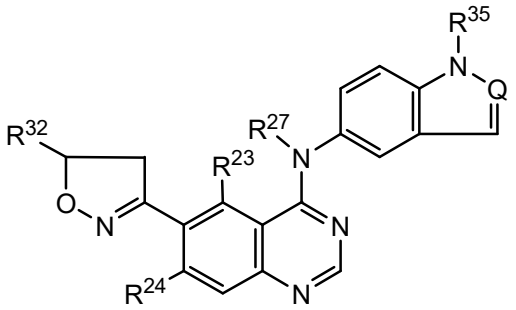


(I-H)

onde R^{23}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, e Y^1 são como definidos acima, seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[0169] Um composto representado pela fórmula (I-I):

Fórmula química 48

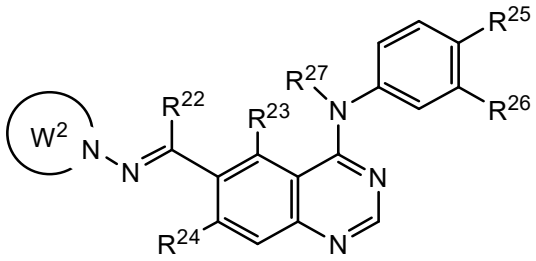


(I-I)

onde R^{23}, R^{24}, R^{27}, R^{32}, R^{35}, e Q são como definidos acima,
seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[0170] Um composto representado pela fórmula (I-J):

Fórmula química 49



(I-J)

onde

R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, e R^{27} são como definidos acima;

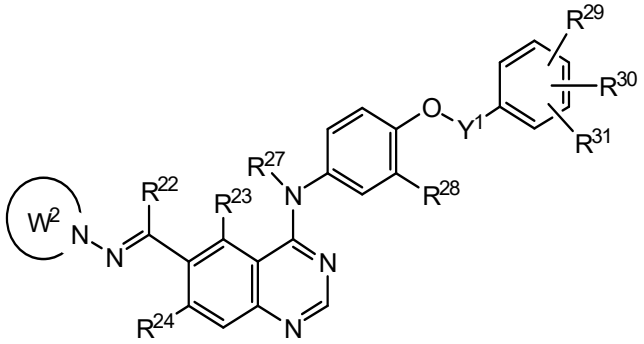
W^2 é pirrolidinila opcionalmente substituído com um

substituinte selecionado do grupo J de substituintes, piperidila opcionalmente substituído com um substituinte selecionado do grupo J de substituintes, piperazinila opcionalmente substituído com um substituinte selecionado do grupo J de substituintes, morfolinila opcionalmente substituído com um substituinte selecionado do grupo J de substituintes, ou triazolila opcionalmente substituído com um substituinte selecionado do grupo J de substituintes,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[0171] Um composto representado pela fórmula (I-K):

Fórmula química 50



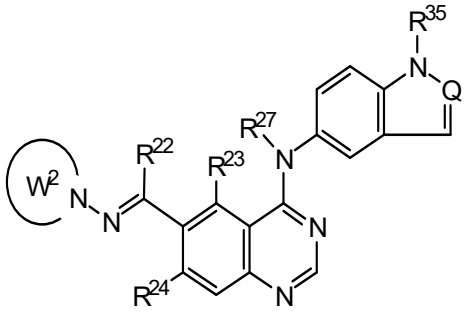
(I-K)

onde R^{22}, R^{23}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, Y^1, e W^2 são como definidos acima,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[0172] Um composto representado pela fórmula (I-L):

Fórmula química 51



(I-L)

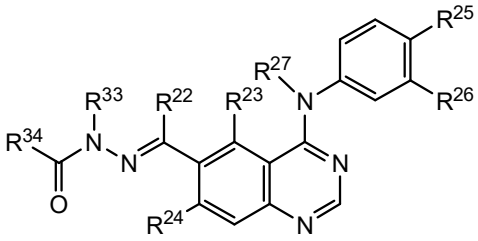
onde

R^{22}, R^{23}, R^{24}, R^{27}, R^{35}, W^2, e Q são como definidos acima,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[0173] Um composto representado pela fórmula (I-M):

Fórmula química 52



(I-M)

onde

R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, e R^{27} são como definidos acima;

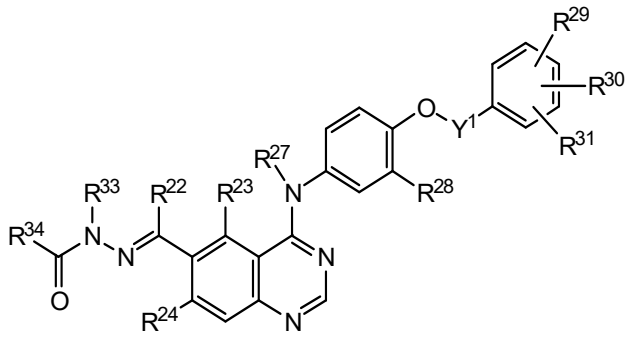
R^{33} é um átomo de hidrogênio, C1-C6 alquila opcionalmente substituída com um substituinte selecionado do grupo L de substituintes, C2-C6 alquenila opcionalmente substituída com um substituinte selecionado do grupo L de substituintes, ou C2-C6 alquinila opcionalmente substituída com um substituinte selecionado do grupo L de substituintes; e

R^{34} é alquila substituída com amina opcionalmente substituída com um substituinte selecionado do grupo C de substituintes, alquila substituída com um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído com um substituinte selecionado do grupo D de substituintes, arila opcionalmente substituída com um substituinte selecionado do grupo F de substituintes, heteroarila opcionalmente substituída com um substituinte selecionado do grupo F de substituintes, ou um grupo heterocíclico não aromático opcionalmente substituído com um substituinte selecionado do grupo F de substituintes,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[0174] Um composto representado pela fórmula (I-N):

Fórmula química 53



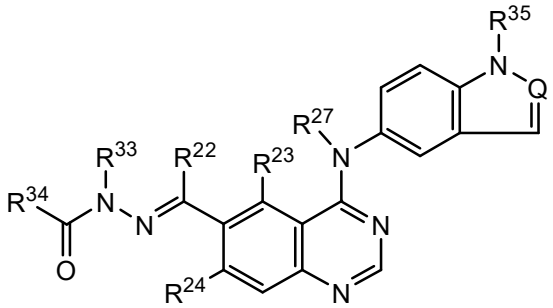
(I-N)

onde R^{22}, R^{23}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{33}, R^{34}, e Y^1 são como definidos acima,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[0175] Um composto representado pela fórmula (I-O):

Fórmula química 54



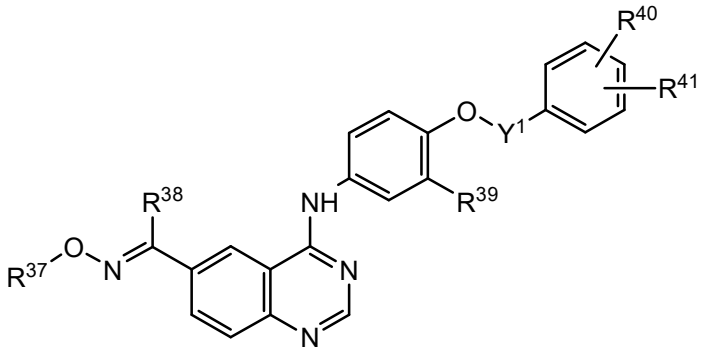
(I-O)

onde R^{22}, R^{23}, R^{24}, R^{27}, R^{34}, R^{35}, e Q são como definidos acima,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[0176] Um composto representado pela fórmula (I-P):

Fórmula química 55



(I-P)

onde

R^{37} é alquila substituída com amina opcionalmente substituída com alquila, hidroxialquila, alquilcarbonilaminoalquila ou um grupo heterocíclico não aromático;

alquila substituída com um grupo heterocíclico contendo nitrogênio não aromático opcionalmente substituído com alquila, hidroxialquila, ou alquilcarbonilamino; ou

um grupo heterocíclico contendo nitrogênio não aromático substituído com hidroxialquila;

R^{38} é C2-C4 alquinila;

R^{39} é halogênio;

R^{40} é um grupo representado pela fórmula: $-Y^3-R^{42}$ onde Y^3 é alquileno que pode ser interposto com -O-; R^{42} é fenila opcionalmente substituída com halogênio, ou piridila opcionalmente substituída com halogênio;

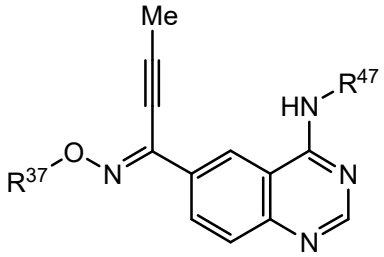
R^{41} é halogênio;

Y^1 é como definido acima,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[0177] Um composto representado pela fórmula (I-Q):

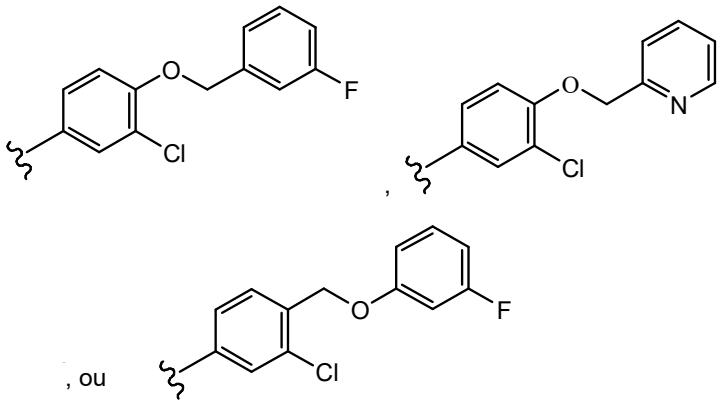
Fórmula química 56



(I-Q)

onde R^{47} é um grupo representado pela fórmula:

Fórmula química 57



, ou

R^{37} é como definido acima,

seu sal farmaceuticamente aceitável, ou um solvato do mesmo.

[0178] Como R^{22} nos compostos representados pela fórmula (I-A) até a fórmula (I-F) e na fórmula (I-J) até a fórmula (I-O), metila, etila, n-propila, isopropila, propinila, butinila, ou fenila é preferido.

[0179] Aqui, o "solvato" inclui, por exemplo, um solvato com um

solvente orgânico, um hidrato e outros. Quando se forma um solvato, o composto pode ser coordenado com um número arbitrário de moléculas de água.

[0180] Quando indicado o "presente composto", um sal farmaceuticamente aceitável, e um hidrato do mesmo também estão incluídos. Exemplos incluem sais de metais alcalinos (lítio, sódio, potássio etc.), ou metais alcalinos-terrosos (magnésio, cálcio etc.), e amônio, bases orgânicas e aminoácido, e sais com ácidos inorgânicos (ácido clorídrico, ácido bromídrico, ácido fosfórico, ácido sulfúrico etc.), ou ácidos orgânicos (ácido acético, ácido cítrico, ácido maléico, ácido fumárico, ácido benzenossulfônico, ácido p-toluenossulfônico etc.). Estes sais podem ser formados por métodos que são normalmente efetuados.

[0181] Além disso, o presente composto não está limitado a isômeros específicos, mas inclui todos os isômeros e racematos possíveis.

[0182] O presente composto, como descrito na seção Exemplos Experimentais descrita adiante, apresenta a excelente atividade inibitória da proliferação celular, e pode ser usado como uma composição farmacêutica útila para tratar câncer" e como um "produto terapêutico para um câncer".

[0183] Quando o presente composto é administrado a um ser humano com o propósito de tratar as doenças acima mencionadas, ele pode ser administrado por via oral como pós, grânulos, comprimidos, cápsulas, pílulas, soluções ou outros, ou podem ser administrados por via parenteral como injetáveis, supositórios, agentes absorventes transdérmicos, inalantes ou outros. E, uma quantidade eficaz do presente composto é misturada, se necessário, com aditivos farmacêuticos tais como excipientes, aglutinantes, agentes umectantes, agentes desintegradores, lubrificantes e outros que são adequados para

uma forma de dosagem, dessa forma, o presente composto pode ser formulado como preparações farmacêuticas. No caso de injetáveis, o presente composto junto com um veículo adequado é submetido a um tratamento de esterilização para obter preparações.

[0184] Uma dose é diferente dependendo da condição de uma doença, da via de administração, e da idade ou peso de um paciente, e geralmente varia de 0,1 a 100 mg/kg/dia, de preferência, 1 a 20 mg/kg/dia quando administrada por via oral a um adulto.

[0185] Os exemplos e exemplos de teste a seguir ilustram a presente invenção mais detalhadamente abaixo, mas a presente invenção não está limitada aos mesmos.

[0186] Nos exemplos, são usadas as seguintes abreviações.

Me: metila

Et: etila

nPr: n-propila

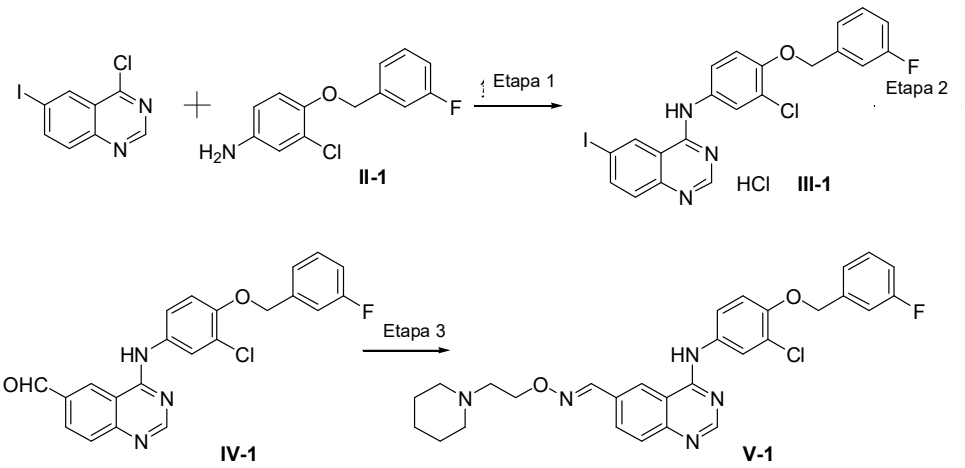
iPr: isopropila

Ph: fenila

Exemplos

Exemplo 1

Fórmula química 58



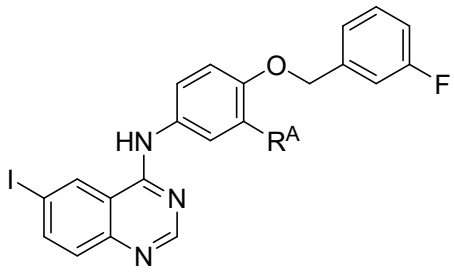
(Etapa 1) Síntese de cloridrato de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-iodoquinazolina (III-1)

[0187] Em 180 ml de tetrahidrofurano foram dissolvidos 4-cloro-6-iodoquinazolina (6,0 g) e 3-cloro-4-(3-fluorbenziloxi)anilina (II-1, 5,2 g), seguido de refluxo térmico por 3 horas. Um precipitado foi filtrado, e lavado com tetrahidrofurano para obter cloridrato de 4-(4-(3-fluorbenziloxi)fenilamino)-6-iodoquinazolina (III-1, 10,5 g) como um sólido amarelo.

^{1}H RMN (d_6-DMSO δ): 11,47 (1H, brs), 9,25 (1H, s), 8,94 (1H, s), 8,36 (1H, dd, J= 1,8 Hz, J= 8,7 Hz), 7,92 (1H, d, J= 2,7 Hz), 7,71 (1H, d, J= 8,7 Hz), 7,66 (1H, dd, J= 2,7 Hz, J= 8,7 Hz), 7,48 (1H, dt, J= 6,0 Hz, J= 7,8 Hz), 7,37-7,30 (3H, m), 7,19 (1H, dt, J= 2,7 Hz, J= 8,7 Hz), 5,30 (2H, s).

[0188] O composto a seguir foi sintetizado de acordo com o mesmo método usado para a primeira etapa acima.

Fórmula química 59



(III)

Tabela 1

Composto Nº	R^A	^{1}H-RMN (d_6-DMSO)
III-2	-F	9,86 (1H, s), 8,95 (1H, d, J=1,5Hz), 8,61 (1H, s), 8,11 (1H, dd, J=1,8Hz, J=8,7Hz), 7,89 (1H, J=2,4Hz, J=13,5Hz), 7,60-7,49 (2H, m), 7,45 (1H, dd, J=6,3Hz, J=8,1Hz), 7,36-7,23 (3H, m), 7,19 (1H, dt, J=8,4Hz, J=2,1Hz), 5,22 (2H, s),

Composto Nº	R^A	^{1}H-RMN (d_6-DMSO)
III-3	-OMe	11,26 (1H, brs), 9,18 (1H, s), 8,89 (1H, s), 8,34 (1H, dd, J=1,5Hz, J=8,7Hz), 7,66 (1H, d, J=8,7Hz), 7,46 (1H, dt, J=6,3Hz, J=8,1Hz), 7,39 (1H, d, J=2,1Hz), 7,34-7,25 (3H, m), 7,22-7,13 (1H, m), 7,13 (1H, d, J=8,7Hz), 5,17 (2H, s), 3,82 (3H, s),

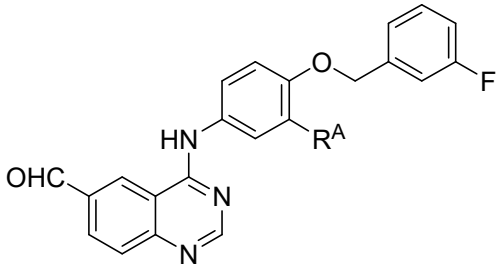
(Etapa 2) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-formilquinazolina (IV-1)

[0189] Em 100 ml de dimetilformamida foi dissolvido cloridrato de 4-(4-(3-fluorbenziloxi)fenilamino)-6-iodoquinazolina (III-1, 5,0 g), e 1,25 g de formiato de sódio, diclorobis(trifenilfosfina)paládio (324 mg), e trietilamina (3,2 ml) foram adicionados. A mistura reacional foi desgaseificada, e agitada sob aquecimento a 80°C por 3 horas em uma atmosfera de monóxido de carbono. Em seguida, a mistura reacional foi despejada em água gelada, e extraída com acetato de etila. O extrato foi lavado com água e solução de cloreto de sódio, e secado com sulfato de magnésio. A solução secada foi filtrada por Celite, concentrada, e pulverizada com acetato de etila-hexano (1:2) para obter 4-(4-(3-fluorbenziloxi)fenilamino)-6-formilquinazolina (IV-1, 2,86 g) como um sólido amarelo.

^{1}H RMN (d_6-DMSO δ): 10,24 (1H, s), 10,13 (1H, s), 9,16 (1H, s), 8,6 9(1H, s), 8,27 (1H, br d, J= 8,7 Hz), 8,03 (1H, d, J= 2,1 Hz), 7,90 (1H, d, J= 9,0 Hz), 7,74 (1H, dd, J= 2,7 Hz, J= 8,7 Hz), 7,48 (1H, dt, J= 6,0 Hz, J= 8,4 Hz), 7,36-7,30 (2H, m), 7,30 (1H, d, J= 8,7 Hz), 7,19 (1H, br t, J= 8,7 Hz), 5,27 (2H, s).

[0190] O composto a seguir foi sintetizado de acordo com o mesmo método usado para a segunda etapa acima.

Fórmula química 60



(IV)

Tabela 2

Composto Nº	R^A	^{1}H-RMN (d_6-DMSO)
IV-2	-F	10,24 (1H, s), 10,14 (1H, s), 9,16 (1H, s), 8,69 (1H, s), 8,26 (1H, dd, J=1,5Hz, J=8,7Hz), 7,94-7,85 (2H, m), 7,55 (1H, br d, J=9,0Hz), 7,47 (1H, dt, J=6,3Hz, J=8,1Hz), 7,36-7,26 (3H, m), 7,23-7,15 (1H, m), 5,23 (2H, s),
IV-3	-OMe	10,13 (2H, s), 9,18 (1H, s), 8,64 (1H, s), 8,25 (1H, dd, J=1,5Hz, J=8,7Hz), 7,88 (1H, d, J=8,4Hz), 7,52-7,38 (3H, m), 7,34-7,26 (2H, m), 7,22-7,12 (1H, m), 7,07 (1H, d, J=8,7Hz), 5,14 (2H, s), 3,83 (3H, s),

(Etapa 3) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(2-(1-piperidila)etoxiimino)quinazolina (V-1)

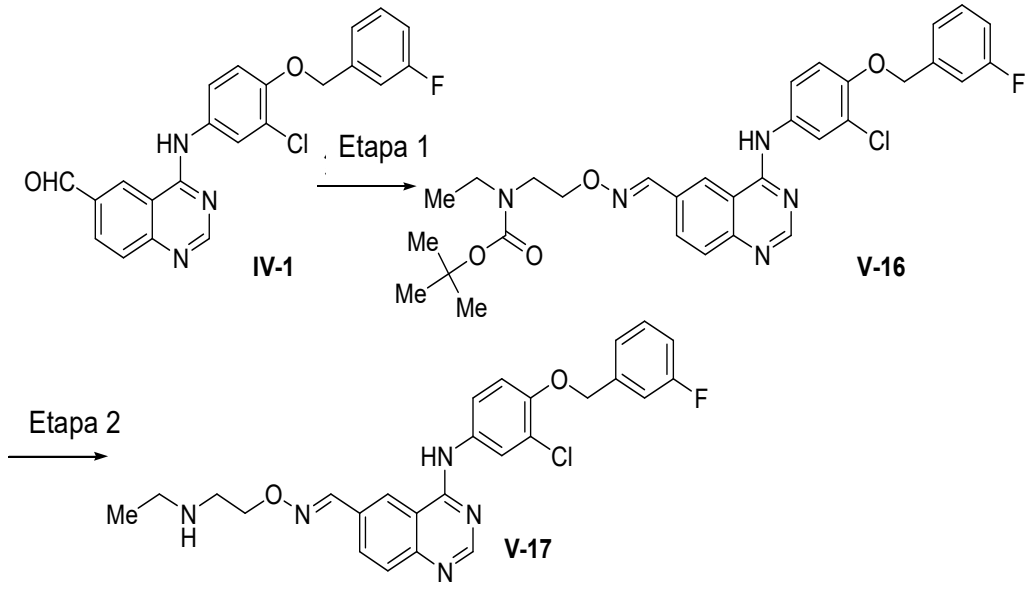
[0191] Em uma mistura de tetrahidrofurano (2 ml) e água (0,1 ml) foram dissolvidos 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-formilquinazolina (IV-1, 50 mg) e dicloridrato de 2-(1-piperidila)etoxiamina (36,5 mg), e a mistura foi agitada à temperatura ambiente por uma noite. A mistura reacional foi diluída com acetato de etila, lavada seqüencialmente com solução aquosa saturada de bicarbonato de sódio, e solução aquosa de cloreto de sódio, e secada em sulfato de magnésio. Depois de concentração, o resíduo foi purificado por cromatografia (eluindo com hexano: acetato de etila = 2:3)

usando uma coluna de amino, e ainda novamente purificado por cromatografia em camada fina para obter 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(2-(1-piperidila)etoxiimino)quinazolina (V-1, 13 mg).

^{1}H RMN (d_6-DMSO, δ): 9,95 (1H, s), 8,63 (1H, s), 8,59 (1H, s), 8,34 (1H, s), 8,10 (1H, d, J= 9,3 Hz), 8,00 (1H, d, J= 2,4 Hz), 7,79 (1H, d, J= 8,7Hz), 7,72 (1H, dd, J= 9,0 Hz, J= 2,1 Hz), 7,51-7,44 (1H, m), 7,36-7,31 (2H, m), 7,28 (1H, d, J= 9,0 Hz), 7,19 (1H, br t, J= 9,0 Hz), 5,26 (2H, s), 4,28 (2H, t, J= 6,0 Hz), 2,63 (2H, t, J= 6,0 Hz), 2,41 (4H, t, J= 4,8 Hz), 1,50 (4H, quin, J= 5,3 Hz), 1,45-1,35 (2H, m).

Exemplo 2

Fórmula química 61



(Etapa 1) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(2-(N-(t-butoxicarbonila)-N-etilamino)etiloxiimino)quinazolina (V-16)

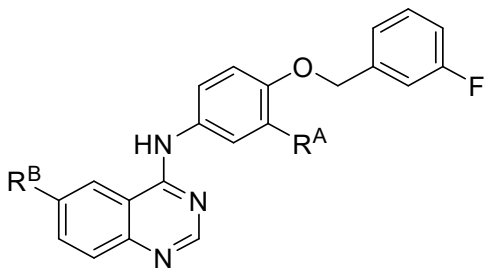
[0192] Em tetrahidrofurano (1,5 ml) foram dissolvidos 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-formilquinazolina (IV-1, 120 mg) e N-(t-butoxicarbonila)etilaminoetoxiamina (110 mg), e 134 μl de 2 mol/l de ácido clorídrico foram adicionados, e em seguida a mistura foi agitada à temperatura ambiente por 4 horas. Depois de completada a reação, a mistura reacional foi despejada em solução aquosa

saturada e gelada de bicarbonato de sódio, e extraída com acetato de etila. A camada orgânica foi lavada com água e solução aquosa de cloreto de sódio, secada em sulfato de magnésio, e concentrada. O resíduo resultante foi purificado por cromatografia de coluna de amino (eluindo com hexano: acetato de etila = 1:1), e ainda novamente purificado por cromatografia sobre sílica-gel (eluindo com hexano: acetato de etila = 1:1) para obter 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(2-(N-(t-butoxicarbonila)-N-etilamino)etiloxiimino)quinazolina (V-16, 96 mg) como um óleo viscoso amarelo.

^{1}H RMN (d_6-DMSO, δ): 9,93 (1H, s), 8,63 (1H, brs), 8,60 (1H, s), 8,34 (1H, s), 8,12 (1H, dd, J= 1,2 Hz, J= 9,0 Hz), 8,01 (1H, d, J= 2,4 Hz), 7,79 (1H, d, J= 8,4 Hz), 7,72 (1H, dd, J= 2,4 Hz, J= 8,4 Hz), 7,48 (1H, dt, J= 6,0 Hz, J= 8,1 Hz), 7,36-7,30 (2H, m), 7,28 (1H, d, J= 9,0 Hz), 7,23-7,14 (1H, m), 5,26 (2H, s), 4,26 (2H, t, J= 5,7 Hz), 3,50 (2H, t, J= 6,3 Hz), 3,23 (2H, q, J= 6,9 Hz), 1,38 (9H, s), 1,12-1,00 (3H, m).

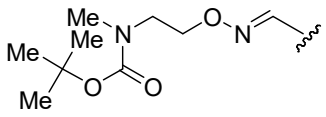
[0193] O composto a seguir foi sintetizado da mesma maneira que para a primeira etapa acima.

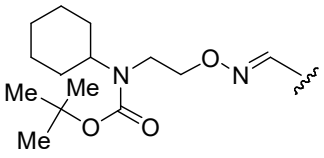
Fórmula química 62

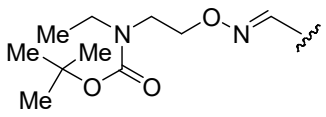
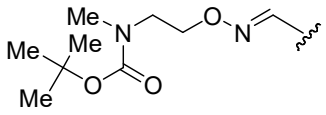


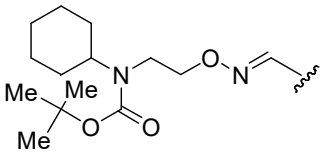
(V)

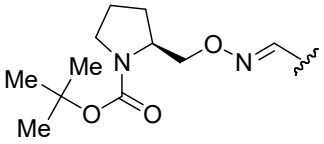
Tabela 3

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-18	Cl		9,92 (1H, s), 8,62 (1H, s), 8,60 (1H, s), 8,34 (1H, s), 8,12 (1H, d, J=8,4Hz), 8,00 (1H, d, J=2,4Hz), 7,79 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=2,4Hz, J=8,7Hz), 7,47 (1H, dt, J=6,0Hz, J=7,8Hz), 7,36-7,30 (2H, m), 7,28 (1H, d, J=9,0Hz), 7,23-7,14 (1H, m), 5,26 (2H, s), 4,28 (2H, t, J=5,7Hz), 3,57-3,48 (2H, m), 2,84 (3H, brs), 1,36 (9H, s),

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-19	Cl		9,92 (1H, s), 8,63 (1H, s), 8,60 (1H, s), 8,33 (1H, s), 8,12 (1H, dd, J=1,5Hz, J=9,0Hz), 8,01 (1H, d, J=2,4Hz), 7,80 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=2,7Hz, J=9,0Hz), 7,47 (1H, dt, J=6,0Hz, J=7,8Hz), 7,36-7,30 (2H, m), 7,28 (1H, d, J=9,0Hz), 7,22-7,14 (1H, m), 5,26 (2H, s), 4,21 (2H, t, J=6,0Hz), 3,8-3,5 (1H, brs), 3,48-3,37 (2H, m), 1,8-1,4 (6H, m), 1,35-1,0 (4H, m),

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-20	OMe		9,83 (1H, s), 8,64 (1H, s), 8,57 (1H, s), 8,34 (1H, s), 8,12 (1H, dd, J=1,5Hz, J=8,7Hz), 7,78 (1H, d, J=8,7Hz), 7,50-7,36 (3H, m), 7,34-7,26 (2H, m), 7,21-7,13 (1H, m), 7,06 (1H, d, J=8,7Hz), 5,13 (2H, s), 4,26 (2H, t, J=5,7Hz), 3,82 (3H, s), 3,50 (2H, t, J=5,7Hz), 3,23 (2H, q, J=7,2Hz), 1,38 (9H, s), 1,12-1,02 (3H, m),
V-21	OMe		9,84 (1H, s), 8,63 (1H, s), 8,56 (1H, s), 8,36 (1H, s), 8,12 (1H, dd, J=1,5Hz, J=8,7Hz), 7,77 (1H, d, J=8,7Hz), 7,50-7,35 (3H, m), 7,33-7,25 (2H, m), 7,20-7,12 (1H, m), 7,05 (1H, d, J=8,7Hz), 5,13 (2H, s), 4,27 (2H, t, J=5,7Hz), 3,82 (3H, s), 3,55-3,47 (2H, m), 2,84 (3H, brs), 1,36 (9H, s),

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-22	OMe		9,82 (1H, s), 8,64 (1H, s), 8,56 (1H, s), 8,33 (1H, s), 8,11 (1H, dd, J=1,5Hz, J=8,7Hz), 7,78 (1H, d, J=8,7Hz), 7,50-7,36 (3H, m), 7,33-7,26 (2H, m), 7,21-7,12 (1H, m), 7,05 (1H, d, J=8,7Hz), 5,13 (2H, s), 4,21 (2H, t, J=6,6Hz), 3,82 (3H, s), 3,8-3,5 (1H, m), 3,47-3,35 (2H, m), 1,8-1,35 (6H, m), 1,41 (9H, s), 1,35-0,95 (4H, m),

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-28	Cl		9,91 (1H, s), 8,62 (1H, brs), 8,60 (1H, s), 8,36 (1H, s), 8,10 (1H, dd, J=8,7Hz), 8,01 (1H, brs), 7,79 (1H, d, J=8,4Hz), 7,73 (1H, d, J=8,1Hz), 7,52-7,44 (1H, m), 7,35-7,27 (3H, m), 7,19 (1H, dt, J=8,1Hz, J=2,4Hz), 5,26 (2H, s), 4,28 (1H, brs), 4,17 (1H, dd, J=10,5Hz, J=6,9Hz), 4,00 (1H, brs), 3,25 (3H, br), 1,92 (3H, br), 1,80 (1H, br), 1,43 (9H, s)

(Etapa 2) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(2-(N-etilamino)etiloxiimino)quinazolina (V-17)

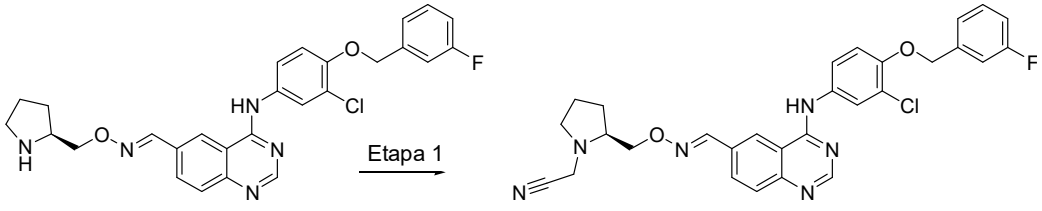
[0194] Em clorofórmio (1,8 ml) foi dissolvida 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(2-(N-(t-butoxicarbonila)-N-etilamino)etiloxiimino)quinazolina (V-16, 54 mg), e ácido trifluoracético (1,8 ml) foi adicionado, seguido de agitação à temperatura ambiente por 1 hora. Depois de completada a reação, a mistura reacional foi concentrada, e diluída com acetato de etila. A mistura foi seqüencialmente lavada com solução aquosa saturada de bicarbonato de sódio, água, e solução aquosa de cloreto de sódio, e secada em sulfato de magnésio. Depois de concentração, o resíduo cristalino foi lavado com uma mistura de diclorometano-hexano (1:4) para obter 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(2-(N-

etilamino)etiloxiimino)quinazolina (V-17, 28 mg) como um sólido branco.

^{1}H RMN (d_6-DMSO, δ): 9,96 (1H, s), 8,65 (1H, brs), 8,60 (1H, s), 8,35 (1H, s), 8,11 (1H, d, J= 9,0 Hz), 8,01 (1H, d, J= 3,0 Hz), 7,80 (1H, d, J= 9,0 Hz), 7,75-7,70 (1H, m), 7,52-7,43 (1H, m), 7,36-7,31 (2H, m), 7,28 (1H, d, J= 9,3 Hz), 7,23-7,14 (1H, m), 5,26 (2H, s), 4,26 (2H, t, J= 6,0 Hz), 2,93 (2H, t, J= 6,0 Hz), 2,66 (2H, q, J= 7,2 Hz), 1,05 (3H, t, J= 7,2 Hz).

Exemplo 3

Fórmula química 63



V-29 V-30

(Etapa 1) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-(N-cianometilpirrolidin-2-il)metoxiimino)metilquinazolina (V-30)

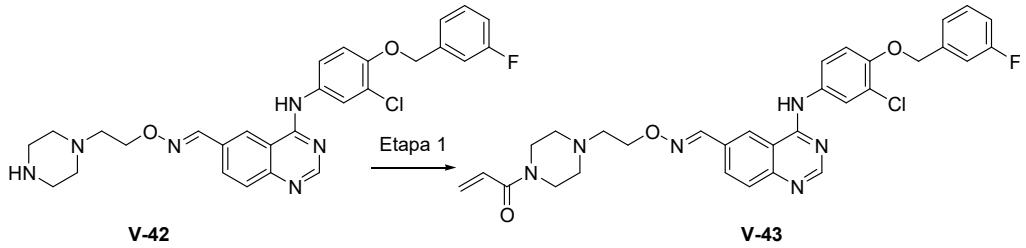
[0195] Em 0,4 ml de N, N-dimetilacetamida foram dissolvidos 40 mg de composto V-29 e 8 μl de iodoacetonitrila, e 15 mg de carbonato de potássio foram adicionados, seguidos de agitação à temperatura ambiente por 1 hora. Depois da reação, solução aquosa saturada de cloreto de sódio foi adicionada, seguida de extração com acetato de etila. A camada orgânica foi desidratada sendo passada por um Presep (marca registrada), e o filtrado foi concentrado. O resíduo concentrado foi purificado por cromatografia sobre sílica-gel (eluindo com hexano: acetato de etila = 2:1) para obter 35 mg de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-(N-cianometilpirrolidin-2-il)metoxiimino)metilquinazolina (V-30).

^{1}H RMN (d_6-DMSO, δ): 9,92 (1H, s), 8,62 (1H, d, J= 1,5 Hz), 8,58 (1H, s), 8,36 (1H, s), 8,09 (1H, dd, J= 8,7 Hz, J= 1,5 Hz), 7,99 (1H, d, J= 2,6 Hz), 7,78 (1H, d, J= 8,7 Hz), 7,71 (1H, dd, J= 9,0 Hz, J= 2,6 Hz), 7,49-7,42 (1H, m), 7,33-7,25 (3H, m), 7,16 (1H, dt, J= 8,1 Hz, J=

1,8 Hz), 5,24 (2H, s), 4,17 (2H, d, J= 5,7 Hz), 3,97 (1H, d, J= 17 Hz), 3,90 (1H, d, J= 17 Hz), 3,00-2,89 (2H, m), 2,01-1,89 (1H, m), 1,78-1,54 (3H, m).

Exemplo 4

Fórmula química 64



V-42 V-43

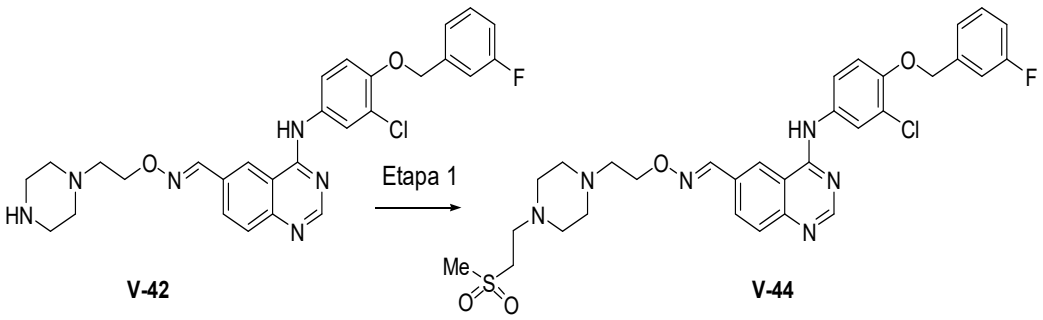
(Etapa 1) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(2-(4-acriloila-1-piperazin-1-ila)etoxiimino)metilquinazolina (V-43)

[0196] Em 1,5 ml de tetrahidrofurano foram dissolvidos 40 mg de composto V-42 e 6 μl de cloreto de acriloíla, seguido de agitação à temperatura ambiente por 2 horas. Depois da reação, solução aquosa saturada de cloreto de sódio foi adicionada, seguida de extração com acetato de etila. A camada orgânica foi desidratada sendo passada por CHEM ELUT (nome comercial), e o filtrado foi concentrado. O resíduo concentrado foi purificado por cromatografia (eluindo com acetato de etila contendo 1% metanol), e o resíduo resultante foi solidificado com hexano-acetato de etila (6:1) para obter 20 mg de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(2-(4-acriloila-1-piperazin-1-ila)etoxiimino)metilquinazolina (V-43).

^{1}H RMN (d_6-DMSO, δ): 9,95 (1H, s), 8,64 (1H, s), 8,59 (1H, s), 8,35 (1H, s), 8,10 (1H, d, J= 8,7 Hz), 8,00 (1H, d, J= 2,4 Hz), 7,78 (1H, d, J= 8,7 Hz), 7,72 (1H, dd, J= 9,0 Hz, 2,7 Hz), 7,44-7,51 (1H, m), 7,26-7,35 (3H, m), 7,15-7,22 (1H, m), 6,79 (1H, dd, J= 16,5 Hz, 10,2 Hz), 6,10 (1H, dd, J= 16,5 Hz, 2,4 Hz), 6,17 (1H, dd, J= 10,5 Hz, 2,4 Hz), 5,26 (2H, s), 4,32 (2H, t, J= 5,7 Hz), 3,55 (4H, m), 2,72 (2H, t, J= 5,7 Hz), 2,50 (4H, m)

Exemplo 5

Fórmula química 65



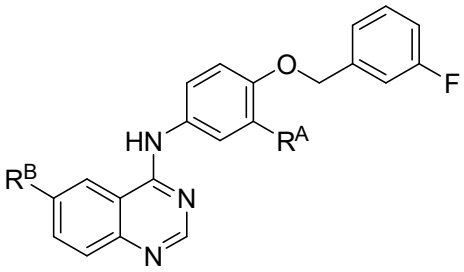
(Etapa 1) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(2-(4-(2-metanosulfoniletila)-1-piperazin-1-ila)etoxiimino)metilquinazolina (V-44)

[0197] Em 1 ml de tetrahidrofurano foram dissolvidos 25 mg de composto V-42 e 4 μl de metilvinilsulfona, seguido de agitação à temperatura ambiente por 21 horas. Além disso, 4 μl de metilvinilsulfona foram adicionados, seguidos de agitação à temperatura ambiente por 29 horas. Depois da reação, solução aquosa saturada de cloreto de sódio foi adicionada, seguida de extração com acetato de etila. A camada orgânica foi lavada seqüencialmente com água, e solução aquosa saturada de cloreto de sódio, e secada em sulfato de magnésio. O resíduo concentrado foi purificado por cromatografia (eluindo com acetato de etila) usando uma coluna de amina, e o resíduo resultante foi solidificado com hexano-acetato de etila (6:1) para obter 15 mg de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(2-(4-(2-metanosulfoniletila)-1-piperazin-1-ila)etoxiimino)metilquinazolina (V-44).

^{1}H RMN (d_6-DMSO, δ): 9,95(1H, s), 8,63(1H, s), 8,59(1H, s), 8,34(1H, s), 8,10(1H, d, J= 9,6 Hz), 8,00 (1H, d, J= 2,4 Hz), 7,79 (1H, d, J= 8,4 Hz), 7,71 (1H, dd, J= 8,7 Hz, 2,7 Hz), 7,44-7,51 (1H, m), 7,26-7,34 (3H, m), 7,15-7,22 (1H, m), 5,26 (2H, s), 4,29 (2H, t, J= 6,0 Hz), 3,27 (2H, t, J= 6,6 Hz), 3,02 (3H, s), 2,67-2,70 (4H, m), 2,46 (8H, m)

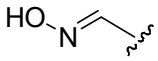
[0198] O composto a seguir foi sintetizado de acordo com os mesmos métodos usados nos exemplos 1 a 5.

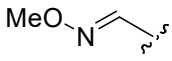
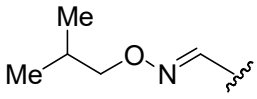
Fórmula química 66

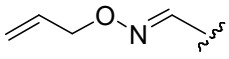


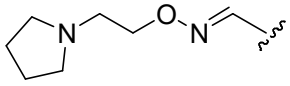
(V)

Tabela 4

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-2	Cl		11,69 (1H,s), 11,11 (1H, brs), 8,84 (1H, s), 8,83 (1H, s), 8,29 (1H, s), 8,26 (1H, d, J=8,7Hz), 7,95 (1H, d, J=2,7Hz), 7,88 (1H, d, J=8,7Hz), 7,67 (1H, dd, J=2,3Hz, J=9,2Hz), 7,48 (1H, dt, J=6,0Hz, J=7,8Hz), 7,37-7,29 (3H, m), 7,20 (1H, br t, J=9,2Hz), 5,30 (2H, s),

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-3	Cl		9,96 (1H, s), 8,65 (1H, s), 8,60 (1H, s), 8,34 (1H, s), 8,10 (1H, br d, J=8,7Hz), 8,01 (1H, d, J=2,4Hz), 7,79 (1H, d, J=8,4Hz), 7,73 (1H, dd, J=2,7Hz, J=9,0Hz), 7,48 (1H, dt, J=6,0Hz, J=8,1Hz), 7,36-7,31 (2H, m), 7,28 (1H, d, J=9,0Hz), 7,19 (1H, br t, J=8,7Hz), 5,26 (2H, s), 3,98 (3H, s),
V-4	Cl		9,95 (1H, s), 8,63 (1H, s), 8,60 (1H, s), 8,36 (1H, s), 8,10 (1H, dd, J=8,7Hz, J=1,2Hz), 8,01 (1H, d, J=2,4Hz), 7,79 (1H, d, J=8,4Hz), 7,72 (1H, dd, J=2,6Hz, J=8,9Hz), 7,48 (1H, dt, J=6,0Hz, J=8,1Hz), 7,36-7,29 (2H, m), 7,28 (1H, d, J=9,0Hz), 7,19 (1H, dt, J=2,4Hz, J=8,6Hz), 5,27 (2H, s), 3,97 (2H, d, J=6,9Hz), 2,05 (1H, m), 0,95 (6H, d, J=6,9Hz),

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-5	Cl		9,96 (1H, s), 8,64 (1H, s), 8,60 (1H, s), 8,39 (1H, s), 8,11 (1H, dd, J=1,5Hz, J=8,7Hz), 8,01 (1H, d, J=2,7Hz), 7,79 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=2,7Hz, J=9,0Hz), 7,48 (1H, dt, J=6,3Hz, J=7,8Hz), 7,36-7,29 (2H, m), 7,28 (1H, d, J=9,0Hz), 7,19 (1H, dt, J=2,2Hz, J=8,6Hz), 6,08 (1H, ddt, J=17,4Hz, J=10,5Hz, J=5,7Hz), 5,38 (1H, ddd, J=17,4Hz, J=3,6Hz, J=1,8Hz), 5,30-5,24 (1H, m), 5,26 (2H, s), 4,72 (2H, dt, J=5,7Hz, J=1,5Hz),

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-6	Cl		9,95 (1H, s), 8,64 (1H, s), 8,60 (1H, s), 8,35 (1H, s), 8,11 (1H, br d, J=8,7Hz), 8,00 (1H, d, J=2,7Hz), 7,79 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=2,7Hz, J=9,0Hz), 7,51-7,44 (1H, m), 7,36-7,31 (2H, m), 7,28 (1H, d, J=9,3Hz), 7,19 (1H, br t, J=8,4Hz), 5,26 (2H, s), 4,29 (2H, t, J=6,3Hz), 2,810 (2H, t, J=4,8Hz), 2,6-2,5 (4H, m), 1,75-1,65 (4H, m),

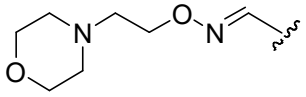
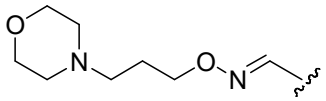
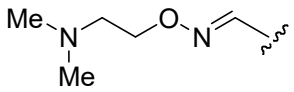
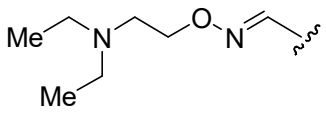
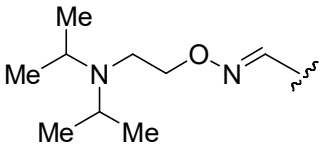
Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-7	Cl		9,95 (1H, s), 8,64 (1H, s), 8,60 (1H, s), 8,35 (1H, s), 8,11 (1H, dd, J=8,7Hz, J=1,5Hz), 8,01 (1H, d, J=2,7Hz), 7,80 (1H, d, J=9,0Hz), 7,72 (1H, dd, J=9,0Hz, J=2,7Hz), 7,48 (1H, dt, J=6,0Hz, J=8,1Hz), 7,36-7,31 (2H, m), 7,28 (1H, d, J=9,3Hz), 7,19 (1H, br t J=9,0Hz), 5,27 (2H, s), 4,31 (2H, t, J=5,7Hz), 3,58 (4H, t, J=5,1Hz), 2,67 (2H, t, J=5,7Hz), 2,46 (4H, t, J=4,5Hz),

Tabela 5

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-8	-Cl		9,94 (1H, s), 8,63 (1H, s), 8,59 (1H, s), 8,33 (1H, s), 8,10 (1H, br d, J=7,2Hz), 8,00 (1H, d, J=2,4Hz), 7,78 (1H, d, J=8,7Hz), 7,71 (1H, dd, J=8,7Hz, J=2,1Hz), 7,47 (1H, dt, J=6,3Hz, J=8,1Hz), 7,36-7,31 (2H, m), 7,28 (1H, d, J=9,0Hz), 7,18 (1H, br t, J=9,0Hz), 5,26 (2H, s), 4,23 (2H, t, J=6,3Hz), 3,57 (4H, t, J=4,5Hz), 2,45-2,35 (6H, m), 1,87 (2H, quin, J=6,8Hz),

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-9	-Cl		9,95 (1H, s), 8,63 (1H, s), 8,60 (1H, s), 8,34 (1H, s), 8,11 (1H, dd, J=8,7Hz, J=1,5Hz), 8,00 (1H, d, J=2,7Hz), 7,79 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=8,7Hz, J=2,7Hz), 7,48 (1H, dt, J=6,0Hz, J=8,1Hz), 7,36-7,31 (2H, m), 7,28 (1H, d, J=9,0Hz), 7,18 (1H, dt, J=2,4Hz, J=8,4Hz), 5,26 (2H, s), 4,28 (2H, t, J=5,7Hz), 2,63 (2H, t, J=5,7Hz), 2,23 (6H, s),

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-10	-Cl		9,93 (1H, s), 8,63 (1H, s), 8,60 (1H, s), 8,33 (1H, s), 8,11 (1H, dd, J=8,7Hz, J=1,5Hz), 8,01 (1H, d, J=2,4Hz), 7,79 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=2,7Hz, J=8,7Hz), 7,47 (1H, dt, J=5,7Hz, J=8,1Hz), 7,36-7,31 (2H, m), 7,28 (1H, d, J=9,3Hz), 7,18 (1H, dt, J=8,7Hz, J=2,7Hz), 5,26 (2H, s), 4,25 (2H, t, J=6,2Hz), 2,79 (2H, brs), 2,57 (4H, q, J=6,6Hz), 0,99 (6H, t, J=7,1Hz),

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-11	-Cl		9,91 (1H, s), 8,61 (1H, d, J=1,5Hz), 8,60 (1H, s), 8,31 (1H, s), 8,12 (1H, dd, J=1,5Hz, J=8,7Hz), 8,01 (1H, d, J=2,4Hz), 7,79 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=2,4Hz, J=8,7Hz), 7,47 (1H, dt, J=5,7Hz, J=8,1Hz), 7,36-7,31 (2H, m), 7,28 (1H, d, J=9,3Hz), 7,18 (1H, dt, J=8,7Hz, J=2,7Hz), 5,26 (2H, s), 4,10 (2H, t, J=6,9Hz), 3,01 (2H, quin, J=6,3Hz), 2,74 (2H, t, J=6,9Hz), 1,99 (12H, d, 6,3Hz),

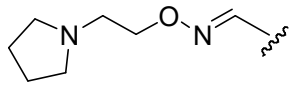
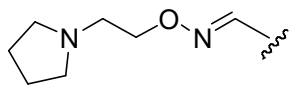
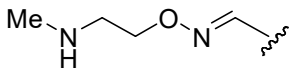
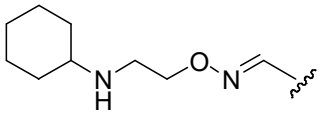
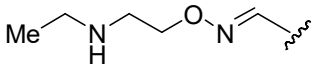
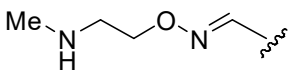
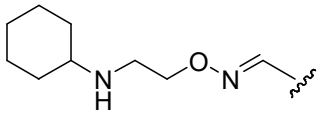
Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-12	-F		9,94 (1H, s), 8,64 (1H, s), 8,60 (1H, s), 8,34 (1H, s), 8,11 (1H, d, J=8,8Hz), 7,88 (1H, d, J=13,2Hz), 7,79 (1H, d, J=8,8Hz), 7,56-7,44 (2H, m), 7,36-7,24 (3H, m), 7,19 (1H, br t, J=8,8Hz), 5,18 (2H, s), 4,32-4,27 (2H, m), 2,82-2,74 (2H, m), 2,55-2,48 (4H, m), 1,73-1,65 (4H, m),
V-13	-OMe		9,84 (1H, s), 8,64 (1H, d, J=1,5Hz), 8,55 (1H, s), 8,34 (1H, s), 8,09 (1H, dd, J=1,5Hz, J=8,7Hz), 7,77 (1H, d, J=8,7Hz), 7,49-7,36 (3H, m), 7,33-7,26 (2H, m), 7,20-7,12 (1H, m), 7,05 (1H, d, J=9,0Hz), 5,13 (2H, s), 4,28 (2H, t, J=6,0Hz), 3,82 (3H, s), 2,76 (2H, t, J=6,0Hz), 2,54-2,46 (4H, m), 1,76-1,62 (4H, m),

Tabela 6

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-23	Cl		9,96 (1H, s), 8,64 (1H, s), 8,60 (1H, s), 8,34 (1H, s), 8,11 (1H, dd, J=1,2Hz, J=8,4Hz), 8,01 (1H, d, J=2,4Hz), 7,79 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=2,4Hz, J=8,7Hz), 7,48 (1H, dt, J=6,0Hz, J=8,4Hz), 7,36-7,30 (2H, m), 7,28 (1H, d, J=9,0Hz), 7,23-7,15 (1H, m), 5,27 (2H, s), 4,24 (2H, t, J=5,7Hz), 2,81 (2H, t, J=5,7Hz), 2,33 (3H, s),

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-24	Cl		9,95 (1H, s), 8,65 (1H, d, J=1,2Hz), 8,60 (1H, s), 8,35 (1H, s), 8,11 (1H, dd, J=1,5Hz, J=8,7Hz), 8,01 (1H, d, J=2,7Hz), 7,79 (1H, d, J=8,7Hz), 7,73 (1H, dd, J=2,7Hz, J=9,0Hz), 7,47 (1H, dt, J=6,0Hz, J=8,1Hz), 7,36-7,30 (2H, m), 7,28 (1H, d, J=9,0Hz), 7,23-7,14 (1H, m), 5,26 (2H, s), 4,25 (2H, t, J=5,7Hz), 2,95 (2H, t, J=5,7Hz), 2,55-2,4 (1H, m), 1,9-1,8 (2H, m), 1,75-1,62 (2H, m), 1,6-1,5 (1H, m), 1,3-0,97 (5H, m),

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-25	OMe		9,86 (1H, s), 8,64 (1H, s), 8,56 (1H, s), 8,34 (1H, s), 8,10 (1H, d, J=8,4Hz), 7,77 (1H, d, J=8,7Hz), 7,5-7,35 (3H, m), 7,34-7,26 (2H, m), 7,21-7,13 (1H, m), 7,06 (1H, d, J=8,7Hz), 5,13 (2H, s), 4,23 (2H, t, J=6,0Hz), 3,82 (3H, s), 2,86 (2H, t, J=6,0Hz), 2,59 (2H, q, J=7,2Hz), 1,02 (3H, t, J=7,2Hz),
V-26	OMe		9,86 (1H, s), 8,64 (1H, s), 8,56 (1H, s), 8,33 (1H, s), 8,10 (1H, d, J=8,7Hz), 7,77 (1H, d, J=9,0Hz), 7,50-7,35 (3H, m), 7,33-7,26 (2H, m), 7,21-7,13 (1H, m), 7,05 (1H, d, J=8,4Hz), 5,13 (2H, s), 4,23 (2H, t, J=5,7Hz), 3,82 (3H, s), 2,81 (2H, d, J=6,0Hz), 2,33 (3H, s),

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-27	Ome		9,86 (1H, s), 8,64 (1H, s), 8,56 (1H, s), 8,34 (1H, s), 8,09 (1H, dd, J=1,5Hz, J=8,7Hz), 7,77 (1H, d, J=8,7Hz), 7,50-7,35 (3H, m), 7,33-7,26 (2H, m), 7,21-7,13 (1H, m), 7,05 (1H, d, J=8,7Hz), 5,13 (2H, s), 4,22 (2H, t, J=5,7Hz), 3,82 (3H, s), 2,88 (2H, t, J=5,7Hz), 2,45-2,35 (1H, m), 1,88-1,76 (2H, m), 1,72-1,62 (2H, m), 1,6-1,5 (2H, m), 1,3-0,93 (4H, m),

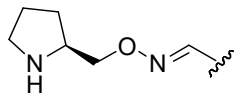
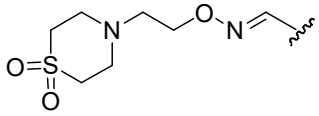
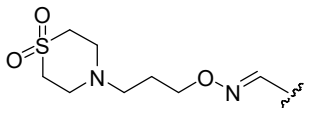
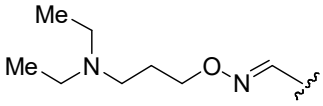
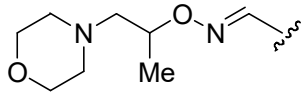
Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-29	Cl		9,94 (1H, s), 8,65 (1H, brs), 8,60 (1H, s), 8,35 (1H, s), 8,11 (1H, dd, J=8,7Hz, J=1,2Hz), 8,00 (1H, d, J=2,4Hz), 7,79 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=9,0Hz, J=2,1Hz), 7,51-7,44 (1H, m), 7,35-7,27 (3H, m), 7,18 (1H, dt, J=8,1Hz, J=1,5Hz), 5,26 (2H, s), 4,12 (2H, d, J=6,3Hz), 3,53-3,44 (1H, m), 2,96-2,82 (2H, m), 1,94-1,64 (3H, m), 1,53-1,41 (1H, m)

Tabela 7

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-30	-Cl		9,95 (1H, s), 8,64 (1H, s), 8,59 (1H, s), 8,35 (1H, s), 8,11 (1H, d, J=8,7Hz), 8,00 (1H, d, J=2,4Hz), 7,79 (1H, d, J=8,7Hz), 7,71 (1H, dd, J=8,4Hz, J=1,8Hz), 7,44-7,51 (1H, m), 7,26-7,35 (3H, m), 7,15-7,22 (1H, m), 5,26 (2H, s), 4,31 (2H, t, J=5,7Hz), 3,08-3,10 (4H, m), 3,02-3,04 (4H, m), 2,91 (2H, t, J=5,7Hz)

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-31	-Cl		9,95 (1H, s), 8,63 (1H, s), 8,60 (1H, s), 8,34 (1H, s), 8,11 (1H, d, J=9,3Hz), 8,00 (1H, d, J=2,7Hz), 7,79 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=9,0 Hz, J=2,4Hz), 7,51-7,44 (1H, m), 7,35-7,27 (3H, m), 7,22-7,15 (1H, m), 5,26 (2H, s), 4,23 (2H, t, J=6,3Hz), 3,09-3,07 (4H, m), 2,92-2,90 (4H, m), 2,59 (2H, t, J=6,9Hz), 1,90-1,85 (2H, m)
V-32	-Cl		9,94 (1H, s), 8,64 (1H, s), 8,59 (1H, s), 8,33 (1H, s), 8,10 (1H, d, J=8,7Hz), 8,00 (1H, d, J=2,7Hz), 7,79 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=8,7Hz, 2,4Hz), 7,44-7,51 (1H, m), 7,26-7,35 (3H, m), 7,15-7,22 (1H, m), 5,26 (2H, s), 4,22 (2H, t, J=6,3Hz), 2,49-2,51 (6H, m), 1,78-1,83 (2H, m), 0,95 (6H, t, J=7,2Hz)

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-33	-Cl		9,94 (1H, s), 8,61 (1H, s), 8,59 (1H, s), 8,31 (1H, s), 8,11 (1H, dd, J=8,4Hz,1,5Hz), 8,00 (1H, d, J=2,7Hz), 7,79 (1H, d, J=8,7Hz), 7,71 (1H, dd, J=9,3Hz, 2,7Hz), 7,44-7,51 (1H, m), 7,26-7,35 (3H, m), 7,15-7,22 (1H, m), 5,26 (2H, s), 4,50-4,56 (1H, m), 3,57 (4H, t, J=4,8Hz), 2,59-2,65 (2H, m), 2,46 (4H, m), 1,31 (3H, d, J=6,0Hz)

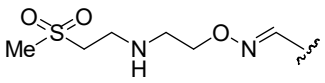
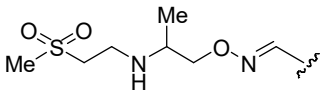
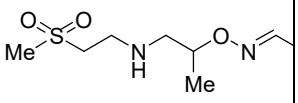
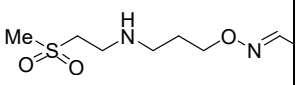
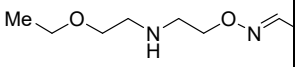
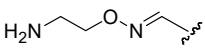
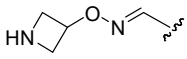
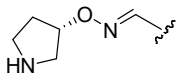
Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-34	-Cl		9,95 (1H, s), 8,65 (1H, s), 8,60 (1H, s), 8,34 (1H, s), 8,12 (1H, dd, J=9,0Hz, 1,8Hz), 8,01 (1H, d, J=2,7Hz), 7,79 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=8,7Hz, J=2,4Hz), 7,44-7,52 (1H, m), 7,27-7,35 (3H, m), 7,16-7,22 (1H, m), 5,27 (2H, s), 4,25 (2H, t, J=5,4Hz), 3,25 (2H, t, J=6,9Hz), 3,02 (3H, s), 2,99 (2H, t, J=6,9Hz), 2,89 (2H, t, J=5,7Hz)
V-35	-Cl		9,95 (1H, s), 8,65 (1H, s), 8,60 (1H, s), 8,36 (1H, s), 8,12 (1H, dd, J=8,7Hz, 1,8Hz), 8,01 (1H, d, J=2,7Hz), 7,80 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=9,0Hz, 2,4Hz), 7,44-7,52 (1H, m), 7,27-7,35 (3H, m), 7,16-7,22 (1H, m), 5,27 (2H, s), 4,04-4,09 (2H, m), 3,20-3,26 (2H, m), 2,98-3,08 (6H, m), 1,06 (3H, d, J=6,3Hz)

Tabela 8

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-36	-Cl		9,95 (1H, s), 8,63 (1H, s), 8,60 (1H, s), 8,32 (1H, s), 8,13 (1H, d, J=9,0Hz), 8,00 (1H, d, J=2,7Hz), 7,80 (1H, d, J=8,4Hz), 7,72 (1H, dd, J=9,3Hz, 2,7Hz), 7,44-7,52 (1H, m), 7,27-7,35 (3H, m), 7,16-7,22 (1H, m), 5,27 (2H, s), 4,40-4,46 (1H, m), 3,27 (2H, t, J=6,9Hz), 2,99-3,02 (5H, m), 2,74-2,90 (2H, m), 1,30 (3H, d, J=6,6Hz)
V-37	-Cl		9,95 (1H, s), 8,64 (1H, s), 8,60 (1H, s), 8,34 (1H, s), 8,11 (1H, dd, J=9,0Hz, 1,2Hz), 8,01 (1H, d, J=2,7Hz), 7,79 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=8,7Hz, 2,7Hz), 7,44-7,51 (1H, m), 7,26-7,34 (3H, m), 7,16-7,22 (1H, m), 5,26 (2H, s), 4,25 (2H, t, J=6,3Hz), 3,25 (2H, t, J=7,2Hz), 3,03 (3H, s), 2,98 (2H, t, J=6,9Hz), 2,70 (2H, t, J=6,9Hz), 1,84-1,91 (2H, m)

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-38	-Cl		9,96 (1H, s), 8,64 (1H, s), 8,60 (1H, s), 8,35 (1H, s), 8,11 (1H, dd, J=8,7Hz, 1,5Hz), 8,01 (1H, d, J=2,4Hz), 7,79 (1H, d, J=8,7Hz), 7,73 (1H, dd, J=9,0Hz, 2,7Hz), 7,44-7,52 (1H, m), 7,27-7,35 (3H, m), 7,16-7,22 (1H, m), 5,27 (2H, s), 4,25 (2H, t, J=5,4Hz), 3,38-3,46 (4H, m), 2,91 (2H, t, J=5,7Hz), 2,73 (2H, t, J=5,4Hz), 1,09 (3H, t, J=6,9Hz)
V-39	-Cl		9,96 (1H, s), 8,63 (1H, brs), 8,60 (1H, s), 8,34 (1H, s), 8,11 (1H, dd, J=8,7Hz, J=1,5Hz), 8,00 (1H, d, J=2,4Hz), 7,79 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=9,0Hz, J=2,4Hz), 7,52-7,44 (1H, m), 7,35-7,27 (3H, m), 7,20 (1H, dt, J=9,3Hz, J=2,7Hz), 5,27 (2H, s), 4,37 (2H, t, J=6,0Hz), 3,51 (2H, t, J=6,0Hz)

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-40	-Cl		9,95 (1H, s), 8,64 (1H, brs), 8,59 (1H, s), 8,40 (1H, s), 8,09 (1H, d, J=6,6Hz), 8,01 (1H, brs), 7,78 (1H, d, J=6,3Hz), 7,72 (1H, d, J=6,3Hz), 7,50-7,45 (1H, m), 7,35-7,26 (3H, m), 7,19 (1H, t, J=6,3Hz), 5,26 (2H, s), 5,09 (1H, m), 3,69 (2H, tipo t, J=5,1Hz), 3,60 (2H, tipo t, J=5,1Hz)
V-41	-Cl		9,93 (1H, s), 8,62 (1H, brs), 8,59 (1H, s), 8,30 (1H, s), 8,11 (1H, d, J=6,3Hz), 8,00 (1H, d, J=1,5Hz), 7,79 (1H, d, J=6,6Hz), 7,72 (1H, dd, J=6,6Hz, J=1,8Hz), 7,50-7,45 (1H, m), 7,35-7,27 (3H, m), 7,19 (1H, t, J=5,7Hz), 5,26 (2H, s), 4,88 (1H, brs), 3,01-2,88 (3H, m), 2,79-2,73 (1H, m), 1,99-1,85 (2H, m)

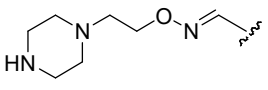
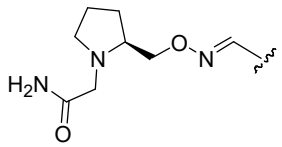
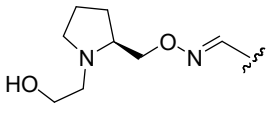
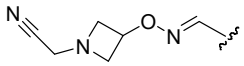
Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-42	-Cl		9,95 (1H, s), 8,63 (1H, brs), 8,60 (1H, s), 8,35 (1H, s), 8,11 (1H, dd, J=8,7Hz, J=1,5Hz), 8,01 (1H, d, J=2,4Hz), 7,79 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=9,3Hz, J=2,7Hz), 7,52-7,44 (1H, m), 7,35-7,27 (3H, m), 7,19 (1H, dt, J=9,3Hz, J=2,7Hz), 5,27 (2H, s), 4,29 (2H, t, J=6,0Hz), 2,69 (4H, t, J=4,8Hz), 2,63 (2H, t, J=6,0Hz), 2,39 (4H, brs)

Tabela 9

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-45	-Cl		9,93 (1H, s), 8,63 (1H, brs), 8,60 (1H, s), 8,33 (1H, s), 8,10 (1H, d, J=6,6Hz), 8,02 (1H, d, J=1,5Hz), 7,79 (1H, d, J=6,6Hz), 7,73 (1H, d, J=6,9Hz), 7,50-7,45 (1H, m), 7,35-7,27 (3H, m), 7,19 (2H, m), 7,08 (1H, brs), 5,26 (2H, s), 4,20 (1H, dd, J=8,1Hz, J=4,2Hz), 4,13 (1H, dd, J=8,1Hz, J=4,2Hz), 3,38 (1H, d, J=12Hz), 3,08-2,93 (3H, m), 2,38 (1H, m), 199-1,89 (1H, m), 1,76-1,57 (3H, m)

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-46	-Cl		9,93 (1H, s), 8,63 (1H, brs), 8,60 (1H, s), 8,34 (1H, s), 8,11 (1H, d, J=6,6Hz), 8,01 (1H, d, J=2,1Hz), 7,80 (1H, d, J=6,6Hz), 7,73 (1H, d, J=8,1Hz), 7,51-7,44 (1H, m), 7,35-7,27 (3H, m), 7,19 (1H, m), 5,27 (2H, s), 4,38 (1H, brs), 4,19 (1H, dd, J=8,1Hz, J=4,2Hz), 4,03 (1H, dd, J=8,1Hz, J=4,2Hz), 3,49 (2H, dd, J=9,3Hz, J=4,5Hz), 3,09-3,05 (1H, m), 2,95-2,90 (1H, m), 2,84-2,82 (1H, m), 2,47-2,40 (1H, m), 2,29-2,22 (1H, m), 1,91-1,85 (1H, m), 1,73-1,57 (3H, m)

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-47	-Cl		9,94 (1H, s), 8,66 (1H, brs), 8,60 (1H, s), 8,43 (1H, s), 8,12 (1H, d, J=6,6Hz), 8,01 (1H, d, J=1,2Hz), 7,79 (1H, d, J=6,9Hz), 7,72 (1H, d, J=6,6Hz), 7,50-7,45 (1H, m), 7,35-7,27 (3H, m), 7,19 (1H, t, J=6,0Hz), 5,27 (2H, s), 4,97 (1H, m), 3,74 (2H, s), 3,68 (2H, tipo t, J=5,1Hz), 3,37 (2H, tipo t, J=5,1Hz)
V-48	-Cl		9,95 (1H, s), 8,64 (1H, brs), 8,60 (1H, s), 8,39 (1H, s), 8,09 (1H, d, J=6,6Hz), 8,01 (1H, brs), 7,79 (1H, d, J=6,3Hz), 7,73 (1H, d, J=6,6Hz), 7,50-7,45 (1H, m), 7,35-7,27 (3H, m), 7,19 (1H, t, J=6,6Hz), 5,26 (2H, s), 4,92 (1H, m), 4,42 (1H, brs), 3,62 (2H, t, J=5,4Hz), 3,14 (2H, t, J=5,4Hz), 2,54 (2H, t, J=4,5Hz)

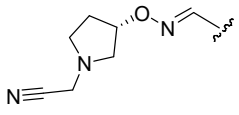
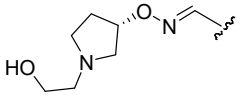
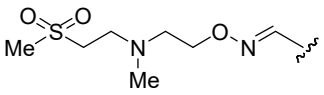
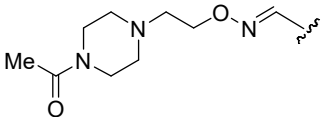
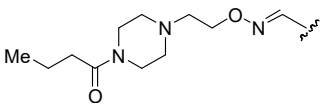
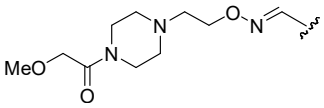
Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-49	-Cl		9,94 (1H, s), 8,63 (1H, brs), 8,60 (1H, s), 8,32 (1H, s), 8,11 (1H, d, J=6,6Hz), 8,01 (1H, d, J=1,8Hz), 7,79 (1H, d, J=6,6Hz), 7,72 (1H, dd, J=6,9Hz, J=1,8Hz), 7,50-7,45 (1H, m), 7,35-7,27 (3H, m), 7,19 (1H, t, J=6,3Hz), 5,26 (2H, s), 4,95 (1H, brs), 3,87 (2H, s), 2,91-2,81 (3H, m), 2,57-2,51 (1H, m), 2,30-2,21 (1H, m), 2,00-1,91 (1H, m)
V-50	-Cl		9,95 (1H, s), 8,62 (1H, brs), 8,59 (1H, s), 8,32 (1H, s), 8,10 (1H, d, J=6,3Hz), 8,00 (1H, brs), 7,79 (1H, d, J=6,3Hz), 7,72 (1H, d, J=6,3Hz), 7,50-7,45 (1H, m), 7,35-7,27 (3H, m), 7,19 (1H, t, J=6,0Hz), 5,26 (2H, s), 4,89 (1H, brs), 4,45 (1H, brs), 3,49 (3H, m), 2,82-2,75 (3H, m), 2,41-2,39 (1H, m), 2,17 (1H, m), 1,86 (1H, brs)

Tabela 10

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-51	-Cl		9,94 (1H, s), 8,64 (1H, s), 8,60 (1H, s), 8,33 (1H, s), 8,12 (1H, d, J=10,2Hz), 8,01 (1H, d, J=2,4Hz), 7,79 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=8,7Hz, 2,4Hz), 7,44-7,51 (1H, m), 7,26-7,34 (3H, m), 7,16-7,22 (1H, m), 5,26 (2H, s), 4,29 (2H, t, J=5,7Hz), 3,27 (2H, t, J=7,2Hz), 3,02 (3H, s), 2,84 (2H, t, J=6,9Hz), 2,75 (2H, t, J=5,7Hz), 2,29 (3H, s)
V-52	-Cl		9,94 (1H, s), 8,64 (1H, s), 8,59 (1H, s), 8,35 (1H, s), 8,10 (1H, dd, J=8,7Hz, 1,5Hz), 8,00 (1H, d, J=2,7Hz), 7,78 (1H, d, J=8,7Hz), 7,71 (1H, dd, J=8,7Hz, 2,4Hz), 7,44-7,51 (1H, m), 7,26-7,35 (3H, m), 7,15-7,21 (1H, m), 5,26 (2H, s), 4,32 (2H, t, J=5,7Hz), 3,42-3,43 (4H, m), 2,71 (2H, t, J=5,7Hz), 2,41 (4H, t, J=5,1Hz), 1,98 (3H, s)

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-53	-Cl		9,95 (1H, s), 8,63 (1H, s), 8,59 (1H, s), 8,35 (1H, s), 8,10 (1H, dd, J=8,4Hz, 1,2Hz), 8,00 (d, 1H, J=2,4Hz), 7,79 (1H, d, J=8,4Hz), 7,71 (1H, dd, J=9,3Hz, 2,4Hz), 7,44-7,51 (1H, m), 7,26-7,34 (3H, m), 7,15-7,22 (1H, m), 5,26 (2H, s), 4,32 (2H, t, J=5,4Hz), 3,43-3,45 (4H, m), 2,70 (2H, t, J=5,7Hz), 2,41-2,46 (4H, m), 2,26 (2H, t, J=7,2Hz), 1,43-1,56 (2H, m), 0,87 (3H, t, J=7,5Hz)
V-54	-Cl		9,94 (1H, s), 8,63 (1H, s), 8,59 (1H, s), 8,35 (1H, s), 8,10 (1H, dd, J=8,7Hz, 1,5Hz), 8,00 (1H, d, J=2,4Hz), 7,78 (1H, d, J=8,7Hz), 7,71 (1H, dd, J=9,0Hz, 2,4Hz), 7,44-7,51 (1H, m), 7,26-7,35 (3H, m), 7,15-7,21 (1H, m), 5,26 (2H, s), 4,32 (2H, t, J=5,7Hz), 4,06 (3H, s), 3,37-3,42 (4H, m), 3,27 (2H, s), 2,71 (2H, t, J=5,7Hz), 2,46 (4H, m)

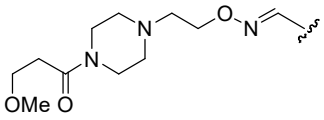
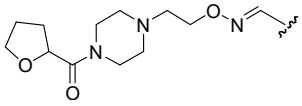
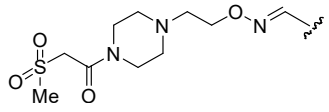
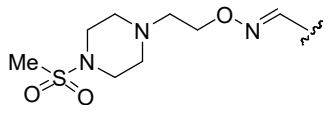
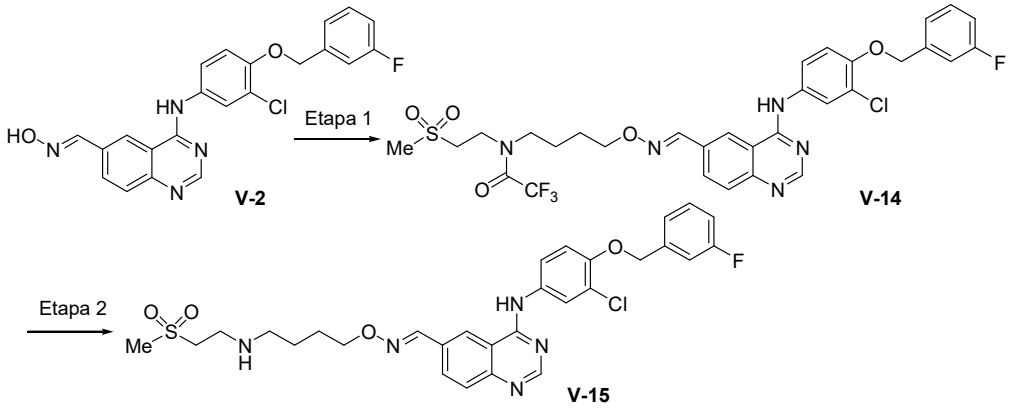
Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-55	-Cl		9,94 (1H, s), 8,63 (1H, s), 8,59 (1H, s), 8,35 (1H, s), 8,10 (1H, dd, J=8,7Hz, 1,5Hz), 8,00 (1H, d, J=2,4Hz), 7,79 (1H, d, J=8,7Hz), 7,71 (1H, dd, J=9,0Hz, 2,4Hz), 7,44-7,51 (1H, m), 7,26-7,35 (3H, m), 7,15-7,21 (1H, m), 5,26 (2H, s), 4,32 (2H, t, J=5,7Hz), 3,53 (2H, t, J=6,6Hz), 3,43-3,47 (4H, m), 3,21 (3H, s), 2,71 (2H, t, J=6,0Hz), 2,55 (2H, t, J=6,6Hz), 2,42-2,50 (4H, m)
V-56	-Cl		9,94 (1H, s), 8,64 (1H, s), 8,59 (1H, s), 8,35 (1H, s), 8,10 (1H, dd, J=8,7Hz, 1,5Hz), 8,00 (1H, d, J=2,7Hz), 7,79 (1H, d, J=9,0Hz), 7,71 (1H, dd, J=8,7Hz, 2,4Hz), 7,44-7,51 (1H, m), 7,26-7,35 (3H, m), 7,15-7,22 (1H, m), 5,26 (2H, s), 4,61-4,66 (1H, m), 4,32 (2H, t, J=5,7Hz), 3,68-3,80 (2H, m), 3,44-3,54 (4H, m), 2,71 (2H, 5,7Hz), 2,44-2,50 (4H, m), 1,95-2,04 (2H, m), 1,75-1,86 (2H, m)

Tabela 11

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
V-57	-Cl		9,94 (1H, s), 8,64 (1H, s), 8,59 (1H, s), 8,35 (1H, s), 8,10 (1H, dd, J=8,7Hz, 1,2Hz), 8,00 (1H, d, J=2,7Hz), 7,79 (1H, d, J=8,7Hz), 7,71 (1H, dd, J=9,0Hz, 2,4Hz), 7,44-7,51 (1H, m), 7,26-7,35 (3H, m), 7,16-7,21 (1H, m), 5,26 (2H, s), 4,45 (2H, s), 4,32 (2H, t, J=5,4Hz), 3,49-3,53 (4H, m), 3,09 (3H, s), 2,72 (2H, t, J=5,7Hz), 2,44-2,50 (4H, m)
V-58	-Cl		9,95 (1H, s), 8,64 (1H, s), 8,59 (1H, s), 8,35 (1H, s), 8,10 (1H, d, J=8,7Hz), 8,00 (1H, d, J=2,7Hz), 7,78 (1H, d, J=8,7Hz), 7,69-7,73 (1H, m), 7,44-7,51 (1H, m), 7,26-7,34 (3H, m), 7,16-7,22 (1H, m), 5,26 (2H, s), 4,31 (2H, t, J=5,7Hz), 3,12 (4H, t, J=5,1Hz), 2,87 (3H, s), 2,75 (2H, t, J=5,4Hz), 2,58 (4H, t, J=5,3Hz)

Exemplo 6

Fórmula química 67



(Etapa 1) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(4-(N-(2-(metanossulfonila)etila)-N-(2, 2, 2-trifluoracetila)amino)butiloxiimino)quinazolina (V-14)

[0199] Em N,N-dimetilacetamida (1,5 ml) foram dissolvidos 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(hidroxiimino)quinazolina (V-2, 84 mg) e N-(4-bromobutila)-N-(2-metanossulfoniletila)-2, 2, 2-trifluoracetamida (71 mg), e carbonato de potássio (41 mg) foi adicionado, seguido de agitação a 60°C por 13 horas com aquecimento. Em seguida, a mistura reacional foi despejada em ácido cítrico 0,5 M, seguida de extração com acetato de etila. A camada orgânica foi lavada com água e solução aquosa de cloreto de sódio, e secada em sulfato de magnésio. O produto bruto foi purificado por cromatografia sobre sílica-gel (eluindo com hexano: acetato de etila = 1:4) para obter 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(4-(N-(2-(metanossulfonila)etila)-2, 2, 2-trifluoracetamido)butiloxiimino)quinazolina (V-14, 41 mg) como um sólido amarelo pálido.

^{1}H RMN (d_6-DMSO, δ): 9,94 (1H, s), 8,63 (1H, s), 8,59 (1H, s), 8,33 (1H, s), 8,10 (1H, dd, J= 8,4 Hz, J= 1,5 Hz), 8,00 (1H, d, J= 2,4 Hz), 7,78 (1H, d, J= 8,7 Hz), 7,71 (1H, dd, J= 2,3 Hz, J= 8,7 Hz), 7,47 (1H, dt, J= 6,0 Hz, J= 8,1 Hz), 7,36-7,31 (2H, m), 7,28 (1H, d, J= 9,0 Hz), 7,18 (1H, dt, J= 2,0 Hz, J= 8,6 Hz), 5,26 (2H, s), 4,26-4,18 (2H, m), 3,79

(2H, t, J= 7,1 Hz), 3,60-3,44 (4H, m), 3,05 (3H, s), 1,78-1,66 (4H, m).

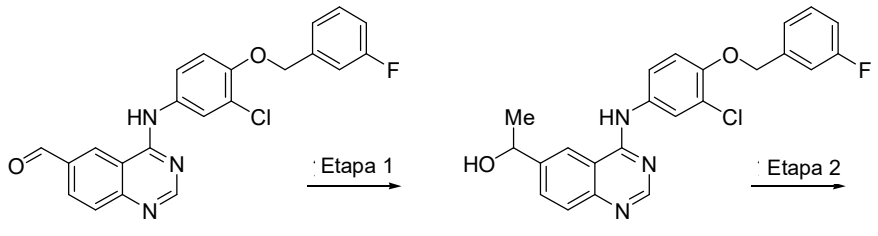
(Etapa 2) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(4-(2-(metanossulfonila)etilamino)butiloxiimino)quinazolina (V-15)

[0200] Em 2,6 ml de uma mistura (1:1) de tetrahidrofurano e metanol foi dissolvida 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(4-(N-(2-(metanossulfonila)etila)-2, 2, 2-trifluoracetamido)butiloxiimino)quinazolina (V-14, 40 mg), e 86 μl de solução aquosa de hidróxido de sódio a 1 mol/l foram adicionados, seguido de agitação à temperatura ambiente por 14 horas, e a 40°C por 2 horas. Depois da reação, a mistura reacional foi extraída com acetato de etila, a camada orgânica foi secada, e o filtrado foi concentrado. O resíduo concentrado foi purificado por cromatografia (eluindo com acetato de etila contendo 0 a 3% metanol) usando uma coluna de amina, e o óleo amarelo pálido resultante foi pulverizado com uma mistura de hexano e acetato de etila para obter 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(4-(2-(metanossulfonila)etilamino)butiloxiimino)quinazolina (V-15, 12 mg) como um sólido amarelo pálido.

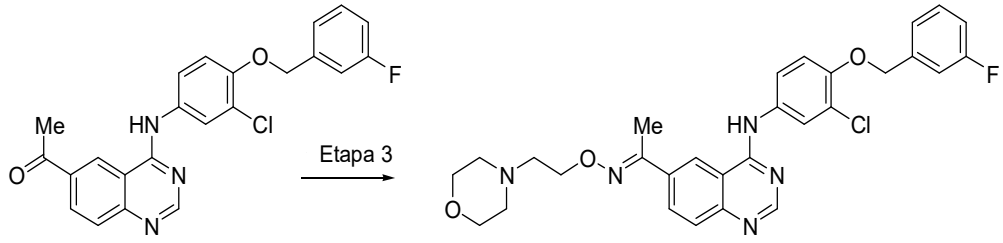
^{1}H RMN (d_6-DMSO, δ): 9,95 (1H, s), 8,63 (1H, s), 8,59 (1H, s), 8,33 (1H, s), 8,11 (1H, d, J= 8,7 Hz), 8,01 (1H, d, J= 2,4 Hz), 7,79 (1H, d, J= 8,7 Hz), 7,72 (1H, br d, J= 9,0 Hz), 7,51-7,44 (1H, m), 7,36-7,31 (2H, m), 7,28 (1H, d, J= 9,0 Hz), 7,19 (1H, br t, J= 9 Hz), 5,26 (2H, s), 4,20 (2H, t, J= 6,6 Hz), 3,21 (2H, t, J= 6,9 Hz), 2,91 (2H, t, J= 6,6 Hz), 2,56 (2H, t, J= 6,9 Hz), 1,73 (2H, quin, J= 7 Hz), 1,51 (2H, quin, J= 7 Hz).

Exemplo 7

Fórmula química 68



IV-1 VI-1



VII-1 VIII-1

(Etapa 1) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-hidroxietan-1-ila)quinazolina (VI-1)

[0201] Em 30 ml de tetrahidrofurano foram dissolvidos 620 mg de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-formilquinazolina (IV-1), a solução foi resfriada para 0°C em uma atmosfera de nitrogênio, e 4,9 ml de brometo de metilmagnésio (solução em tetrahidrofurano 0,93 M) foram adicionados em gotas. Depois da reação a 0°C por 1 hora em uma atmosfera de nitrogênio, água e acetato de etila foram adicionados para separar as camadas. A camada orgânica foi lavada sequencialmente com água e solução aquosa saturada de cloreto de sódio, e secada em sulfato de magnésio. Depois de concentração, o cristal resultante foi lavado com clorofórmio para obter 330 mg de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-hidroxietan-1-ila)quinazolina (VI-1).

^{1}H RMN (d_6-DMSO δ): 9,81 (1H, s), 8,55 (1H, s), 8,44 (1H, s), 8,03 (1H, d, J= 2,4 Hz), 7,86 (1H, dd, J= 8,7 Hz, J= 1,2 Hz), 7,78-7,73 (2H, m), 7,51-7,44 (1H, m), 7,35-7,25 (3H, m), 7,18 (1H, dt, J= 8,4 Hz, J= 2,4 Hz), 5,44 (1H, d, J= 3,9 Hz), 5,26 (2H, s), 4,93 (1H, m), 1,45 (3H, d, J= 6,6 Hz)

(Etapa 2) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(etano-4-ona)quinazolina (VII-1)

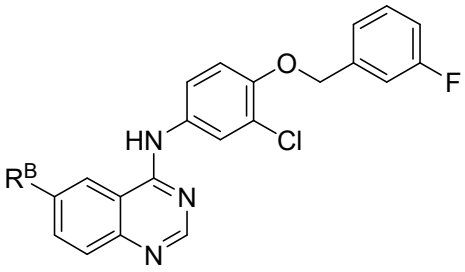
[0202] Em 150 ml de tetrahidrofurano foram dissolvidos 360 mg de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino-6-(1-hidroxietan-1-ila)quinazolina (VI-1), e 3,7 g de dióxido de manganês foram adicionados, seguido de agitação à temperatura ambiente por uma noite.

Depois da reação, as substâncias inorgânicas foram filtradas, e o filtrado foi concentrado. O cristal resultante foi lavado com clorofórmio para obter 320 mg de 4-(3-cloro-4-(3- fluorbenziloxi)fenilamino)-6-(etano-4-ona)quinazolina (VII-1).

^{1}H RMN (d_6-DMSO δ): 10,18 (1H, s), 9,16 (1H, d, J= 1,5 Hz), 8,64 (1H, s), 8,31 (1H, dd, J= 8,4 Hz, J= 2,4 Hz), 7,97 (1H, d, J= 2,4 Hz), 7,83 (1H, d, J= 8,7 Hz), 7,71 (1H, dd, J= 8,7 Hz, J= 2,4 Hz), 7,51-7,44 (1H, m), 7,35-7,29 (3H, m), 7,19 (1H, dt, J= 8,1 Hz, J= 2,7 Hz), 5,27 (2H, s), 2,74 (3H, s)

[0203] Os compostos a seguir foram sintetizados da mesma maneira que aquela descrita na primeira etapa e na segunda etapa acima.

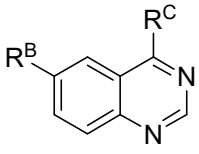
Fórmula química 69



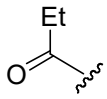
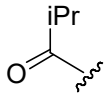
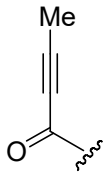
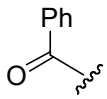
(VII)

Tabela 12

Fórmula química 70



(VII)

Composto Nº	R^A	^{1}H-RMN(d_6-DMSO)
VII-2		10,17 (1H, s), 9,17 (1H, d, J=1,5Hz), 8,64 (1H, s), 8,32 (1H, dd, J=8,7Hz, J=1,5Hz), 7,97 (1H, d, J=2,7Hz), 7,84 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=8,7Hz, J=2,7Hz), 7,52-7,44 (1H, m), 7,35-7,29 (3H, m), 7,20 (1H, dt, J=8,7Hz, J=2,7Hz), 5,28 (2H, s), 3,22 (2H, q, J=7,2Hz), 1,17 (3H, t, J=7,2Hz)
VII-3		($CDCl_3$) 8,76 (1H, s), 8,65 (1H, brs), 8,29 (1H, d, J=9,0Hz), 7,97 (1H, d, J=8,4Hz), 7,88 (1H, brs), 7,52 (1H, d, J=9,0Hz), 7,40-7,33 (1H, m), 7,25-7,19 (3H, m), 7,05-6,97 (2H, m), 5,16 (2H, s), 3,72-3,63 (1H, m), 1,28 (3H, d, J=1,8Hz), 1,26 (3H, d, J=1,8Hz)
VII-4		10,34 (1H, s), 9,23 (1H, s), 8,66 (1H, s), 8,44 (1H, dd, J=9 Hz, J=1,5Hz), 7,99 (1H, d, J=2,7Hz), 7,88 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=9 Hz, J=2,4Hz), 7,43-7,52 (1H, m), 7,14-7,36 (4H, m), 5,28 (2H, s), 2,28 (3H, s)
VII-5		10,14 (1H, s), 8,98 (1H, s), 8,67 (1H, s), 8,11 (1H, dd, J=8,7 Hz, J=0,9Hz), 7,98-7,82 (4H, m), 7,78-7,58 (4H, m), 7,52-7,43 (1H, m), 7,36-7,14 (4H, m), 5,26 (2H, s)

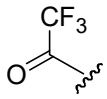
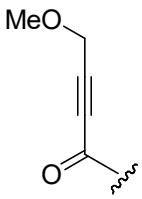
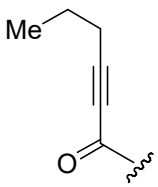
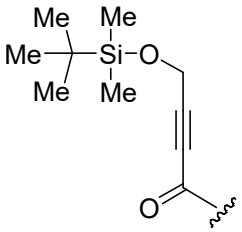
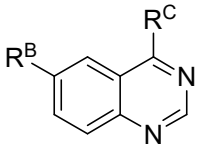
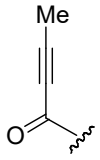
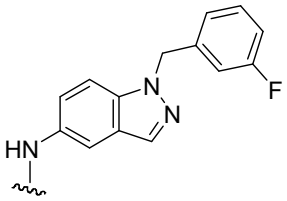
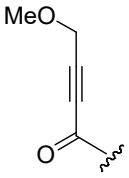
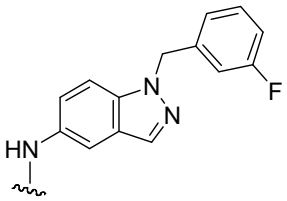
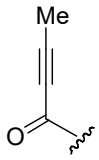
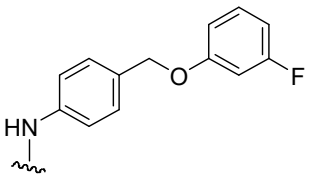
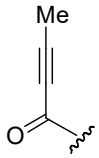
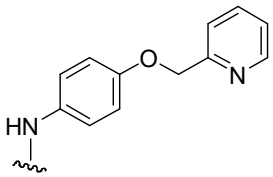
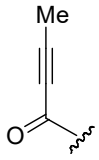
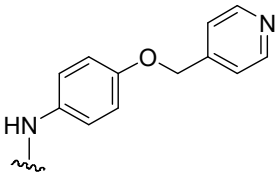
Composto Nº	R^A	^{1}H-RMN(d_6-DMSO)
VII-6		10,50 (1H, s), 9,27 (1H, s), 8,67 (1H, s), 8,35 (1H, d, J=9,3Hz), 7,99 (1H, d, J=2,7Hz), 7,88 (1H, brs), 7,70 (1H, d, J=7,5Hz), 7,52-7,43 (1H, m), 7,36-7,14 (4H, m), 5,28 (2H, s)
VII-8		10,36 (1H, s), 9,26 (1H, s), 8,67 (1H, s), 8,44 (1H, dd, J=8,7Hz, J=1,8Hz), 8,00 (1H, d, J=2,4Hz), 7,91 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=9,0Hz, J=2,4Hz), 7,51-7,44 (1H, m), 7,35-7,28 (3H, m), 7,22-7,15 (1H, m), 5,27 (2H, s), 4,55 (2H, s),
VII-9		10,4 (1H, s), 9,24 (1H, s), 8,67 (1H, s), 8,46 (1H, d, J=8,7Hz), 8,01 (1H, d, J=2,7Hz), 7,90 (1H, d, J=8,7Hz), 7,70-7,80 (1H, m), 7,44-7,54 (1H, m), 7,15-7,40 (4H, m), 5,27 (2H, s), 2,64 (2H, t, J=6,9Hz), 1,63-1,75 (2H, m), 1,05 (3H, t, J=7,5Hz)
VII-10		10,34 (1H, s), 9,24 (1H, s), 8,67 (1H, s), 8,42 (1H, d, J=8,4Hz), 7,99 (1H, s), 7,88 (1H, d, J=8,7Hz), 7,73 (1H, d, J=9,0Hz), 7,48-7,44 (1H, m), 7,34-7,27 (3H, m), 7,21-7,16 (1H, m), 5,27 (2H, s), 4,76 (2H, s), 0,94 (9H, s), 0,16 (6H, s),

Tabela 13



(VII)

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
VII-11			10,44 (1H, s), 9,24 (1H, s), 8,60 (1H, s), 8,43 (1H, dd, J=2,4, 11,6Hz), 8,17 (2H, s), 7,87 (1H, d, J=12,0Hz), 7,78-7,67 (2H, m), 7,41-7,34 (1H, m), 7,14-7,04 (3H, m), 5,72 (2H, s), 2,28 (3H, s)
VII-12			10,47 (1H, s), 9,29 (1H, d, J=1,8Hz), 8,62 (1H, s), 8,43 (1H, dd, J=1,5Hz, J=9,0Hz), 8,21-8,17 (2H, m), 7,89 (1H, d, J=8,7Hz), 7,78-7,68 (2H, m), 7,41-7,33 (1H, m), 7,15-7,04 (3H, m), 5,71 (2H, s), 4,55 (2H, s), 3,42 (3H, s),

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
VII-13			10,44 (1H, s), 9,25 (1H, s), 8,73 (1H, s), 8,44 (1H, d, J=8,8Hz), 8,16 (1H, s), 7,89 (1H, d, J=8,4Hz), 7,62 (1H, d, J=8,4Hz), 7,34 (1H, dd, J=8,4, 16,0Hz), 6,95-6,86 (2H, m), 6,82-6,77 (1H, m), 5,15 (2H, s), 2,27 (3H, s),
VII-14			10,34 (1H, s), 9,22 (1H, s), 8,64-8,59 (2H, m), 8,43-8,41 (1H, m), 7,98 (1H, s), 7,87-7,85 (2H, m), 7,71-7,68 (1H, m), 7,59-7,58 (1H,m), 7,40-7,34 (1H, m), 7,29-7,27 (1H, m), 5,30 (2H, s),
VII-15			9,21 (1H, s), 8,64-8,58 (2H, m), 8,45-8,39 (1H, m), 7,97 (1H, s), 7,88-7,84 (1H, m), 7,71-7,66 (1H, m), 7,45-7,51 (1H,m), 7,27-7,23 (1H, m), 7,29-7,27 (1H, m), 5,30 (2H, s),

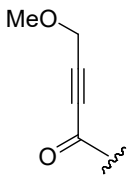
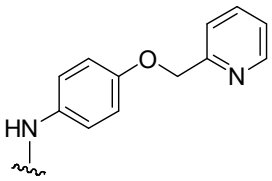
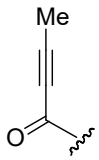
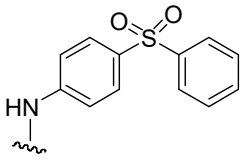
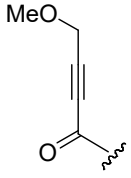
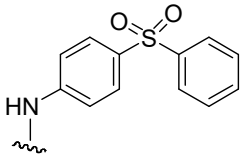
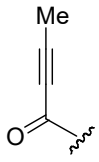
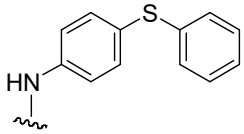
Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
VII-16			10,35 (1H, s), 9,24 (1H, s), 8,67 (1H, s), 8,60 (1H, d, J=4,4Hz), 8,42 (1H, d, J=8,8Hz), 8,01 (1H, s), 7,91-7,87 (2H, m), 7,73-7,71 (1H, m), 7,59 (1H, d, J=8,0Hz), 7,39-7,36 (1H, m), 7,29 (1H, d, J=8,8Hz), 5,31 (2H, s), 4,55 (2H, s), 3,42 (3H, s),

Tabela 14

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
VII-17			10,32 (1H, s), 8,85 (1H, s), 8,74 (1H, s), 8,20 (2H, d, J=6,0Hz), 8,01-7,96 (4H, m), 7,87 (1H, d, J=6,0Hz), 7,68-7,64 (3H, m), 3,56 (3H, s),
VII-18			10,52 (1H, s), 9,14 (1H, s), 8,60 (1H, s), 8,31 (1H, d, J=8,4Hz), 8,40 (2H, d, J=8,4Hz), 7,84-7,78 (5H, m), 7,52-7,43 (3H, m), 4,37 (2H, s), 3,24 (3H, s),

Composto Nº	R^A	R^B	^{1}H-RMN (d_6-DMSO)
VII-19			10,44 (1H, s), 9,28 (1H, s), 8,70 (1H, s), 8,45 (1H, d, J=8,8Hz), 7,92 (3H, t, J=8,8Hz), 7,46 (2H, d, J=8,8Hz), 7,37 (2H, t, J=7,6Hz), 7,30-7,26 (3H, m), 4,24-4,20 (2H, m), 2,28 (3H, s),

(Etapa 3) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-(2-(1-morfolino)etoxiimino)etila)quinazolina (VIII-1)

[0204] Em 6 ml (20:1) de uma mistura de tetrahidrofurano e água foram dissolvidos 100 mg de composto VII-1 e 78 mg de dicloridrato de 2-(1-morfolino)etoxiamina, seguido de agitação à temperatura ambiente por uma noite. A mistura reacional foi diluída com acetato de etila, lavada com solução aquosa saturada de bicarbonato de sódio, e secada em sulfato de magnésio. Depois de concentração, o sólido foi lavado com uma mistura (2:1) de hexano e acetato de etila para obter 72 mg de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-(2-(1-morfolino)etoxiimino)etila)quinazolina (VIII-1).

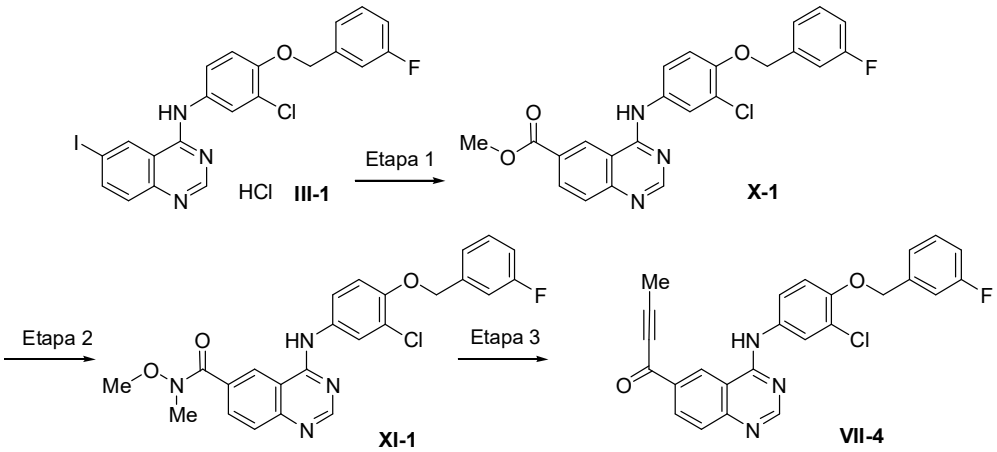
^{1}H RMN (d_6-DMSO, δ): 9,93 (1H, s), 8,62 (1H, brs), 8,58 (1H, s), 8,22 (1H, d, J= 6,6 Hz), 7,96 (1H, d, J= 1,8 Hz), 7,76 (1H, d, J= 6,6 Hz), 7,70 (1H, dd, J= 6,6 Hz, J= 1,8 Hz), 7,51-7,45 (1H, m), 7,35-7,28 (3H, m), 7,19 (1H, t, J= 6,0 Hz), 5,27 (2H, s), 4,33 (2H, t, J= 6,0 Hz), 3,59 (4H, t, J= 4,5 Hz), 2,69 (2H, t, J= 6,0 Hz), 2,47 (4H, t, J= 4,5 Hz), 2,36 (3H, s)

Exemplo de referência 1

[0205] Como um método para obter um derivado tipo cetona (VII),

o método a seguir é exemplificado além da primeira etapa e da segunda etapa do exemplo 7.

Fórmula química 71



(Etapa 1) Síntese de éster metílico do ácido 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-quinazolina-6-carboxílico (X-1)

[0206] Em uma mistura de 200 ml de dimetilformamida e 200 ml de metanol foram dissolvidos cloridrato de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-iodoquinazolina (III-1, 20 g) e 1,29 g de diclorobis(trifenilfosfina)paládio, e 25,7 ml de trietilamina foram adicionados. O interior de um vaso de reação foi suficientemente substituído com um gás monóxido de carbono, seguido de uma reação a 80°C por 15 horas sob a atmosfera de monóxido de carbono. A mistura reacional foi filtrada por Celite, e o filtrado foi resfriado para 0°C com agitação. Um precipitado foi filtrado, lavado com metanol frio, e secado para obter éster metílico do ácido 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)quinazolina-6-carboxílico (X-1, 13,5 g) como um sólido incolor.

^{1}H RMN (d_6-DMSO, δ): 10,26 (1H, s), 9,25 (1H, d, J= 1,5 Hz), 8,65 (1H, s), 8,31 (1H, dd, J= 1,5 Hz, J= 8,7 Hz), 8,02 (1H, d, J= 2,7 Hz), 7,85 (1H, d, J= 2,7 Hz), 7,77 (1H, dd, J= 2,7 Hz, J= 8,7 Hz), 7,49-7,44 (1H, m), 7,35-7,27 (3H, m), 7,20-7,16 (1H, m), 5,27 (2H, s), 3,96 (3H, s).

(Etapa 2) Síntese de metóxi metila amida de ácido 4-(3-cloro-4-(3-

fluorbenziloxi)fenilamino)quinazolina-6-carboxílico (XI-1)

[0207] Em tetrahidrofurano (230 ml) foi dissolvido o éster metílico do ácido 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-quinazolina-6-carboxílico (X-1, 11,6 g), cloridrato de N, O-dimetilhidroxilamina (7,8 g) foi adicionado, e solução de iPrMgCl a 2 mol/l em tetrahidrofurano (79,8 ml) foi adicionada em gotas por 30 minutos com resfriamento em gelo. Depois de completada a adição, a mistura foi agitada por 20 minutos com resfriamento em gelo e, depois de completada a reação, 200 ml de solução aquosa saturada de cloreto de amônio foram adicionados. Depois que 100 ml de água foram adicionados à mistura, a mistura foi extraída com acetato de etila, e a camada orgânica foi secada em sulfato de sódio. O filtrado foi concentrado para obter metóxi metila amida de ácido 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-quinazolina-6-carboxílico (XI-1, 12,7 g) como um sólido amarelo pálido.

^{1}H RMN (d_6-DMSO, δ): 10,01 (1H, s), 8,79 (1H, d, J= 1,5 Hz), 8,64 (1H, s), 8,05 (1H, d, J= 2,7 Hz), 8,00 (1H, dd, J= 1,5 Hz, J= 8,7 Hz), 7,81 (1H, d, J= 8,7 Hz), 7,76 (1H, dd, J= 2,7 Hz, J= 8,7 Hz), 7,52-7,44 (1H, m), 7,35-7,26 (3H, m), 7,22-7,16 (1H, m), 5,27 (2H, s), 3,57 (3H, s), 3,34 (3H, s).

(Etapa 3) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-oxo-2-butin-1-ila)quinazolina (VII-4)

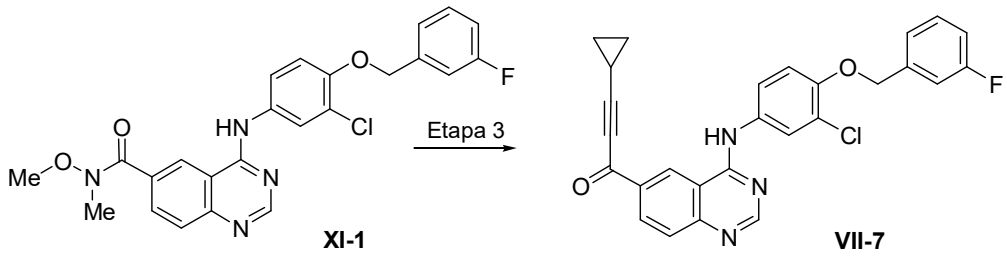
[0208] A uma solução de 4,22 ml de N,N-diisopropilamina em tetrahidrofurano (25 ml) resfriada para -78°C foram adicionados em gotas 18,8 ml de solução de n-BuLi a 1,6 mol/l em hexano. Depois de completada a adição, a temperatura foi aumentada para 0°C, e a mistura foi agitada a 0°C por 20 minutos, e novamente resfriada para -78°C. 1,33 ml de 2-bromo-1-propeno em tetrahidrofurano (25 ml) foi adicionado, e a mistura foi agitada a -78°C por 2 horas. À mistura foi adicionada em gotas uma solução de metóxi metila amida de ácido 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-quinazolina-6-carboxílico (XI-1,

2,33 g) em tetrahidrofurano (50 ml) e, depois de completada a adição, a temperatura foi aumentada para 0°C, seguido de agitação por 3 horas. Depois de completada a reação, a mistura reacional foi despejada em água gelada, neutralizada com ácido clorídrico a 2 mol/l, e extraída com acetato de etila. A camada orgânica foi secada em sulfato de sódio, o filtrado foi concentrado, e o resíduo cristalino resultante foi lavado com cloreto de metileno para obter 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-oxo-2-butin-1-ila)quinazolina (VII-4, 1,71 g) como um sólido amarelo.

Exemplo de referência 2

[0209] Como outro método da terceira etapa do Exemplo de referência 1, temos o seguinte método.

Fórmula química 72



(Etapa 3) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-oxo-2-propino-3-ciclopropila-1-ila)quinazolina (VII-7)

[0210] A uma solução de 0,16 ml de etinilciclopropano em tetrahidrofurano (3 ml) resfriada para -78°C foi adicionado em gotas 1,25 ml de solução de n-BuLi a 1,54 mol/l em hexano. Depois de completada a adição, a mistura foi agitada a -78°C por 1 hora. À mistura foi adicionada em gotas uma solução de metóxi metila amida de ácido 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-quinazolina-6-carboxílico (XI-1, 300 mg) em tetrahidrofurano (3 ml) e, depois de completada a adição, a temperatura foi aumentada para 0°C, e a mistura foi agitada por 3 horas. Depois de completada a reação, 10 ml de água e 10 ml de acetato de etila foram adicionados à mistura reacional para separar as camadas.

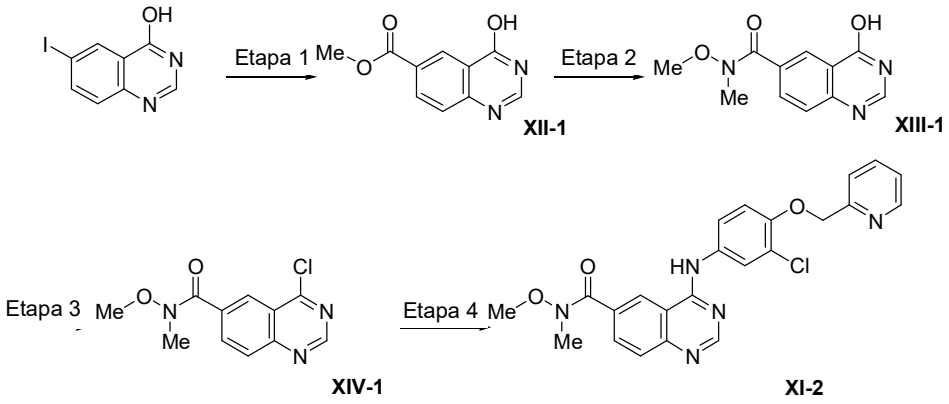
Depois que a camada aquosa foi novamente extraída com 10 ml de acetato de etila duas vezes, todas as camadas orgânicas foram combinadas, e secadas em sulfato de sódio, e o filtrado foi concentrado. O resíduo foi purificado por cromatografia de coluna sobre sílica-gel para obter 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-oxo-2-propino-3-ciclopropila-1-ila)quinazolina) (VII-7, 265 mg) como um sólido amarelo.

^{1}H RMN (d_6-DMSO, δ): 10,4 (1H, s), 9,21 (1H, s), 8,67 (1H, s), 8,41 (1H, d, J= 8,7 Hz), 8,01 (1H, d, J= 2,7 Hz), 7,88 (1H, d, J= 8,7 Hz), 7,73 (1H, dd, J= 8,7 Hz, J= 3 Hz), 7,40-7,52 (1H, m), 7,15-7,4 (4H, m), 5,28 (2H, s), 1,77-1,87 (1H, m), 1,05-1,20 (3H, m).

Exemplo de referência 3

[0211] Como um método para obter um derivado tipo amida (XI), temos o método a seguir além da primeira etapa e da segunda etapa do Exemplo de referência 1.

Fórmula química 73



(Etapa 1) Síntese de éster metílico do ácido 4-hidroxiquinazolina-6-carboxílico (XII-1)

[0212] 4-Hidroxi-6-iodoquinazolina (250 mg), uma quantidade catalítica de acetato de paládio (II) e 1,3-bis(difenilfosfino)propano foram dissolvidos em N,N-dimetilformamida (3,8 ml) e metanol (1,5 ml) e 1,5 ml de trietilamina foi adicionado. Depois que o interior de um vaso de reação foi suficientemente substituído com gás monóxido de carbono,

uma reação foi realizada a 80°C por 20 horas sob atmosfera de monóxido de carbono. Depois de completada a reação, a mistura reacional foi despejada em ácido cítrico aquoso a 10%, seguida de extração com acetato de etila. A camada orgânica foi lavada com água, e secada em sulfato de sódio, e o filtrado foi concentrado. O resíduo resultante foi purificado por cromatografia de coluna sobre sílica-gel (eluindo com acetato de etila) para obter éster metílico do ácido 4-hidroxiquinazolina-6-carboxílico (XII-1, 157 mg) como um sólido castanho.

^{1}H RMN (d_6-DMSO, δ): 12,48 (1H¤ s), 8,63 (1H, s), 8,26 (1H, d, J= 8,4 Hz), 8,19 (1H, s), 7,73 (1H, d, J= 8,4 Hz).

(Etapa 2) Síntese de metoximetilamida de ácido 4-hidroxiquinazolina-6-carboxílico (XIII-1)

[0213] Éster metílico do ácido 4-Hidroxiquinazolina-6-carboxílico (XII-1, 4,0 g) foi dissolvido em tetrahidrofurano (120 ml), cloridrato de N,O-dimetila hidroxilamina (5,7 g) foi adicionado, e solução de iPrMgCl a 2 mol/l em tetrahidrofurano (59 ml) foi adicionada em gotas durante 30 minutos. Depois de completada a adição, a mistura foi agitada por 30 minutos com resfriamento em gelo e, depois de completada a reação, 40 ml de ácido clorídrico a 2 mol/l foram adicionados em gotas. A mistura foi neutralizada com solução aquosa saturada de bicarbonato de sódio, e extraída com clorofórmio, e a camada orgânica foi lavada com solução aquosa de cloreto de sódio, e secada em sulfato de sódio. Depois de concentração, o resíduo cristalino foi purificado por cromatografia de coluna sobre sílica-gel (eluindo com acetato de etila: metanol = 9:1) para obter metoximetilamida de ácido 4-hidroxiquinazolina-6-carboxílico (XIII-1, 2,9 g) como um sólido branco.

^{1}H RMN (d_6-DMSO, δ): 12,42 (1H, s), 8,36 (1H, s), 8,18 (1H, s), 8,02 (1H, d, J= 8,4 Hz), 7,73 (1H, d, J= 8,4 Hz), 3,57 (3H, s), 3,32 (3H, s).

(Etapa 3) Síntese de metoximetilamida de ácido 4-cloroquinazolina-6-carboxílico (XIV-1)

[0214] Metoximetilamida de ácido 4-Hidroxiquinazolina-6-carboxílico (XIII-1, 2,9 g) foi suspendida em tolueno (57 ml), e 6,8 ml de trietilamina e 3,4 ml de oxicloreto de fósforo foram adicionados, seguido de agitação a 130°C por 30 minutos. Depois de completada a reação, a mistura reacional foi resfriada para a temperatura ambiente, e 50 ml de solução aquosa saturada de bicarbonato de sódio e acetato de etila foram adicionados. Bicarbonato de sódio foi adicionado até a camada aquosa apresentar um pH 8, seguido de extração com acetato de etila. A camada orgânica foi lavada com solução aquosa saturada de bicarbonato de sódio, secada em sulfato de sódio. Depois de concentração, o resíduo cristalino foi lavado com éter dietílico, e secado para obter metoximetilamida de ácido 4-cloroquinazolina-6-carboxílico (XIV-1, 2,3 g) como um sólido branco.

^{1}H RMN (d_6-DMSO, δ): 8,75 (1H, s), 8,36 (1H, s), 8,11 (1H, dd, J= 2,0 Hz, J= 8,4 Hz), 7,87 (1H, d, J= 8,4 Hz), 3,56 (3H, s), 3,32 (3H, s).

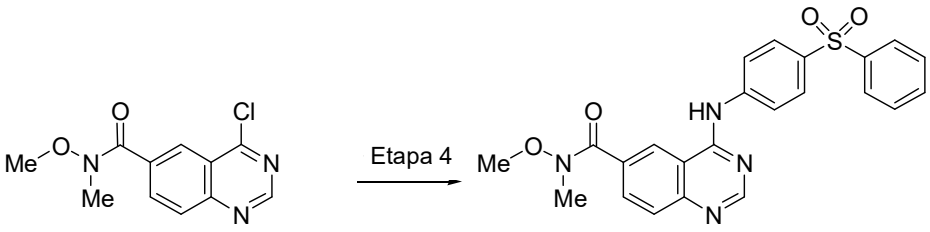
(Etapa 4) Síntese de metoximetilamida de ácido 4-(3-cloro-4-(piridin-2-ilmetoxi)fenilamino)-quinazolina-6-carboxílico (XI-2)

[0215] Metoximetilamida de ácido 4-Cloroquinazolina-6-carboxílico (XIV-1, 5,78 g) foi dissolvida em tetrahidrofurano (100 ml), e 5,39 g de 3-cloro-4-(piridin-2-ilmetoxi)anilina foram adicionados, seguido de agitação a 60°C por 1 hora. Um precipitado foi filtrado, e lavado com tetrahidrofurano para obter metoximetilamida de ácido 4-(3-cloro-4-(piridin-2-ilmetoxi)fenilamino)-quinazolina-6-carboxílico (XI-2, 7,87 g) como um sólido branco. O filtrado foi deixado repousar à temperatura ambiente, e o precipitado resultante foi recolhido por filtração, para de novo obter 2,21 g de XI-2.

^{1}H RMN (d_6-DMSO, δ): 10,02 (1H, s), 8,79 (1H, s), 8,62-8,59 (2H, m), 8,04 (1H, s), 8,00-7,98 (1H, m), 7,90-7,86 (1H, s), 7,80-7,78

(1H, m), 7,75-7,73 (1H, m), 7,59-7,57 (1H, m), 7,37-7,35 (1H, m), 7,28-7,26 (1H, m), 5,29 (2H, s), 3,57 (3H, s).

Fórmula química 74



XIV-1 XI-3

Exemplo de referência 4

[0216] Como outro método da quarta etapa do Exemplo de referência 3, temos o método a seguir.

(Etapa 4) Síntese de metoximetilamida de ácido 4-(4-benzenossulfonilfenilamino)-quinazolina-6-carboxílico (XI-3)

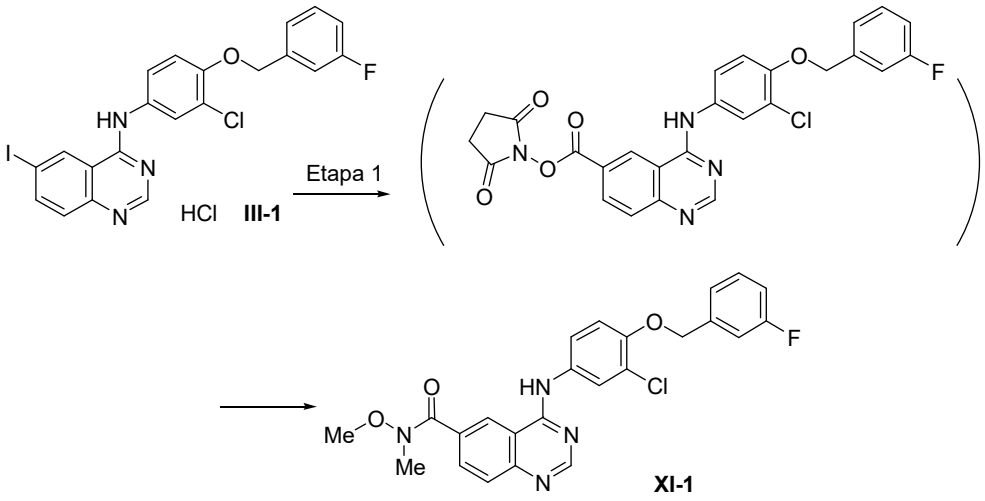
[0217] Metoximetilamida de ácido 4-Cloroquinazolina-6-carboxílico (XIV-1, 550 mg), 611 mg de 4-benzenossulfonilfenilamina, 49 mg de acetato de paládio (II), 190 mg de Xant phos e 997 mg de carbonato de césio foram adicionados a 1, 4-dioxano (30 ml), e o interior de um vaso de reação foi substituído com nitrogênio gasoso, seguido de agitação a 100°C por 2,5 horas. A mistura reacional foi filtrada com Celite, e água foi adicionada ao filtrado, seguida de extração com acetato de etila. A camada orgânica foi lavada com solução aquosa saturada de cloreto de sódio, e secada em sulfato de sódio. O filtrado foi concentrado, e o resíduo foi purificado por cromatografia de coluna sobre sílica-gel (eluindo com acetato de etila: metanol = 95:5) para obter metoximetilamida de ácido 4-(4-benzenossulfonilfenilamino)-quinazolina-6-carboxílico (XI-3, 651 mg) como um sólido amarelo pálido.

^{1}H RMN (d_6-DMSO, δ): 10,66 (1H, s), 9,29 (1H, s), 8,80 (1H, s), 8,48 (1H, d, J= 7,7 Hz), 8,16 (2H, d, J= 7,7 Hz), 7,99-7,94 (5H, m), 7,80-7,61 (3H, m), 2,27 (3H, s).

Exemplo de referência 5

[0218] Como um método para obter um derivado tipo amida (XI), temos ainda o método a seguir além da primeira etapa e da segunda etapa do Exemplo de referência 1, e do Exemplo de referência 3.

Fórmula química 75



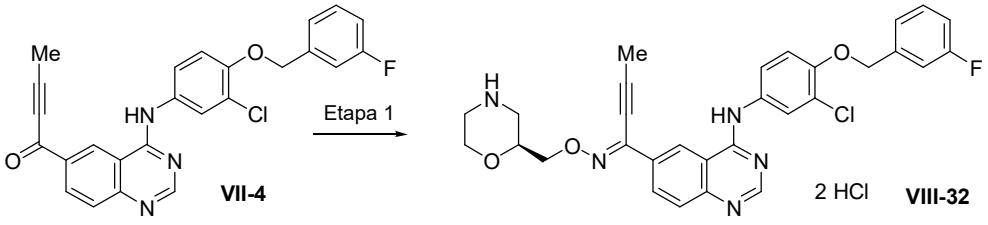
(Etapa 1) Síntese de metoximetilamida de ácido 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-quinazolina-6-carboxílico (XI-1)

[0219] Cloridrato de 4-(3-Cloro-4-((3-fluorbenziloxi)fenilamino)-6-iodoquinazolina (III-1, 500 mg), 32 mg de diclorobis(trifenilfosfina)paládio, e 191 mg de N-hidroxissuccinimida foram dissolvidos em 10 ml de dimetilformamida, e 360 μl de trietilamida foram adicionados. O interior de um vaso de reação foi suficientemente substituído como gás monóxido de carbono, seguido de uma reação a 80°C por 3 horas sob atmosfera de monóxido de carbono. A 1/5 da mistura reacional foi adicionado 0,3 ml de uma solução aquosa de N,O-dimetilhidroxilamina a 40%, seguido de agitação à temperatura ambiente por uma noite. Depois de completada a reação, água foi adicionada à mistura reacional, seguida de extração com acetato de etila. A camada orgânica foi lavada com água e solução aquosa saturada de cloreto de sódio nesta ordem, e secada em sulfato de sódio. O resíduo concentrado do filtrado foi purificado por cromatografia de coluna sobre sílica-gel (eluindo com acetato de etila) para obter

metoximetilamida de ácido 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-quinazolina-6-carboxílico (XI-1, 74 mg) como um sólido amarelo pálido.

Exemplo 8

Fórmula química 76



(Etapa 1) Síntese de dicloridrato de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-((S)-morfolin-2-ilmetoxiimino)-2-butin-1-ila)quinazolina (VIII-32)

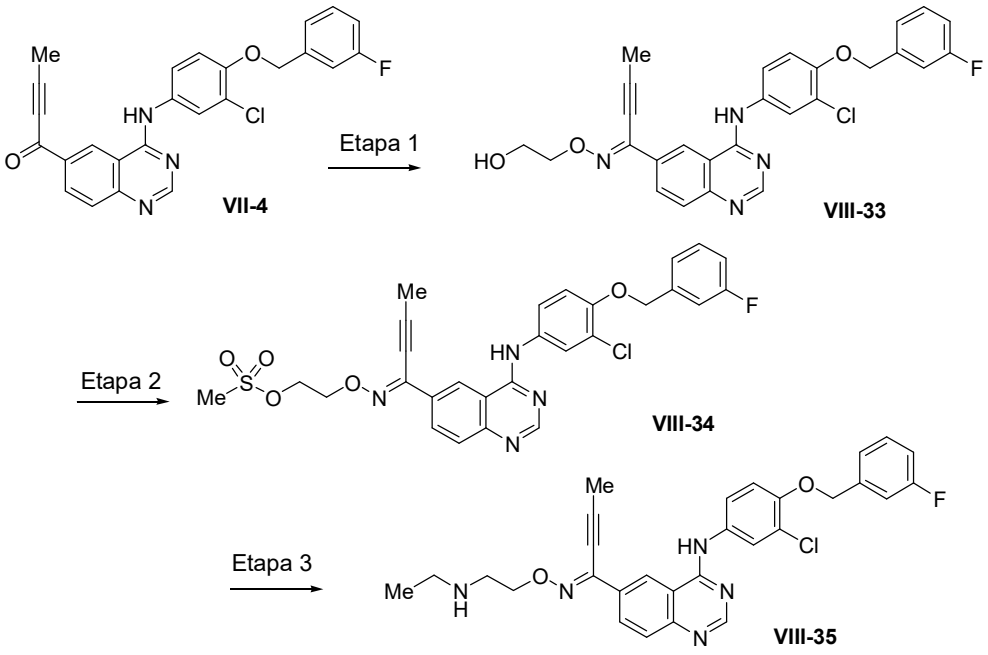
[0220] A uma suspensão de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-oxo-2-butin-1-ila)quinazolina (VII-4, 786 mg) e 614 mg de éster ter-butílico do ácido (S)-2-aminooximetila-morfolina-4-carboxílico em 31 ml de 1,4-dioxano foram adicionados 2,21 ml de solução aquosa de ácido metanossulfônico a 2 mol/l, seguidos de agitação a 80°C por 22 horas. E, 1,32 ml de solução aquosa de ácido metanossulfônico a 2 mol/l foi adicionalmente adicionado, seguido de mais agitação por 5,5 horas. Depois de completada a reação, a mistura reacional foi despejada em solução aquosa de bicarbonato de sódio, seguida de extração com acetato de etila. Depois que uma camada aquosa foi novamente extraída com acetato de etila, todas as camadas orgânicas foram combinadas, lavadas com água, e secadas em sulfato de magnésio anidro. Depois que o filtrado foi concentrado, o resíduo foi purificado por cromatografia de coluna sobre sílica-gel (eluindo com clorofórmio: metanol = 9:1) para obter um óleo amarelo. Este óleo foi dissolvido em 50 ml de acordo com, e filtrado, e 0,95 ml de solução de ácido clorídrico a 4 mol/l em acetato de etila foi adicionada com agitação, seguida de agitação à temperatura ambiente por 1 hora. Um precipitado foi filtrado, e lavado com acetato de etila e hexano nesta

ordem. Uma substância recolhida por filtração foi recristalizada com metanol-acetato de etila para obter dicloridrato de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-((S)-morfolin-2-ilmetoxiimino)-2-butin-1-ila)quinazolina (VIII-32, 839 mg) como um cristal amarelo.

^{1}H RMN (d_6-DMSO, δ): 11,69 (1H, bs), 9,49-9,37 (2H, m), 9,05 (1H, s), 8,88 (1H, s), 8,38 (1H, dd, J= 1,5 Hz, J= 8,7 Hz), 7,96 (1H, d, J= 8,7 Hz), 7,89 (1H, d, J= 2,7 Hz), 7,64 (1H, dd, J= 2,4 Hz, J= 9,0 Hz), 7,52-7,45 (1H, m), 7,36-7,30 (3H, m), 7,23-7,16 (1H, m), 5,31 (2H, s), 4,36-4,34 (1H, m), 4,25-4,22 (1H, m), 4,04-3,98 (1H, m), 3,84-3,77 (1H, m), 3,04-2,85 (3H, m), 2,28 (3H, s).

Exemplo 9

Fórmula química 77



(Etapa 1) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-(2-hidroxietoxiimino)-2-butin-1-ila)quinazolina (VIII-33)

[0221] 4-(3-Cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-oxo-2-butin-1-ila)quinazolina (VII-4, 10 g) foi dissolvida em 300 ml de 1,4-dioxano, 1,5 equivalente de 2-(acetoxi)etoxiamina foi adicionado, e 28 ml de solução aquosa de ácido metanossulfônico a 2 mol/l foram adicionados, seguidos de agitação a 60°C por 17 horas. A mistura reacional foi

despejada em solução aquosa saturada de bicarbonato de sódio, e a mistura foi extraída com acetato de etila. A camada orgânica foi lavada com água, e secada em sulfato de sódio. O resíduo obtido por concentração do filtrado foi recristalizado de etanol hidratado-água, filtrado, e secado para obter 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-(2-hidroxietoxiimino)-2-butin-1-ila)quinazolina (VIII-33, 7,6 g) como um sólido incolor.

^{1}H RMN (d_6-DMSO, δ): 10,07 (1H, s), 8,74 (1H, s), 8,58 (1H, s), 8,22 (1H, d, J= 8,8 Hz), 7,96 (1H, d, J= 2,4 Hz), 7,80 (1H, d, J= 8,8 Hz), 7,69 (1H, dd, J= 2,4 Hz, J= 8,8 Hz), 7,50-7,45 (1H, m), 7,35-7,24 (3H, m), 7,20-7,16 (1H, m), 5,27 (2H, s), 4,79 (1H, t. J= 5,6 Hz), 4,29 (2H, t. J= 5,6 Hz), 3,75 (2H, dd, J= 5,2 Hz, J= 10,4 Hz), 2,26 (3H, s).

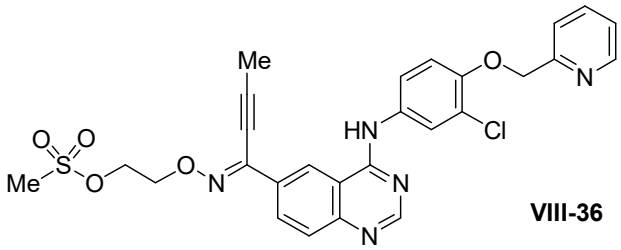
(Etapa 2) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-(2-sulfoniloxietoxiimino)-2-butin-1-ila)quinazolina (VIII-34)

[0222] 4-(3-Cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-(2-hidroxietoxiimino)-2-butin-1-ila)quinazolina (VIII-33, 7,6 g) foi dissolvida em 150 ml de tetrahidrofurano, e 4,19 ml de trietilamina e 2,33 ml de cloreto de metanossulfonila foram adicionados, seguidos de agitação por 3,5 horas. Depois de completada a reação, a mistura reacional foi despejada em água, e solução aquosa saturada de bicarbonato de sódio foi adicionada, seguida de extração com acetato de etila. A camada orgânica foi secada em sulfato de sódio, e o filtrado foi concentrado. Acetato de etila foi adicionado ao resíduo concentrado, este foi deixado repousar à temperatura ambiente, um cristal foi precipitado, e diluído com hexano, e o cristal foi recolhido por filtração para obter 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-(2-sulfoniloxietoxiimino)-2-butin-1-ila)quinazolina (VIII-34, 7,66 g) como um cristal amarelo pálido.

^{1}H RMN (d_6-DMSO, δ): 10,07 (1H, s), 8,77 (1H, s), 8,60 (1H, s), 8,24 (1H, d, J= 8,8 Hz), 7,97 (1H, d, J= 2,4 Hz), 7,81 (1H, d, J= 8,8 Hz), 7,69 (1H, dd, J= 2,4 Hz, J= 8,8 Hz), 7,51-7,45 (1H, m), 7,35-7,27

(3H, m), 7,21-7,17 (1H, m), 5,27 (2H, s), 4,58 (2H, t. J= 4,8 Hz), 4,54 (2H, t. J= 4,8Hz), 3,24 (3H, s), 2,27 (3H, s).

Fórmula química 78



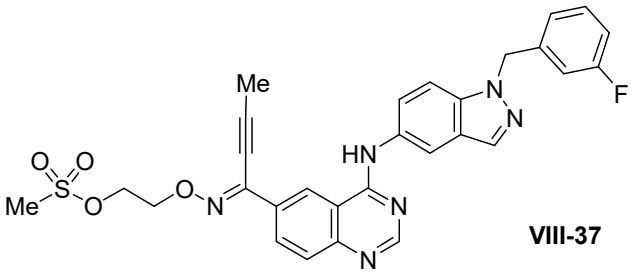
VIII-36

4-(3-Cloro-4-(piridin-2-ilmetoxi)fenilamino)-6-(1-(2-sulfoniloxietoxiimino)-2-butin-1-ila)quinazolina (VIII-36)

[0223] O composto foi sintetizado da mesma maneira que a descrita para a primeira etapa e para a segunda etapa.

^{1}H RMN (d_6-DMSO, δ): 10,09 (1H, s), 8,77 (1H, s), 8,61 (1H, s), 8,59 (1H, s), 8,24 (1H, d, J= 8,1 Hz), 7,97 (1H, d, J= 2,4 Hz), 7,89 (1H, t, J= 7,5 Hz), 7,81 (1H, d, J= 9,0 Hz), 7,68 (1H, dd, J= 2,4 Hz, J= 9,0 Hz), 7,59 (1H, d, J= 8,1 Hz), 7,40-7,35 (1H, m), 7,29 (1H, d, J= 9,0 Hz), 5,31 (2H, s), 4,57 (2H, bs), 4,55 (2H, bs), 3,24 (3H, s), 2,27 (3H, s).

Fórmula química 79



VIII-37

4-(1-(3-Fluorbenzila)-1H-indazol-5-ilamino)-6-(1-(2-sulfoniloxietoxiimino)-2-butin-1-ila)quinazolina (VIII-37)

[0224] O composto foi sintetizado da mesma maneira que a descrita para a primeira etapa e para a segunda etapa.

^{1}H RMN (d_6-DMSO, δ): 10,20 (1H, s), 8,81 (1H, s), 8,53 (1H, s), 8,24 (1H, d, J= 8,7 Hz), 8,17 (1H, s), 8,13 (1H, s), 7,80 (1H, d, J= 8,7 Hz), 7,75 (1H, d, J= 8,7 Hz), 7,67 (1H, d, J= 9,3 Hz), 7,41-7,36 (1H, m), 7,14-7,04 (3H, m), 5,72 (2H, s), 4,58 (2H, t. J= 5,4 Hz), 4,54 (2H, t. J= 5,4 Hz),

3,24 (3H, s), 2,26 (3H, s).

(Etapa 3) Síntese de 4-(3-cloro-4-3-fluorbenziloxi)fenilamino)-6-(1-2-etilaminoetoxiimino)-2-butin-1-ila)quinazolina (VIII-35)

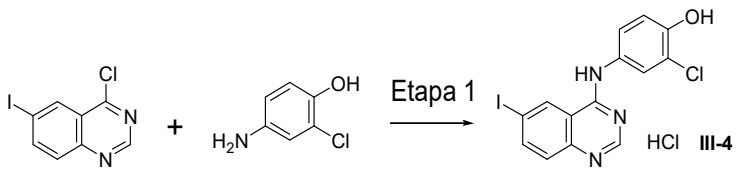
[0225] 4-(3-Cloro-4-(3-fluorbenziloxi)fenilamino)-6-(1-(2-sulfoniloxietoxiimino)-2-butin-1-ila)quinazolina (VIII-34, 100 mg) foi dissolvida em 3 ml de N,N-dimetilformamida, e 160 μg de solução aquosa de etilamina a 70% foram adicionados, seguidos de agitação a 60°C por 14 horas. Água foi adicionada à mistura reacional, seguida de extração com acetato de etila. A camada orgânica foi secada em sulfato de magnésio, e o resíduo concentrado do filtrado foi purificado por cromatografia (eluindo com acetato de etila) usando uma coluna de amina para obter 4-(3-cloro-4-3-fluorbenziloxi)fenilamino)-6-(1-(2-etilaminoetoxiimino)-2-butin-1-ila)quinazolina (VIII-35, 53 mg) como um sólido incolor.

^{1}H RMN (d_6-DMSO, δ): 10,08 (1H, s), 8,74 (1H, s), 8,59 (1H, s), 8,21 (1H, d, J= 8,4 Hz), 7,96 (1H, s), 7,80 (1H, d, J= 8,8 Hz), 7,69 (1H, d, J= 8,0 Hz), 7,51-7,45 (1H, m), 7,35-7,27 (3H, m), 7,21-7,16 (1H, m), 5,27 (2H, s), 4,31 (2H, t. J= 5,6 Hz), 2,89 (2H, t, J= 6,0 Hz), 2,61 (2H, q, J= 7,2 Hz), 2,26 (3H, s), 1,02 (3H, t, J= 7,6 Hz).

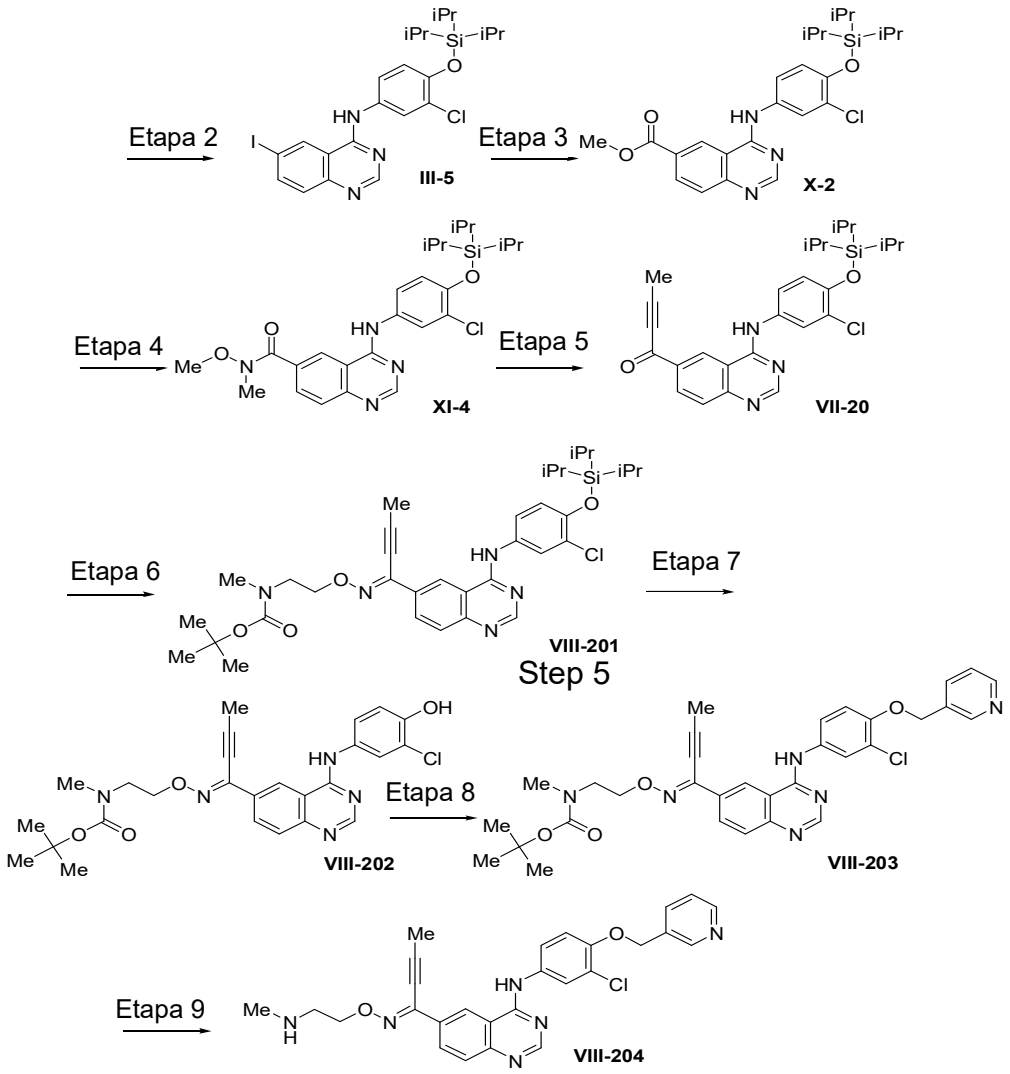
[0226] Na aminação de uma terceira etapa, pode ser usada uma amina que está comercialmente disponível ou uma amina que pode ser sintetizada de acordo com o método descrito em J. Syn. Org. Chem., Jpn., 2001, 59:779-789, Tetrahedron Lett., 1995, 36:6373-6374, Synlett, 1999:1301-1303, Tetrahedron, 2002, 58:6267-6276 ou um sal da mesma.

Exemplo 10

Fórmula química 80



III-4



(Etapa 1) Síntese de 4-(3-Cloro-4-hidroxifenilamino)-6-iodoquinazolina (III-4)

[0227] Da mesma maneira que para a primeira etapa do Exemplo 1 e usando 20,3 g de 4-cloro-6-iodoquinazolina e 10 g de 3-cloro-4-hidroxianilina, cloridrato de 4-(3-cloro-4-hidroxifenilamino)-6-iodoquinazolina (III-4, 26,6 g) foi obtido como um sólido amarelo.

^{1}H RMN (d_6-DMSO, δ): 11,4 (1H, s), 10,5 (1H, s), 9,21 (1H, s), 8,93 (1H, s), 8,35 (1H, d, J= 8,4 Hz), 7,79 (1H, s), 7,69 (1H, d, J= 9,0 Hz), 7,48 (1H, d, J= 9,0 Hz), 7,10 (1H, d, J= 8,4 Hz).

(Etapa 2) Síntese de 4-(3-cloro-4-triisopropilsililoxifenilamino)-6-iodoquinazolina (III-5)

[0228] Cloridrato de 4-(3-Cloro-4-3-fluorbenziloxi)fenilamino)-6-

iodoquinazolina (III-4, 20 g), 13,3 g de cloreto de triisopropilsilano, e 12,6 g de imidazol foram dissolvidos em 200 ml de N, N-dimetilformamida, seguidos de agitação à temperatura ambiente por 4 horas. Depois de completada a reação, 200 ml de solução aquosa saturada de bicarbonato de sódio e 200 ml de acetato de etila foram adicionados para separar as camadas. A camada aquosa foi novamente extraída com 200 ml de acetato de etila duas vezes, e todas as camadas orgânicas foram combinadas, lavadas com água e solução aquosa saturada de cloreto de sódio nesta ordem, e secadas em sulfato de magnésio anidro. O filtrado foi concentrado, e o resíduo foi lavado com hexano-acetato de etila (2:1) para obter 4-(3-cloro-4-triisopropilsililoxifenilamino)-6-iodoquinazolina (III-5, 25,3 g) como um sólido incolor.

^{1}H RMN (d_6-DMSO, δ): 9,8 (1H, s), 8,96 (1H, s), 8,62 (1H, s), 8,12 (1H, d, J= 8,7 Hz), 8,02 (1H, d, J= 2,7 Hz), 7,70 (1H, dd, J= 8,7 Hz, J= 2,7 Hz), 7,56 (1H, d, J= 8,7 Hz), 7,04 (1H, d, J= 8,7 Hz), 1,25-1,40 (3H, m), 1,11 (18H, d, J= 7,2 Hz).

(Etapa 3) Síntese de éster metílico do ácido 4-(3-cloro-4-triisopropilsililoxifenilamino)-quinazolina-6-carboxílico (X-2)

[0229] De 4-(3-cloro-4-triisopropilsililoxifenilamino)-6-iodoquinazolina (III-5, 21,8 g), éster metílico do ácido 4-(3-cloro-4-triisopropilsililoxifenilamino)-quinazolina-6-carboxílico (X-2, 20,4 g) foi obtido como um sólido amarelo da mesma maneira que para a primeira etapa do Exemplo de referência 1.

^{1}H RMN (d_6-DMSO, δ): 10,2 (1H, s), 9,26 (1H, s), 8,66 (1H, s), 8,30 (1H, d, J= 8,7 Hz), 8,01 (1H, d, J= 2,4 Hz), 7,84 (1H, d, J= 8,7 Hz), 7,71 (1H, dd, J= 9 Hz, J= 2,1 Hz), 7,04 (1H, d, J= 8,7 Hz), 3,96 (3H, s), 1,29-1,41 (3H, m), 1,11 (18H, d, J= 7,2 Hz).

(Etapa 4) Síntese de metoximetilamida de ácido 4-(3-cloro-4-triisopropilsililoxifenilamino)-quinazolina-6-carboxílico (XI-4)

[0230] De éster metílico do ácido 4-(3-cloro-4-triisopropilsililoxifenilamino)-quinazolina-6-carboxílico (X-2, 10 g), metoximetilamida de ácido 4-(3-cloro-4-triisopropilsililoxifenilamino)-quinazolina-6-carboxílico (XI-4, 4,1 g) foi obtida como um sólido incolor da mesma maneira que para a segunda etapa do Exemplo de referência 1.

^{1}H RMN (d_6-DMSO, δ): 10,0 (1H, s), 8,80 (1H, s), 8,65 (1H, s), 7,97-8,08 (2H, m), 7,81 (1H, d, J= 8,7 Hz), 7,70-7,75 (1H, m), 7,04 (1H, d, J= 9,0 Hz), 3,58 (3H, s), 3,35 (3H, s), 1,29-1,41 (3H, m), 1,11 (18H, d, J= 7,5 Hz).

(Etapa 5) Síntese de 4-(3-cloro-4-triisopropilsililoxifenilamino)-6-(1-oxo-2-butin-1-ila)quinazolina (VII-20)

[0231] De metoximetilamida de ácido 4-(3-cloro-4-triisopropilsililoxifenilamino)-quinazolina-6-carboxílico (XI-4, 4,1 g), 4-(3-cloro-4-triisopropilsililoxifenilamino)-6-(1-oxo-2-butin-1-ila)quinazolina (VII-20, 1,3 g) foi obtida como um óleo amarelo da mesma maneira que para a terceira etapa do Exemplo de referência 1.

^{1}H RMN (d_6-DMSO, δ): 10,3 (1H, s), 9,24 (1H, s), 8,67 (1H, s), 8,45 (1H, d, J= 8,7 Hz), 7,99 (1H, s), 7,88(1H, s, J= 8,7 Hz), 7,68 (1H, d, J= 9,0 Hz), 7,06 (1H, d, J= 9,0 Hz), 2,28 (3H, s), 1,29-1,41 (3H, m), 1,11 (18H, d, J= 6,9 Hz).

(Etapa 6) Síntese de 4-(3-cloro-4-triisopropilsililoxifenilamino)-6-(1-(2-(N-(ter-butoxicarbonila)-N-metilaminoetoxiimino)-2-butin-1-ila)quinazolina (VIII-201)

[0232] De 4-(3-cloro-4-triisopropilsililoxifenilamino)-6-(1-oxo-2-butin-1-ila)quinazolina (VII-20, 1,3 g), 4-(3-cloro-4-triisopropilsililoxifenilamino)-6-(1-(2-(N-(ter-butoxicarbonila)-N-metilaminoetoxiimino)-2-butin-1-ila)quinazolina (VIII-201, 1,1 g) foi obtida como um sólido amarelo da mesma maneira que para a segunda etapa do Exemplo 2.

ESI-MS (M/Z): (M+) = 666,71, (M+H) = 667,73

(Etapa 7) Síntese de 4-(3-cloro-4-hidroxifenilamino)-6-(1-(2-(N-(terc-butoxicarbonila)-N-metilaminoetoxiimino)-2-butin-1-ila)quinazolina (VIII-202)

[0233] 4-(3-Cloro-4-triisopropilsililoxifenilamino)-6-(1-(2-(N-(terc-butoxicarbonila)-N-metilaminoetoxiimino)-2-butin-1-ila)quinazolina (VIII-201, 1,1 g) foi dissolvida em 20 ml de tetrahidrofurano, e 6,7 ml de solução de fluoreto de tetrabutilamônio a 1 mol/l em tetrahidrofurano foram adicionados, seguidos de agitação à temperatura ambiente por 30 minutos. Depois de completada a reação, 10 ml de água e 10 ml de acetato de etila foram adicionados para separar as camadas. A camada aquosa foi novamente extraída com 10 ml de acetato de etila duas vezes, e todas as camadas orgânicas foram combinadas, lavadas com água e solução aquosa saturada de cloreto de sódio, e secadas em sulfato de magnésio anidro. O filtrado foi concentrado, e o resíduo foi lavado com hexano-acetato de etila (1:1) para obter 4-(3-cloro-4-hidroxifenilamino)-6-(1-(2-(N-(ter-butoxicarbonila)-N-metilaminoetoxiimino)-2-butin-1-ila)quinazolina (VIII-202, 0,7 g) como um sólido amarelo.

^{1}H RMN (d_6-DMSO, δ): 9,96 (1H, s), 8,73 (1H, s), 8,55 (1H, s), 8,21 (1H, d, J= 8,7 Hz), 7,75-7,86 (2H, m), 7,50 (1H, d, J= 7,8 Hz), 7,00 (1H, d, J= 8,7 Hz), 4,36 (2H, bs), 3,56 (2H, bs), 2,86 (3H, bs), 2,25 (3H, bs), 1,36 (9H, s).

(Etapa 8) Síntese de 4-(3-cloro-4-(piridin-3-ilmetoxi)fenilamino)-6-(1-(2-(N-(terc-butoxicarbonila)-N-metilaminoetoxiimino)-2-butin-1-ila)quinazolina (VIII-203)

[0234] 4-(3-Cloro-4-hidroxifenilamino)-6-(1-(2-(N-(terc-butoxicarbonila)-N-metilaminoetoxiimino)-2-butin-1-ila)quinazolina (VIII-202, 70 mg), 87 mg de bromidrato de 3-bromometilpiridina, e 223 mg de carbonato de césio foram dissolvidos em 1,1 ml de N, N-dimetilformamida-água (10,1), seguidos de agitação à temperatura

ambiente por 3 horas. Depois de completada a reação, 5 ml de água e 5 ml de acetato de etila foram adicionados para separar as camadas. A camada aquosa foi novamente extraída com 5 ml de acetato de etila duas vezes, e todas as camadas orgânicas foram combinadas, lavadas com água e solução aquosa saturada de cloreto de sódio nesta ordem, e secadas em sulfato de magnésio anidro. O filtrado foi concentrado, e o resíduo foi purificado por cromatografia de coluna sobre sílica-gel (eluindo com hexano: acetato de etila = 1:1) para obter 4-(3-cloro-4-(piridin-3-ilmetoxi)fenilamino)-6-(1-(2-(N-(terc-butoxicarbonila)-N-metilaminoetoxiimino)-2-butin-1-ila)quinazolina (VIII-203, 70 mg) como um óleo amarelo.

^{1}H RMN (d_6-DMSO, δ): 10,0 (1H, bs), 8,74 (1H, bs), 8,72 (1H, bs), 8,60 (1H, s), 8,57 (1H, d, J= 4,4 Hz), 8,23 (1H, d, J= 8,8 Hz), 7,97 (1H, bs), 7,91 (1H, d, J= 8,0 Hz), 7,80 (1H, d, J= 8,8 Hz), 7,72 (1H, d, J= 8,8 Hz), 7,46 (1H, dd, J= 7,6 Hz, J= 4,4 Hz), 7,33 (1H, d, J= 8,8 Hz), 5,29 (2H, s), 4,37 (2H, bs), 3,56 (2H, bs), 2,86 (3H, bs), 2,25 (3H, bs), 1,36 (9H, s).

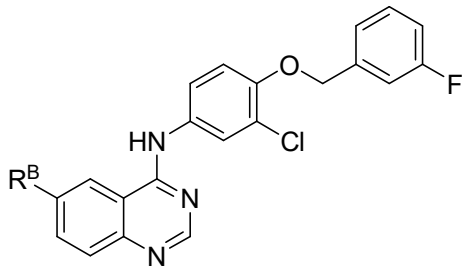
(Etapa 9) Síntese de 4-(3-cloro-4-(piridin-3-ilmetoxi)fenilamino)-6-(1-(2-N-metilaminoetoxiimino)-2-butin-1-ila)quinazolina (VIII-204)

[0235] Partindo de 4-(3-cloro-4-(piridin-3-ilmetoxi)fenilamino)-6-(1-(2-(N-(terc-butoxicarbonila)-N-metilaminoetoxiimino)-2-butin-1-ila)quinazolina (VIII-203, 70 mg), e da mesma maneira que para a segunda etapa do Exemplo 2, a reação foi realizada, e purificação foi efetuada por recristalização de hexano-acetato de etila para obter 4-(3-cloro-4-(piridin-3-ilmetoxi)fenilamino)-6-(1-(2-N-metilaminoetoxiimino)-2-butin-1-ila)quinazolina (VIII-204, 7 mg) como um sólido amarelo.

10,3 (1H, s), 8,84 (1H, s), 8,72 (1H, s), 8,42-8,65 (2H, m), 8,26 (1H, d, J= 7,6 Hz), 7,98 (1H, s), 7,91 (1H, brs), 7,81 (1H, brs), 7,71 (1H, brs), 7,47 (1H, brs), 7,34 (1H, d, J= 8,0 Hz), 5,30 (2H, s), 4,53 (2H, brs), 3,38 (2H, brs), 2,68 (3H, s), 2,26 (3H, s).

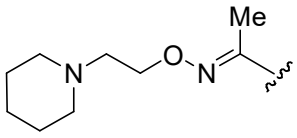
[0236] Da mesma maneira que para os exemplos 7 a 10, foi sintetizado o seguinte composto.

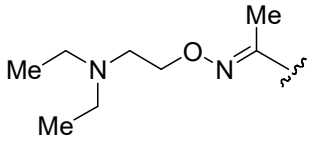
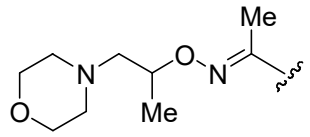
Fórmula química 81

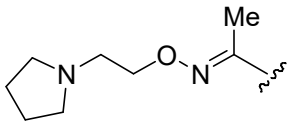
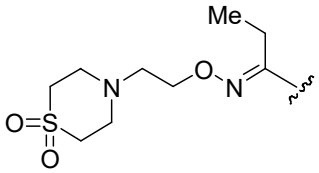


(VIII)

Tabela 15

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-2		9,92 (1H, s), 8,65 (1H, brs), 8,62 (1H, s), 8,22 (1H, d, J=6,6Hz), 7,96 (1H, d, J=2,1Hz), 7,76 (1H, d, J=6,6Hz), 7,70 (1H, dd, J=6,6Hz, J=1,8Hz), 7,53-7,45 (1H, m), 7,35-7,28 (3H, m), 7,18 (1H, t, J=5,7Hz), 5,27 (2H, s), 4,30 (2H, t, J=4,5Hz), 2,64 (2H, t, J=4,5Hz), 2,43 (4H, brs), 2,35 (3H, s), 1,53-1,47 (4H, m), 1,40-1,36 (2H, m),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-3		9,92 (1H, s), 8,62 (1H, brs), 8,58 (1H, s), 8,23 (1H, d, J=6,6Hz), 7,96 (1H, d, J=1,8Hz), 7,76 (1H, d, J=6,6Hz), 7,70 (1H, d, J=6,9Hz), 7,50-7,45 (1H, m), 7,35-7,28 (3H, m), 7,18 (1H, t, J=6,9Hz), 5,27 (2H, s), 4,26 (2H, t, J=4,5Hz), 2,77 (2H, t, J=4,5Hz), 2,55 (4H, q, J=5,4Hz), 2,36 (3H, s), 0,96 (2H, t, J=5,4Hz)
VIII-4		(mono-HCl salt) 11,4 (1H, brs), 10,82 (1H, brs), 9,07 (1H, s), 8,82 (1H, s), 8,40 (1H, d, J=10,2Hz), 7,94 (1H, d, J=2,7Hz), 7,88 (1H, d, J=9,0Hz), 7,70 (1H, dd, J=8,7Hz, 2,7Hz), 7,45-7,52 (1H, m), 7,31-7,36 (3H, m), 7,17-7,23 (1H, m), 5,30 (2H, s), 4,94 (1H, m), 3,85 (4H, m), 3,36-3,60 (6H, m), 2,44 (3H, s), 1,38 (3H, d, J=6,3Hz)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-5		9,93 (1H, s), 8,62 (1H, brs), 8,58 (1H, s), 8,22 (1H, d, J=6,6Hz), 7,96 (1H, d, J=1,8Hz), 7,76 (1H, d, J=6,6Hz), 7,70 (1H, dd, J=6,6Hz, J=1,8Hz), 7,50-7,45 (1H, m), 7,35-7,28 (3H, m), 7,19 (1H, t, J=6,6Hz), 5,27 (2H, s), 4,31 (2H, t, J=4,5Hz), 2,78 (2H, t, J=4,5Hz), 2,50 (4H, br), 2,36 (3H, s), 1,69 (4H, br)
VIII-6		9,95 (1H, s), 8,62 (1H, brs), 8,58 (1H, s), 8,21 (1H, d, J=6,9Hz), 7,94 (1H, d, J=1,5Hz), 7,77 (1H, d, J=6,6Hz), 7,69 (1H, d, J=6,9Hz), 7,51-7,45 (1H, m), 7,35-7,28 (3H, m), 7,19 (1H, t, J=6,3Hz), 5,28 (2H, s), 4,32 (2H, t, J=4,2Hz), 3,09 (4H, brd, J=4,5Hz), 3,05 (4H, brd, J=4,5Hz), 2,97-2,89 (4H, m), 1,13 (3H, t, J=5,4Hz)

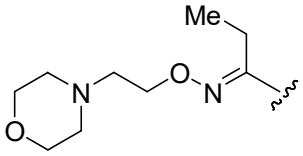
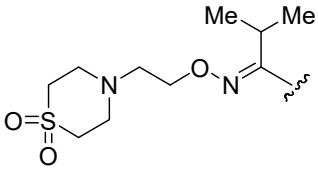
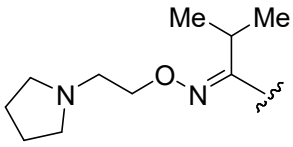
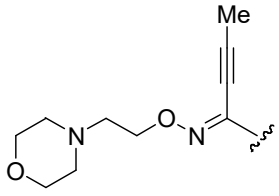
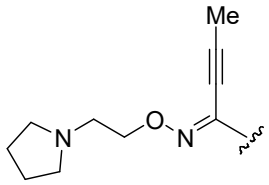
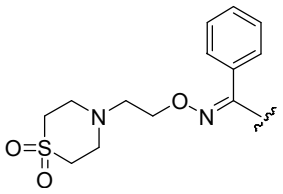
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-7		9,95 (1H, s), 8,61 (1H, brs), 8,58 (1H, s), 8,20 (1H, d, J=6,6Hz), 7,94 (1H, brs), 7,77 (1H, d, J=6,6Hz), 7,69 (1H, d, J=6,9Hz), 7,51-7,45 (1H, m), 7,35-7,28 (3H, m), 7,19 (1H, t, J=6,0Hz), 5,27 (2H, s), 4,32 (2H, t, J=4,2Hz), 3,59 (4H, t, J=3,3Hz), 2,91 (2H, q, J=5,4Hz), 2,68 (2H, t, J=4,2Hz), 1,13 (3H, t, J=5,4Hz)

Tabela 16

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-8		(Mistura E/Z) 8,61 (0,5H, s), 8,58 (0,5H, s), 8,48 (0,5H, s), 8,25 (0,5H, s), 7,99 (0,5H, d, J = 2,4Hz), 7,97 (0,5H, d, J = 2,4 Hz), 7,90 (0,5H, d, J = 7,9 Hz), 7,65-7,73 (2,5H, m), 7,50-7,55 (0,5H, m), 7,26-7,34 (3,5H, m), 7,16 (1H, d,t J = 7,9,2,4 Hz), 5,26 (2H, s), 4,29 (1H, t, J = 7,0 Hz), 4,15 (1H, t, J = 7,0 Hz), 3,50-3,55 (1H, m) , 3,28-3,35 (2H, m), 3,20-3,28 (2H, m), 3,10-3,20 (2H, m), 2,99-3,07 (2H, m), 2,90-2,96 (1H, m), 2,87-2,95 (1H, m), 1,21 (3H, d, J = 7,0Hz), 1,16 (3H, d, J = 7,0Hz)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-9		(Mistura E/Z) 8,58 (0,5H, s), 8,56 (0,5H, s), 8,44 (0,5H, s), 8,36 (0,5H, s), 7,99 (0,5H, d, J = 2,4Hz), 7,97 (0,5H, d, J = 2,4 Hz), 7,90 (0,5H, d, J = 7,9 Hz), 7,65-7,73 (2,5H, m), 7,50-7,55 (0,5H, m), 7,26-7,34 (3,5H, m), 7,16 (1H, d,t J = 7,9,2,4 Hz), 5,24 (2H, s), 4,21 (1H, t, J = 7,0 Hz), 4,05 (1H, t, J = 7,0 Hz), 2,73 (1H, t, J = 7,2Hz) , 2,57 (1H, t, J = 7,2Hz), 2,45-2,55 (2H, m), 2,30-2,35 (2H, m), 1,64-1,70 (2H, m), 1,50-1,58 (2H, m), 1,21 (3H, d, J = 7,0Hz), 1,16 (3H, d, J = 7,0Hz)
VIII-10		(Mistura E/Z) 10,09 (1H, s, principal), 10,00 (1H, s, secundário), 8,74 (1H, s, principal), 8,59 (1H, s), 8,22 (1H, d, J=9Hz, principal), 7,94-8,02 (1H, m), 7,64-7,82 (2H, m), 7,44-7,52 (1H, m), 7,16-7,36 (4H, m), 5,27 (2H, s), 4,32-4,43 (2H, m), 3,56-3,62 (4H, m), 2,66-2,74 (2H, m), 2,34 (3H, s, secundário), 2,25 (3H, s, principal)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-11		10,08 (1H, s), 8,74 (1H, s), 8,58 (1H, s), 8,22 (1H, d, J=8,4Hz), 7,96 (1H, brs), 7,80 (1H, d, J=8,4Hz), 7,68 (1H, d, J=9,6Hz), 7,43-7,52 (1H, m), 7,14-7,36 (4H, m), 5,27 (2H, s), 4,37 (2H, t, J=6,0Hz), 2,80 (2H, t, J=6,0Hz), 2,25 (3H, s), 1,69 (4H, brs), 1,24 (4H, brs)
VIII-12		(Mistura E/Z) 9,95 (1H, s, principal), 9,80 (1H, s, secundário), 8,65 (1H, s, secundário), 8,58 (1H, s, principal), 8,54 (1H, s, principal), 8,44 (1H, s, secundário), 7,99 (1H, d, J=1,5Hz, secundário), 7,91 (1H, d, J=1,8Hz, principal), 7,15-7,92 (14H, m), 5,26 (2H, s), 5,25 (2H, s), 4,32 (2H, d, J=3,9Hz, principal), 4,27 (2H, t, J=4,2Hz, secundário), 2,82-3,06 (10H, m)

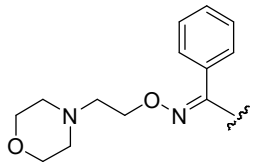
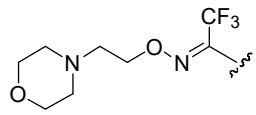
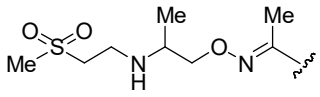
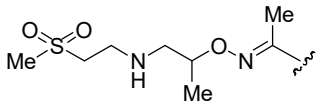
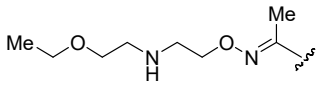
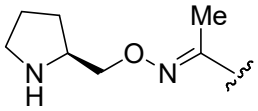
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-13		(Mistura E/Z) 9,96 (1H, s, principal), 9,82 (1H, s, secundário), 8,64 (1H, s, secundário), 8,57 (1H, s, principal), 8,53 (1H, brs, principal), 8,44 (1H, brs, secundário), 7,99 (1H, d, J=2,7Hz, secundário), 7,90 (1H, d, J=2,4Hz, principal), 7,14-7,88 (13H, m), 5,26 (2H, s, principal), 5,24 (2H, s, secundário), 4,32 (2H, t, J=5,7Hz, principal), 4,27 (2H, t, J=5,4Hz, secundário), 3,53-3,58 (4H, m, principal), 3,44-3,50 (4H, m, secundário), 2,56-2,70 (2H, m), 2,32-2,46 (4H, m)

Tabela 17

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-14		9,99 (1H, s), 8,65 (s, 1H), 8,61 (1H, s), 7,98 (1H, brs), 7,90 (1H, d, J=6,9Hz), 7,87 (1H, d, J=6,9Hz), 7,70 (1H, d, J=6,3Hz), 7,40-7,51 (1H, m), 7,27-7,35 (3H, m), 7,15-7,21 (1H, m), 5,27 (2H, s), 4,38 (2H, t, J=3,9Hz), 3,47-3,51 (4H, m), 2,57-2,65 (2H, m), 2,33-2,40 (4H, m)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-15		9,94 (1H, s), 8,63 (1H, s), 8,58 (1H, s), 8,23 (1H, dd, J=8,7Hz, 1,2Hz), 7,96 (1H, d, J=2,4Hz), 7,76 (1H, d, J=9,0Hz), 7,70 (1H, dd, J=8,4Hz, 2,4Hz), 7,44-7,52 (1H, m), 7,28-7,35 (3H, m), 7,16-7,22 (1H, m), 5,27 (2H, s), 4,07-4,10 (2H, m), 3,23 (2H, t, J=6,9Hz), 3,01-3,04 (6H, m), 2,38 (3H, s), 1,05 (3H, d, J=6,3Hz)
VIII-16		9,94 (1H, s), 8,62 (1H, s), 8,58 (1H, s), 8,25 (1H, dd, J=9,0Hz, 1,5Hz), 7,95 (1H, d, J=2,7Hz), 7,76 (1H, d, J=8,7Hz), 7,69 (1H, dd, J=8,7Hz, 2,4Hz), 7,44-7,52 (1H, m), 7,28-7,35 (3H, m), 7,16-7,22 (1H, m), 5,27 (2H, s), 4,39-4,45 (1H, m), 3,25 (2H, t, J=6,9Hz), 2,95-3,01 (5H, m), 2,73-2,92 (2H, m), 2,36 (3H, s), 1,30 (3H, d, J=6,3Hz)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-17		(sal di-HCl) 11,09 (1H, brs), 9,00 (1H, s), 8,90 (2H, brs), 8,75 (1H, s), 8,34 (1H, d, J=9,3Hz), 7,96 (1H, d, J=2,7Hz), 7,85 (1H, d, J=8,7Hz), 7,72 (1H, dd, J=9,0Hz, 2,7Hz), 7,45-7,52 (1H, m), 7,31-7,35 (3H, m), 7,17-7,22 (1H, m), 5,29 (2H, s), 4,49 (2H, t, J=5,4Hz), 3,67 (2H, t, J=5,4Hz), 3,49 (2H, q, J=6,9Hz), 3,21-3,23 (4H, m), 2,45 (3H, s), 1,13 (3H, t, J=6,9Hz)
VIII-18		9,93 (1H, s), 8,62 (1H, brs), 8,58 (1H, s), 8,22 (1H, d, J=6,9Hz), 7,95 (1H, brs), 7,76 (1H, d, J=6,0Hz), 7,70 (1H, d, J=6,3Hz), 7,50-7,45 (1H, m), 7,35-7,28 (3H, m), 7,18 (1H, t, J=5,4Hz), 5,27 (2H, s), 4,11-4,03 (2H, m), 2,87-2,67 (2H, m), 2,37 (3H, s), 1,85-1,76 (1H, m), 1,73-1,59 (2H, m), 1,48-1,39 (1H, m)

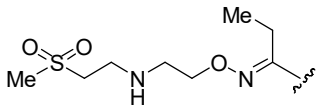
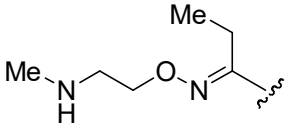
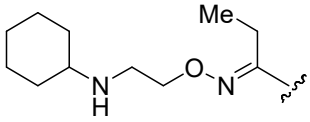
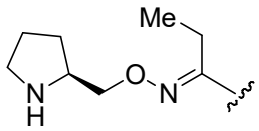
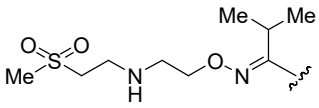
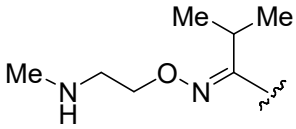
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-19		(sal bis-trifluoroacetato) 11,40 (1H, s), 9,10 (2H, s), 8,89 (1H, s), 8,81 (1H, s), 8,42 (1H, d, J=6,0Hz), 7,90-7,87 (2H, m), 7,62 (1H, d, J=6,6Hz), 7,51-7,46 (1H, m), 7,38-7,31 (3H, m), 7,20 (1H, t, J=6,3Hz), 5,32 (2H, s), 4,48 (2H, brs), 3,61-3,46 (6H, m), 3,13 (3H, s), 2,97 (2H, q, J=5,7Hz), 1,14 (3H, t, J=5,7Hz),
VIII-20		(sal bis-trifluoroacetato) 11,07 (1H, s), 8,82 (1H, s), 8,78 (3H, brs), 8,37 (1H, d, J=6,6Hz), 7,89-7,86 (2H, m), 7,64 (1H, d, J=6,6Hz), 7,51-7,46 (1H, m), 7,36-7,32 (3H, m), 7,20 (1H, t, J=6,3Hz), 5,31 (2H, s), 4,45 (2H, brs), 2,97 (2H, q, J=5,4Hz), 2,67 (3H, brs), 1,13 (3H, t, J=5,4Hz),

Tabela 18

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-21		(sal bis-trifluoroacetato) 11,03 (1H, s), 8,81 (1H, s), 8,78 (1H, s), 8,71 (2H, s), 8,37 (1H, d, J=6,6Hz), 7,88-7,86 (2H, m), 7,64 (1H, d, J=6,6Hz), 7,51-7,46 (1H, m), 7,36-7,31 (3H, m), 7,20 (1H, t, J=6,3Hz), 5,31 (2H, s), 4,46 (2H, brs), 3,39 (2H, brs), 3,10 (1H, brs), 2,97 (2H, q, J=6,3Hz), 2,06 (2H, brd, J=8,4Hz), 1,78 (2H, brd, J=8,4Hz), 1,37-1,04 (9H, m),
VIII-22		9,95 (1H, s), 8,61 (1H, brs), 8,58 (1H, s), 8,19 (1H, d, J=6,3Hz), 7,94 (1H, brs), 7,77 (1H, d, J=6,6Hz), 7,69 (1H, d, J=6,6Hz), 7,50-7,45 (1H, m), 7,35-7,28 (3H, m), 7,19 (1H, t, J=6,0Hz), 5,27 (2H, s), 4,14-4,07 (2H, m), 3,43 (1H, br), 2,95-2,82 (4H, m), 1,86-1,80 (1H, m), 1,69 (2H, m), 1,46 (1H, m), 1,14 (3H, t, J=5,4Hz)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-23		(Mistura E/Z) 8,60 (0,5H, s), 8,58 (0,5H, s), 8,47 (0,5H, s), 8,39 (0,5H, s), 7,96 (0,5H, d, J = 2,4Hz), 7,93 (0,5H, d, J = 2,4 Hz), 7,88 (0,5H, d, J = 7,9 Hz), 7,65-7,73 (2,5H, m), 7,50-7,55 (0,5H, m), 7,26-7,34 (3,5H, m), 7,16 (1H, d,t J = 7,9,2,4 Hz), 5,26 (2H, s), 4,19 (1H, t, J = 7,0 Hz), 4,03 (1H, t, J = 7,0 Hz), 3,50-3,55 (1H, m) , 3,22-3,30 (1H, m) , 3,16-3,23 (1H, m), 2,96-3,03 (1H, m), 3,04 (1,5H, s), 2,90-2,95 (2H, m), 2,93 (1,5H, s), 2,70-2,80 (1H, m), 1,21 (3H, d, J = 7,0Hz), 1,16 (3H, d, J = 7,0Hz)
VIII-24		(Mistura E/Z) 8,61 (0,5H, s), 8,59 (0,5H, s), 8,47 (0,5H, s), 8,41 (0,5H, s), 7,99 (0,5H, d, J = 2,4Hz), 7,97 (0,5H, d, J = 2,4 Hz), 7,90 (0,5H, d, J = 7,9 Hz), 7,65-7,73 (2,5H, m), 7,50-7,55 (0,5H, m), 7,26-7,34 (3,5H, m), 7,16 (1H, d,t J = 7,9,2,4 Hz), 5,26 (2H, s), 4,29 (1H, t, J = 7,0 Hz), 4,13 (1H, t, J = 7,0 Hz), 3,50-3,55 (1H, m) , 3,14-3,30 (1H, m) , 2,96-3,04 (1H, m) , 2,54 (1,5H, s) , 2,49 (1,5H, s), 1,21 (3H, d, J = 7,0Hz), 1,16 (3H, d, J = 7,0Hz), 1,00 (3H, t, J = 7,2Hz)

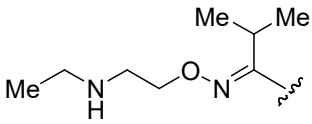
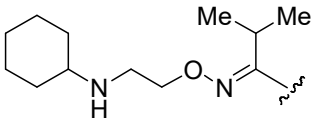
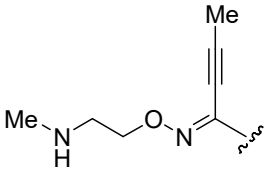
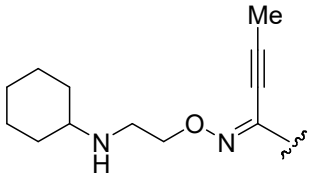
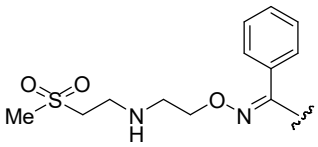
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-25		(Mistura E/Z) 8,61 (0,5H, s), 8,58 (0,5H, s), 8,48 (0,5H, s), 8,31 (0,5H, s), 7,99 (0,5H, d, J = 2,4Hz), 7,97 (0,5H, d, J = 2,4 Hz), 7,90 (0,5H, d, J = 7,9 Hz), 7,65-7,73 (2,5H, m), 7,50-7,55 (0,5H, m), 7,26-7,34 (3,5H, m), 7,16 (1H, d,t J = 7,9,2,4 Hz), 5,26 (2H, s), 4,29 (1H, t, J = 7,0 Hz), 4,15 (1H, t, J = 7,0 Hz), 3,50-3,55 (1H, m) , 3,24-3,30 (1H, m) , 3,10-3,14 (1H, m) , 2,99 (1H, q, J = 7,2Hz) , 2,89 (1H, q, J = 7,2Hz), 1,21 (3H, d, J = 7,0Hz), 1,16 (3H, d, J = 7,0Hz), 1,00 (3H, t, J = 7,2Hz)

Tabela 19

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-26		(Mistura E/Z) 8,61 (0,5H, s), 8,58 (0,5H, s), 8,48 (0,5H, s), 8,31 (0,5H, s), 7,99 (0,5H, d, J = 2,4Hz), 7,94 (0,5H, d, J = 2,4 Hz), 7,90 (0,5H, d, J = 7,9 Hz), 7,65-7,73 (2,5H, m), 7,50-7,55 (0,5H, m), 7,26-7,34 (3,5H, m), 7,16 (1H, d,t J = 7,9,2,4 Hz), 5,26 (2H, s), 4,29 (1H, t, J = 7,0 Hz), 4,11 (1H, t, J = 7,0 Hz), 3,50-3,55 (1H, m) , 3,14-3,17 (1H, m) , 3,00-3,04 (1H, m) , 2,00-2,10 (2H, m), 1,70-1,85 (2H, m), 1,00-1,30 (6H, m), 1,23 (3H, d, J = 7,0Hz), 1,16 (3H, d, J = 7,0Hz)
VIII-27		10,10 (1H, s), 8,76 (1H, s), 8,60 (1H, s), 8,25 (1H, d, J=8,7Hz), 7,96 (1H, brs), 7,82 (1H, d, J=9,0Hz), 7,69 (1H, d, J=9,0Hz), 7,43-7,52 (1H, m), 7,14-7,36 (4H, m), 5,28 (2H, s), 4,43 (2H, brs), 2,98 (2H, brs), 2,54 (3H, s), 2,27 (3H, brs), 1,60 (1H, s)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-28		10,10 (1H, s), 8,77 (1H, s), 8,60 (1H, s), 8,25 (1H, d, J=8,7Hz), 7,95 (1H, brs), 7,82 (1H, d, J=9,6Hz), 7,69 (1H, d, J=9,3Hz), 7,43-7,52 (1H, m), 7,14-7,36 (4H, m), 5,28 (2H, s), 4,45 (2H, brs), 2,91 (2H, brs), 2,27 (3H, s), 2,00 (2H, brs), 1,73 (2H, brs), 1,60 (1H, brs), 1,23 (7H, brs)
VIII-29		(Mistura E/Z) 9,94 (1H, s, principal), 9,78 (1H, s, secundário), 8,62 (1H, s, secundário), 8,56 (1H, s, principal), 8,51 (1H, brs, principal), 8,42 (1H, brs, secundário), 7,12-7,53 (14H, m), 5,24 (2H, s,), 4,15-4,28 (2H, m), 3,13-3,25 (2H, m), 2,80-3,00 (7H, m)

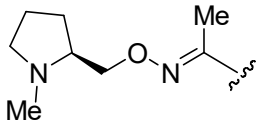
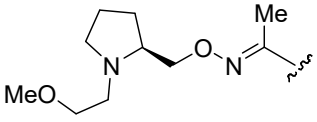
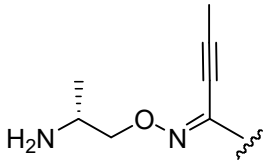
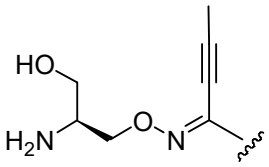
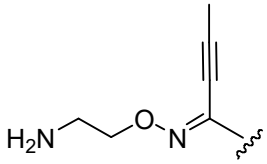
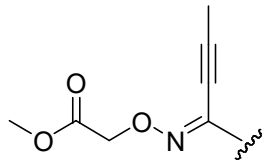
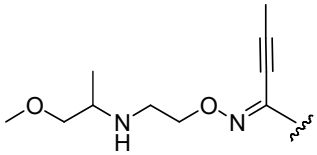
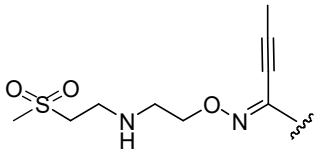
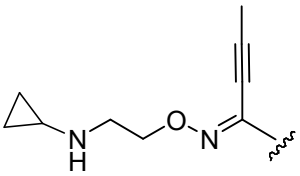
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-30		9,93 (1H, s), 8,62 (1H, brs), 8,58 (1H, s), 8,22 (1H, d, J=6,3Hz), 7,96 (1H, d, J=1,2Hz), 7,76 (1H, d, J=6,6Hz), 7,70 (1H, d, J=6,6Hz), 7,50-7,45 (1H, m), 7,35-7,28 (3H, m), 7,19 (1H, t, J=6,6Hz), 5,27 (2H, s), 4,23 (1H, dd, J=8,1Hz, J=4,2Hz), 4,11 (1H, dd, J=8,1Hz, J=4,2Hz), 2,98-2,93 (1H, m), 2,59-2,54 (1H, m), 2,36 (6H, s), 2,17 (1H, dd, J=13Hz, J=6,6Hz), 1,97-1,88 (1H, m), 1,71-1,54 (3H, m)
VIII-31		9,92 (1H, s), 8,62 (1H, brs), 8,58 (1H, s), 8,22 (1H, d, J=6,9Hz), 7,96 (1H, brs), 7,76 (1H, d, J=6,6Hz), 7,70 (1H, d, J=6,6Hz), 7,50-7,45 (1H, m), 7,35-7,28 (3H, m), 7,19 (1H, t, J=6,6Hz), 5,27 (2H, s), 4,18 (1H, dd, J=7,8Hz, J=4,5Hz), 4,06 (1H, dd, J=7,8Hz, J=4,5Hz), 3,43 (1H, t, J=4,8Hz), 3,24 (3H, s), 3,08-2,99 (2H, m), 2,88-2,81 (1H, m), 2,36 (3H, s), 2,27 (1H, dd, J=13Hz, J=6,6Hz), 1,93-1,84 (1H, m), 1,72-1,54 (3H, m)

Tabela 20

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-40		10,08 (1H, bs), 8,74 (1H, s), 8,58 (1H, s), 8,21 (1H, d, J=8,8Hz), 7,96 (1H, s), 7,80 (1H, d, J=8,8Hz), 7,51-7,45 (1H, m), 7,35-7,27 (3H, m), 7,19 (1H, t, J=8,0Hz), 5,27 (2H, s), 4,04 (2H, t, J=5,6Hz), 3,08-3,05 (1H, m), 2,22 (3H, s), 1,04 (3H, d, J=6,4Hz),
VIII-41		10,13-10,09 (1H, m), 8,82 (1H, s), 8,74 (1H, s), 8,21 (1H, d, J=14,0Hz), 7,69-7,62 (1H, m), 7,50-7,45 (1H, m), 7,35-7,26 (3H, m), 7,18 (1H, t, J=8,2Hz), 5,27 (2H, s), 4,69 (1H, bs), 4,25-4,21 (1H, m), 4,13-4,09 (1H, m), 3,46-3,44 (2H, m), 3,09 (1H, t, J=5,6Hz), 2,26 (3H, s)
VIII-42		10,2 (1H, s), 8,78 (1H, s), 8,59 (1H, s), 8,24 (1H, d, J=8,8Hz), 7,96 (1H, s), 7,81 (1H, d, J=8,8Hz), 7,66-7,73 (1H, m), 7,43-7,50 (1H, m), 7,23-7,36 (3H, m), 7,15-7,22 (1H, m), 5,27 (2H, s), 4,31-4,48 (2H, m), 3,07-3,15 (2H, m), 2,27 (3H, s)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-43		10,10 (1H, brs), 8,75 (1H, d, J=2,0Hz), 8,59 (1H, s), 8,17 (1H, dd, J=2,4, 11,6Hz), 7,96 (1H, d, J=3,2Hz), 7,80 (1H, d, J=12,0Hz), 7,68 (1H, dd, J=3,6, 12,0Hz), 7,51-7,44 (1H, m), 7,34-7,26 (3H, m),7,22-7,15 (1H, m), 5,27 (2H, s), 4,94 (2H, s), 3,71 (3H, s), 2,27 (3H, s)
VIII-44		(CDCl3) 8,71 (1H, s), 8,53 (1H, s), 8,39 (1H, s), 8,23 (1H, d, J=9,0Hz), 7,88 (1H, d, J=9,0Hz), 7,81 (1H, d, J=2,4Hz), 7,57 (1H, dd, J=2,4, 9,0Hz), 7,40-7,33 (1H, m), 7,26-7,21 (2H, m), 7,06-6,97 (2H, m), 5,17 (2H, s), 4,49 (2H, t, J=5,4Hz), 3,40 (2H, d, J=6,0Hz), 3,25 (3H, s), 3,14-2,98 (3H, m), 2,25 (3H, s), 1,06 (3H, d, J=6,6Hz),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-45		(sal di-HCl) 12,2 (1H, s), 9,61 (2H, brs), 9,38 (1H, s), 8,93 (1H, s), 8,46 (1H, d, J=8,8Hz), 8,03 (1H, d, J=8,4Hz), 7,93 (1H, d, J=2,4Hz), 7,69 (1H, dd, J=8,8Hz, J=2,4Hz), 7,44-7,52 (1H, m), 7,30-7,36 (3H, m), 7,15-7,23 (1H, m), 5,32 (2H, s), 4,61 (2H, brs), 3,65-3,70 (2H, m), 3,45-3,56 (5H, m), 3,12 (3H, s), 2,28 (3H, s)
VIII-46		10,07 (1H, brs), 8,73 (1H, s), 8,58 (1H, s), 8,21 (1H, d, 6,6Hz), 7,96 (1H, s), 7,79 (1H, d, J=6,6Hz), 7,68 (1H, d, J=6,6Hz), 7,49-7,44 (1H, m), 7,34-7,25 (3H, m), 7,19-7,15 (1H, m), 5,26 (2H, s), 4,31 (2H, t, 4,5 Hz), 2,95 (2H, t, 4,5 Hz), 2,25 (3H, s), 2,16 (1H, m), 0,36 (2H, m), 0,25 (2H, m)

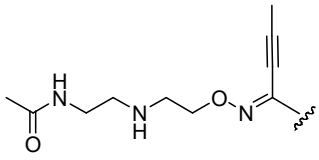
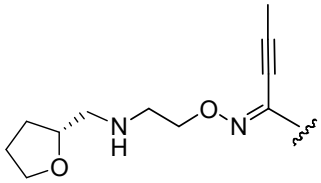
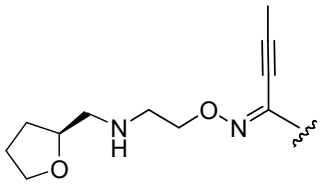
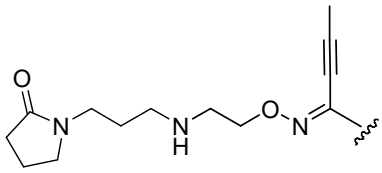
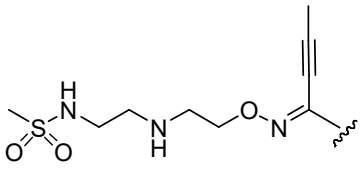
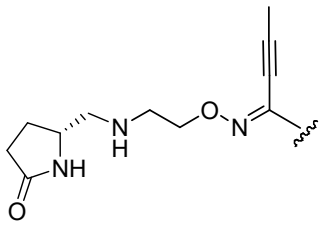
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-47		(sal di-HCl) 12,26 (1H, brs), 9,36 (1H, s), 8,91 (1H, s), 8,45 (1H, d, 6,6Hz), 8,29 (1H, m), 8,00 (1H, d, J=6,6Hz), 7,91 (1H, s), 7,68 (1H, d, J=6,6Hz), 7,51-7,45 (1H, m), 7,36-7,31 (3H, m), 7,23-7,17 (1H, m), 5,32 (2H, s), 4,59 (2H, m), 3,48 (2H, m), 3,41 (2H, m), 3,10 (2H, m), 2,28 (3H, s), 1,82 (3H, s)

Tabela 21

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-48		(sal di-HCl) 12,49 (1H, brs), 9,43 (1H, s), 8,93 (1H, s), 8,43 (1H, d, 6,6Hz), 8,09 (1H, d, J=6,6Hz), 7,93 (1H, s), 7,70 (1H, d, J=6,6Hz), 7,51-7,45 (1H, m), 7,36-7,31 (3H, m), 7,23-7,17 (1H, m), 5,32 (2H, s), 4,61 (2H, m), 4,24 (1H, m), 3,80 (1H, m), 3,68 (1H, m), 3,49 (2H, m), 3,20 (1H, m), 3,05 (1H, m), 2,28 (3H, s), 1,99 (1H, m), 1,83 (2H, m), 1,58 (1H, m)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-49		(sal di-HCl) 12,44 (1H, brs), 9,41 (1H, s), 8,92 (1H, s), 8,43 (1H, d, 6,6Hz), 8,08 (1H, d, J=6,6Hz), 7,92 (1H, s), 7,70 (1H, d, J=6,6Hz), 7,51-7,45 (1H, m), 7,36-7,31 (3H, m), 7,23-7,16 (1H, m), 5,31 (2H, s), 4,61 (2H, m), 4,24 (1H, m), 3,80 (1H, m), 3,68 (1H, m), 3,48 (2H, m), 3,19 (1H, m), 3,05 (1H, m), 2,28 (3H, s), 1,99 (1H, m), 1,84 (2H, m), 1,58 (1H, m),
VIII-50		(sal di-HCl) 12,37 (1H, brs), 9,41 (1H, s), 8,91 (1H, s), 8,41 (1H, d, 6,0Hz), 8,04 (1H, d, J=6,0Hz), 7,91 (1H, s), 7,68 (1H, d, J=6,0Hz), 7,45 (1H, m), 7,36-7,31 (3H, m), 7,20-7,14 (1H, m), 5,29 (2H, s), 4,58 (2H, m), 3,44 (2H, m), 3,31 (2H, m), 3,22 (2H, m), 2,95 (2H, m), 2,27-1,55 (9H, m)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-51		(sal di-HCl) 10,07 (1H, brs), 8,74 (1H, s), 8,58 (1H, s), 8,20 (1H, d, 6,6Hz), 7,96 (1H, s), 7,79 (1H, d, J=6,6Hz) 7,69 (1H, d, J=6,6Hz), 7,66 (1H, s), 7,49-7,43 (1H, m), 7,34-7,24 (3H, m), 7,19-7,15 (1H, m), 5,26 (2H, s), 4,32 (2H, m), 3,61 (1H, m), 2,93 (2H, m), 2,61 (2H, d, 4,5Hz), 2,25 (3H, s), 2,09 (3H, m), 1,70 (1H, m)
VIII-52		10,07 (1H, brs), 8,74 (1H, s), 8,58 (1H, s), 8,20 (1H, d, 6,6Hz), 7,96 (1H, s), 7,79 (1H, d, J=6,6Hz) 7,69 (1H, d, J=6,6Hz), 7,66 (1H, s), 7,49-7,43 (1H, m), 7,34-7,24 (3H, m), 7,19-7,15 (1H, m), 5,26 (2H, s), 4,32 (2H, m), 3,61 (1H, m), 2,93 (2H, m), 2,61 (2H, d, 4,5Hz), 2,25 (3H, s), 2,09 (3H, m), 1,70 (1H, m)

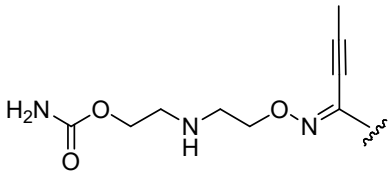
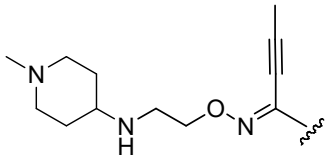
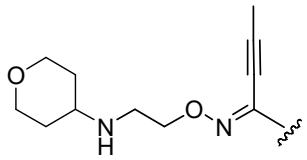
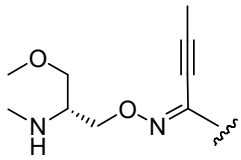
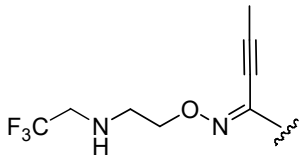
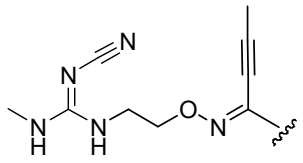
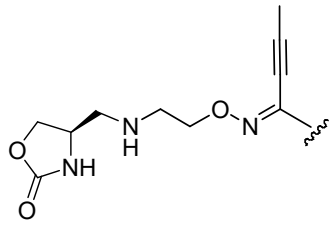
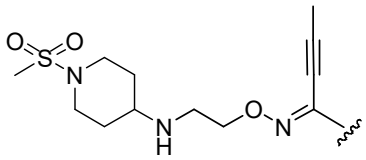
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-53		(sal di-HCl) 12,04 (1H, brs), 9,26 (1H, s), 8,91 (1H, s), 8,45 (1H, d, 10,5Hz), 7,99 (1H, d, 9,0Hz), 7,91 (1H, s), 7,67 (1H, d, J=9,0Hz), 7,53-7,45 (1H, m), 7,37-7,31 (3H, m), 7,23-7,17 (1H, m), 6,65 (2H, s), 5,32 (2H, s), 4,58 (2H, m), 4,23 (2H, m), 3,50 (2H, m), 3,30 (2H, m), 2,28 (3H, s)
VIII-54		(sal tri-HCl) 10,88 (1H, bs), 9,68 (1H, bs), 9,33 (1H, s), 8,83 (1H, s), 8,61 (1H, bs), 8,54 (2H, d, J=5,2Hz), 8,00 (1H, d, J=7,96Hz), 7,95 (1H, s), 7,71 (1H, d, J=8,4Hz), 7,49-7,45 (1H, m), 7,33 (2H, d, J=5,6Hz), 7,24-7,17 (1H, m), 5,31 (2H, s), 4,61 (2H, bs), 2,91 (2H, bs), 2,68 (3H, s), 2,37-2,33 (2H, m), 2,29 (3H, s), 2,05-1,79 (5H, m), 1,24 (2H, s),

Tabela 22

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-55		10,07 (1H, bs), 8,74 (1H, s), 8,59 (1H, s), 8,31 (1H, s), 8,21 (1H, d, J=8,8Hz), 7,96 (1H, s), 7,80 (1H, d, J=8,4Hz), 7,69 (1H, d, J=9,2Hz), 7,50-7,45 (3H, m), 7,18 (1H, t, J=6,4Hz), 5,27 (2H, s), 4,33-4,30 (2H, m), 3,81 (2H, d, J=7,2Hz), 2,93 (2H, t, J=5,9Hz), 2,67-2,65 (1H, m), 2,33 (3H, s), 1,76 (2H, d, J=11,6Hz), 1,24-1,16 (4H, m),
VIII-56		10,08 (1H, s), 8,75 (1H, s), 8,59 (1H, s), 8,21 (1H, d, J=10,0Hz), 7,80 (1H, d, J=10,0Hz), 7,69 (1H, d, J=8,4Hz), 7,47 (1H, t, J=6,8Hz), 7,35-7,17 (4H, m), 5,27 (2H, s), 3,29 (3H, s), 3,08-2,93 (1H, m), 2,41 (3H, s), 2,26 (3H, s),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-57		10,1 (1H, s), 8,75 (1H, s), 8,59 (1H, s), 8,22 (1H, d, J=8,4Hz), 7,96 (1H, s), 7,80 (1H, d, J=8,8Hz), 7,69 (1H, d, J=8,8Hz), 7,43-7,51 (1H, m), 7,23-7,36 (3H, m), 7,18 (1H, t, J=6,4Hz), 5,27 (2H, s), 4,33 (2H, t, J=5,6Hz), 3,30-3,33 (2H, m), 2,98-3,05 (2H, m), 2,25 (3H, s)
VIII-58		10,1 (1H, s), 8,75 (1H, s), 8,59 (1H, s), 8,23 (1H, d, J=8,8Hz), 7,96 (1H, s), 7,80 (1H, d, J=8,8Hz), 7,74 (1H, d, J=8,8Hz), 7,43-7,50 (1H, m), 7,25-7,35 (3H, m), 7,18 (1H, t, J=7,6Hz), 6,99-7,08 (2H, m), 5,27 (2H, s), 4,35 (2H, t, J=5,6Hz), 3,48-3,53 (2H, m), 2,68 (3H, d, J=4,4Hz), 2,26 (3H, s)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-59		(sal di-HCl) 11,83 (1H, brs), 9,02 (1H, s), 8,93 (1H, s), 8,45 (1H, d, J=8,7Hz), 7,89 (1H, d, 8,7Hz), 7,87 (1H, d, J=2,4Hz), 7,62 (1H, dd, J=2,4Hz, J=9,0Hz), 7,53-7,45 (1H, m), 7,38-7,31 (3H, m), 7,82-7,20 (1H, m), 5,32 (2H, s), 4,37 (2H, m), 3,56-3,25 (10H, m), 2,26 (3H, s),
VIII-60		10,08 (1H, s), 8,74 (1H, s), 8,59 (1H, s), 8,22 (1H, d, J=8,8Hz), 7,76 (1H, s), 7,81 (1H, d, J=8,8Hz), 7,69 (1H, d, J=7,2Hz), 7,47 (1H, t, J=7,2Hz), 7,35-7,27 (2H, m), 7,22-7,17 (1H, m), 5,27 (2H, s), 4,31-4,26 (2H, m), 3,51-3,44 (2H, m), 2,93-2,88 (2H, m), 2,83 (3H, s), 2,63-2,59 (1H, m), 2,26 (3H, s), 1,91-1,88 (2H, m), 1,33-1,24 (2H, m),

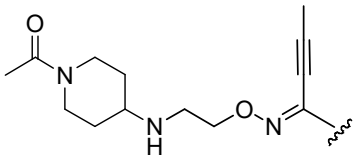
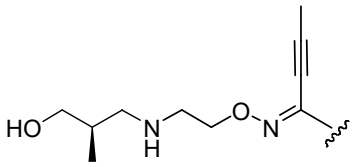
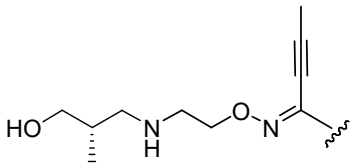
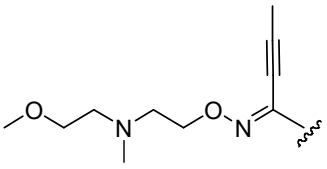
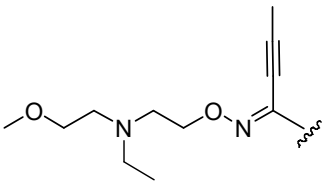
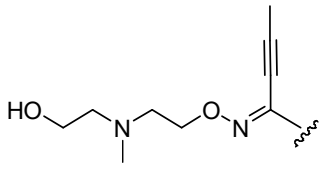
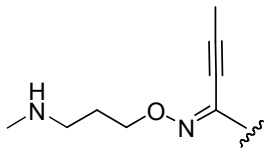
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-61		10,07 (1H, s), 8,75 (1H, s), 8,59 (1H, s), 8,21 (1H, d, J=7,2Hz), 7,96 (1H, s), 7,80 (1H, d, J=7,2Hz), 7,69 (1H, d, J=8,8Hz),7,48 (1H, dd, J=8,4Hz, J=7,2Hz), 7,34-7,27 (3H, m), 7,18 (1H, t, J=7,2Hz), 5,27 (2H, s), 4,32 (2H, t, J=6,8Hz), 4,15 (1H, bs), 3,72 (1H, d, J=12,8Hz), 3,05 (1H, t, J=10,8Hz), 2,94 (1H, t, J=5,6Hz), 2,26 (3H, s), 1,97 (3H, s), 1,24 (2H, bs),

Tabela 23

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-62		(sal di-HCl) 12,14 (1H, bs), 9,16-9,08 (1H, m), 8,91 (2H, s), 8,44 (1H, d, J=8,0Hz), 8,91 (2H, s), 8,44 (1H, d, J=8,0Hz), 8,02 (1H, d, J=8,8Hz), 7,91 (1H, s), 7,68 (1H, d, J=8,4Hz), 7,51-7,46 (1H, m), 7,37-7,31 (2H, m), 7,21-7,18 (1H, m), 5,32 (2H, s), 4,62 (2H, bs), 3,44-3,38 (2H, m), 3,32-3,21 (2H, m), 3,08-3,07 (1H, m), 2,99-2,91 (1H, m), 2,28 (3H, s), 2,08-2,02 (1H, m), 1,24-1,19 (1H, m), 0,91 (3H, d, J=6,4Hz),
VIII-63		10,08 (1H, s), 8,75 (1H, s), 8,68 (1H, s), 8,22 (1H, d, J=8,8Hz), 7,79 (1H, s), 7,80 (1H, d, J=7,2Hz), 7,70 (1H, d, J=8,8Hz), 7,50-7,45 (1H, m), 7,35-7,27 (3H, m), 7,18 (1H, t, J=8,8Hz), 5,27 (2H, s), 4,34 (2H, t, J=5,6Hz), 3,35-3,32 (2H, m), 2,92 (2H, t, J=5,6Hz), 2,65-2,61 (1H, m), 2,26 (3H, s), 1,75-1,70 (1H, bs), 0,84 (3H, d, J=5,6Hz),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-64		10,09 (1H, s), 8,58 (1H, s), 8,22 (1H, dd, J=8,7Hz, 1,8Hz), 7,95 (1H, d, J=2,7Hz), 7,80 (1H, d, J=9,0Hz), 7,68 (1H, dd, J=8,7Hz, 2,7Hz), 7,51-7,44 (1H, m), 7,35-7,16 (4H, m), 3,22 (3H, s), 2,77 (2H, t, J=5,7Hz), 2,60 (2H, t, J=5,7Hz), 2,29 (3H, s), 2,24 (3H, s),
VIII-65		10,09 (1H, bs), 8,74 (1H, s), 8,58 (1H, s), 7,96 (1H, d, J=2,1Hz), 7,80 (1H, d, J=8,7Hz), 7,68 (1H, d, J=9,0Hz), 7,48 (1H, dd, J=8,1Hz), 7,35-7,26 (3H, m), 7,19 (1H, t, J=8,1Hz), 5,27 (2H, s), 4,32 (2H, t, J=6,0Hz), 3,23 (3H, s), 2,85 (2H, t, J=6,0Hz), 2,87-2,59 (4H, m), 2,24 (3H, s), 0,98 (3H, t, J=7,2Hz),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-66		(sal di-HCl) 10,70 (1H, brs), 9,92 (1H, brs), 8,94 (1H, s), 8,69 (1H, s), 8,30 (1H, d, J=12), 7,95-7,94 (1H, m), 786 (1H, d, J=12), 7,71-7,68 (1H,m), 7,52-7,44 (1H, m), 7,35-7,28 (3H, m), 7,22-7,15 (1H, m), 5,40 (1H, br), 5,30 (2H, s), 4,74-4,60 (2H, m), 3,83-3,75 (2H, m), 3,70-3,55 (2H, m), 2,92 (3H, s), 2,28 (3H, s)
VIII-67		10,09 (1H, s), 8,75 (1H, s), 8,59 (1H, s), 8,22 (1H, d, J=8,7Hz), 7,95 (1H, d, J=2,1Hz), 7,81 (1H, d, J=9,0Hz), 7,69 (1H, d, J=8,7Hz), 7,51-7,34 (1H, m), 7,34-7,26 (2H, m), 7,21-7,16 (1H, m), 5,27 (2H, s), 4,34 (2H, t, J=6,3Hz), 2,96 (2H, t,, J=6,9Hz), 2,56 (3H, s), 2,26 (3H, s),

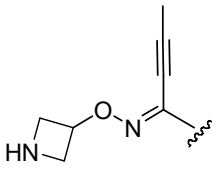
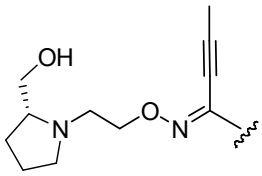
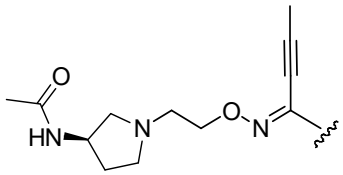
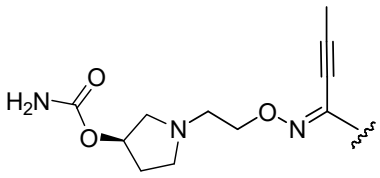
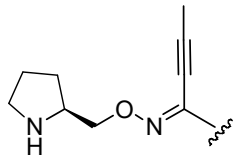
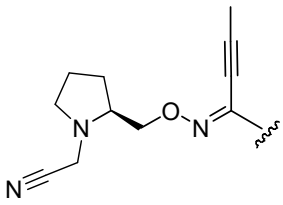
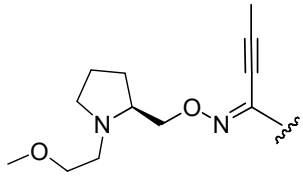
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-68		10,4 (1H, s), 9,06 (1H, s), 8,59 (1H, s), 8,30 (1H, d J=8Hz), 8,01 (1H, s), 7,81 (1H, d, J=8,8Hz), 7,74 (1H, d, J=8,8Hz), 7,44-7,50 (1H, m), 7,24-7,36 (3H, m), 7,18 (1H, t, J=7,2Hz), 5,27 (2H, s), 4,21-4,36 (4H, m), 3,98-4,04 (1H, m), 2,25 (3H, s)

Tabela 24

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-69		(sal di-HCl) 9,37 (1H, s), 8,91 (1H, s), 8,42 (1H, d, 7,8Hz), 8,00 (1H, d, J=6,6Hz), 7,92 (1H, s), 7,69 (1H, d, J=7,8Hz), 7,51-7,45 (1H, m), 7,36-7,31 (3H, m), 7,22-7,17 (1H, m), 5,32 (2H, s), 4,75-4,60 (2H, m), 3,85-3,10 (7H, m), 2,27 (3H, s), 2,15-1,74 (4H, m)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-70		10,07 (1H, bs), 8,74 (1H, bs), 8,59 (1H, s), 8,22 (1H, d, J=8,8Hz), 7,98-7,96 (2H, m), 7,80 (1H, d, J=8,8Hz), 7,68 (1H, d J=8,8Hz), 7,50-7,45 (1H, m), 7,35-7,27 (3H, m), 7,20-7,16 (1H, m), 5,27 (2H, s), 4,37 (2H, t, J=5,6Hz), 4,16 (1H, bs), 2,79-2,66 (4H, m), 2,46-2,42 (3H, m), 2,25 (3H, s), 2,06 (1H, bs), 1,78 (3H, s), 1,56-1,51 (1H, m),
VIII-71		(sal di-HCl) 9,29 (1H, m), 8,91 (1H, s), 8,42 (1H, m), 7,99 (1H, d, 8,7Hz), 7,92 (1H, s), 7,67 (1H, d, J=9,0Hz), 7,53-7,45 (1H, m), 7,37-7,31 (3H, m), 7,23-7,17 (1H, m), 6,68 (2H, brs), 5,32 (2H, s), 5,11 (1H, m), 4,66 (3H, m), 3,72-3,70 (5H, m), 3,51 (1H, m), 3,26 (2H, m), 2,28 (3H, s)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-72		10,08 (1H, bs), 8,74 (1H, s), 8,56 (1H, s), 8,21 (1H, d, J=8,0Hz), 7,93 (1H, s), 7,79 (1H, d, J=8,8Hz), 7,67-7,65 (1H, m), 7,50-7,40 (1H, m), 7,33-7,24 (2H, m), 7,20-7,12 (1H, m), 5,25 (2H, s), 4,36-4,30 (1H, m), 4,22-4,17 (1H, m), 4,08-3,92 (2H, m), 2,98 (2H, bs), 2,24 (3H, s), 2,00-1,90 (1H, m), 1,80-1,70 (2H, m), 1,62-1,52 (1H, m)
VIII-73		10,08 (1H, bs), 8,80 (1H, s), 8,57 (1H, s), 8,21 (1H, d, J=8,8Hz), 7,97 (1H, s), 7,79 (1H, d, J=8,8Hz), 7,71-7,68 (1H, m), 7,46 (1H, dd, J=8,0, J=14,4), 7,34-7,25 (2H, m), 7,19-7,15 (1H, m), 5,26 (2H, s), 4,22-4,20 (2H, m), 2,98-2,84 (2H, m), 2,25 (2H, s), 1,92-1,82 (1H, m), 1,79-1,62 (2H, m), 1,54-1,45 (1H, m),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-74		10,07 (1H, bs), 8,74 (1H, s), 8,58 (1H, s), 8,21 (1H, d, J=8,4Hz), 7,95 (1H, s), 7,79 (1H, d, J=8,8Hz), 7,69-7,67 (1H, m), 7,47 (1H, dd, J=8,4, J=15,2), 7,34-7,26 (2H, m), 7,19-7,15 (1H, m), 5,26 (2H, s), 4,23-4,13 (2H, m), 3,43 (2H, t, J=6,0), 3,23 (3H, s), 3,11-3,03 (2H, m), 2,91-2,86 (1H, m), 2,53-2,47 (1H, m), 2,30-2,24 (1H, m), 2,24 (3H, s), 1,90-1,83 (1H, m), 1,72-1,67 (2H, m), 1,59-1,53 (1H, m),

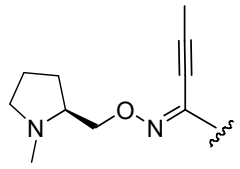
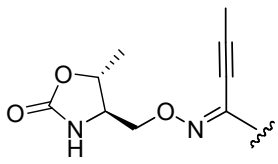
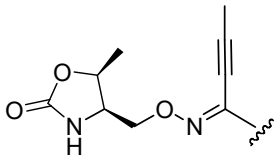
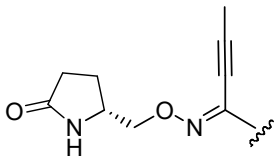
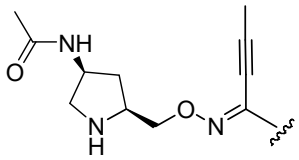
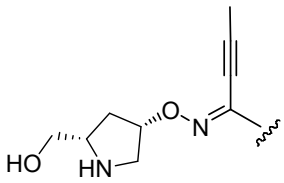
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-75		10,07 (1H, s), 8,73 (1H, s), 8,57 (1H, s), 8,20 (1H, d, J=8,8Hz), 7,95-7,94 (1H, m), 7,79 (1H, d, J=8,8Hz), 7,68-7,63 (1H, m), 7,46 (1H, dd, J=8,0, J=14,0), 7,33-7,25 (2H, m), 7,19-7,14 (1H, m), 5,26 (2H, s), 4,27-4,18 (2H, m), 2,95-2,92 (1H, m), 2,62-2,57 (1H, m), 2,41 (3H, s), 2,23 (3H, s), 2,19-2,15 (1H, m), 1,96-1,87 (1H, m), 1,74-1,61 (2H, m), 1,59-1,53 (1H, m),

Tabela 25

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-76		10,09 (1H, bs), 8,76 (1H, d, J=1,8Hz), 8,58 (1H, s), 8,22 (1H, dd, J=1,8Hz, J=8,7Hz), 7,96 (1H, d, J=2,4Hz), 7,87-7,78 (2H, m), 7,68 (1H, dd, J=2,1Hz, J=9,0Hz), 7,52-7,44 (1H, m), 7,35-7,26 (3H, m), 7,22-7,16 (1H, m), 5,27 (2H, s), 4,57-4,49 (1H, m), 4,35-4,27 (2H, m), 3,77-3,71 (1H, m), 2,26 (3H, s), 1,36 (3H, d, J=6,3Hz),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-77		10,08 (1H, bs), 8,75 (1H, d, J=1,8Hz), 8,58 (1H, s), 8,22 (1H, dd, J=1,8Hz, J=9,0Hz), 7,96 (1H, d, J=2,4Hz), 7,80 (1H, d, J=9,0Hz), 7,76 (1H, dd, J=2,4Hz, J=9,0Hz), 7,51-7,44 (1H, m), 7,35-7,26 (3H, m), 7,21-7,15 (1H, m), 5,26 (2H, s), 4,85-4,76 (1H, m), 4,39 (1H, dd, J=5,7Hz, J=11,4Hz), 4,30 (1H, dd, J=4,5Hz, J=11,4Hz), 4,11-4,07 (1H, m), 2,25 (3H, s), 1,40 (3H, d, J=6,6Hz),
VIII-78		10,07 (1H, brs), 8,74 (1H, s), 8,58 (1H, s), 8,21 (1H, d, 9,0Hz), 7,97 (1H, s), 7,82-7,78 (2H, m), 7,69 (1H, d, 9,0Hz), 7,51-7,44 (1H, m), 7,35-7,26 (3H, m), 7,22-7,15 (1H, m), 5,27 (2H, s), 4,24 (2H, d, 4,8 Hz), 3,91 (1H, m), 2,31-2,06 (6H, m), 1,95-1,87 (1H, m)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-79		10,09 (1H, s), 8,74 (1H, s), 8,59 (1H, s), 8,21 (1H, d, J=8,8Hz), 7,97 (1H, s), 7,91-7,89 (1H, m), 7,80 (1H, d, J=8,4Hz), 7,69 (1H, d, J=8,8Hz), 7,51-7,45 (1H, m), 7,35-7,27 (3H, m), 7,20-7,17 (1H, m), 5,27 (2H, s), 4,26-4,06 (3H, m), 3,46 (1H, t, J=6,8Hz), 3,02-2,98 (1H, m), 2,58 (1H, dd, J=12,0Hz, J=5,6Hz), 2,26 (3H, s), 2,20-2,10 (1H, m), 1,77 (3H, m), 1,38-1,31 (1H, m),
VIII-80		10,3 (1H, s), 8,95 (1H, s), 8,57 (1H, s), 8,22 (1H, d, J=9,6), 8,01 (1H, s), 7,80-7,73 (2H, m), 7,47-7,41 (1H,m), 7,34-7,25 (2H, m), 7,20-7,12 (1H, m), 5,37 (1H, br), 5,26 (2H, s), 5,10 (1H, brs), 3,78-3,48 (5H, m), 2,45-2,35 (1H, m), 2,26 (3H, s), 2,05-1,96 (1H, m),

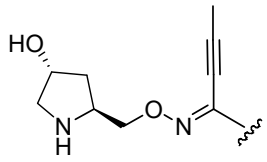
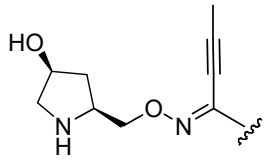
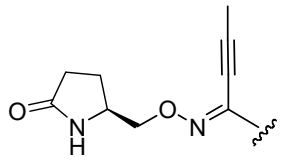
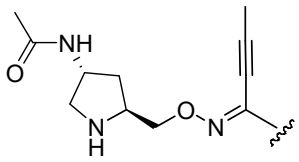
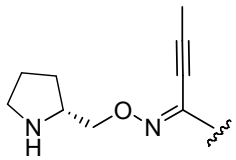
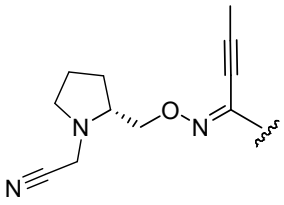
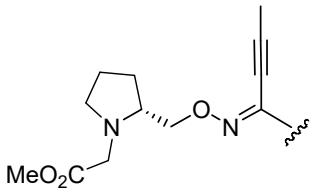
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-81		10,45 (1H, s), 8,92 (1H, s), 8,65 (1H, s), 8,31 (1H, d, J=8,4Hz), 7,97 (1H, s), 7,77 (1H, d, J=8,8Hz), 7,71 (1H, d, J=9,2Hz), 7,51-7,45 (1H, m), 7,35-7,28 (2H, m), 7,19 (1H, t, J=8,4Hz), 5,28 (2H, s), 4,56-4,47 (3H, m), 4,15 (1H, bs), 3,60 (1H, bs), 3,12 (1H, bs), 2,28 (3H, s), 2,09 (1H, dd, J=13,2Hz, J=6,0Hz), 1,862-1,81 (1H, m),
VIII-82		10,08 (1H, s), 8,75 (1H, s), 8,59 (1H, s), 8,22 (1H, d, J=8,8Hz), 7,97 (1H, s), 7,80 (1H, d, J=8,8Hz), 7,69 (1H, d, J=8,0Hz), 7,51-7,45 (1H, m), 7,35-7,27 (m, 3H), 7,20-7,17 (1H, m), 5,27 (2H, s), 4,67 (1H, bs), 4,29-4,19 (3H, m), 3,45-4,40 (1H, m), 2,88 (1H, dd, J=11,2Hz, J=5,6Hz), 2,70 (1H, dd, J=11,0, J=3,6Hz), 2,27 (3H, s), 2,10-2,02 (1H, m), 1,46-1,39 (1H, m),

Tabela 26

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-83		10,07 (1H, brs), 8,74 (1H, s), 8,58 (1H, s), 8,21 (1H, d, 8,7Hz), 7,97 (1H, s), 7,82-7,78 (2H, m), 7,69 (1H, d, 9,0Hz), 7,51-7,44 (1H, m), 7,35-7,26 (3H, m), 7,22-7,15 (1H, m), 5,27 (2H, s), 4,24 (2H, d, 4,8 Hz), 3,91 (1H, m), 2,31-2,06 (6H, m), 1,95-1,87 (1H, m)
VIII-84		10,35 (1H, s), 9,08 (1H, s), 8,60 (1H, s), 8,40 (1H, s), 8,22 (1H, d, J=8,4Hz), 8,09 (1H, s), 7,83-7,82 (2H, m), 7,49-7,47 (1H, m), 7,33-7,19 (4H, m), 5,27 (2H, s), 4,43-4,16 (4H, m), 3,01-2,98 (2H,, M), 2,28 (3H, s), 1,92 (2H, bs), 1,83 (3H, s),
VIII-85		10,1 (1H, brs), 8,82 (1H, s), 8,58 (1H, s), 8,21 (1H, d, J=8,8), 7,98 (1H, s), 7,80 (1H, d, J=8,4), 7,72-7,70 (1H,m), 7,50-7,44 (1H, m), 7,34-7,26 (3H, m), 7,20-7,15 (1H, m), 5,26 (2H, s), 4,22 (2H, s), 3,57 (1H, br), 2,96-2,89 (2H, m), 2,26 (3H, s), 1,98-1,62 (3H, m), 1,58-1,45 (1H, m),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-86		10,07 (1H, bs), 8,75 (1H, s), 8,57 (1H, s), 8,21 (1H, d, J=8,8Hz), 7,95 (1H, s), 7,79 (1H, d, J=8,8Hz), 7,71-7,68 (1H, m), 7,50-7,44 (1H, m), 7,34-7,26 (2H, m), 7,19-7,15 (1H, m), 5,26 (2H, s), 4,22-4,20 (2H, m), 3,03-2,95 (2H, m), 2,26 (3H, s), 2,02-1,93 (1H, m), 1,80-1,73 (2H, m), 1,62-1,56 (1H, m)
VIII-87		10,0 (1H, brs), 8,73 (1H, s), 8,57 (1H, s), 8,19 (1H, d, J=9,2), 7,95 (1H, s), 7,79 (1H, d, J=8,8), 7,69-7,67 (1H, m), 7,50-7,44 (1H, m), 7,34-7,26 (3H, m), 7,20-7,16 (1H, m), 5,26 (2H, s), 4,24-4,17 (2H, m), 3,77 (1H, d, J=17,2), 3,58 (1H, s), 3,50 (1H, d, J=17,6), 3,22-3,12 (1H, m), 3,10-3,00 (1H, m), 2,58-2,52 (1H, m), 2,23 (3H, s), 1,98-1,89 (1H, m), 1,77-1,70 (2H, m), 1,59-1,52 (1H, m),

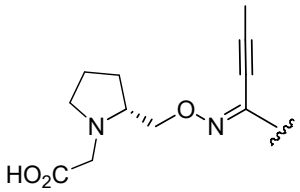
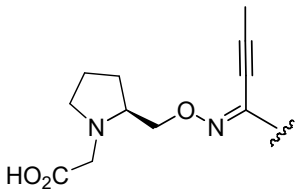
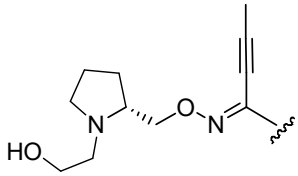
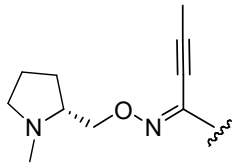
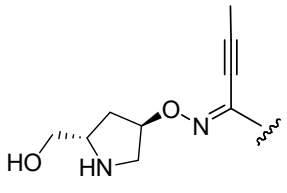
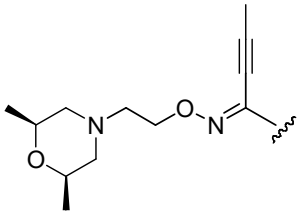
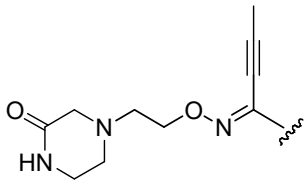
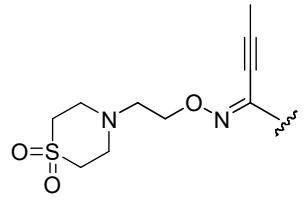
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-88		10,8 (1H, s), 8,98 (1H, s), 8,58 (1H, s), 8,20-8,16 (2H, m), 7,91-7,88 (1H, m), 7,80 (1H, d, J=7,6), 7,50-7,44 (1H,m), 7,34-7,30 (2H, m), 7,23 (1H, d, J=8,8), 7,20-7,15 (1H, m), 5,26 (2H, s), 4,23-4,41 (2H, m), 3,76 (1H, d, J=16,4), 3,52 (1H, d, J=16,4), 3,61-3,52 (1H, m), 3,45-3,36 (1H, m), 2,91-2,85 (1H, m), 2,25 (3H, s), 2,09-2,02 (1H, m), 1,91-1,79 (2H, m), 1,73-1,66 (1H, m),
VIII-89		10,87 (1H, s), 8,97 (1H, s), 8,58 (1H, s), 8,20-8,15 (2H, m), 7,91-7,88 (1H, m), 7,80 (1H, d, J=8,8), 7,50-7,44 (1H,m), 7,34-7,30 (2H, m), 7,23 (1H, d, J=8,8), 7,20-7,15 (1H, m), 5,26 (2H, s), 4,22-4,41 (2H, m), 3,76 (1H, d, J=16,4), 3,52 (1H, d, J=16,4), 3,61-3,52 (1H, m), 3,45-3,36 (1H, m), 2,91-2,85 (1H, m), 2,25 (3H, s), 2,09-2,02 (1H, m), 1,91-1,79 (2H, m), 1,73-1,66 (1H, m),

Tabela 27

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-90		10,0 (1H, s), 8,72 (1H, s), 8,56 (1H, s), 8,21-8,19 (1H, m), 7,93 (1H, s), 7,80-7,78 (1H, m), 7,67-7,65 (1H, m), 7,49-7,42 (1H,m), 7,33-7,25 (3H, m), 7,19-7,14 (1H, m), 5,26 (2H, s), 4,40 (1H, brs), 4,27-4,19 (1H, m), 4,16-4,09 (1H, m), 3,10-2,94 (2H, m), 2,90-2,80 (1H, m), 2,23 (3H, s), 1,93-1,82 (1H, m), 1,75-1,62 (2H, m), 1,61-1,52 (1H, m),
VIII-91		10,08 (1H, s), 8,74 (1H, s), 8,56 (1H, s), 8,21 (1H, d, J=8,8Hz), 7,93 (1H, s), 7,89 (1H, d, J=8,8Hz), 7,68-7,63 (1H, m), 7,46 (1H, dd, J=8,0, J=14,0), 7,33-7,24 (2H, m), 7,19-7,14 (1H, m), 5,25 (2H, s), 4,27-4,18 (2H, m), 2,95-2,92 (1H, m), 2,62-2,57 (1H, m), 2,41 (3H, s), 2,23 (3H, s), 2,46-2,39 (1H, m), 2,04-1,95 (1H, m), 1,78-1,73 (2H, m), 1,65-1,56 (1H, m)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-92		10,0 (1H, s), 8,72 (1H, s), 8,57 (1H, s), 8,21 (1H, d, J=8,4), 7,94 (1H, s), 7,79 (1H, d, J=8,8), 7,68-7,66 (1H,m), 7,49-7,44 (1H, m), 7,34-7,25 (3H, m), 7,19-7,15 (1H, m), 5,26 (2H, s), 4,93 (1H, brs), 3,02 (1H, d, J=10,7), 2,25 (3H, s), 2,09-2,01 (1H, m), 1,77-1,70 (1H, m)
VIII-93		10,07 (1H, bs), 8,74 (1H, bs), 8,59 (1H, s), 8,22 (1H, d, J=7,6Hz), 7,96 (1H, d, J=2,4Hz), 7,80 (1H, d, J=8,8Hz), 7,69 (1H, dd, J=2,4Hz, J=8,8Hz), 7,50-7,45 (1H, m), 7,35-7,27 (3H, m), 7,20-7,17 (1H, m), 5,27 (2H, s), 4,40 (2H, t, J=5,6Hz), 3,56 (2H, t, J=8,0Hz), 2,85 (2H, t, J=8,4Hz), 2,69 (2H, t, J=5,6Hz), 2,25 (3H, s), 1,04 (6H, d, J=5,6Hz),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-94		10,07 (1H, bs), 8,74 (1H, bs), 8,59 (1H, s), 8,22 (1H, d, J=8,8Hz), 7,97 (1H, d, J=2,4Hz), 7,80 (1H, d, J=8,8Hz), 7,72 (1H, bs), 7,69 (1H, dd, J=2,4Hz, J=8,8Hz), 7,50-7,45 (1H, m), 7,35-7,27 (3H, m), 7,21-7,16 (1H, m), 5,27 (2H, s), 4,41 (2H, t, J=5,6Hz), 3,17 (2H, bs), 3,10 (2H, s), 2,80 (2H, t, J=5,6Hz), 2,70 (2H, t, J=5,6Hz), 2,26 (3H, s),
VIII-95		10,27 (1H, brs), 8,74 (1H, s), 8,58 (1H, s), 8,23-8,21 (1H, m), 7,95 (1H, s), 7,80 (1H, d, J=8,8), 7,69-7,67 (1H,m), 7,50-7,44 (1H, m), 7,34-7,26 (2H, m),7,20-7,16 (1H, m), 5,27 (2H, s), 4,39 (2H, t, J=5,6Hz), 3,18 (8H, brs), 2,96 (2H, t, J=5,6Hz), 2,55 (3H, s)

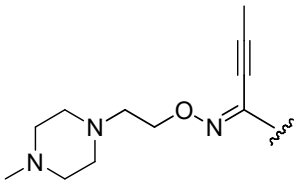
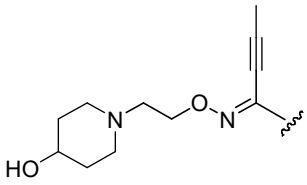
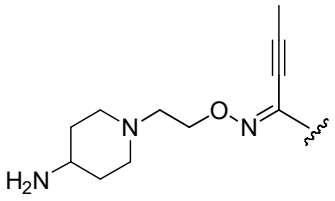
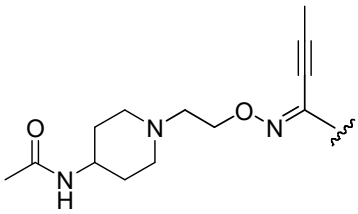
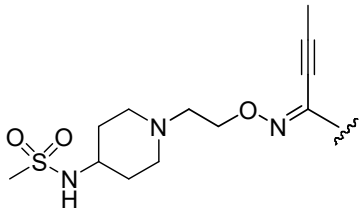
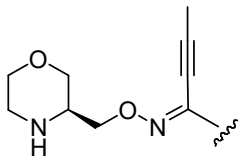
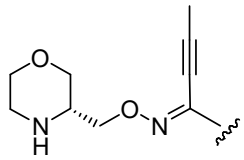
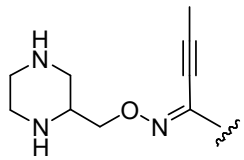
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-96		10,1 (1H, s), 8,79 (1H, s), 8,59 (1H, s), 8,21 (1H, d, J=8Hz), 7,96 (1H, s), 7,79 (1H, d, J=8,8Hz), 7,68 (1H, d, J=8,8Hz), 7,44-7,50 (1H, m), 7,24-7,36 (3H, m), 7,18 (1H, t, J=7,2Hz), 5,27 (2H, s), 4,37 (2H, t, J=10Hz), 3,29-3,34 (2H, m), 2,70 (2H, t, J=6,4Hz), 2,26-2,35 (4H, m), 2,25 (3H, s), 2,14 (3H, s)
VIII-97		10,1 (1H, s), 8,74 (1H, s), 8,59 (1H, s), 8,21 (1H, d, J=8,8Hz), 7,96 (1H, s), 7,80 (1H, s), 7,69 (1H, s), 7,42-7,50 (1H, m), 7,13-7,36 (4H, m), 5,27 (2H, s), 4,52 (1H, s), 4,36 (2H, brs), 3,40-3,50 (1H, brs), 2,80 (2H, brs), 2,69 (2H, brs), 2,10-2,27 (5H, m), 1,69 (2H, brs), 1,40 (2H, brs)

Tabela 28

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-98		8,74 (1H, s), 8,58 (1H, s), 8,21 (1H, d, J=9,2Hz), 7,96 (1H, s), 7,79 (1H, d, J=9,2Hz), 7,68 (1H, d, J=9,2Hz), 7,48 (1H, dd, J=5,8Hz, J=7,2Hz), 7,35-7,26 (3H, m), 7,18 (1H, t, J=9,2Hz), 5,27 (2H, s), 4,36 (2H, t, J=9,2Hz), 3,38 (1H, dd, J=5,8Hz, J=7,2Hz), 2,86 (2H, d, J=11,6Hz), 2,68 (2H, t, J=6,0Hz), 2,25 (3H, s), 2,06 (2H, t, J=11,2Hz), 1,66 (2H, d, J=11,7Hz), 1,09 (2H, t, J=7,2Hz),
VIII-99		10,1 (1H, bs), 8,78 (1H, bs), 8,59 (1H, s), 8,22 (1H, d, J=8,0Hz), 7,97 (1H, s), 7,81 (1H, d, J=8,8Hz), 7,70 (1H, d, J=6,4Hz), 7,49-7,45 (1H, m), 5,27 (2H, s), 4,49-4,12 (2H, m), 3,41-3,38 (1H, m), 2,82-2,65 (2H, m), 2,25 (3H, s), 1,79 (3H, s), 1,09 (2H, t, J=7,2Hz),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-100		10,07 (1H, s), 8,74 (1H, s), 8,59 (1H, s), 8,21 (1H, d, J=9,2Hz), 8,59 (1H, s), 8,21 (1H, d, J=9,2Hz), 7,96 (1H, s), 7,80 (1H, d, J=8,4Hz), 7,68 (1H, d, J=8,4Hz), 7,50-7,45 (1H, m), 7,35-7,27 (3H, m), 7,19 (1H, t, J=8,0Hz), 7,04 (1H, t, J=6,0Hz), 5,20 (2H, s), 4,30 (2H, bs), 3,10 (1H, bs), 2,91 (3H, s), 2,63 (2H, d, J=2,4Hz), 2,55 (3H, s), 2,03-1,99 (2H, m), 1,77 (2H, d, J=22,0Hz), 1,48-1,38 (2H, m), 1,24 (2H, bs),
VIII-101		10,09 (1H, bs), 8,75 (1H, s), 8,58 (1H, s), 8,20 (1H, d, J=8,7Hz), 7,95 (1H, d, J=2,1Hz), 7,80 (1H, d, J=8,7Hz), 7,68 (1H, d, J=9,0Hz), 7,51-7,44 (1H, m), 7,35-7,26 (3H, m), 7,21-7,16 (1H, m), 5,27 (2H, s), 4,20-4,09 (2H, m), 3,79 (1H, dd, J=2,7Hz, J=10,8Hz), 3,68-3,64 (1H, m), 3,13-3,08 (1H, m), 2,82-2,71 (3H, m), 2,26 (3H, s),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-102		10,11 (1H, bs), 8,74 (1H, s), 8,57 (1H, s), 8,22-8,19 (1H, m), 7,96 (1H, m), 7,80 (1H, d, J=9,0Hz), 7,69-7,66 (1H, m), 7,51-7,44 (1H, m), 7,35-7,26 (3H, m), 7,21-7,16 (1H, m), 5,27 (2H, s), 4,20-4,09 (2H, m), 3,79 (1H, dd, J=3,0Hz, J=10,8Hz), 3,68-3,64 (1H, m), 3,25-3,18 (1H, m), 3,13-3,05 (1H, m), 2,82-2,71 (2H, m), 2,26 (3H, s),
VIII-103		10,09 (1H, brs), 8,74 (1H, s), 8,59 (1H, s), 8,21 (1H, d, 9,0Hz), 7,96 (1H, s), 7,79 (1H, d, J=9,0Hz) 7,68 (1H, d, J=9,0Hz), 7,49-7,44 (1H, m), 7,34-7,22 (3H, m), 7,19-7,15 (1H, m), 5,27 (2H, s), 4,11 (2H, d, J=4,8Hz), 2,95-2,50 (6H, m), 2,34-2,26 (4H, m)

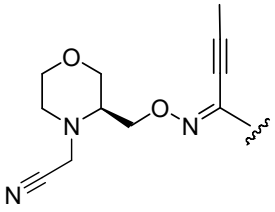
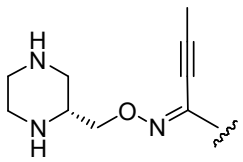
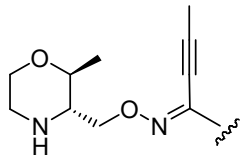
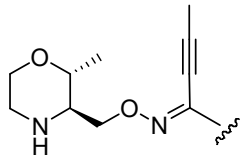
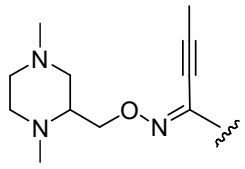
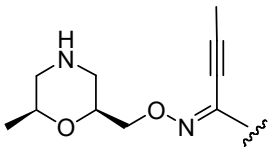
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-104		10,07 (1H, s), 8,75 (1H, d, J=1,8Hz), 8,58 (1H, s), 8,22 (1H, dd, J=1,8Hz, J=9,0Hz), 7,96 (1H, d, J=2,4Hz), 7,79 (1H, d, J=8,7Hz), 7,68 (1H, dd, J=1,8Hz, J=9,3Hz), 7,51-7,44 (1H, m), 7,35-7,26 (3H, m), 7,21-7,15 (1H, m), 5,27 (2H, s), 4,35 (1H, dd, J=2,7Hz, J=11,7Hz), 4,24 (1H, dd, J=3,9Hz, J=11,7Hz), 4,12 (1H, d, J=17,4Hz), 3,90-3,76 (3H, m), 3,50 (1H, dt, J=2,4Hz, J=11,1Hz), 2,83-2,71 (2H, m), 2,26 (3H, s),

Tabela 29

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-105		10,09 (1H, brs), 8,73 (1H, s), 8,58 (1H, s), 8,20 (1H, d, 7,8Hz), 7,96 (1H, s), 7,79 (1H, d, J=9,0Hz), 7,69 (1H, d, J=8,4Hz), 7,51-7,42 (1H, m), 7,35-7,25 (3H, m), 7,22-7,16 (1H, m), 5,27 (2H, s), 4,31 (2H, d, 4,5 Hz), 2,95-2,53 (5H, m), 2,34-2,10 (5H, m)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-106		10,1 (1H, s), 8,75 (1H, s), 8,59 (1H, s), 8,21 (1H, d, J=8,8Hz), 7,97 (1H, s), 7,80 (1H, d, J=8,4Hz), 7,69 (1H, d, J=8,8Hz), 7,43-7,52 (1H, m), 7,15-7,37 (4H, m), 5,27 (2H, s), 4,23-4,29 (1H, m), 4,11-4,17 (1H, m), 3,69 (1H, d, J=12Hz), 3,37-3,45 (1H, m), 3,23-3,32 (1H, m), 2,66-2,80 (3H, m), 2,28-2,40 (1H, m), 2,26 (3H, s), 1,16 (3H, d, J=6Hz)
VIII-107		10,1 (1H, s), 8,75 (1H, s), 8,59 (1H, s), 8,21 (1H, d, J=8,8Hz), 7,97 (1H, s), 7,80 (1H, d, J=8,4Hz), 7,69 (1H, d, J=8,8Hz), 7,43-7,52 (1H, m), 7,15-7,37 (4H, m), 5,27 (2H, s), 4,23-4,29 (1H, m), 4,11-4,17 (1H, m), 3,69 (1H, d, J=12Hz), 3,37-3,45 (1H, m), 3,23-3,32 (1H, m), 2,66-2,80 (3H, m), 2,28-2,40 (1H, m), 2,26 (3H, s), 1,16 (3H, d, J=6Hz)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-108		10,09 (1H, brs), 8,75 (1H, s), 8,59 (1H, s), 8,21 (1H, d, 10,5Hz), 7,96 (1H, s), 7,80 (1H, d, J=9,0Hz), 7,68 (1H, d, J=9,0Hz), 7,52-7,44 (1H, m), 7,35-7,25 (3H, m), 7,22-7,16 (1H, m), 5,27 (2H, s), 4,44 (1H, m), 4,18 (1H, m), 2,80-2,60 (4H, m), 2,32-2,00 (12H, m)
VIII-109		10,1 (1H, s), 8,74 (1H, s), 8,59 (1H, s), 8,21 (1H, d, J=8,0Hz), 7,96 (1H, s), 7,80 (1H, d, J=8,8Hz), 7,66-7,70 (1H, m), 7,43-7,50 (1H, m), 7,15-7,36 (4H, m), 5,72 (2H, s), 4,10-4,27 (2H, m), 3,75-3,82 (1H, m), 3,45-3,55 (1H, m), 2,85 (1H, d, J=10Hz), 2,74 (1H, d, J=11Hz), 2,37 (1H, t, J=11Hz), 2,26 (4H, brs), 1,03 (3H, d, J=6,4Hz),

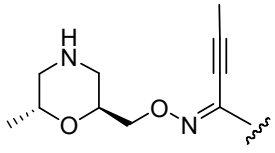
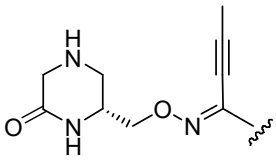
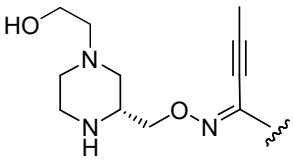
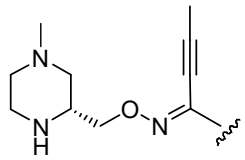
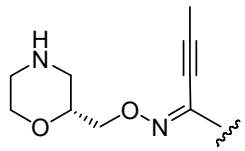
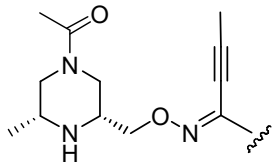
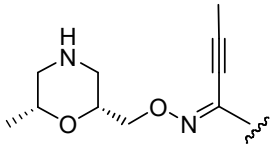
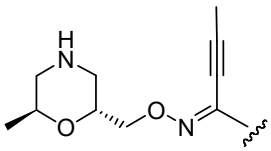
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-110		10,1 (1H, s), 8,74 (1H, s), 8,58 (1H, s), 8,21 (1H, d, J=8,8Hz), 7,96 (1H, s), 7,80 (1H, d, J=8,4Hz), 7,68 (1H, s, J=9,6Hz), 7,42-7,52 (1H, m), 7,14-7,37 (4H, m), 5,27 (2H, s), 4,38-4,55 (2H, m), 3,80-4,05 (2H, m), 2,75-2,85 (2H, m), 2,65-2,72 (1H, m), 2,30-2,40 (1H, m), 2,26 (3H, s), 1,06 (3H, d, J=5Hz)
VIII-111		10,08 (1H, s), 8,74 (1H, s), 8,59 (1H, s), 8,20 (1H, d, J=8,7Hz), 7,98 (1H, d, J=0,9Hhz), 7,83-7,72 (2H, m), 7,10 (1H, dd, J=2,7Hz, J=9,0Hz), 7,51-7,44 (1H, m), 7,34-7,26 (3H, m), 7,22-7,16 (1H, m), 5,27 (2H, s), 4,32 (2H, m), 3,65 (1H, m), 3,17 (2H, s), 3,10-2,84 (3H, m), 2,26 (3H, s),
VIII-112		(sal di-HCl) 12,03 (1H, brs), 8,93 (1H, s), 8,46 (1H, d, J=9,0Hz), 8,02 (1H, d, J=8,7Hz), 7,92 (1H, d, J=2,4Hz), 7,68-7,67 (1H, m9, 7,52-7,36 (1H, m), 7,35-7,31 (3H, m), 7,23-7,19 (1H, m), 5,31 (2H, s), 4,58 (2H, m), 4,33 (1H, brs), 3,99-3,23 (12H, m), 2,29 (3H, s),

Tabela 30

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-113		10,09 (1H, brs), 8,74 (1H, s), 8,58 (1H, s), 8,20 (1H, d, J=8,7Hz), 7,96 (1H, d, J=2,4Hz), 7,79 (1H, d, J=8,7Hz), 7,68 (1H, dd, J=2,7Hz, J=9,0Hz), 7,51-7,44 (1H, m), 7,36-7,16 (4H, m), 5,27 (2H, s), 4,15 (2H, m), 3,07 (1H, m), 2,87-2,55 (4H, m), 2,26 (3H, s),2,15 (3H, s), 1,90 (1H, m), 1,71 (1H, m),
VIII-114		(sal di-HCl) 11,65 (1H, bs), 9,46-9,35 (2H, m), 9,04 (1H, s), 8,88 (1H, s), 7,95 (1H, d, J=9,0Hz), 7,89 (1H, d, J=2,4Hz), 7,66-7,62 (1H, m), 7,52-7,45 (1H, m), 7,36-7,31 (3H, m), 7,23-7,17 (1H, m), 5,31 (2H, s), 4,35-4,34 (2H, m), 4,24-4,21 (1H, m), 4,04-3,98 (1H, m), 3,85-3,77 (1H, m), 3,05-2,85 (3H, m), 2,28 (3H, s),
VIII-115		

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-116		10,1 (1H, s), 8,74 (1H, s), 8,59 (1H, s), 8,21 (1H, d, J=8,0Hz), 7,96 (1H, s), 7,80 (1H, d, J=8,8Hz), 7,66-7,70 (1H, m), 7,43-7,50 (1H, m), 7,15-7,36 (4H, m), 5,72 (2H, s), 4,10-4,27 (2H, m), 3,75-3,82 (1H, m), 3,45-3,55 (1H, m), 2,85 (1H, d, J=10Hz), 2,74 (1H, d, J=11Hz), 2,37 (1H, t, J=11Hz), 2,26 (4H, brs), 1,03 (3H, d, J=6,4Hz),
VIII-117		10,1 (1H, s), 8,74 (1H, s), 8,58 (1H, s), 8,21 (1H, d, J=8,8Hz), 7,96 (1H, s), 7,80 (1H, d, J=8,4Hz), 7,68 (1H, s, J=9,6Hz), 7,42-7,52 (1H, m), 7,14-7,37 (4H, m), 5,27 (2H, s), 4,38-4,55 (2H, m), 3,80-4,05 (2H, m), 2,75-2,85 (2H, m), 2,65-2,72 (1H, m), 2,30-2,40 (1H, m), 2,26 (3H, s), 1,06 (3H, d, J=5Hz)

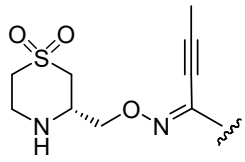
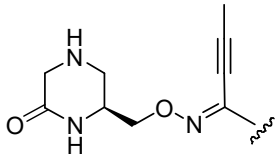
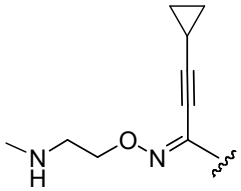
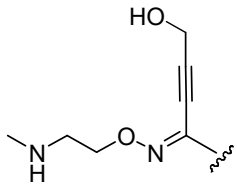
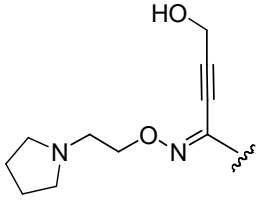
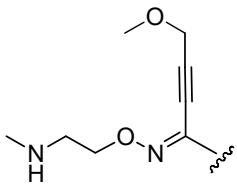
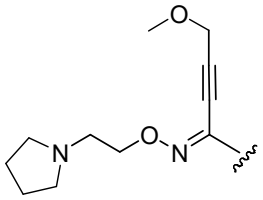
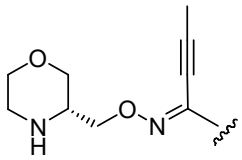
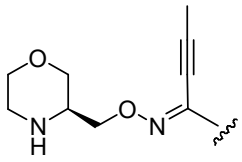
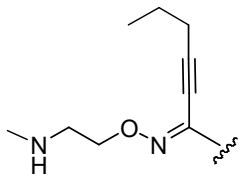
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-118		10,10 (1H, s), 8,76 (1H, s), 8,59 (1H, s), 8,22 (1H, d, J=8,7Hz), 7,96 (1H, d, J=2,1Hz), 7,81 (2H, d, J=8,7Hz), 7,69 (1H, dd, J=2,1Hz, J=8,7Hz), 7,44-7,52 (1H, m), 7,27-7,35 (2H, m), 7,16-7,22 (1H, m), 5,27 (2H, s), 4,20-4,35 (2H, m), 3,84-3,98 (1H, m), 2,85-3,15 (6H, m), 2,28 (3H, m),
VIII-119		(sal di-HCl) 9,14 (1H, s), 8,91 (1H, s), 8,61-8,55 (1H, m), 8,41 (1H, d, J=9,0Hz), 8,22 (1H, d, J=9,0Hz), 8,00-7,97 (1H, m), 7,91 (1H, s), 7,66 (1H, d, J=9,0Hz), 7,52-7,45 (1H, m), 7,37-7,30 (3H, m), 7,23-7,17 (1H, m), 5,32 (2H, s), 4,40 (2H, m), 4,18 (1H, m), 3,65-3,20 (4H, m), 2,287 (3H, s)
VIII-120		10,1 (1H, s), 8,71 (1H, s), 8,59 (1H, s), 8,16 (1H, d, J=8,8Hz), 7,98 (1H, s), 7,80 (1H, d, J=9,2Hz), 7,69 (1H, d, J=9,2Hz), 7,44-7,51 (1H, m), 7,14-7,36 (4H, m), 5,27 (2H, s), 4,31 (2H, t, J=5,6Hz), 2,85 (2H, t, J=5,6Hz), 2,35 (3H, s), 1,70-1,78 (1H, m), 1,02-1,07 (2H, m), 0,90-0,95 (2H, m)

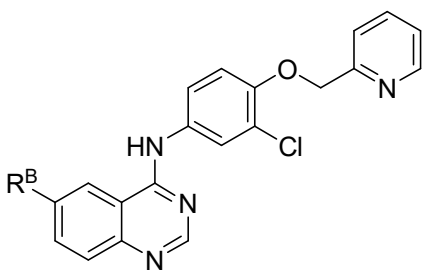
Tabela 31

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-121		10,1 (1H, s), 8,82 (1H, s), 8,61 (1H, s), 8,27 (1H, d, J=7,6Hz), 7,97 (1H, s), 7,84 (1H, d, J=9,6Hz), 7,70 (1H, d, J=7,6Hz), 7,43-7,51 (1H, m), 7,25-7,36 (3H, m), 7,15-7,22 (1H, m), 5,62 (1H, s), 5,72 (2H, s), 4,49-4,55 (4H, m), 3,29-3,40 (2H, m), 2,66 (3H s)
VIII-122		10,05 (1H, s), 8,76 (1H, s), 8,60 (1H, s), 8,20 (1H, d, J=9,2Hz), 7,97 (1H, s), 7,82 (1H, d, J=8,8Hz), 7,68 (1H, d, J=9,2Hz), 7,53-7,45 (1H, m), 7,37-7,27 (3H, m), 7,19 (1H, t, J=8,4Hz), 5,63 (1H, t, J=5,2Hz), 5,27 (2H, s), 4,70 (2H, d, J=5,2Hz), 4,40 (2H, t, J=6,0Hz), 2,81 (2H, t, J=6,0Hz), 2,53 (4H, bs), 1,68 (4H, bs),
VIII-123		10,02 (1H, s), 8,89 (1H, s), 8,60 (1H, s), 8,22 (1H, d, J=9,3Hz), 8,00 (1H, s), 7,83 (1H, d, J=8,7Hz), 7,73 (1H, d, J=9,6Hz), 7,51-7,44 (1H, m), 7,35-7,29 (2H, m), 7,22-7,16 (1H, m), 5,2782H, s), 4,53 (2H, s), 3,40 (5H, bs), 2,51 (5H, bs),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-124		10,13 (1H, s), 8,80 (1H, s), 8,61 (1H, s), 8,21 (1H, d, J=8,4Hz), 7,99 (1H, s), 7,83 (1H, d, J=8,8Hz), 7,71 (1H, d, J=8,8Hz), 7,51-7,45 (1H, m), 7,35-7,27 (3H, m), 7,19 (1H, t, J=8,4Hz), 5,27 (2H, s), 4,53 (2H, s), 4,46 (2H, t, J=5,6Hz), 2,93 (2H, bs), 2,65 (4H, bs), 1,72 (4H, bs),
VIII-125		10,09 (1H, s), 8,76 (1H, bs), 8,59 (1H, s), 8,19 (1H, d, J=9,0Hz), 7,96 (1H, bs), 7,82 (1H, d, J=8,7Hz), 7,67 (1H, bd, J=7,5Hz), 7,51-7,44 (1H, m), 7,35-7,26 (3H, m), 7,21-7,16 (1H, m), 5,27 (2H, s), 4,52 (2H, s), 4,23 (1H, dd, J=5,7Hz, J=10,8Hz), 4,17 (1H, dd, J=6,3Hz, J=10,8Hz), 3,79 (1H, dd, J=3,0Hz, J=10,8Hz), 3,65 (1H, bd, J=7,8Hz), 3,40 (3H, s), 3,27-3,20 (1H, m), 3,13-3,04 (1H, m),

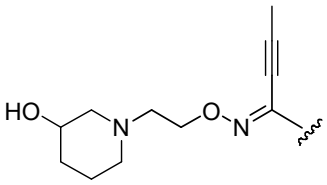
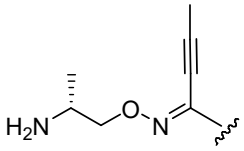
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-126		10,10 (1H, bs), 8,76 (1H, d, J=1,5Hz), 8,59 (1H, s), 8,19 (1H, dd, J=1,8Hz, J=8,7Hz), 7,96 (1H, d, J=2,1Hz), 7,83 (1H, d, J=9,0Hz), 7,71-7,64 (1H, m), 7,52-7,44 (1H, m), 7,35-7,27 (3H, m), 7,22-7,16 (1H, m), 5,27 (2H, s), 4,53 (2H, s), 4,23 (1H, dd, J=6,3Hz, J=11,4Hz), 4,17 (1H, dd, J=6,3Hz, J=10,8Hz), 3,80 (1H, dd, J=3,0Hz, J=10,8Hz), 3,68-3,64 (1H, m), 3,12-3,07 (1H, m), 2,82-2,70 (2H, m),
VIII-127		10,1 (1H, s), 8,76 (1H, s), 8,59 (1H, t, J=5,6Hz), 8,20 (1H, d, J=8,8Hz), 7,98 (1H, s), 7,81 (1H, d, J=8,8Hz), 7,70 (1H, d, J=8,8Hz), 7,44-7,51 (1H, m), 7,15-7,37 (4H, m), 5,27 (2H, s), 4,34 (2H, t, J=6Hz), 2,86 (2H, t, J=5,6Hz), 2,61 (2H, t, J=7,2Hz), 2,36 (3H, s), 1,67 (2H, q, J=7,2Hz), 1,05 (3H, t, J=7,2Hz)

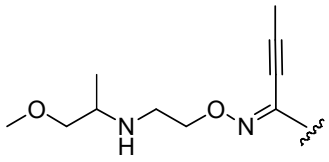
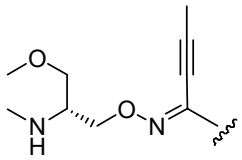
Fórmula química 82

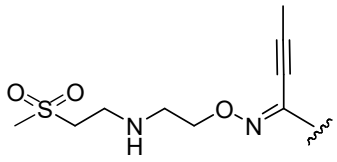
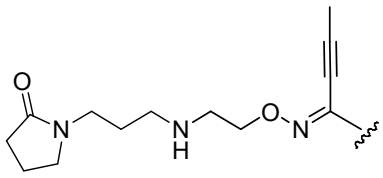


(VIII)

Tabela 32

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-128		10,0 (1H, s), 8,74 (1H, s), 8,60-8,58 (2H, m), 8,21 (1H, d, J=8,8), 7,96 (1H, s), 7,90-7,86 (1H, m), 7,79 (1H, d, J=8,8), 7,68-7,66 (1H, m), 7,58 (1H, d, J=7,6), 7,38-7,35 (1H, m), 7,27 (1H, d, J=8,8), 5,30 (2H, s), 4,61-4,60 (1H, m), 4,37-4,35 (2H, m), 3,52-3,38 (1H, m), 2,93-2,92 (1H, m), 2,76-2,66 (2H, m), 2,24 (3H, s), 2,00-1,95 (1H, m), 1,89-1,84 (1H, m), 1,79-1,77 (1H, m), 1,62-1,59 (1H, m), 1,45-1,36 (1H, m), 1,10-1,02 (1H, m),
VIII-129		10,09 (1H, s), 8,61-8,59 (2H, m), 8,21 (1H, d, J=9,2Hz), 8,07 (1H, s), 7,89 (1H, d, J=7,6Hz), 7,80 (1H, d, J=8,4Hz), 7,68 (1H, d, J=9,2Hz), 7,37 (1H, t, J=7,6Hz), 7,28 (1H, d, J=8,8Hz), 5,31 (2H, s), 4,60 (2H, d J=6,0Hz), 2,27 (3H, s), 0,89 (3H, d, J=7,6Hz),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-130		(sal tri-HCl) 12,58 (1H, s), 9,44 (1H, s), 9,33 (1H, bs), 9,09 (1H, bs), 8,95 (1H, s), 8,78 (1H, d, J=4,4Hz), 8,46 (1H, d, J=8,8Hz), 8,23 (1H, t, J=6,8Hz), 8,09 (1H, d, J=8,4Hz), 7,94 (1H, d, J=2,4Hz), 7,86 (1H, d, J=8,0Hz), 7,72-7,67 (2H, m), 7,39 (1H, d, J=9,2Hz), 5,51 (2H, s), 4,61 (2H, bs), 3,61-3,47 (5H, m), 2,28 (3H, s), 1,28 (3H, d, J=6,4Hz),
VIII-131		10,0 (1H, s), 8,74 (1H, s), 8,60-8,58 (2H, m), 8,20 (1H, d, J=8,8), 7,97 (1H, s), 7,90-7,86 (1H,m), 7,79 (1H, d, J=8,4), 7,69-7,67 (1H, m), 7,58 (1H, d, J=7,6), 7,38-7,35 (1H, m), 7,27 (1H, d, J=9,2), 5,30 (2H, s), 4,24-4,23 (2H, m), 3,44-3,34 (2H, m), 2,97-2,92 (1H, m), 2,38 (3H, s), 2,26 (3H, s),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-132		10,08 (1H, s), 8,98 (1H, s), 8,61-8,59 (2H, m), 8,23 (1H, d, J=8,8Hz), 7,98 (1H, s), 7,89 (1H, t, J=7,2Hz), 7,80 (1H, d, J=8,8Hz), 7,69 (1H, d, J=9,2Hz), 7,59 (1H, t, J=8,0Hz), 7,37 (1H, d, J=7,6Hz), 7,28 (1H, d, J=8,8Hz), 5,31 (2H, s), 4,33 (2H, t J=4,8Hz), 3,26 (2H, t, J=6,4Hz), 3,03 (5H, bs), 2,94 (2H, bs), 2,26 (3H, s),
VIII-133		10,0 (1H, s), 8,74 (1H, s), 8,60-8,58 (2H, m), 8,21 (1H, d, J=8,0), 7,97 (1H, m), 7,90-7,86 (1H, m), 7,80 (1H, d, J=8,8), 7,69-7,67 (1H, m), 7,59 (1H, d, J=8,0), 7,38-7,35 (1H, m), 7,28 (1H, d, J=9,2), 5,30 (2H, s), 4,32-4,29 (2H, m), 3,22-3,18 (2H, m), 2,90-2,87 (2H, m), 2,57-2,53 (2H, m), 2,25 (3H, s), 2,20-2,16 (2H, m), 1,91-1,84 (2H, m), 1,62-1,55 (1H, m)

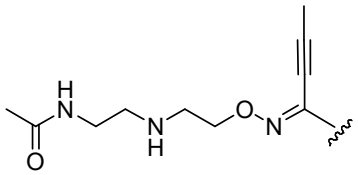
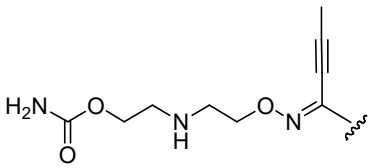
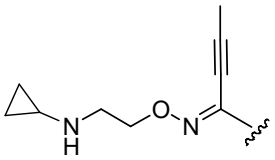
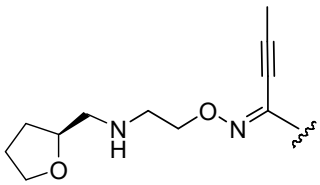
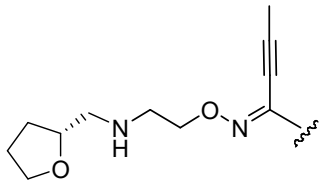
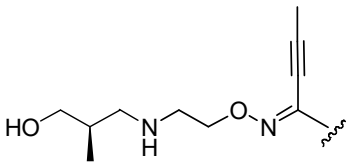
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-134		10,11 (1H, brs), 8,75 (1H, s), 8,61-8,59 (2H, m), 8,22 (1H, d, J=9,0Hz), 7,91-7,78 (3H, m), 7,67 (1H, d, J=9,0Hz), 7,59 (1H, d, J=7,8Hz), 7,40-7,36 (1H, m), 7,29 (1H, d, J=9,0Hz), 5,31 (2H, s), 4,32 (2H, m), 3,13 (2H, m), 2,93 (2H, m), 2,66 (2H, m), 2,26 (3H, s), 1,78 (3H, s)

Tabela 33

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-135		10,09 (1H, brs), 8,75 (1H, s), 8,61-8,59 (2H, m), 8,22 (1H, d, J=9,0Hz), 7,97 (1H, s), 7,92-7,86 (1H, m), 7,81 (1H, d, J=9,0Hz), 7,69 (1H, d, J=9,0Hz), 7,59 (1H, d, J=7,8Hz), 7,40-7,36 (1H, m), 7,29 (1H, d, J=9,0Hz), 6,47 (2H, brs), 5,31 (2H, s), 4,34 (2H, m), 3,99 (2H, m), 2,99 (2H, m), 2,84 (2H, m), 2,26 (3H, s)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-136		10,10 (1H, brs), 8,75 (1H, s), 8,61-8,59 (2H, m), 8,22 (1H, d, J=9,0Hz), 7,97 (1H, s), 7,92-7,86 (1H, m), 7,81 (1H, d, J=9,0Hz), 7,69 (1H, d, J=9,0Hz), 7,59 (1H, d, J=7,8Hz), 7,40-7,36 (1H, m), 7,29 (1H, d, J=9,0Hz), 5,31 (2H, s), 4,33 (2H, t, 6,0Hz), 3,00 (2H, t, 6,0Hz), 2,25 (3H, s), 2,23 (1H, m), 0,408 (2H, m), 0,29 (2H, m)
VIII-137		(sal tri-HCl) 12,14 (1H, brs), 9,28 (1H, s), 8,93 (1H, s), 8,64 (1H, d, J=4,2Hz), 8,44 (1H, d, J=10,5Hz), 8,02-7,91 (3H, m), 7,69-7,62 (1H, m), 7,46-7,42 (1H, m), 7,37 (1H, d, 9,0Hz), 5,38 (2H, s), 4,59 (2H, m), 4,19 (1H, m), 3,81 (1H, m), 3,71 (1H, m), 3,47 (2H, m), 3,21 (1H, m), 3,02 (1H, m), 2,28 (3H, s), 2,02 (1H, m), 1,84 (2H, m), 1,56 (1H, m)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-138		(sal tri-HCl) 9,28 (1H, s), 8,93 (1H, s), 8,64 (1H, d, J=4,2Hz), 8,44 (1H, d, J=10,5Hz), 8,02-7,91 (3H, m), 7,69-7,62 (1H, m), 7,46-7,42 (1H, m), 7,37 (1H, d, 9,0Hz), 5,38 (2H, s), 4,59 (2H, m), 4,19 (1H, m), 3,81 (1H, m), 3,71 (1H, m), 3,47 (2H, m), 3,21 (1H, m), 3,02 (1H, m), 2,28 (3H, s), 2,02 (1H, m), 1,84 (2H, m), 1,56 (1H, m)
VIII-139		10,08 (1H, s), 8,75 (1H, s), 8,61-8,58 (2H, m), 8,22 (1H, d, J=8,8Hz), 7,98 (1H, s), 7,89 (1H, t, J=8,0Hz), 7,68 (1H, d, J=8,4Hz), 7,37 (1H, t, J=6,4Hz), 7,37 (1H, t, J=6,4Hz), 7,28 (1H, d, J=8,4Hz), 5,31 (2H, s), 4,34 (2H, t, J=6,4Hz), 3,33 (1H, t, J=6,4Hz), 2,92 (2H, t, J=5,2Hz), 2,65-2,61 (1H, m), 2,26 (3H, s), 1,75-1,70 (1H, m), 0,83 (3H, d, J=6,8Hz),

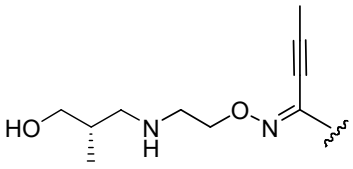
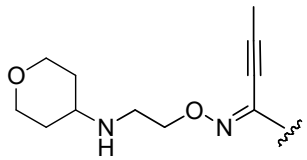
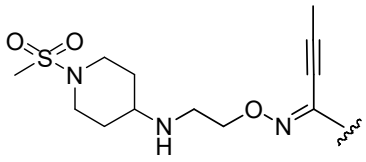
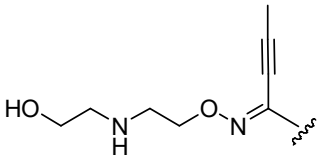
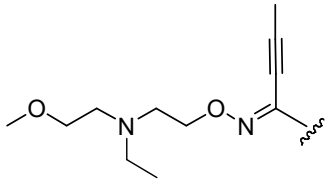
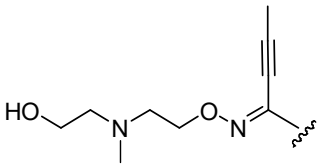
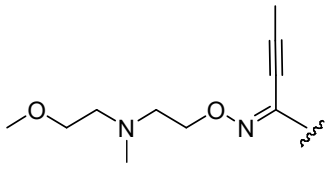
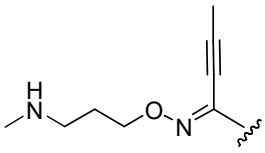
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-140		10,09 (1H, s), 8,75 (1H, s), 8,59 (2H, bs), 8,22 (1H, d, J=8,8Hz), 7,98 (1H, s), 7,89 (1H, t, J=6,4Hz), 7,80 (1H, d, J=8,8Hz), 7,69 (1H, t, J=8,4Hz), 7,59 (1H, t, J=8,4Hz), 7,37 (1H, d, J=5,2Hz), 7,28 (1H, d, J=8,8Hz), 5,31 (2H, s), 4,34 (2H, t, J=6,4Hz), 3,32 (2H, t, J=6,4Hz), 2,92 (2H, t, J=5,6Hz), 2,65-2,61 (1H, m), 2,26 (3H, s), 1,75-1,68 (1H, m), 1,24 (1H, bs), 0,83 (3H, d, J=6,8Hz),
VIII-141		(sal tri-HCl) 12,48 (1H, s), 9,48 (1H, s), 9,42 (1H, bs), 9,29 (2H, bs), 8,94 (1H, s), 8,72 (1H, s), 8,47 (1H, s), 8,13-8,06 (1H, m), 7,92 (1H, s), 7,76 (1H, bs), 7,68 (1H, bs), 7,59 (1H, bs), 7,39 (1H, bs), 5,46 (2H, s), 4,62 (2H, bs), 3,88 (4H, bs), 2,28 (3H, s), 2,01-1,94 (4H, m), 1,69-1,60 (4H, m),

Tabela 34

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-142		10,07 (1H, s), 8,74 (1H, s), 8,59 (2H, s), 8,20 (1H, bs), 7,97 (1H, s), 7,89 (1H, bs), 7,80 (1H, d, J=8,0Hz), 7,68 (1H, bs), 7,58 (1H, d, J=8,8Hz), 7,38 (1H, bs), 7,28 (1H, d, J=9,2Hz), 5,31 (2H, s), 4,31 (2H, bs), 3,45 (2H, bs), 2,94 (2H, bs), 2,85-2,81 (5H, m), 2,26 (3H, s), 1,89-1,85 (2H, m), 1,36-1,28 (2H, m),
VIII-143		10,09 (1H, brs), 8,74 (1H, s), 8,61-8,59 (2H, m), 8,22 (1H, d, J=9,0Hz), 7,97 (1H, s), 7,92-7,86 (1H, m), 7,81 (1H, d, J=9,0Hz), 7,69 (1H, d, J=9,0Hz), 7,59 (1H, d, J=7,8Hz), 7,40-7,36 (1H, m), 7,29 (1H, d, J=9,0Hz), 5,31 (2H, s), 4,23 (2H, t, 5,4Hz), 3,47 (2H, t, 5,4Hz)), 2,91 (2H, t, 5,4Hz), 2,65 (2H, m), 2,25 (3H, s)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-144		(sal tri-HCl) 12,4 (1H, s), 10,5 (1H, s), 9,34 (1H, s), 8,93 (1H, s), 8,68-8,67 (1H, m), 8,45 (1H, d, J=9,2), 8,05-8,02 (2H, m), 7,92-7,91 (1H, m), 7,71-7,66 (2H, m), 7,52-7,49 (1H, m), 7,37 (1H, d, J=8,8), 5,41 (2H, s), 4,73-4,67 (1H, m), 3,30 (6H, s), 2,27 (3H, s),1,29-1,25 (1H, m),
VIII-145		10,08 (1H, s), 8,75 (1H, s), 8,59 (2H, bs), 8,22 (1H, d, J=8,4Hz), 7,98 (1H, bs), 7,89 (1H, t, J=8,0Hz), 7,80 (1H, d, J=9,2Hz), 7,68 (1H, d, J=8,8Hz), 7,38 (1H, d, J=6,4Hz), 7,28 (1H, d, J=8,8Hz), 5,31 (2H, s), 4,36 (4H, t J=6,4Hz), 3,49 (2H, bs), 2,79 (2H, t, J=6,0Hz), 2,30 (3H, s), 2,25 (3H, s),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-146		(sal tri-HCl) 12,70 (1H, s), 10,83 (1H, bs), 9,49 (1H, s), 8,95 (1H, s), 8,77 (1H, bs), 8,44 (1H, d, J=8,84Hz), 8,23 (1H, bs), 8,10 (1H, d, J=8,8Hz), 7,95 (1H,s), 7,85 (1H, d, J=6,8Hz), 7,74-7,68 (2H, m), 7,39 (1H, d, J=8,4Hz), 5,51 (2H, s), 4,70 (2H, bs), 7,75-7,42 (4H, m), 3,48-3,44 (1H, m), 3,40 (1H, bs), 3,30 (3H, s), 2,90 (3H, s), 2,28 (3H, s),
VIII-147		10,28-10,03 (1H, m), 8,75 (1H, s), 8,61-8,58 (2H, m), 8,21 (1H, d, J=8,8Hz), 7,98 (1H, s), 7,89 (1H, t, J=8,0Hz), 7,79 (1H, d, J=7,2Hz), 7,68 (1H, d, J=8,0Hz), 7,37 (1H, t, J=6,0Hz), 7,28 (1H, t, J=8,8Hz), 5,31 (2H, s), 4,33 (2H, t J=6,4Hz), 2,31 (3H, s), 2,06 (3H, s), 1,88 (2H, t, J=6,4Hz),

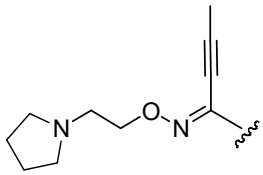
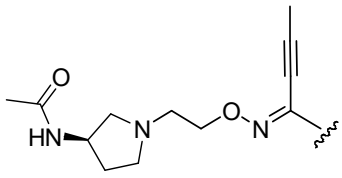
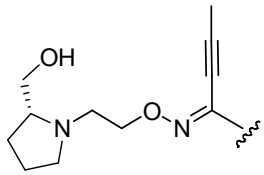
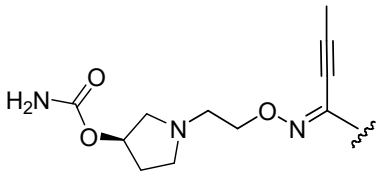
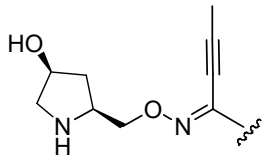
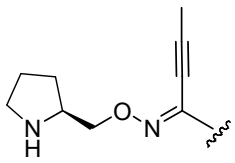
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-148		10,09 (1H, brs), 8,75 (1H, s), 8,61-8,57 (2H, m), 8,22 (1H, d, J=9,0Hz), 7,98 (1H, s), 7,92-7,86 (1H, m), 7,80 (1H, d, J=9,0Hz), 7,68 (1H, d, J=9,0Hz), 7,59 (1H, d, J=7,8Hz), 7,40-7,36 (1H, m), 7,28 (1H, d, J=9,0Hz), 5,31 (2H, s), 4,37 (2H, m), 2,82 (2H, m), 2,54 (4H, m), 2,25 (3H, s), 1,69 (4H, m)

Tabela 35

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-149		10,09 (1H, s), 8,75 (1H, s), 8,70 (2H, s), 8,20 (1H, d, J=8,0Hz), 8,07 (2H, s), 7,98 (1H, t, J=4,8Hz), 7,88 (1H, t, J=8,0Hz), 7,68 (1H, d, J=8,0Hz), 7,38 (1H, s), 7,28 (1H, d, J=9,6Hz), 5,31 (2H, s), 4,42 (2H, s), 4,29-4,24 (1H, m), 2,91-2,76 (2H, m), 2,25 (3H, s), 2,17-2,12 (1H, m), 1,75 (3H, s), 1,53-1,34 (1H, m), 1,11 (2H, d, J=4,4Hz),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-150		10,09 (1H, s), 8,75 (1H, s), 8,59 (2H, s), 8,21 (1H, bs), 7,98 (1H, s), 7,89 (1H, s), 7,79 (1H, s), 7,68 (1H, s), 7,58 (1H, s), 7,37 (1H, s), 7,28 (1H, s), 5,31 (2H, s), 4,36 (2H, bs), 2,71 (2H, bs), 2,25 (3H, s), 1,81 (1H, bs), 1,66 (2H, bs), 1,52 (1H, bs), 1,24 (2H, bs),
VIII-151		10,09 (1H, brs), 8,75 (1H, s), 8,61-8,59 (2H, m), 8,22 (1H, d, J=9,0Hz), 7,97 (1H, s), 7,92-7,86 (1H, m), 7,80 (1H, d, J=9,0Hz), 7,69 (1H, d, J=9,0Hz), 7,59 (1H, d, J=7,8Hz), 7,40-7,36 (1H, m), 7,28 (1H, d, J=9,0Hz), 6,48 (2H, brs), 5,31 (2H, s), 4,94 (1H, m), 4,37 (2H, m), 2,81-2,63 (5H, m), 2,44 (1H, m), 2,25 (3H, s), 2,14 (1H, m), 1,69 (1H, m)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-152		10,13 (1H, brs), 8,79 (1H, s), 8,61-8,58 (2H, m), 8,23 (1H, dd, J=1,8Hz, J=8,7Hz), 7,98 (1H, d, J=2,7Hz), 7,92-7,86 (1H, m), 8,80 (1H, d, J=8,7Hz), 7,79 (1H, dd, J=2,7Hz, J=9,0Hz), 7,59 (1H, d, J=7,8Hz), 7,39-7,35 (1H, m), 7,28 (1H,d, J=9,0Hz), 5,31 (2H, s), 4,91 (1H, brs), 4,36-4,24 (3H, m), 3,59 (1H, m), 2,99-2,812 (2H, m), 2,26 (3H, s), 2,13 (1H, m), 1,50 (1H,m),
VIII-153		10,0 (1H, br), 8,64 (1H, s), 8,62-8,55 (2H, m), 8,20 (1H, d, J=8,8), 7,96 (1H, s), 7,90-7,87 (1H, m), 7,79 (1H, d, J=8,4), 7,68-7,66 (1H,m), 7,58 (1H, d, J=8,4), 7,38-7,35 (1H, m), 7,27 (1H, d, J=8,8), 5,30 (2H, s), 4,18-4,08 (2H, m), 3,43-3,40 (1H, m), 3,69 (3H, s), 2,84-2,77 (2H, m), 2,25 (3H, s), 1,88-1,55 (3H, m), 1,50-1,38 (1H, m),

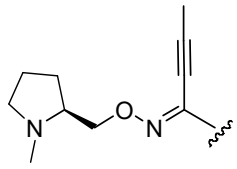
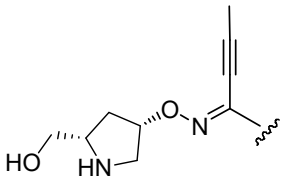
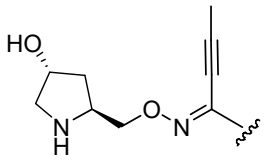
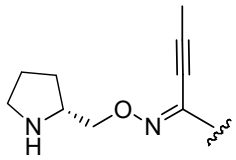
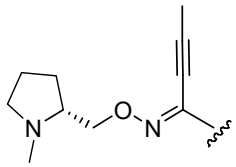
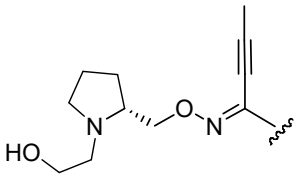
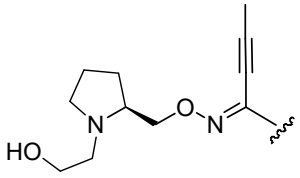
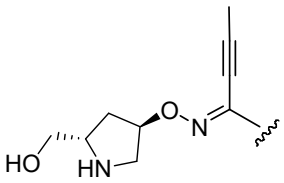
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-154		10,08 (1H, br), 8,75 (1H, s), 8,60-8,58 (2H, m), 8,21-8,19 (1H,m), 7,98-7,97 (1H, m), 7,93-7,86 (1H, m), 7,79 (1H, d, J=8,8), 7,70-7,67 (1H, m), 7,58 (1H, d, J=8,0), 7,38-7,35 (1H, m), 7,27 (1H, d, J=9,2), 5,30 (2H, s), 4,30-4,20 (2H, m), 3,01-2,96 (1H, m), 2,68 (1H, br), 2,41 (3H, s), 2,24 (3H, s), 1,99-1,89 (1H, m), 1,73-1,66 (2H, m), 1,62-1,53 (1H, m),
VIII-155		10,0 (1H, brs), 8,73 (1H, s), 8,60-8,58 (2H, m), 8,31 (1H, s), 8,22-8,20 (1H, m), 7,96 (1H, s), 7,90-7,86 (1H, m), 7,79 (1H, d, J=8,8), 7,68-7,66 (1H, m), 7,59 (1H, d, J=7,6), 7,38-7,35 (1H, m), 7,28 (1H, d, J=9,2), 5,30 (2H, s), 4,93 (1H, brs), 3,02 (1H, d, J=11,6), 2,24 (3H, s), 2,06-2,01 (1H, m), 1,77-1,70 (1H, m),

Tabela 36

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-156		10,13 (1H, brs), 8,81 (1H, s), 8,61-8,59 (2H, m), 8,24 (1H, d, J=10,5Hz), 7,99 (1H, s), 7,92-7,88 (1H, m), 7,81 (1H, d, J=9,0Hz), 7,70 (1H, d, J=9,0Hz), 7,59 (1H, d, J=7,8Hz), 7,38-7,36 (1H, m), 7,28 (1H, d, J=9,0Hz), 5,31 (2H, s), 4,92 (1H, s), 4,28 (3H, m), 3,82 (1H, m), 3,09 (1H, d, 11,4Hz), 3,83 (1H, d, 11,4Hz), 2,27 (3H, s), 1,87 (1H, m), 1,65 (1H, m)
VIII-157		10,03 (1H, br), 8,73 (1H, s), 8,59-8,58 (1H, m), 8,55 (1H, s), 8,20 (1H, d, J=8,8), 7,94 (1H, s), 7,89-7,85 (1H, m), 7,78 (1H, d, J=8,4), 7,66-7,64 (1H, m), 7,57 (1H, d, J=7,6), 7,38-7,35 (1H, m), 7,25 (1H, d, J=8,8), 5,28 (2H, s), 4,20-4,08 (2H, m), 2,85-2,74 (2H, m), 2,24 (3H, s), 1,82-1,76 (1H, m), 1,73-1,58 (2H, m), 1,48-1,39 (1H, m)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-158		10,07 (1H, br), 8,74 (1H, s), 8,60-8,58 (2H, m), 8,22-8,19 (1H,m), 7,98-7,97 (1H, m), 7,93-7,86 (1H, m), 7,80 (1H, d, J=9,2), 7,70-7,67 (1H, m), 7,59 (1H, d, J=7,6), 7,38-7,35 (1H, m), 7,28 (1H, d, J=9,2), 5,30 (2H, s), 4,30-4,20 (2H, m), 3,01-2,96 (1H, m), 2,65 (1H, br), 2,40 (3H, s), 2,24 (3H, s), 1,99-1,89 (1H, m), 1,73-1,66 (2H, m), 1,62-1,53 (1H, m),
VIII-159		10,08 (1H, s), 8,73 (1H, s), 8,59-8,56 (2H, m), 8,21-8,19 (1H, m), 7,94 (1H, s), 7,90-7,86 (1H, m), 7,79 (1H, d, J=8,8), 7,66-7,64 (1H, m), 7,58 (1H, d, J=7,6), 7,38-7,35 (1H, m), 7,26 (1H, d, J=9,2), 5,29 (2H, s), 4,44 (1H, brs), 4,25-4,21 (1H, m), 4,15-4,11 (1H, m), 3,05-2,96 (2H, m), 2,46-2,39 (1H, m), 2,23 (2H, s), 1,92-1,82 (1H, m), 1,73-1,63 (2H, m), 1,59-1,54 (1H, m),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-160		10,0 (1H, s), 8,72 (1H, s), 8,61-8,53 (2H, m), 8,21-8,19 (1H, m), 7,94 (1H, s), 7,89-7,86 (1H, m), 7,79 (1H, d, J=8,8), 7,66-7,64 (1H,m), 7,58 (1H, d, J=8,0), 7,38-7,35 (1H, m), 7,26 (1H, d, J=9,2), 5,29 (2H, s), 4,44 (1H, brs), 4,25-4,21 (1H, m), 4,15-4,11 (1H, m), 3,05-2,96 (2H, m), 2,45-2,39 (1H, m), 2,23 (3H, s), 1,92-1,82 (1H, m), 1,73-1,63 (2H, m), 1,60-1,53 (2H, m),
VIII-161		10,0 (1H, brs), 8,73 (1H, s), 8,60-8,57 (2H, m), 8,21 (1H, d, J=8,4), 7,95 (1H, s), 7,90-7,86 (1H, m), 7,79 (1H, d, J=8,8), 7,67-7,65 (1H, m), 7,58 (1H, d, J=7,6), 7,38-7,35 (1H, m), 7,27 (1H, d, J=8,8), 5,30 (2H, s), 4,93 (1H, brs), 3,02 (1H, d, J=11,6), 2,24 (3H, s), 2,06-2,01 (1H, m), 1,77-1,70 (1H, m)

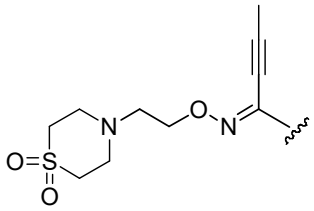
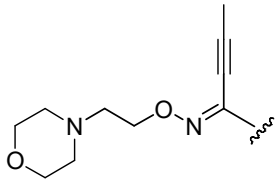
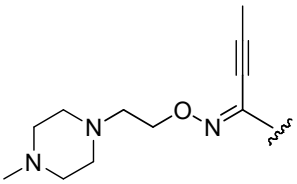
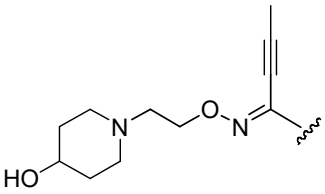
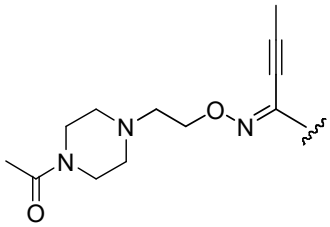
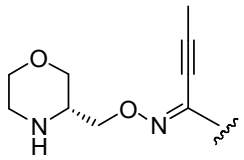
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-162		10,07 (1H, s), 8,75 (1H, s), 8,61-8,59 (2H, m), 8,23 (1H, d, J=8,8Hz), 7,98 (1H, d, J=2,4Hz), 7,89 (1H, t, J=8,4Hz), 7,80 (1H, d, J=8,8Hz), 7,68 (1H, d, J=6,4Hz), 7,57 (1H, t, J=11,8Hz), 7,28 (1H, d, J=8,8Hz), 5,31 (2H, s), 4,40 (2H, t J=5,2Hz), 3,32 (4H, s), 3,09 (4H, bs), 2,96 (2H, t, J=5,6Hz), 2,26 (3H, s),

Tabela 37

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-163		10,07 (1H, s), 8,75 (1H, s), 8,59 (2H, bs), 8,21 (1H, d, J=4,8Hz), 7,98 (1H, s), 7,89 (1H, t, J=7,6Hz), 7,80 (1H, d, J=8,4Hz), 7,68 (1H, d, J=8,4Hz), 7,60 (1H, t, J=8,4Hz), 7,37 (1H, t, J=7,6Hz), 7,28 (1H, d, J=8,8Hz), 5,31 (2H, s), 4,40 (2H, t J=4,8Hz), 3,60 (4H, bs), 2,72 (4H, t, J=4,8Hz), 2,25 (3H, s),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-164		10,0 (1H, s), 8,73 (1H, s), 8,60-8,57 (2H, m), 8,20 (1H, d, J=8,8), 7,96 (1H, s), 7,90-7,86 (1H, m), 7,79 (1H, d, J=8,4), 7,67-7,65 (1H, m), 7,58 (1H, d, J=7,6), 7,38-7,35 (1H, m), 7,27 (1H, d, J=8,8), 5,30 (2H, s), 4,38-4,35 (2H, m), 2,71-2,68 (2H, m), 2,31 (1H, br), 2,24 (3H, s), 2,13 (3H, s),
VIII-165		10,0 (1H, s), 8,73 (1H, s), 8,62-8,54 (2H, m), 8,21-8,19 (1H, m), 7,96 (1H, s), 7,90-7,86 (1H, m), 7,80-7,78 (1H, m), 7,68-7,66 (1H, m), 7,59 (1H, d, J=8,0), 7,38-7,36 (1H, m), 7,27 (1H, d, J=8,8), 5,30 (2H, s), 4,54 (1H, brs), 4,37-4,34 (2H, m), 2,83-2,75 (2H, m), 2,69-2,66 (2H, m), 2,24 (3H, s), 2,17-2,11 (2H, m), 1,71-1,69 (2H, m), 1,71-1,69 (2H, m), 1,44-1,32 (2H, m),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-166		10,08 (1H, s), 8,75 (1H, s), 8,59 (2H, bs), 8,22 (1H, d, J=8,8Hz), 7,80 (1H, s), 7,89 (1H, t, J=6,4Hz), 7,80 (1H, d, J=8,4Hz), 7,70-7,67 (1H, m), 7,59 (1H, d, J=8,4Hz), 7,37 (1H, bs), 7,28 (1H, d, J=8,0Hz), 5,31 (2H, s), 4,41 (2H, t J=4,4Hz), 3,43 (2H, bs), 2,76 (2H, bs), 2,26 (3H, s), 1,99 (3H, s),
VIII-167		10,10 (1H, s), 8,73 (1H, s), 8,60-8,56 (2H, m), 8,20 (1H, d, J=8,8), 7,94 (1H, s), 7,90-7,86 (1H,m), 7,79 (1H, d, J=8,8), 7,68-7,64 (1H, m), 7,58 (1H, d, J=7,6), 7,38-7,35 (1H, m), 7,27 (1H, d, J=9,2), 5,29 (2H, s), 4,20-4,08 (2H, m), 3,79 (1H, d, J=10,4), 3,65 (1H, d, J=11,2), 3,25-3,20 (1H, m), 3,09 (1H, br), 2,83-2,70 (2H, m), 2,25 (3H, s)

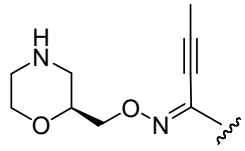
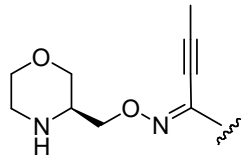
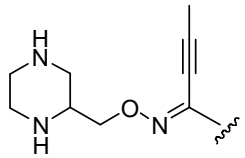
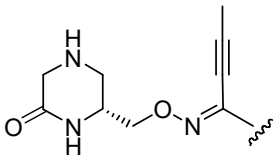
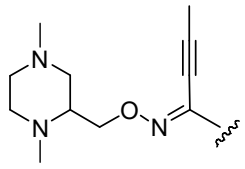
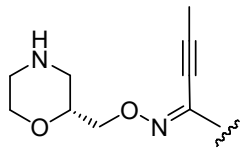
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-168		10,0 (1H, s), 8,73 (1H, s), 8,59-8,57 (2H, m), 8,19 (1H, d, J=8,8), 7,95 (1H, s), 7,89-7,85 (1H,m), 7,78 (1H, d, J=8,8), 7,68-7,65 (1H, m), 7,58 (1H, d, J=7,6), 7,37-7,34 (1H, m), 7,26 (1H, d, J=8,8), 5,29 (2H, s), 4,26-4,14 (2H, m), 3,75-3,72 (2H, m), 2,85 (1H, d, J=12,4), 2,69-2,61 (2H, m), 2,45 (1H, d, J=10,8), 2,25 (3H, s),
VIII-169		10,0 (1H, s), 8,74 (1H, s), 8,60-8,58 (2H, m), 8,20 (1H, d, J=8,8), 7,96 (1H, s), 7,90-7,86 (1H,m), 7,80 (1H, d, J=8,8), 7,68-7,66 (1H, m), 7,59 (1H, d, J=7,6), 7,38-7,35 (1H, m), 7,27 (1H, d, J=9,2), 5,30 (2H, s), 4,20-4,08 (2H, m), 3,79 (1H, d, J=10,4), 3,65 (1H, d, J=11,2), 3,25-3,20 (1H, m), 3,09 (1H, br), 2,83-2,70 (2H, m), 2,26 (2H, s),

Tabela 38

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-170		10,09 (1H, brs), 8,74 (1H, s), 8,61-8,58 (2H, m), 8,22 (1H, d, J=10,5Hz), 7,97 (1H, s), 7,92-7,86 (1H, m), 7,80 (1H, d, J=9,0Hz), 7,68 (1H, d, J=10,5Hz), 7,59 (1H, d, J=8,1Hz), 7,39-7,35 (1H, m), 7,28 (1H, d, J=9,0Hz), 5,31 (2H, s), 4,12 (2H, d, 4,5Hz), 2,95-2,53 (5H, m), 2,34-2,09 (5H, m)
VIII-171		10,08 (1H, brs), 8,74 (1H, s), 8,61-8,59 (2H, m), 8,21 (1H, d, J=9,0Hz), 7,98 (1H, s), 7,92-7,86 (1H, m), 7,81 (1H, d, J=9,0Hz), 7,75 (1H, s), 7,67 (1H, d, J=9,0Hz), 7,59 (1H, d, J=7,8Hz), 7,40-7,36 (1H, m), 7,29 (1H, d, J=9,0Hz), 5,31 (2H, s), 4,31 (2H, m), 3,66 (1H, m), 3,27-3,10 (2H, m), 2,99-2,80 (2H, m)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-172		10,09 (1H, brs), 8,74 (1H, s), 8,61-8,59 (2H, m), 8,22 (1H, d, J=9,0Hz), 7,97 (1H, s), 7,92-7,86 (1H, m), 7,81 (1H, d, J=9,0Hz), 7,68 (1H, d, J=9,0Hz), 7,59 (1H, d, J=7,8Hz), 7,40-7,36 (1H, m), 7,29 (1H, d, J=9,0Hz), 5,31 (2H, s), 4,44 (1H, m), 4,16 (1H, m), 2,70-2,51 (4H, m), 2,30-2,16 (10H, m), 2,09-1,88 (2H, m)
VIII-173		10,0 (1H, br), 8,74 (1H, s), 8,60-8,58 (2H, m), 8,20 (1H, d, J=8,8), 7,97 (1H, s), 7,90-7,86 (1H, m), 7,80 (1H, d, J=8,4), 7,68-7,66 (1H,m), 7,59 (1H, d, J=8,0), 7,38-7,35 (1H, m), 7,28 (1H, d, J=9,2), 5,30 (2H, s), 4,26-4,14 (2H, m), 3,75-3,72 (2H, m), 3,48-3,42 (2H, m), 2,85 (1H, d, J=12,4), 2,69-2,60 (2H, m), 2,45 (1H, d, J=10,4), 2,26 (3H, s)

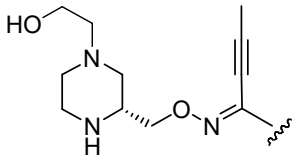
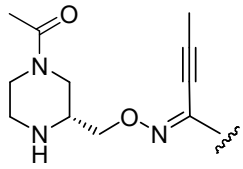
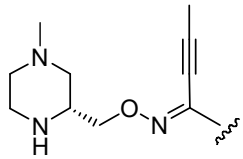
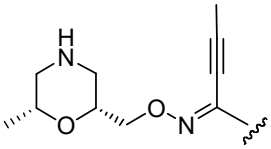
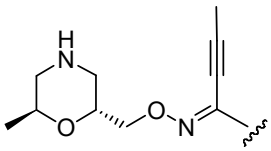
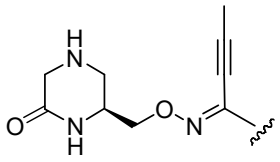
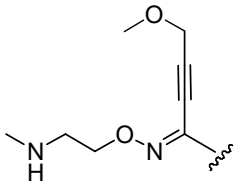
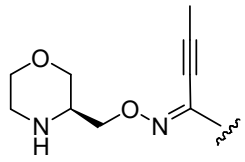
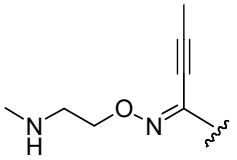
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-174		(sal tri-HCl) 12,31 (1H, brs), 9,41 (1H, s), 8,97 (1H, s), 8,73 (1H, d, J=1,8Hz), 8,49 (1H, d, 8,7Hz), 8,17-8,05 (2H, m), 7,94 (1H, s), 7,77 (1H, d, J=7,5Hz), 7,69 (1H, d, 8,7Hz), 7,59 (1H, t, J=5,7Hz), 7,38 (1H, d, J=8,7Hz), 5,46 (2H, s), 4,60 (2H, m), 4,35-3,31 (12H, m), 2,30 (3H, s),
VIII-175		
VIII-176		(sal tri-HCl) 12,31 (1H, brs), 9,41 (1H, s), 8,97 (1H, s), 8,73 (1H, d, J=5,4Hz), 8,49 (1H, d, J=8,7Hz), 8,13 (1H, s), 8,07 (1H, d, J=9,0Hz), 7,94 (1H, s), 7,72 (1H, d, J=8,7Hz), 7,02 (1H, d, J=9,0Hz), 7,59 (1H, s), 7,38 (1H, d, J=9,0Hz), 5,46 (2H, s), 4,65-3,62 (10H, m), 2,89 (3H, s), 2,30 (3H,s),

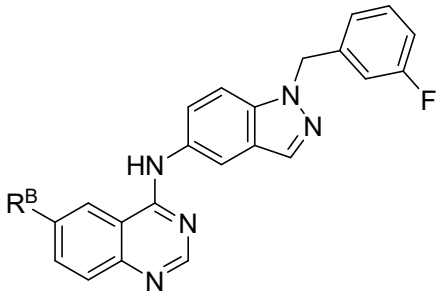
Tabela 39

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-177		10,1 (1H, s), 8,74 (1H, s), 8,59 (2H, brs), 8,21 (1H, d, J=8,8Hz), 7,97 (1H, s), 7,85-7,92 (1H, m), 7,80 (1H, d, J=8,4Hz), 7,67 (1H, d, J=9,6Hz), 7,59 (1H, d, J=6,4Hz), 7,34-7,40 (1H, m), 7,29 (1H, d, J=8,8Hz), 5,31 (2H, m), 4,10-4,35 (2H, m), 3,75-3,82 (1H, m), 3,48 (1H, m), 2,85 (1H, d, J=12Hz), 2,74 (1H, d, J=13Hz), 2,34-2,41 (1H, m), 2,26 (4H, brs), 1,03 (3H, d, J=6,0Hz)
VIII-178		10,1 (1H, s), 8,74 (1H, s), 8,59 (2H, brs), 8,21 (1H, d, J=8,8Hz), 7,97 (1H, s), 7,79-7,93 (2H, m), 7,66-7,70 (1H, m), 7,59 (1H, d, J=6,4Hz), 7,38 (1H, brs), 7,29 (1H, d, J=8,8Hz), 5,31 (2H, m), 4,37-4,56 (2H, m), 3,95-4,02 (1H, m), 3,80-3,88 (1H, m), 2,62-2,85 (3H, m), 2,31-2,4 (1H, m), 2,26 (3H, s), 1,06 (3H, d, J=5,2Hz)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-179		10,06 (1H, brs), 8,75 (1H, s), 8,61-8,59 (2H, m), 8,22 (1H, d, J=9,0Hz), 7,97 (1H, s), 7,92-7,86 (1H, m), 7,81 (1H, d, J=9,0Hz), 7,76 (1H, s), 7,69 (1H, d, J=9,0Hz), 7,59 (1H, d, J=7,8Hz), 7,40-7,36 (1H, m), 7,29 (1H, d, J=9,0Hz), 5,31 (2H, s), 4,30 (2H, m), 3,65 (1H, m), 3,16 (2H, m), 2,99-2,80 (2H, m), 2,26 (3H, s)
VIII-180		10,0 (1H, brs), 8,76 (1H, s), 8,60-8,58 (2H, m), 8,19 (1H, d, J=8,8), 7,97 (1H, s), 7,89-7,86 (1H,m), 7,81 (1H, d, J=8,8), 7,68-7,66 (1H, m), 7,58 (1H, d, J=7,6), 7,38-7,35 (1H, m), 7,27 (1H, d, J=8,8), 5,30 (2H, s), 4,51 (2H, s), 4,38-4,35 (2H, m), 3,40 (3H, s), 2,87-2,84 (2H, m), 2,34 (3H, s)

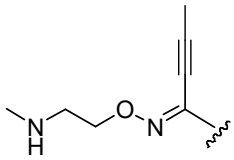
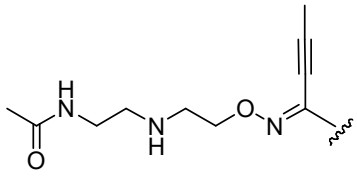
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-181		10,0 (1H, s), 8,76 (1H, s), 8,59 (2H, s), 8,19 (1H, d, J=8,8), 7,97 (1H, s), 7,90-7,86 (1H, m), 7,82 (1H, d, J=8,8), 7,69-7,66 (1H, m), 7,59 (1H, d, J=8,0), 7,38-7,35 (1H, m), 7,28 (1H, d, J=8,8), 5,30 (2H, s), 4,52 (2H, s), 4,25-4,15 (2H, m), 3,82-3,79 (1H, m), 3,67-3,64 (1H, m), 3,40 (3H, s), 3,26-3,21 (2H, m), 3,14-3,05 (1H, m), 2,81-2,72 (2H, m)
VIII-182		10,1 (1H, s), 8,79 (1H, s), 8,60 (2H, s), 8,25 (1H, d, J=7,6Hz), 7,98 (1H, s), 7,89 (1H, bs), 7,81 (1H, d, J=7,6Hz), 7,69 (1H, d, J=7,6Hz), 7,60 (1H, d, J=7,2Hz), 7,38 (1H, bs), 7,29 (1H, d, J=8,4Hz), 5,31 (2H, s), 4,43 (2H, bs), 3,14 (2H, bs), 2,52 (3H, s), 2,27 (3H, s)

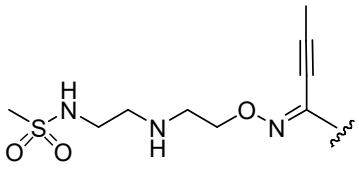
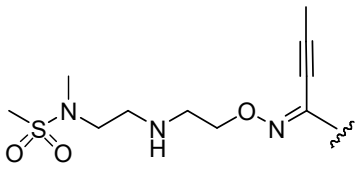
Fórmula química 83

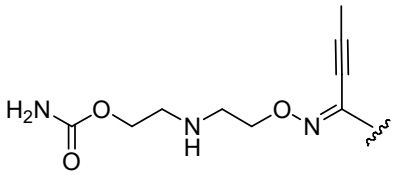
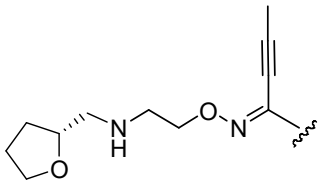


(VIII)

Tabela 40

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-183		10,19 (1H, s), 8,78 (1H, s), 8,53 (1H, s), 8,23 (1H, dd, J=8,4Hz, J=4,0Hz), 8,17 (1H, s), 8,14 (1H, s), 7,80-7,65 (3H, m), 7,40-7,35 (1H, m), 7,13-7,04 (3H, m), 5,72 (2H, s), 4,32 (2H, t, J=6,0Hz), 2,86 (2H, t, J=6,0Hz), 2,35 (3H, s), 2,25 (3H, s),
VIII-184		(sal di-HCl) 12,46 (1H, s), 9,37 (1H, s), 8,87 (1H, s), 8,48 (1H, d, J=8,7Hz), 8,27 (1H, t, J=5,4Hz), 8,24 (1H, s), 8,03 (2H, m), 7,85 (1H, d, J=9,0Hz), 7,68 (1H, d, 9,0Hz), 7,35 (1H, s), 7,13-7,05 (3H, m), 5,75 (2H, s), 4,58 (2H, m), 7,13-7,05 (3H, m), 5,75 (2H, s), 4,58 (2H, m), 3,51-3,37 (4H, m), 3,11 (2H, m), 2,27 (3H, s), 1,01 (1H, s),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-185		(sal di-HCl) 10,12 (1Hs), 8,82 (1H, d, J=1,5Hz), 8,52 (1H, s), 8,22 (1H, dd, J=1,8Hz, J=8,7Hz), 8,14 (1H, s), 7,80 (1H, s), 7,80 (1H, s), 7,77-7,68 (3H, m), 7,40-7,33 (1H, m), 7,12-7,04 (3H, m), 5,71 (2H, s), 4,86 (1H, brs), 4,28 (3H, m), 3,58 (1H, m), 2,95-2,78 (2H, m), 2,25 (3H, s), 2,11 (1H, m), 1,47 (1H, m),
VIII-186		10,18 (1H, s), 8,78 (1H, s), 8,52 (1H, s), 8,23-8,12 (3H, m), 7,79-7,65 (3H, m), 7,41-7,32 (1H, m), 7,18 (7,02) (3H, m), 5,71 (2H, s), 4,31 (2H, m), 3,14 (2H, m), 2,29 (2H, m), 2,87 (3H, s)2,77 (6H, m), 2,24 (3H, s),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-187		10,19 (1Hs), 8,78 (1H, s), 8,52 (1H, s), 8,23-8,12 (3H, m), 7,80-7,65 (3H, m), 7,38-7,33 (1H, m), 713-7,03 (3H, m), 6,49 (2H, brs), 5,71 (2H, s), 4,31 (2H, m), 4,04-3,95 (2H, m), 2,92 (2H, m), 2,78 (2H, m), 2,25 (3H, s),
VIII-188		(sal di-HCl) 12,09 (1H, s), 8,96 (1H, s), 8,83 (1H, s), 8,43 (1H, d, J=8,7Hz), 8,06 (1H, s), 7,97 (1H, d, J=8,4Hz), 7,83 (1H, d, J=9,0Hz), 7,67 (1H, d, J=1,8Hz), 7,65 (1H, dd, J=2,1Hz, J=9,0Hz), 7,41-7,34 (1H, m), 7,14-7,05 (3H, m), 5,71 (2H, s), 4,54 (2H, m), 4,19 (1H, m), 3,83-3,70 (2H, m), 3,68-2,95 (5H, m), 2,27 (3H, s), 2,04 (1H, m), 1,93 (1H, m), 1,56 (1H, m),

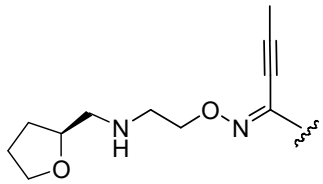
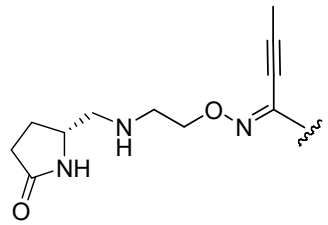
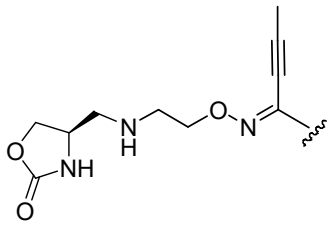
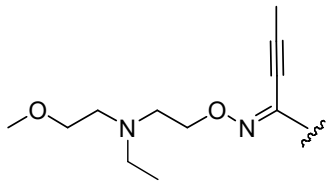
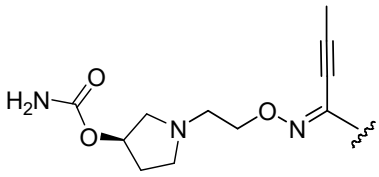
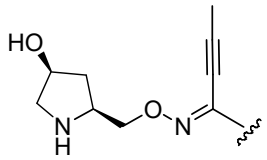
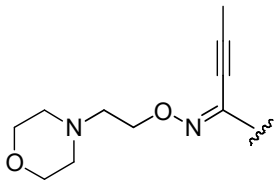
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-189		(sal di-HCl) 12,21 (1H, brs), 8,97 (1H, brs), 8,84 (1H, s), 8,43 (1H, dd, J=1,5Hz, J=9,0Hz), 8,07 (1H, s), 8,01 (1H, s), 7,99 (1H, d, J=9,0Hz), 7,84 (1H, d, J=9,0Hz), 7,67 (1H, dd, J=1,8Hz, J=9,0Hz), 7,41-7,32 (1H, m), 7,14-7,05 (3H, m), 5,74 (2H, s), 4,59 (2H, m), 4,21 (1H, m), 3,82-3,65 (2H, m), 3,62-3,05 (8H, m), 2,28 (3H, s), 2,02 (1H, m), 1,83 (1H, M), 1,55 (1H, m),

Tabela 41

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-190		(sal di-HCl) 12,18 (1H, s), 9,29 (1H, s), 8,45 (1H, dd, J=1,2, J=9,0Hz), 8,23 (1H, s), 8,06 (1H, s), 8,06 (1H, d, J=1,2Hz), 7,99 (1H, d, J=8,7Hz), 7,87-7,82 (1H, m), 7,67 (1H, dd, J=1,2Hz, J=9,0Hz), 7,39-7,14 (1H, m), 7,14-7,05 (3H, m), 5,74 (2H, s), 4,61 (2H (, m), 3,95 (1H, m), 8,23 (2H, m), 3,13 (3H, m), 2,28 (3H, s), 2,17 (1H, m), 1,78 (1H, m),
VIII-191		(sal di-HCl) 12,18 (1H, s), 9,12 (1H, s), 8,87 (1H, s), 8,46 (1H, d, J=8,7Hz), 8,43 (1H, s), 8,23 (1H, s), 8,04-7,97 (2H, m), 7,87-7,82 (1H, m), 7,64 (1H, dd, J=1,2Hz, J=9,0Hz), 7,37-7,14 (1H, m), 7,11-7,05 (3H, m), 5,74 (2H, s), 4,61 (2H (, m), 4,09-3,26 (7H, m), 2,26 (3H, s), 2,17 (1H, m), 1,79 (1H, s),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-192		10,17 (1H, s), 8,78 (1H, s), 8,51 (1H,s), 8,20 (1H, dd, J=1,8Hz, J=8,7Hz), 8,14 (1H, s), 7,80-7,65 (3H, m), 7,40-7,33 (1H, m), 7,13-7,03 (3H, m), 5,71 (2H, s), 4,31 (2H, t, J=5,7Hz), 3,41 (2H, t, J=6,3Hz), 3,22 (3H, s), 2,85 (2H, m), 2,70-2,57 (4H, m), 2,23 (3H, s), 0,99 (2H, t, J=7,2Hz),
VIII-193		10,19 (1H, s), 8,78 (1H, s), 8,52 (1H, s), 8,21 (1H, d, J=8,4Hz), 8,16 (1H, s), 8,13 (1H, s), 7,78-7,65 (3H, m), 7,49-7,33 (1H, m), 7,13-7,04 (3H, m), 6,48 (2H,brs), 5,71 (2H, s), 4,93 (1H, m), 4,36 (2H, t, J=5,7Hz), 2,80 (3H, m), 2,71 (2H, m), 2,42 (1H, m), 2,24 (3H, s), 2,10 (1h, m), 1,66 (1H, m),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-194		10,21 (1H, s), 8,,82 (1H, d, J=1,5Hz), 8,52 (1H, s), 8,22 (1H, dd, J=1,8Hz, J=8,7Hz), 8,14 (1H, s), 7,80 (1H, s), 7,77-7,66 (3H, m), 7,40-7,33 (1H, m), 7,12-7,04 (3H, m), 5,71 (2H, s), 4,86 (1H,brs), 4,28 (3H, m), 3,58 (1H, m), 2,95-2,78 (2H, m), 2,25 (3H, s), 2,11 (1H, m), 1,47 (1H, m),
VIII-195		10,17 (1H, s), 8,78 (1H, d, J=1,8Hz), 8,52 (1H, s), 8,19 (1H, dd, J=1,8Hz, J=10,5Hz), 8,13 (1H, s), 7,80 (1H, s), 7,77-7,33 (1H, m), 7,12-7,03 (3H, m), 5,71 (2H, s), 439 (2H, t, J=5,7Hz), 3,58 (4H, t, J=4,8Hz), 2,71 (2H, t, J=6,0Hz), , 2,50 (2H, m), 2,24 (3H, s),

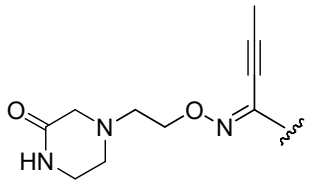
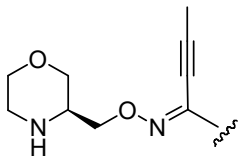
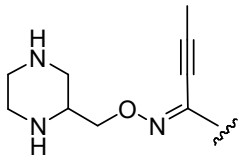
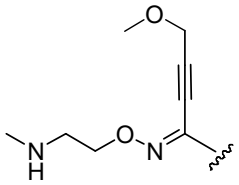
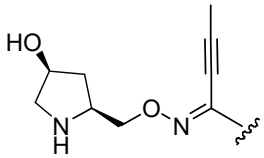
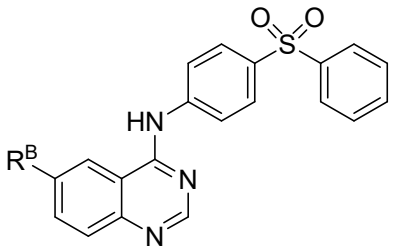
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-196		10,19 (1H, s), 8,78 (1H, d, J=1,5Hz), 8,19 (1H, dd, J=1,8Hz, J=10,5Hz), 8,16 (1H, s), 8,13 (1H, d, J=1,5Hz), 7,80 (1H, s), 7,80-7,66 (4H, m), 7,40-7,33 (1H, m), 7,13-7,06 (3H, m), 5,71 (2H, s), 4,41 (2H, t, J=5,2Hz), 3,16 (2H, m), 3,10 (2H, s), 2,80 (1H, t, J=5,7Hz), 2,67 (3H, s), 2,25 (3H, s),

Tabela 42

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-197		10,21 (1H, s), 8,79 (1H, d, J=1,8Hz), 8,53 (1H, s), 8,21 (1H, dd, J=1,8Hz, J=8,7Hz), 8,17 (1H, s), 8,13 (1H, d, J=1,5Hz), 7,79 (1H, d, J=13,2Hz), 7,76 (1H, d, J=13,2Hz), 7,67 (1H, dd, J=1,8Hz, J=9,0Hz), 7,41-7,34 (1H, m), 7,16-7,04 (3H, m), 5,72 (2H, s), 4,20-4,09 (2H, m), 3,79 (1H, dd, J=2,7Hz, J=10,8Hz), 3,68-3,64 (1H, m), 3,30-3,19 (1H, m), 3,13-3,10 (1H, m), 2,78-2,74 (3H, m), 2,26 (3H, s),

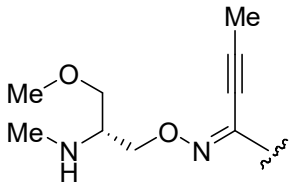
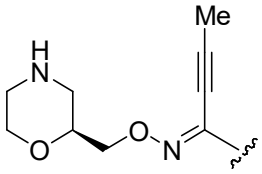
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-198		10,20 (1H, brs), 8,79 (1H, s), 8,53 (1H, s), 8,22-8,13 (3H, m), 7,81-7,66 (3H, m), 7,41-7,33 (1H, m) 7,13-7,04 (3H, m), 5,72 (2H, s), 4,13 (2H, d, J=5,2Hz), 3,00-2,51 (6H, m), 2,39-2,26 (4H, m)
VIII-199		(sal di-HCl) 12,69 (1Hbrs), 9,44 (1H, s), 8,69 (1H, s), 8,47 (1H, d, J=8,1Hz), 8,23 (1H, d, J=2,1Hz), 7,38 (1H, s), 7,19-7,01 (1H, m), 5,74 (2H, s), 4,64 (5H, m), 4,01 (1H, m), 3,39-3,21 (4H, m), 2,59 (3H, s),
VIII-200		10,19 (1H, s), 8,81 (1H, s), 8,53 (1H, s), 8,21-8,14 (3H, m), 7,82 (7,82-7,65 (3H, m), 7,41 (1H, m), 7,15-7,04 (13H, m), 5,71 (2H, s), 4,68 (1H, brs), 4,51 (2H, s), 4,27 (2H, m), 4,18 (1H, m), 3,42 (2H, m), 3,45 (3H, s), 2,87 (1H, m), 2,69 (1H, m), 2,04 (1H, m), 1,41 (1H, m),

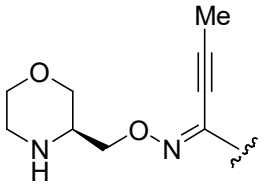
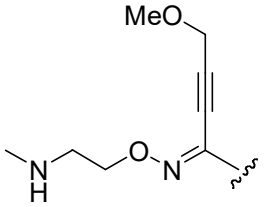
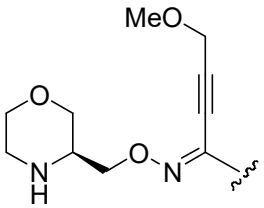
Fórmula química 84



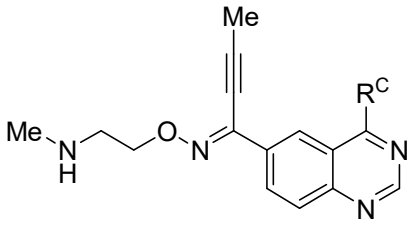
(VIII)

Tabela 43

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-205		10,43-10,40 (1H, m), 8,79 (1H, s), 8,70 (1H, s), 8,25 (1H, d, J=8,4Hz), 8,11 (2H, bs), 7,98-7,96 (4H, m), 7,85 (1H, d, J=7,2Hz), 7,69-7,62 (3H, m), 4,24-4,20 (2H, m), 3,28 (3H, s), 2,94 (1H, t, J=6,4Hz), 2,38 (3H, s), 2,25 (3H, s),
VIII-206		10,44 (1H, bs), 8,78 (1H, d, J=1,5Hz), 8,67 (1H, bs), 8,24 (1H, d, J=9,0Hz), 8,16-8,05 (2H, m), 7,99-7,94 (4H, m), 7,84 (1H, d, J=8,7Hz), 7,71-7,60 (3H, m), 4,24 (1H, dd, J=6,3Hz, J=11,7Hz), 4,16 (1H, dd, J=4,8Hz, J=11,7Hz), 3,75-3,71 (2H, m), 3,51-3,37 (1H, m), 2,84 (1H, dd, J=2,4Hz, J=12,3Hz), 2,73-2,58 (2H, m), 2,50-2,42 (1H, m), 2,25 (3H, s),

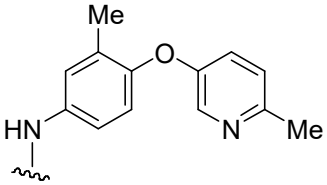
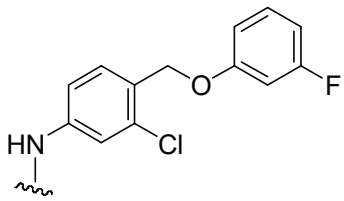
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-207		10,45 (1H, bs), 8,78 (1H, d, J=1,5Hz), 8,67 (1H, bs), 8,24 (1H, dd, J=1,5Hz, J=8,7Hz), 8,12-8,09 (2H, m), 7,99-7,95 (4H, m), 7,85 (1H, d, J=8,7Hz), 7,71-7,61 (3H, m), 4,18 (1H, dd, J=6,0Hz, J=11,1Hz), 4,12 (1H, dd, J=6,3Hz, J=11,1Hz), 3,78 (1H, dd, J=2,7Hz, J=10,5Hz), 3,65 (1H, dt, J=11,1Hz, J=2,7Hz), 3,11-3,07 (1H, m), 2,81-2,69 (3H, m), 2,25 (3H, s),
VIII-208		10,42 (1H, s), 8,84 (1H, s), 8,69 (1H, s), 8,25 (1H, d, J=8,8Hz), 8,13 (1H, d, J=8,4Hz), 8,00-7,97 (3H, m), 7,87 (1H, d, J=8,8Hz), 7,97-7,62 (5H, m), 4,51 (2H, s), 4,42 (2H, t,, J=5,2Hz), 3,37 (3H, s), 2,97 (2H, t, J=4,8Hz), 2,41 (3H, s),
VIII-209		10,45 (1H, bs), 8,80 (1H, bs), 8,68 (1H, bs), 8,23 (1H, d, J=7,5Hz), 8,14-8,06 (2H, m), 7,99-7,95 (4H, m), 7,87 (1H, d, J=9,0Hz), 7,69-7,60 (3H, m), 4,52 (2H, s), 4,23 (1H, dd, J=6,3Hz, J=10,8Hz), 4,17 (1H, dd, J=6,3Hz, J=10,8Hz), 3,80 (1H, dd, J=2,7Hz, J=11,1Hz), 3,67-3,64 (1H, m), 3,40 (3H, s), 3,12-3,07 (1H, m),

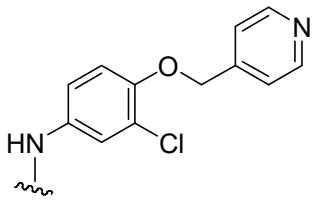
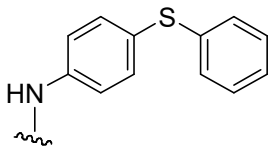
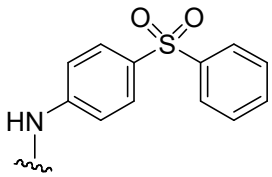
Fórmula química 85



(VIII)

Tabela 44

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-210		10,13 (1H, s), 8,82 (1H, s), 8,60 (1H, s), 8,26 (1H, d, J=9,2Hz), 8,18 (1H, s), 7,82 (1H, d, J=8,8Hz), 7,74 (1H, s), 7,64 (1H, d, J=9,2Hz), 7,27-7,22 (2H, m), 6,99 (1H, d, J=8,4Hz), 4,50 (2H, t, J=5,2Hz), 2,64 (3H, s), 2,50 (2H, bs), 2,45 (3H, s), 2,28 (3H, s), 2,23 (3H, s),
VIII-211		10,26 (1H, brs), 8,80 (1H, s), 8,66 (1H, s), 8,26-8,23 (1H, m), 8,14 (1H, s), 7,88-7,79 (2H, m), 7,62 (1H, d, J=8,4), 7,34 (1H, dd, J=8,4, 15,2), 6,95-6,88 (2H, m), 6,82-6,78 (1H, m), 5,16 (2H, s), 4,35 (2H, t, J=6,0Hz), 2,92 (2H, t, J=6,0Hz), 2,38 (3H, s), 2,26 (3H, s), 2,26 (3H, s),

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-212		10,0 (1H, brs), 8,74 (1H, s), 8,62-8,58 (3H, m), 8,21 (1H, d, J=8,8), 7,97 (1H, s), 7,80 (1H, d, J=8,8), 7,69-7,67 (1H, m), 7,48-7,47 (2H, m), 7,25 (1H, d, J=9,2), 5,32 (2H, s), 4,34-4,31 (2H, s), 2,89-2,86 (2H, m), 2,36 (3H, s), 2,25 (3H, s),
VIII-213		10,43 (1H, s), 9,23 (1H, s), 9,21 (1H, s), 8,64 (1H, s), 8,26 (1H, d, J=6,6Hz), 7,93 (2H, d, J=3,9Hz), 7,84 (1H, d, J=6,9Hz), 7,45 (2H, d, J=5,7Hz), 7,35 (1H, d, J=5,4Hz), 7,27 (2H, t, J=5,7Hz), 4,56 (2H, d, J=3,9Hz), 2,64 (3H, s), 2,28 (3H, s), 1,99 (3H, s),
VIII-214		8,85 (1H, s), 8,80 (1H, s), 8,26 (1H, d, J=6,6Hz), 8,12 (1H, d, J=6,3Hz), 7,99-7,96 (4H, m), 7,85 (1H, d, J=6,6Hz), 7,71-7,62 (3H, m), 4,33 (2H, t, J=4,2Hz), 2,86 (2H, t, J=4,5Hz), 2,35 (3H, s), 2,25 (3H, s),

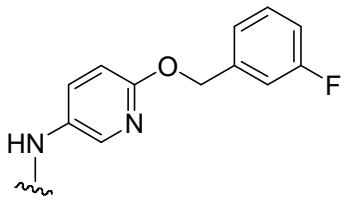
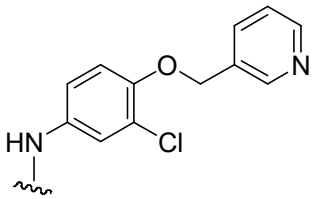
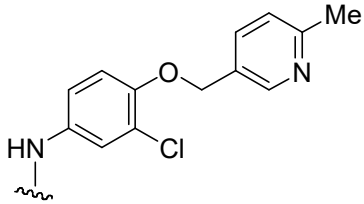
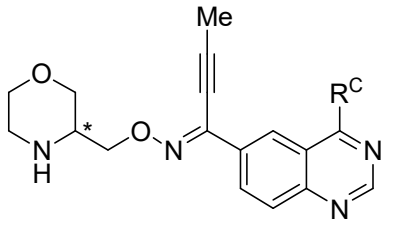
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-215		10,15 (1H, s), 8,77 (1H, s), 8,55 (1H, s), 8,47 (1H, s), 8,24 (1H, d, J=9,2Hz), 8,07 (1H, d, J=9,2Hz), 7,81 (1H, d, J=9,2Hz), 7,47-7,39 (1H, m), 7,32-7,28 (2H, m), 7,16 (1H, t, J=7,6Hz), 7,00 (1H, d, J=8,8Hz), 5,41 (1H, s), 4,41 (2H, t, J=5,6Hz), 3,10 (2H, t, J=5,2Hz), 2,49 (3H, s), 2,26 (3H, s),
VIII-216		10,3 (1H, s), 8,84 (1H, s), 8,72 (1H, s), 8,42-8,65 (2H, m), 8,26 (1H, d, J=7,6Hz), 7,98 (1H, s), 7,91 (1H, brs), 7,81 (1H, brs), 7,71 (1H, brs), 7,47 (1H, brs), 7,34 (1H, d, J=8,0Hz), 5,30 (2H, s), 4,53 (2H, brs), 3,38 (2H, brs), 2,68 (3H, s), 2,26 (3H, s),

Tabela 45

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
VIII-217		10,1 (1H, s), 8,76 (1H, s), 8,59 (1H, s), 8,57 (1H, s), 8,24 (1H, d, J=10Hz), 7,94 (1H, bs), 7,67-7,73 (3H, m), 7,29-7,35 (2H, m), 5,24 (2H, s), 4,40 (2H, t, J=5,6Hz), 3,06 (2H, t, J=5,2Hz), 2,49 (3H, s), 2,48 (3H, s), 2,26 (3H, s)

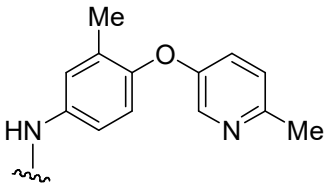
Fórmula química 86

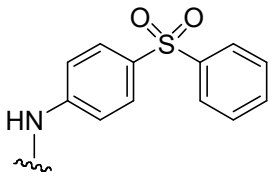


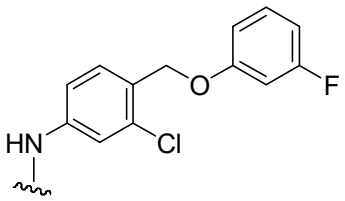
(VIII)

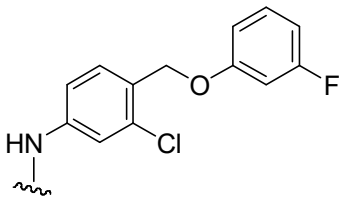
(onde um átomo assinado com * é um átomo de carbono assimétrico)

Tabela 46

Composto Nº	*	R□	^{1}H-RMN (d_6-DMSO)
VIII-218	S		(sal tri-HCl) 12,18 (1H, bs), 9,78 (1H, m), 9,61 (1H, m), 9,36 (1H, s), 8,94 (1H, s), 8,48 (1H, dd, J=1,8Hz, J=9,0Hz), 8,41 (1H, d, J=3Hz), 8,03 (1H, d, J=9Hz), 7,76-7,73 (2H, m), 7,64-7,60 (2H, m), 7,13 (1H, d, J=8,7Hz), 4,51-4,49 (2H, m), 2,60 (3H, s), 2,29 (3H, s), 2,27 (3H, s),

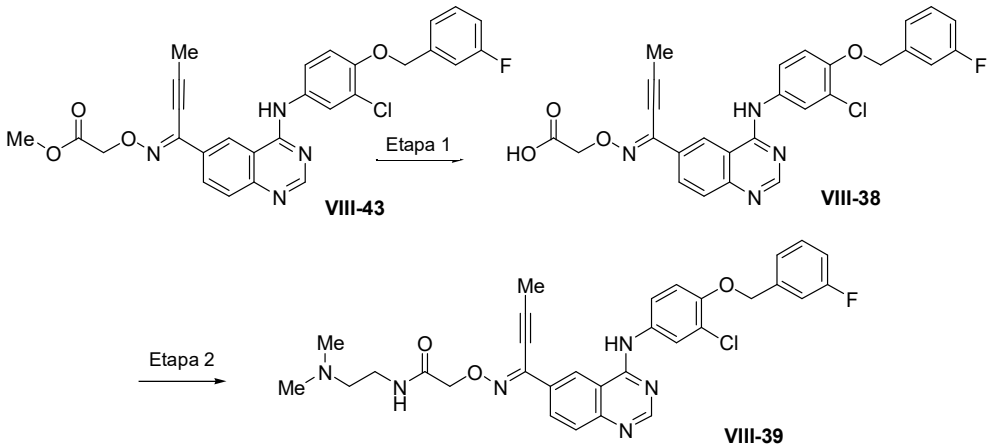
Composto Nº	*	R□	^{1}H-RMN (d_6-DMSO)
VIII-219	R		10,46 (1H, bs), 8,78 (1H, d, J=1,5Hz), 8,67 (1H, s), 8,24 (1H, dd, J=1,5Hz, J=8,7Hz), 8,12-8,09 (2H, m), 7,99-7,95 (4H, m), 7,85 (1H, d, J=8,7Hz), 7,71-7,60 (3H, m), 4,17 (1H, dd, J=5,7Hz, J=11,1Hz), 4,12 (1H, dd, J=6,3Hz, J=11,1Hz), 3,78 (1H, dd, J=2,7Hz, J=10,5Hz), 3,65 (1H, dt, J=10,8Hz, J=2,7Hz), 3,26-3,18 (1H, m), 3,13-3,05 (1H, m), 2,82-2,70 (2H, m), 2,25 (3H, s),

Composto Nº	*	R□	^{1}H-RMN (d_6-DMSO)
VIII-220	S		10,26 (1H, bs), 8,79 (1H, s), 8,67 (1H, s), 8,23 (1H, d, J=8,8Hz), 8,14 (1H, s), 7,84 (1H, d, J=8,8Hz), 7,62 (1H, d, J=8,8Hz), 7,35 (1H, dd, J=8,0, J=15,6), 6,96-6,86 (2H, m), 6,82-6,78 (1H, m), 5,16 (2H, s), 4,20-4,11 (2H, m), 3,79 (1H, d, J=10,8Hz), 3,66 (1H, d, J=11,2Hz), 3,22 (2H, t, d=10,4), 3,10-3,02 (1H, m), 2,81-2,68 (2H, m), 2,26 (3H, s),

Composto Nº	*	R□	^{1}H-RMN (d_6-DMSO)
VIII-221	R		10,26 (1H, bs), 8,79 (1H, s), 8,67 (1H, s), 8,23 (1H, d, J=9,6Hz), 8,14 (1H, s), 7,85-7,83 (1H, m), 7,62 (1H, d, J=8,8Hz), 7,35 (1H, dd, J=8,0, J=15,6), 6,95-6,88 (2H, m), 6,82-6,78 (1H, m), 5,16 (2H, s), 4,20-4,11 (2H, m), 3,79 (1H, d, J=10,8Hz), 3,66 (1H, d, J=11,2Hz), 3,22 (2H, t, d=10,4), 3,10-3,02 (1H, m), 2,81-2,68 (2H, m), 2,26 (3H, s)

Exemplo 11

Fórmula química 87



(Etapa 1) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(carboximetoxiimino)-2-butin-1-ila)quinazolina (VIII-38)

[0237] 4-(3-Cloro-4-(3-fluorbenziloxi)fenilamino)-6-

(metoxicarbonilmetoxiimino)-2-butin-1-ila)quinazolina (VIII-43, 1,2 g) foi dissolvida em uma mistura de 12 ml de tetrahidrofurano e 12 ml de metanol, e 1,5 ml de solução aquosa de hidróxido de sódio a 2 mol/l foi adicionado, seguido de agitação à temperatura ambiente por 1,5 hora. A mistura reacional foi diluída com 20 ml de acetato de etila, 1,6 ml de ácido clorídrico a 2 mol/l foi adicionado, e água foi adicionada, dessa forma, uma substância desejada foi precipitada. Um precipitado foi recolhido por filtração, lavado com água e acetato de etila, e secado para obter 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(carboximetoxiimino)-2-butin-1-ila)quinazolina (VIII-38, 0,9 g) como um sólido amarelo.

^{1}H RMN (d_6-DMSO, δ): 10,18 (1H, brs), 8,77 (1H, s), 8,60 (1H, s), 8,19 (1H, dd, J= 2,0, 11,6 Hz), 7,95 (1H, d, J= 3,2 Hz), 7,80 (1H, d, J= 11,6 Hz), 7,67 (1H, dd, J= 3,2, 11,6 Hz), 7,51-7,44 (1H, m), 7,35-7,26 (3H, m), 7,22-7,15 (1H, m), 5,27 (2H, s), 4,83 (2H, s), 2,27 (3H, s).

(Etapa 2) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-((2-dimetilaminoetilcarbamoila)metoxiimino)-2-butin-1-ila)quinazolina (VIII-39)

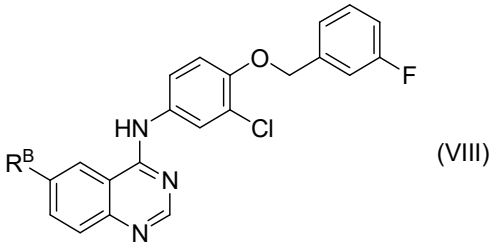
[0238] 4-(3-Cloro-4-(3-fluorbenziloxi)fenilamino)-6-(carboximetoxiimino)-2-butin-1-ila)quinazolina (VIII-38, 70 mg), 24 mg de 1-hidroxibenzotriazol, e 27 mg de cloridrato de 1-etila 3-(3-dimetilaminopropila)carbodiimida foram dissolvidos em 1,4 ml de N,N-dimetilformamida, a mistura foi agitada à temperatura ambiente por 5 minutos, e 22 μl de N,N-dimetiletilenodiamina foram adicionados, seguidos de agitação à temperatura ambiente por 2 horas. Depois de completada a reação, a mistura reacional foi diluída com acetato de etila, e água e solução aquosa saturada de bicarbonato de sódio foram adicionadas para separar as camadas. A camada orgânica foi lavada com água, e secada em sulfato de sódio, e o filtrado foi concentrado. Acetato de etila foi adicionado ao resíduo concentrado para solidificar o material, e o sólido foi recolhido por filtração, e secado obter 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-((2-

dimetilaminoetilcarbamoila)metoxiimino)-2-butin-1-ila)quinazolina (VIII-39, 30 mg) como um cristal incolor.

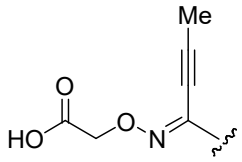
^{1}H RMN (d_6-DMSO, δ): 10,12 (1H, s), 8,77 (1H, s), 8,59 (1H, s), 8,19 (1H, dd, J= 2,0, 12,0 Hz), 8,08 (1H, brs), 7,95 (1H, d, J= 3,2 Hz), 7,80 (1H, d, J= 11,6 Hz), 7,70-7,62 (2H, m), 7,51-7,44 (1H, m), 7,34-7,26 (3H, m), 7,21-7,15 (1H, s), 5,27 (2H, s), 4,69 (2H, s), 3,22 (2H, dd, J= 8,4, 16,0 Hz) 2,31 (1H, t, J= 8,4 Hz), 2,28 (3H, s), 2,11 (6H, s).

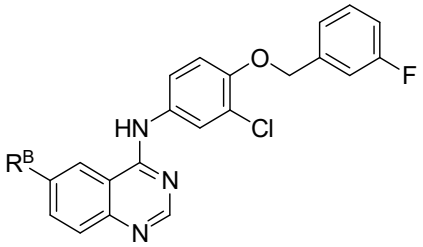
[0239] Da mesma maneira que para o exemplo 11, foi sintetizado o seguinte composto.

Tabela 47

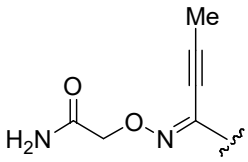
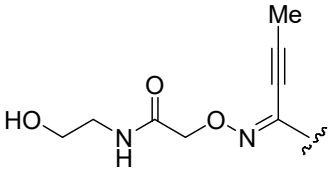


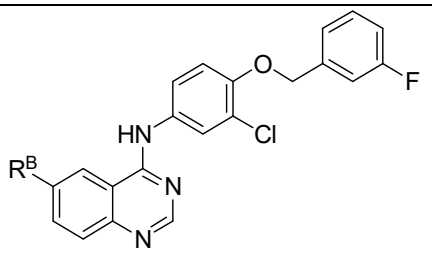
(VIII)

Composto Nº	R^B	^{1}H-RMN (d_6-DMSO)
VIII-222		10,18 (1H, brs), 8,77 (1H, s), 8,60 (1H, s), 8,19 (1H, dd, J=2,0, 11,6Hz), 7,95 (1H, d, J=3,2Hz), 7,80 (1H, d, J=11,6Hz), 7,67 (1H, dd, J=3,2, 11,6Hz), 7,51-7,44 (1H, m), 7,35-7,26 (3H, m),7,22-7,15 (1H, m), 5,27 (2H, s), 4,83 (2H, s), 2,27 (3H, s),

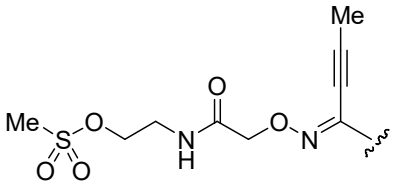
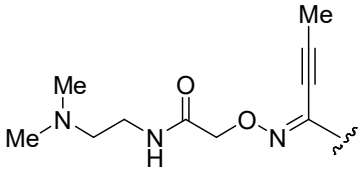


(VIII)

Composto Nº	R^B	^{1}H-RMN (d_6-DMSO)
VIII-223		10,12 (1H, bs), 8,76 (1H, d, J=1,5Hz), 8,59 (1H, s), 8,20 (1H, dd, J=1,8Hz, J=8,7Hz), 7,96 (1H, d, J=2,4Hz), 7,81 (1H, d, J=8,7Hz), 7,68 (1H, dd, J=2,7Hz, J=9,0Hz), 7,52-7,44 (1H, m), 7,35-7,16 (6H, m), 5,27 (2H, s), 4,65 (2H, s), 2,28 (3H, s),
VIII-224		10,10 (1H, s), 8,59 (1H, s), 8,19 (1H, dd, J=2,4, 11,6Hz), 7,95 (1H, d, J=3,2Hz), 7,80 (1H, d, J=11,6), 7,76-7,73 (1H, m), 7,68 (1H, dd, J=3,6, 12Hz), 7,48-7,44 (1H, m),7,35-7,26 (3H, m), 7,21-7,15 (1H, m), 5,27 (2H, s), 4,73 (1H, t, J=7,2Hz), 4,70 (2H, s), 3,44 (2H, dd, J=8,0, 15,6Hz), 3,21 (2H, dd, J=8,0, 15,6Hz), 2,28 (3H, s)

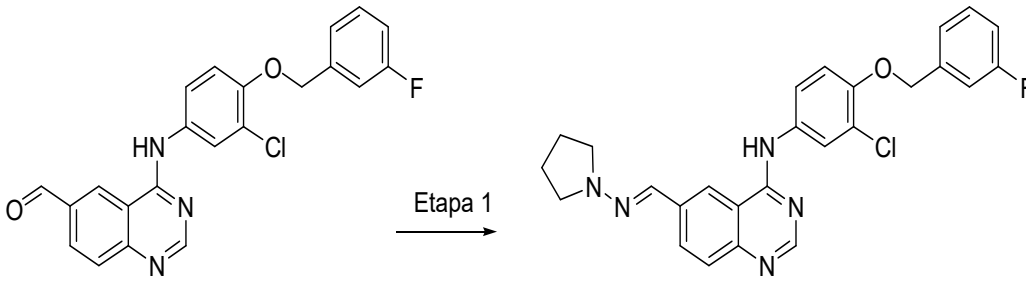


(VIII)

Composto Nº	R^B	^{1}H-RMN (d_6-DMSO)
VIII-225		10,10 (1H, s), 8,76 (1H, s), 8,59 (1H, s), 8,19 (1H, d, J=12,0Hz), 8,08 (1H, brs), 7,95 (1H, s), 7,80 (1H, d, J=11,6Hz), 7,69-7,66 (1H, m),7,51-7,44 (1H, m), 7,34-7,26 (3H, m), 7,21-7,16 (1H, s), 5,27 (2H, s), 4,71 (2H, s), 3,60-3,53 (1H, m), 2,99 (3H, s), 2,28 (3H, s)
VIII-226		10,12 (1H, s), 8,77 (1H, s), 8,59 (1H, s), 8,19 (1H, dd, J=2,0, 12,0Hz), 8,08 (1H, brs), 7,95 (1H, d, J=3,2Hz), 7,80 (1H, d, J=11,6Hz), 7,70-7,62 (2H, m),7,51-7,44 (1H, m), 7,34-7,26 (3H, m), 7,21-7,15 (1H, s), 5,27 (2H, s), 4,69 (2H, s), 3,22 (2H, dd, J=8,4, 16,0Hz) 2,31 (1H, t, J=8,4Hz), 2,28 (3H, s), 2,11 (6H, s),

Exemplo 12

Fórmula química 88



IV-1 **IX-1**

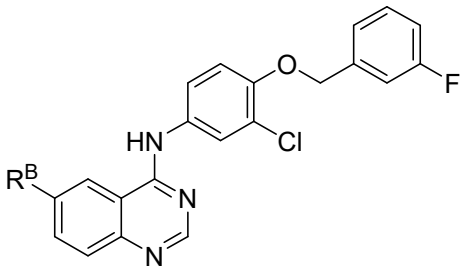
(Etapa 1) Síntese de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(pirrolidin-1-iliminometila)quinazolina (IX-1)

[0240] Em uma mistura de 1 ml de tetrahidrofurano e 0,1 ml de água foram dissolvidos 40 mg de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-formilquinazolina (IV-1) e 13 mg de cloridrato de 1-amino-pirrolidina, seguido de uma reação à temperatura ambiente por uma noite. Depois da reação, solução saturada aquosa de bicarbonato de sódio foi adicionada, seguida de extração com acetato de etila. A camada orgânica foi desidratada sendo passada por Presep (marca registrada), e o filtrado foi concentrado. O resíduo concentrado foi purificado por cromatografia (eluindo com hexano: acetato de etila = 2:1 $\rightarrow$ 1:1) usando uma coluna de amina para obter 38 mg de 4-(3-cloro-4-(3-fluorbenziloxi)fenilamino)-6-(pirrolidin-1-iliminometila)quinazolina (IX-1) como um sólido amarelo.

^{1}H RMN (d_6-DMSO, δ): 9,76 (1H, s), 8,52 (1H, s), 8,40 (1H, brs), 8,08 (1H, d, J= 6,6 Hz), 8,06 (1H, d, J= 1,8 Hz), 7,76 (1H, dd, J= 6,6 Hz, J= 1,8 Hz), 7,69 (1H, dd, J= 6,6 Hz), 7,50-7,45 (1H, m), 7,35-7,26 (3H, m), 7,19 (1H, t, J= 6,6 Hz), 5,26 (2H, s), 3,39 (4H, br), 1,94 (4H, br)

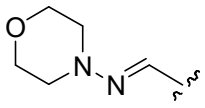
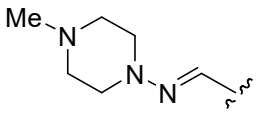
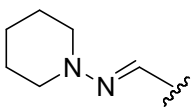
[0241] Da mesma maneira que para o exemplo 12, foi sintetizado o seguinte composto.

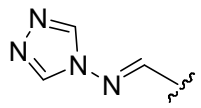
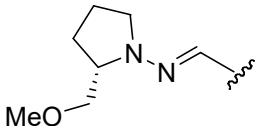
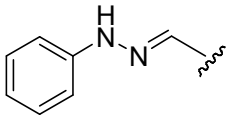
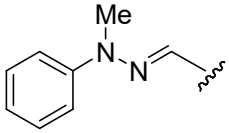
Fórmula química 89



(IX)

Tabela 48

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
IX-2		9,86 (1H, s), 8,56 (1H, s), 8,55 (1H, brs), 8,14 (1H, d, J=6,6Hz), 8,05 (1H, d, J=1,8Hz), 7,78-7,74 (3H, m), 7,50-7,45 (1H, m), 7,35-7,26 (3H, m), 7,19 (1H, t, J=6,3Hz), 5,26 (2H, s), 3,18 (4H, tipo t, J=3,6Hz), 3,20 (4H, tipo t, J=3,6Hz)
IX -3		9,83 (1H, s), 8,56 (1H, s), 8,52 (1H, brs), 8,13 (1H, d, J=6,6Hz), 8,05 (1H, brs), 7,77-7,73 (3H, m), 7,50-7,45 (1H, m), 7,35-7,26 (3H, m), 7,19 (1H, t, J=6,3Hz), 5,26 (2H, s), 3,21 (4H, brs), 2,53 (4H, brs), 2,25 (3H, s)
IX -4		9,83 (1H, s), 8,54 (1H, s), 8,50 (1H, brs), 8,13 (1H, d, J=8,7Hz), 8,04 (1H, d, J=2,7Hz), 7,76-7,70 (3H, m), 7,52-7,43 (1H, m), 7,36-7,25 (3H, m), 7,22-7,15 (1H, m), 5,26 (2H, s), 3,25-3,17 (4H, m), 1,76-1,65 (4H, m), 1,58-1,49 (2H, m)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
IX -5		9,19 (3H, brs), 9,16 (1H, s), 8,95 (1H, brs), 8,52 (1H, brs), 8,20 (1H, d, J=8,4Hz), 7,95 (1H, s), 7,79 (1H, d, J=6,9Hz), 7,66-7,60 (1H, m), 7,52-7,43 (1H, m), 7,36-7,14 (4H, m), 5,23 (2H, s)
IX -6		9,73 (1H, s), 8,52 (1H, s), 8,38 (1H, brs), 8,13 (1H, d, J=6,6Hz), 8,05 (1H, d, J=1,8Hz), 7,75 (1H, dd, J=6,9Hz, J=1,8Hz), 7,70 (1H, dd, J=6,6Hz, J=1,8Hz), 7,50-7,45 (1H, m), 7,33-7,26 (3H, m), 7,18 (1H, t, J=6,6Hz), 5,26 (2H, s), 3,72 (1H, brs), 3,64 (1H, dd, J=6,9Hz, J=2,7Hz), 3,46 (2H, dd, J=7,2Hz, J=5,1Hz), 3,13 (1H, br), 1,99 (3H, br,), 1,80 (1H, br)
IX -7		10,59 (1H, s), 9,84 (1H, s), 8,56 (1H, s), 8,53 (1H, brs), 8,29 (1H, d, J=6,9Hz), 8,03 (2H, brs), 7,78-7,73 (2H, m), 7,51-7,45 (1H, m), 7,35-7,16 (8H, m), 6,79 (1H, t, J=5,4Hz), 5,27 (2H, s)
IX -8		9,86 (1H, s), 8,61 (1H, s), 8,57 (1H, brs), 8,32 (1H, d, J=7,2Hz), 8,05 (2H, J=2,1Hz), 7,80-7,73 (3H, m), 7,52-7,45 (3H, m), 7,37-7,28 (5H, m), 7,19 (1H, t, J=6,3Hz), 6,94 (1H, t, J=5,4Hz), 5,27 (2H, s), 3,51 (3H, s)

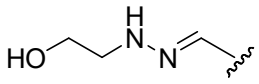
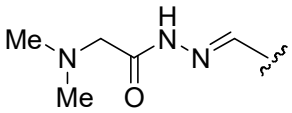
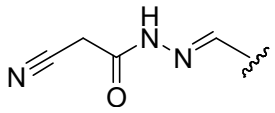
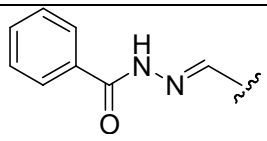
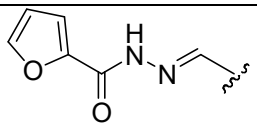
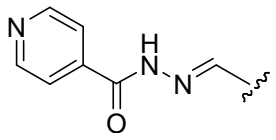
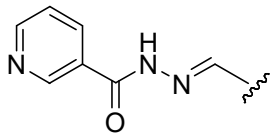
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
IX -9		9,77 (1H, s), 8,53 (1H, s), 8,39 (1H, brs), 8,09 (1H, d, J=6,3Hz), 8,04 (1H, s), 7,75-7,69 (3H, m), 7,55-7,45 (2H, m), 7,34-7,26 (3H, m), 7,18 (1H, t, J=6,3Hz), 5,21 (2H, s), 4,69 (1H, t, J=3,6Hz), 3,61 (2H, dd, J=8,4Hz, J=4,5Hz), 3,29 (2H, m)

Tabela 49

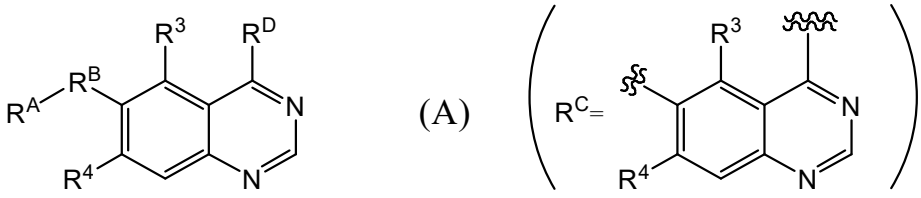
Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
IX -10		(Mistura E/Z) 11,51 (1H, s, secundário), 11,45 (1H, s, principal), 10,00 (1H, s, principal), 9,89 (1H, s, secundário), 8,65 (1H, brs, secundário), 8,60 (1H, brs), 8,53 (1H, brs, principal), 8,26 (1H, d, J=6,6Hz, secundário), 8,22 (1H, d, J=6,6Hz, principal), 8,04 (1H, brs, secundário), 8,00 (1H, d, J=1,8Hz, principal), 7,80 (1H, d, J=6,6Hz), 7,73 (1H, d, J=6,6Hz), 7,51-7,45 (1H, m), 7,35-7,27 (3H, m), 7,19 (1H, t, J=6,6Hz), 5,27 (2H, s), 3,58 (2H, s, secundário), 3,08 (2H, s, principal), 2,34 (3H, s, secundário), 2,28 (3H, s, principal)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
IX -11		12,04 (1H, s), 9,88 (1H, s), 8,64 (1H, brs), 8,61 (1H, s), 8,31 (1H, d, J=6,3Hz), 8,17 (1H, s), 8,01 (1H, d, J=2,1Hz), 7,80 (1H, d, J=6,6Hz), 7,72 (1H, d, J=6,6Hz), 7,50-7,45 (1H, m), 7,35-7,28 (3H, m), 7,19 (1H, t, J=5,4Hz), 5,27 (2H, s), 4,31 (2H, s)
IX -12		12,02 (1H, s), 10,00 (1H, s), 8,70 (1H, brs), 8,65 (1H, brs), 8,61 (1H, s), 8,31 (1H, d, J=6,0Hz), 8,02 (1H, d, J=1,8Hz), 7,96-7,94 (2H, m), 7,84 (1H, d, J=6,0Hz), 7,72 (1H, d, J=13,8Hz), 7,65-7,55 (3H, m), 7,51-7,45 (1H, m), 7,35-7,28 (3H, m), 7,19 (1H, t, J=6,3Hz), 5,27 (2H, s)
IX -13		12,04 (1H, s), 10,01 (1H, s), 8,68 (1H, brs), 8,65 (1H, brs), 8,61 (1H, s), 8,28 (1H, d, J=6,9Hz), 8,02 (1H, d, J=1,8Hz), 7,99 (1H, s), 7,83 (1H, d, J=6,6Hz), 7,74 (1H, dd, J=6,6Hz, J=1,8Hz), 7,51-7,45 (1H, m), 7,35-7,28 (4H, m), 7,19 (1H, t, J=6,3Hz), 6,74 (1H, brs), 5,27 (2H, s)

Composto Nº	R^B	^{1}H-RMN(d_6-DMSO)
IX -14		12,22 (1H, s), 10,02 (1H, s), 8,82 (2H, m), 8,73 (1H, brs), 8,65 (1H, s), 8,62 (1H, s), 8,31 (1H, d, J=7,2Hz), 8,01 (1H, d, J=1,8Hz), 7,86-7,84 (2H, m), 7,73-7,72 (2H, m), 7,51-7,45 (1H, m), 7,35-7,28 (3H, m), 7,19 (1H, t, J=6,9Hz), 5,27 (2H, s)
IX -15		12,18 (1H, s), 10,01 (1H, s), 9,11 (1H, s), 8,80 (1H, d, J=3,3Hz), 8,72 (1H, brs), 8,64-8,62 (2H, m), 8,32-8,28 (2H, m), 8,02 (1H, d, J=1,8Hz), 7,85 (1H, d, J=6,3Hz), 7,73 (1H, dd, J=6,6Hz, J=1,8Hz), 7,62-7,59 (1H, m), 7,51-7,45 (1H, m), 7,35-7,28 (3H, m), 7,19 (1H, t, J=6,9Hz), 5,27 (2H, s)

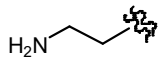
[0242] Da mesma maneira que para o exemplo acima, é possível sintetizar o seguinte composto. Isto é, no composto representado pela fórmula geral (A) a seguir:

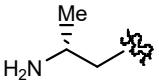
Fórmula química 90

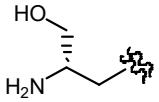


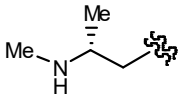
os seguintes compostos representados por uma combinação de um grupo no qual R^A é um grupo selecionado de a1 a a90:

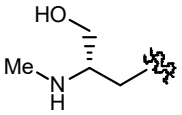
Fórmula química 91

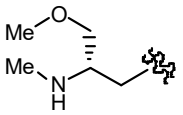
a1 

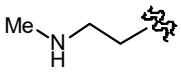
a2 

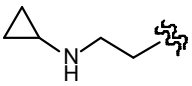
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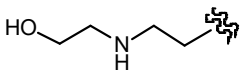
a4 

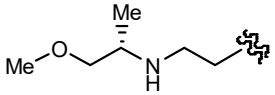
a5 

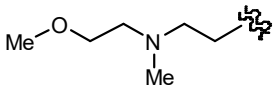
a6 

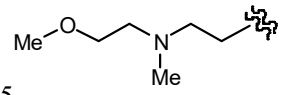
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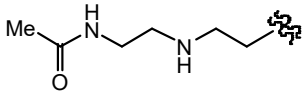
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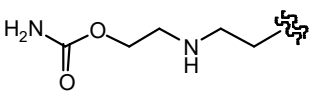
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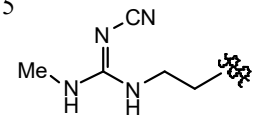
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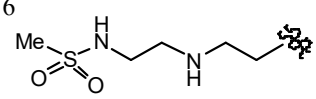
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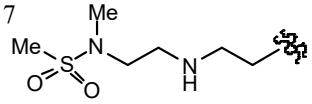
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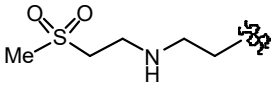
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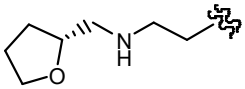
a14 

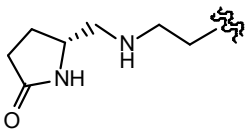
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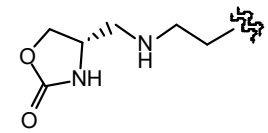
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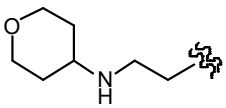
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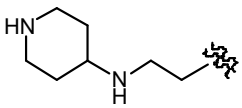
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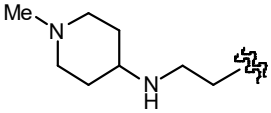
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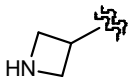
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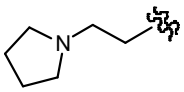
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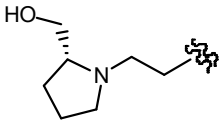
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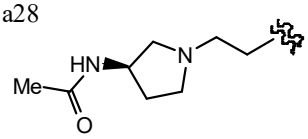
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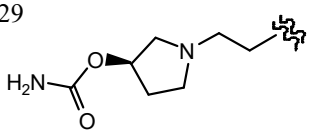
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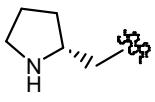
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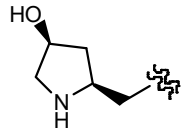
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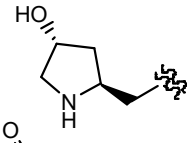
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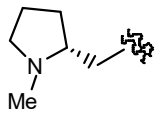
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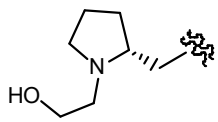
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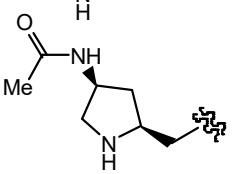
Fórmula química 92

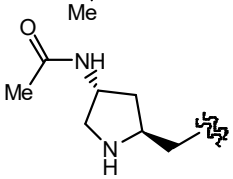
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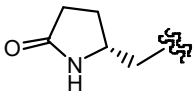
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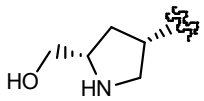
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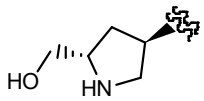
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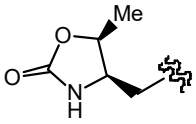
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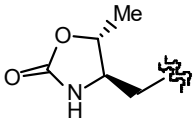
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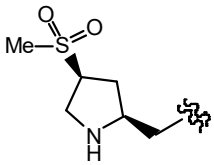
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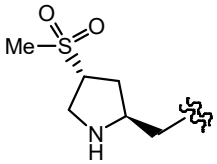
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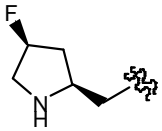
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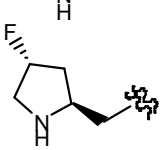
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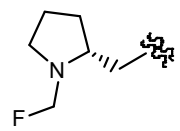
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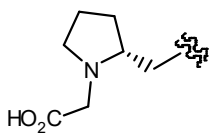
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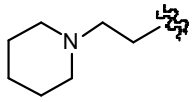
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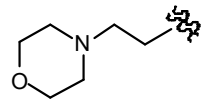
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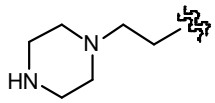
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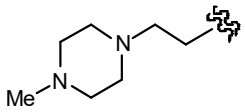
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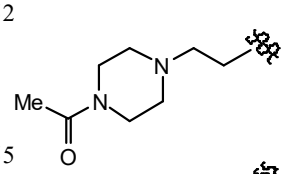
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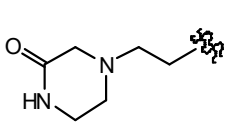
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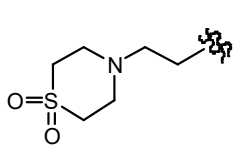
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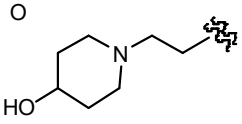
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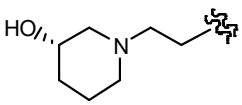
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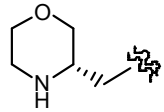
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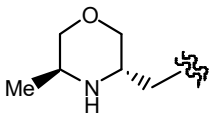
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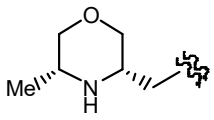
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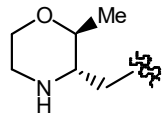
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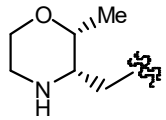
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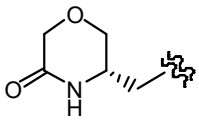
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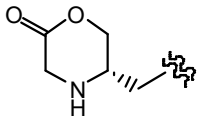
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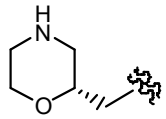
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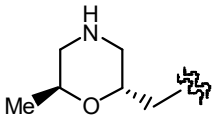
Fórmula química 93

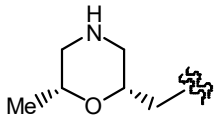
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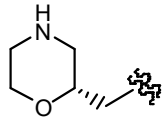
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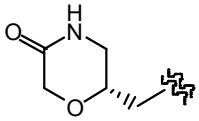
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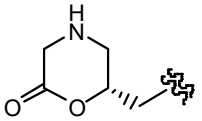
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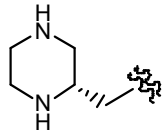
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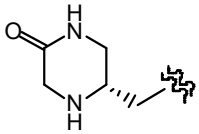
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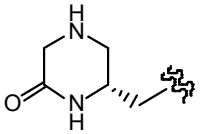
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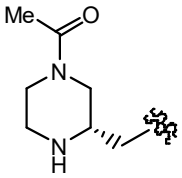
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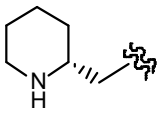
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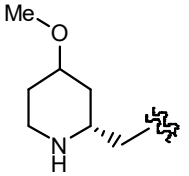
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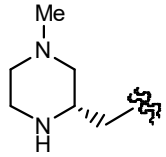
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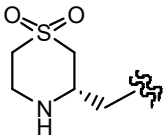
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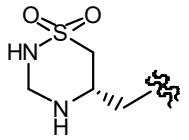
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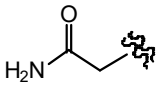
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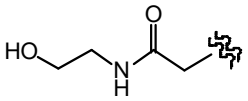
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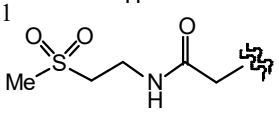
a76 

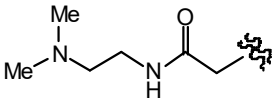
a77 

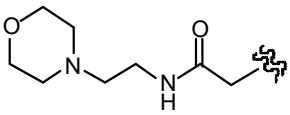
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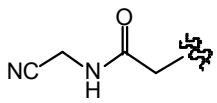
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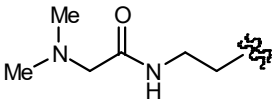
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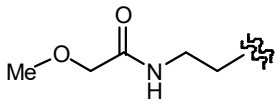
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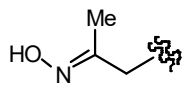
a82 

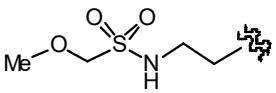
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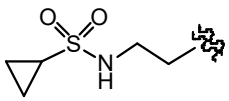
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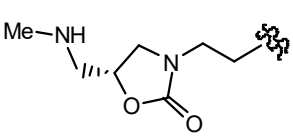
a85 

a86 

a87 

a88 

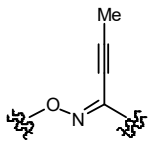
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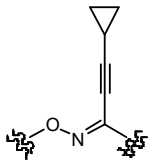
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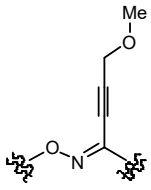
onde Me é metila,

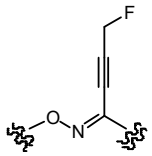
um grupo no qual R^B é selecionado de b1 a b6 a seguir:

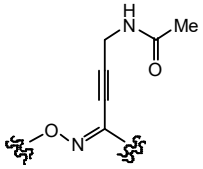
Fórmula química 94

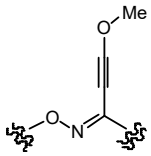
b1 

b2 

b3 

b4 

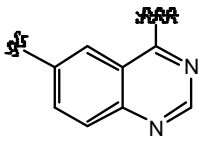
b5 

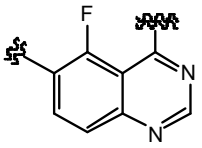
b6 

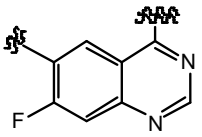
onde Me é metila,

um grupo no qual R^C é selecionado de c1 a c3 a seguir:

Fórmula química 95

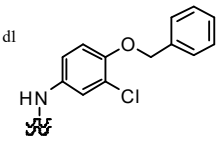
c1 

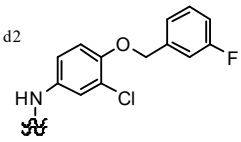
c2 

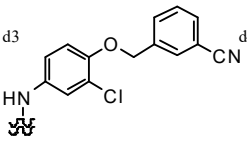
c3  ,

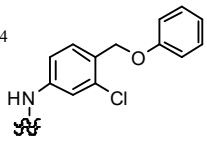
um grupo no qual R^D é selecionado de d1 a d22 a seguir:

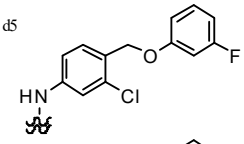
Fórmula química 96

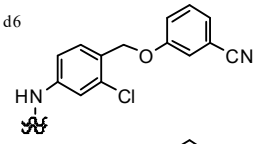
d1 

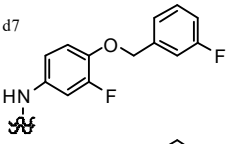
d2 

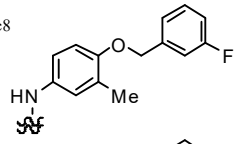
d3 

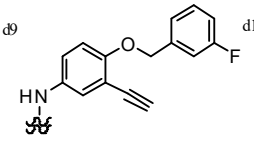
d4 

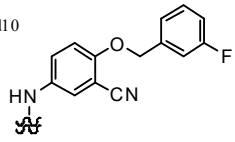
d5 

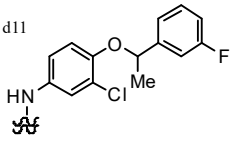
d6 

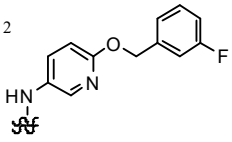
d7 

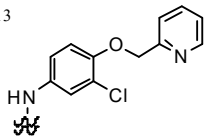
c8 

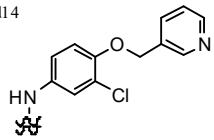
d9 

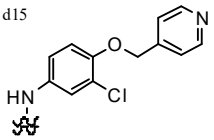
d10 

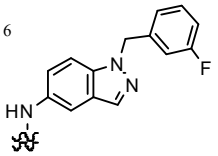
d11 

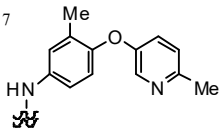
d12 

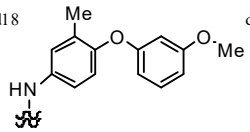
d13 

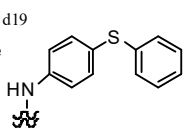
d14 

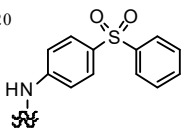
d15 

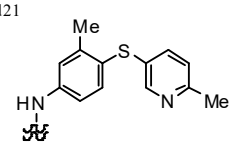
d16 

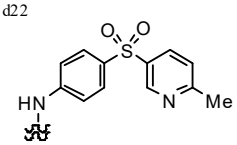
d17 

d18 

d19 

d20 

d21 

d22 

onde Me é metila

podem ser sintetizados.

(a1, b1, c1, d1), (a1, b1, c1, d2), (a1, b1, c1, d3), (a1, b1, c1, d4), (a1, b1, c1, d5), (a1, b1, c1, d6), (a1, b1, c1, d7), (a1, b1, c1, d8), (a1, b1, c1, d9), (a1, b1, c1, d10), (a1, b1, c1, d11), (a1, b1, c1, d12), (a1, b1, c1, d13), (a1, b1, c1, d14), (a1, b1, c1, d15), (a1, b1, c1, d16), (a1, b1, c1, d17), (a1, b1, c1, d18), (a1, b1, c1, d19), (a1, b1, c1, d20), (a1, b1, c1, d21), (a1, b1, c1, d22), (a1, b1, c2, d1), (a1, b1, c2, d2), (a1, b1, c2, d3), (a1, b1, c2, d4), (a1, b1, c2, d5), (a1, b1, c2, d6), (a1, b1, c2, d7), (a1, b1, c2, d8), (a1, b1, c2, d9), (a1, b1, c2, d10), (a1, b1, c2, d11), (a1, b1, c2, d12), (a1, b1, c2, d13), (a1, b1, c2, d14), (a1, b1, c2, d15), (a1, b1, c2, d16), (a1, b1, c2, d17), (a1, b1, c2, d18), (a1, b1, c2, d19), (a1, b1, c2, d20), (a1, b1, c2, d21), (a1, b1, c2, d22), (a1, b1, c3, d1), (a1, b1, c3, d2), (a1, b1, c3, d3), (a1, b1, c3, d4), (a1, b1, c3, d5), (a1, b1, c3, d6), (a1, b1, c3, d7), (a1, b1, c3, d8), (a1, b1, c3, d9), (a1, b1, c3, d10), (a1, b1, c3, d11), (a1, b1, c3, d12), (a1, b1, c3, d13), (a1, b1, c3, d14), (a1, b1, c3, d15), (a1, b1, c3, d16), (a1, b1, c3, d17), (a1, b1, c3, d18), (a1, b1, c3, d19), (a1, b1, c3, d20), (a1, b1, c3, d21), (a1, b1, c3, d22), (a1, b2, c1, d1), (a1, b2, c1, d2), (a1, b2, c1, d3), (a1, b2, c1, d4), (a1, b2, c1, d5), (a1, b2, c1, d6), (a1, b2, c1, d7), (a1, b2, c1, d8), (a1, b2, c1, d9), (a1, b2, c1, d10), (a1, b2, c1, d11), (a1, b2, c1, d12), (a1, b2, c1, d13), (a1, b2, c1, d14), (a1, b2, c1, d15), (a1, b2, c1, d16), (a1, b2, c1, d17), (a1, b2, c1, d18), (a1, b2, c1, d19), (a1, b2, c1, d20), (a1, b2, c1, d21), (a1, b2, c1, d22), (a1, b2, c2, d1), (a1, b2, c2, d2), (a1, b2, c2, d3), (a1, b2, c2, d4), (a1, b2, c2, d5), (a1, b2, c2, d6), (a1, b2, c2, d7), (a1, b2, c2, d8), (a1, b2, c2, d9), (a1, b2, c2, d10), (a1, b2, c2, d11), (a1, b2, c2, d12), (a1, b2, c2, d13), (a1, b2, c2, d14), (a1, b2, c2, d15), (a1, b2, c2, d16), (a1, b2, c2, d17), (a1, b2, c2, d18), (a1, b2, c2, d19), (a1, b2, c2, d20), (a1, b2, c2, d21), (a1, b2, c2, d22), (a1, b2, c3, d1), (a1, b2, c3, d2), (a1, b2, c3, d3), (a1, b2, c3, d4), (a1, b2, c3, d5), (a1, b2, c3, d6), (a1, b2, c3,

d7), (a1, b2, c3, d8), (a1, b2, c3, d9), (a1, b2, c3, d10), (a1, b2, c3, d11), (a1, b2, c3, d12), (a1, b2, c3, d13), (a1, b2, c3, d14), (a1, b2, c3, d15), (a1, b2, c3, d16), (a1, b2, c3, d17), (a1, b2, c3, d18), (a1, b2, c3, d19), (a1, b2, c3, d20), (a1, b2, c3, d21), (a1, b2, c3, d22), (a1, b3, c1, d1), (a1, b3, c1, d2), (a1, b3, c1, d3), (a1, b3, c1, d4), (a1, b3, c1, d5), (a1, b3, c1, d6), (a1, b3, c1, d7), (a1, b3, c1, d8), (a1, b3, c1, d9), (a1, b3, c1, d10), (a1, b3, c1, d11), (a1, b3, c1, d12), (a1, b3, c1, d13), (a1, b3, c1, d14), (a1, b3, c1, d15), (a1, b3, c1, d16), (a1, b3, c1, d17), (a1, b3, c1, d18), (a1, b3, c1, d19), (a1, b3, c1, d20), (a1, b3, c1, d21), (a1, b3, c1, d22), (a1, b3, c2, d1), (a1, b3, c2, d2), (a1, b3, c2, d3), (a1, b3, c2, d4), (a1, b3, c2, d5), (a1, b3, c2, d6), (a1, b3, c2, d7), (a1, b3, c2, d8), (a1, b3, c2, d9), (a1, b3, c2, d10), (a1, b3, c2, d11), (a1, b3, c2, d12), (a1, b3, c2, d13), (a1, b3, c2, d14), (a1, b3, c2, d15), (a1, b3, c2, d16), (a1, b3, c2, d17), (a1, b3, c2, d18), (a1, b3, c2, d19), (a1, b3, c2, d20), (a1, b3, c2, d21), (a1, b3, c2, d22), (a1, b3, c3, d1), (a1, b3, c3, d2), (a1, b3, c3, d3), (a1, b3, c3, d4), (a1, b3, c3, d5), (a1, b3, c3, d6), (a1, b3, c3, d7), (a1, b3, c3, d8), (a1, b3, c3, d9), (a1, b3, c3, d10), (a1, b3, c3, d11), (a1, b3, c3, d12), (a1, b3, c3, d13), (a1, b3, c3, d14), (a1, b3, c3, d15), (a1, b3, c3, d16), (a1, b3, c3, d17), (a1, b3, c3, d18), (a1, b3, c3, d19), (a1, b3, c3, d20), (a1, b3, c3, d21), (a1, b3, c3, d22), (a1, b4, c1, d1), (a1, b4, c1, d2), (a1, b4, c1, d3), (a1, b4, c1, d4), (a1, b4, c1, d5), (a1, b4, c1, d6), (a1, b4, c1, d7), (a1, b4, c1, d8), (a1, b4, c1, d9), (a1, b4, c1, d10), (a1, b4, c1, d11), (a1, b4, c1, d12), (a1, b4, c1, d13), (a1, b4, c1, d14), (a1, b4, c1, d15), (a1, b4, c1, d16), (a1, b4, c1, d17), (a1, b4, c1, d18), (a1, b4, c1, d19), (a1, b4, c1, d20), (a1, b4, c1, d21), (a1, b4, c1, d22), (a1, b4, c2, d1), (a1, b4, c2, d2), (a1, b4, c2, d3), (a1, b4, c2, d4), (a1, b4, c2, d5), (a1, b4, c2, d6), (a1, b4, c2, d7), (a1, b4, c2, d8), (a1, b4, c2, d9), (a1, b4, c2, d10), (a1, b4, c2, d11), (a1, b4, c2, d12), (a1, b4, c2, d13), (a1, b4, c2, d14), (a1, b4, c2, d15), (a1, b4, c2, d16), (a1, b4, c2, d17), (a1, b4, c2, d18), (a1, b4, c2, d19), (a1, b4, c2, d20), (a1, b4, c2,

d21), (a1, b4, c2, d22), (a1, b4, c3, d1), (a1, b4, c3, d2), (a1, b4, c3, d3), (a1, b4, c3, d4), (a1, b4, c3, d5), (a1, b4, c3, d6), (a1, b4, c3, d7), (a1, b4, c3, d8), (a1, b4, c3, d9), (a1, b4, c3, d10), (a1, b4, c3, d11), (a1, b4, c3, d12), (a1, b4, c3, d13), (a1, b4, c3, d14), (a1, b4, c3, d15), (a1, b4, c3, d16), (a1, b4, c3, d17), (a1, b4, c3, d18), (a1, b4, c3, d19), (a1, b4, c3, d20), (a1, b4, c3, d21), (a1, b4, c3, d22), (a1, b5, c1, d1), (a1, b5, c1, d2), (a1, b5, c1, d3), (a1, b5, c1, d4), (a1, b5, c1, d5), (a1, b5, c1, d6), (a1, b5, c1, d7), (a1, b5, c1, d8), (a1, b5, c1, d9), (a1, b5, c1, d10), (a1, b5, c1, d11), (a1, b5, c1, d12), (a1, b5, c1, d13), (a1, b5, c1, d14), (a1, b5, c1, d15), (a1, b5, c1, d16), (a1, b5, c1, d17), (a1, b5, c1, d18), (a1, b5, c1, d19), (a1, b5, c1, d20), (a1, b5, c1, d21), (a1, b5, c1, d22), (a1, b5, c2, d1), (a1, b5, c2, d2), (a1, b5, c2, d3), (a1, b5, c2, d4), (a1, b5, c2, d5), (a1, b5, c2, d6), (a1, b5, c2, d7), (a1, b5, c2, d8), (a1, b5, c2, d9), (a1, b5, c2, d10), (a1, b5, c2, d11), (a1, b5, c2, d12), (a1, b5, c2, d13), (a1, b5, c2, d14), (a1, b5, c2, d15), (a1, b5, c2, d16), (a1, b5, c2, d17), (a1, b5, c2, d18), (a1, b5, c2, d19), (a1, b5, c2, d20), (a1, b5, c2, d21), (a1, b5, c2, d22), (a1, b5, c3, d1), (a1, b5, c3, d2), (a1, b5, c3, d3), (a1, b5, c3, d4), (a1, b5, c3, d5), (a1, b5, c3, d6), (a1, b5, c3, d7), (a1, b5, c3, d8), (a1, b5, c3, d9), (a1, b5, c3, d10), (a1, b5, c3, d11), (a1, b5, c3, d12), (a1, b5, c3, d13), (a1, b5, c3, d14), (a1, b5, c3, d15), (a1, b5, c3, d16), (a1, b5, c3, d17), (a1, b5, c3, d18), (a1, b5, c3, d19), (a1, b5, c3, d20), (a1, b5, c3, d21), (a1, b5, c3, d22), (a1, b6, c1, d1), (a1, b6, c1, d2), (a1, b6, c1, d3), (a1, b6, c1, d4), (a1, b6, c1, d5), (a1, b6, c1, d6), (a1, b6, c1, d7), (a1, b6, c1, d8), (a1, b6, c1, d9), (a1, b6, c1, d10), (a1, b6, c1, d11), (a1, b6, c1, d12), (a1, b6, c1, d13), (a1, b6, c1, d14), (a1, b6, c1, d15), (a1, b6, c1, d16), (a1, b6, c1, d17), (a1, b6, c1, d18), (a1, b6, c1, d19), (a1, b6, c1, d20), (a1, b6, c1, d21), (a1, b6, c1, d22), (a1, b6, c2, d1), (a1, b6, c2, d2), (a1, b6, c2, d3), (a1, b6, c2, d4), (a1, b6, c2, d5), (a1, b6, c2, d6), (a1, b6, c2, d7), (a1, b6, c2, d8), (a1, b6, c2, d9), (a1, b6, c2, d10), (a1, b6, c2, d11), (a1, b6, c2, d12), (a1, b6, c2, d13), (a1, b6, c2,

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c3, d9), (a90, b5, c3, d10), (a90, b5, c3, d11), (a90, b5, c3, d12), (a90, b5, c3, d13), (a90, b5, c3, d14), (a90, b5, c3, d15), (a90, b5, c3, d16), (a90, b5, c3, d17), (a90, b5, c3, d18), (a90, b5, c3, d19), (a90, b5, c3, d20), (a90, b5, c3, d21), (a90, b5, c3, d22), (a90, b6, c1, d1), (a90, b6, c1, d2), (a90, b6, c1, d3), (a90, b6, c1, d4), (a90, b6, c1, d5), (a90, b6, c1, d6), (a90, b6, c1, d7), (a90, b6, c1, d8), (a90, b6, c1, d9), (a90, b6, c1, d10), (a90, b6, c1, d11), (a90, b6, c1, d12), (a90, b6, c1, d13), (a90, b6, c1, d14), (a90, b6, c1, d15), (a90, b6, c1, d16), (a90, b6, c1, d17), (a90, b6, c1, d18), (a90, b6, c1, d19), (a90, b6, c1, d20), (a90, b6, c1, d21), (a90, b6, c1, d22), (a90, b6, c2, d1), (a90, b6, c2, d2), (a90, b6, c2, d3), (a90, b6, c2, d4), (a90, b6, c2, d5), (a90, b6, c2, d6), (a90, b6, c2, d7), (a90, b6, c2, d8), (a90, b6, c2, d9), (a90, b6, c2, d10), (a90, b6, c2, d11), (a90, b6, c2, d12), (a90, b6, c2, d13), (a90, b6, c2, d14), (a90, b6, c2, d15), (a90, b6, c2, d16), (a90, b6, c2, d17), (a90, b6, c2, d18), (a90, b6, c2, d19), (a90, b6, c2, d20), (a90, b6, c2, d21), (a90, b6, c2, d22), (a90, b6, c3, d1), (a90, b6, c3, d2), (a90, b6, c3, d3), (a90, b6, c3, d4), (a90, b6, c3, d5), (a90, b6, c3, d6), (a90, b6, c3, d7), (a90, b6, c3, d8), (a90, b6, c3, d9), (a90, b6, c3, d10), (a90, b6, c3, d11), (a90, b6, c3, d12), (a90, b6, c3, d13), (a90, b6, c3, d14), (a90, b6, c3, d15), (a90, b6, c3, d16), (a90, b6, c3, d17), (a90, b6, c3, d18), (a90, b6, c3, d19), (a90, b6, c3, d20), (a90, b6, c3, d21), (a90, b6, c3, d22).

[0243] O composto representado pela fórmula geral (A) inclui um isômero ótico do mesmo e um racemato do mesmo.

Exemplos de teste 1 - Atividade inibitória de enzima do composto de teste em EGFR e HER2

[0244] EGFR e HER2 purificadas de um sistema de expressão de células de inseto, e um substrato biotinilado (peptídio sintético de ácido glutâmico:tirosina = 4:1) foram adicionados a uma placa de 384 compartimentos com ATP adicionado à mesma, e uma reação enzimática foi realizada à temperatura ambiente. Depois de completada

a reação enzimática, um anticorpo de tirosina anti-fosforilado marcado com európio e estreptavidina marcada com alficocianina foram adicionados, e um resíduo de tirosina fosforilado foi quantificado por um método de fluorescência com resolução temporal.

Preparação do composto de teste

[0245] Um composto de teste foi ajustado em 10 mM usando DMSO.

[0246] Além disso, usando uma solução de DMSO a 10%, foi preparada uma solução 1 mM, e esta foi considerada como o ponto de concentração máxima.

[0247] Como uma série de diluições, foi uma preparada uma série de diluições 4 vezes até o estágio 10.

Preparação do reagente

Preparação do tampão:

[0248] Como tampão, foi usado TBS contendo 10 mM $MgCl_2$, 5 mM $MnCl_2$, 0,2 mM Na_3VO_4, e 0,1% BSA.

Enzima:

[0249] Como enzimas EGFR e HER2, aquelas purificadas de um sistema de expressão de células de inseto foram adquiridas na Carna Biosciences, Inc.

[0250] Uma solução de enzima EGFR foi ajustada em 250 ng/ml usando um tampão.

[0251] A cinase HER2 foi ajustada em 1000 ng/ml usando um tampão.

Solução de substrato:

[0252] Como substrato, foi usado poli-Glu-Tyr biotinilado (4:1, produzido por CISbio). Um concentração foi ajustada em 3,125 μg/ml usando o tampão acima.

Solução de ATP:

[0253] Uma concentração de ATP no estudo da enzima EGFR foi

ajustada em 125 μM usando o tampão.

[0254] Uma concentração de ATP no estudo da enzima HER2 foi ajustada em 290 μM.

Reagente de detecção:

[0255] Para preparar um reagente de detecção, foi usado TBS contendo 30mM EDTA, 0,8M KF e 0,1% BSA.

[0256] Um anticorpo de tirosina antifosforilado marcado com európio, PT-66K (CISbio) foi ajustado em 195 ng/ml, e estreptavidina marcada com alficocianina, SA-XL(CISbio) foi ajustada em 5 μg/ml.

Método de ensaio

[0257] Como placa de ensaio, foi usada uma placa de 384 compartimentos. Por uma cavidade, foram adicionados 1,1 μl de um composto de teste, 4 μl de uma solução de substrato, e 4 μl de uma solução de enzima, e 2 μl de uma solução de ATP para iniciar uma reação enzimática. A reação enzimática foi realizada à temperatura ambiente por 60 minutos, e 10 μl de um reagente de detecção foram adicionados para completar a reação. Uma hora depois de completada a reação, foi efetuada a medida fluorescente com resolução temporal.

Método de avaliação

[0258] Usando 10% DMSO no lugar de um composto de teste, e deixando um sinal com a adição de ATP ser 0% de inibição (atividade enzimática 100%), e deixando um sinal na ausência de ATP ser 100% de inibição (atividade enzimática 0%), foi calculada a atividade inibitória com a adição de um composto de teste.

[0259] A atividade inibitória (valor de IC_{50}, nM) dos compostos descritos nos Exemplos em EGFR e HER2 está mostrada abaixo.

Tabela 50

Composto Nº	EGFR (nM)	HER2 (nM)	Composto Nº	EGFR (nM)	HER2 (nM)
V-6	6,5	3,6	VIII-74	164	150

Composto Nº	EGFR (nM)	HER2 (nM)	Composto Nº	EGFR (nM)	HER2 (nM)
V-7	36	76	VIII-75	50	34
V-43	186	151	VIII-76	162	216
VIII-7	103	348	VIII-77	217	246
VIII-10	409	484	VIII-78	111	410
VIII-11	43	45	VIII-80	23	29
VIII-12	209	227	VIII-81	9,8	17,7
VIII-13	300	888	VIII-82	7,6	7,5
VIII-19	89	115	VIII-83	164	121
VIII-20	29	31	VIII-84	44	47
VIII-27	33	43	VIII-85	32	33
VIII-28	162	167	VIII-86	244	304
VIII-29	102	513	VIII-87	642	476
VIII-32	50	46	VIII-88	47	56
VIII-35	11	25	VIII-89	27	24
VIII-40	9,3	19,2	VIII-90	93	97
VIII-41	12	15	VIII-91	74	83
VIII-42	10	11	VIII-92	32	36
VIII-44	26	6,3	VIII-93	453	321
VIII-45	58	152	VIII-94	213	150
VIII-46	82	104	VIII-95	209	176
VIII-47	12	23	VIII-96	20	20
VIII-48	44	15	VIII-97	19	22
VIII-49	28	31	VIII-98	21	21
VIII-50	19	15	VIII-99	84	84
VIII-51	45	64	VIII-100	208	203
VIII-52	19	28	VIII-101	56	129
VIII-53	79	80	VIII-102	72	121

Composto Nº	EGFR (nM)	HER2 (nM)	Composto Nº	EGFR (nM)	HER2 (nM)
VIII-55	19	68	VIII-103	3,9	5,6
VIII-56	7,9	13,8	VIII-104	238	202
VIII-57	301	303	VIII-105	14	14
VIII-58	207	236	VIII-106	160	148
VIII-59	115	278	VIII-107	150	135
VIII-60	54	30	VIII-108	53	56
VIII-61	30	24	VIII-109	23	18
VIII-62	22	22	VIII-110	29	35
VIII-63	9,6	9,2	VIII-111	37	55
VIII-64	52	88	VIII-112	11	13
VIII-65	97	98	VIII-113	9,7	12
VIII-66	27	43	VIII-114	57	69
VIII-67	16	14	VIII-116	37	25
VIII-68	19	25	VIII-117	47	53
VIII-69	43	28	VIII-118	197	223
VIII-70	63	31	VIII-119	81	77
VIII-71	130	199	VIII-120	33	29
VIII-72	6,3	11	VIII-121	17	18
VIII-73	275	199	VIII-122	29	24

Tabela 51

Composto Nº	EGFR (nM)	HER2 (nM)	Composto Nº	EGFR (nM)	HER2 (nM)
VIII-123	24	38	VIII-174	25	28
VIII-124	40	38	VIII-176	23	26
VIII-125	118	103	VIII-177	7,3	5,8
VIII-126	101	123	VIII-178	8,1	8,2
VIII-127	37	35	VIII-179	4,6	5

Composto Nº	EGFR (nM)	HER2 (nM)	Composto Nº	EGFR (nM)	HER2 (nM)
VIII-128	15	17	VIII-180	7,8	6
VIII-129	7,1	6,3	VIII-181	6,2	5,9
VIII-130	8,1	5,2	VIII-182	4,7	7,3
VIII-131	5,8	4,4	VIII-183	7,1	8,3
VIII-132	14	14	VIII-184	10	7
VIII-133	8,4	7,1	VIII-185	6,8	12,5
VIII-134	7,1	7,4	VIII-186	19	26
VIII-135	7,6	8,1	VIII-187	10	9
VIII-136	21	21	VIII-188	20	30
VIII-137	13	14	VIII-189	17	27
VIII-139	5	3,8	VIII-190	8,9	11,1
VIII-140	5,5	4,3	VIII-191	17	42
VIII-141	10	7,9	VIII-192	6,2	14,2
VIII-142	5,5	4,4	VIII-193	14	15
VIII-143	3,5	3,6	VIII-194	8,6	13
VIII-145	9,4	8,9	VIII-195	45	43
VIII-146	12	10	VIII-196	11	20
VIII-147	13	13	VIII-197	9	21
VIII-148	6,1	5,8	VIII-198	3,6	4,6
VIII-149	13	14	VIII-199	6,3	5,2
VIII-150	12	11	VIII-200	9,7	9,6
VIII-151	20	19	VIII-205	17	13
VIII-152	2,4	4,3	VIII-207	21	17
VIII-153	10	11	VIII-208	28	23
VIII-154	9,5	9	VIII-209	38	30
VIII-155	10	8	VIII-210	42	14
VIII-156	7	6,4	VIII-211	23	18

Composto Nº	EGFR (nM)	HER2 (nM)	Composto Nº	EGFR (nM)	HER2 (nM)
VIII-157	4,1	4	VIII-213	18	25
VIII-158	3,8	3,8	VIII-214	4,5	3,3
VIII-159	16	19	VIII-216	22	7
VIII-160	17	18	VIII-218	76	22
VIII-161	14	15	VIII-219	26	20
VIII-162	51	62	VIII-220	263	449
VIII-163	23	27	VIII-221	143	168
VIII-164	7,3	7,6	VIII-223	253	217
VIII-165	11	11	VIII-224	122	118
VIII-167	4,8	4,2	VIII-225	47	70
VIII-168	8	9	VIII-226	20	10
VIII-169	13	15	IX-1	138	203
VIII-170	5	5,6	IX-4	193	334
VIII-171	9,9	11,7	IX-6	344	326
VIII-172	14	16	IX-8	426	549
VIII-173	4,8	3,9			

Exemplo de teste 2 - Teste de inibição de proliferação celular in vitro do composto de teste

[0260] Como a cepa de célula de câncer humano, foi usada a BT-474. As células foram todas cultivadas em uma incubadora a 37°C e 5% de CO_2 em um meio no qual 10% de soro fetal bovino (ICN) e 50 unidades/ml de penicilina/50 μg/ml a solução de estreptomicina (GIBCO) foram adicionados ao meio essencial modificado da Dulbecco (DMEM, Nacalai Tesque, Inc). Cada 3000/cavidade de células foram semeadas em uma placa de 96 cavidades (Sumitomo Bakelite Co., Ltd.) e, no dia seguinte, um fármaco foi adicionado a uma concentração máxima de 3×10^{-10} a 10^{-5}M. Depois de cultivadas por 3 dias, o ensaio de WST (sal de tetrazólio solúvel em água) foi realizado, e um valor de IC_{50} foi calculado.

[0261] A atividade inibitória de proliferação (valor de IC_{50}, nM) dos compostos descritos nos exemplos em BT-474 está mostrada abaixo.

Tabela 52

Composto Nº	BT-474 (nM)	Composto Nº	BT-474 (nM)	Composto Nº	BT-474 (nM)
V-6	110	VIII-75	22	VIII-124	14
V-7	134	VIII-76	12	VIII-125	10
V-43	71	VIII-77	11	VIII-126	9
VIII-7	63	VIII-78	35	VIII-127	61
VIII-10	27	VIII-80	35	VIII-128	37
VIII-11	26	VIII-81	8	VIII-129	12
VIII-12	69	VIII-82	16	VIII-130	50
VIII-13	64	VIII-83	13	VIII-131	14
VIII-20	37	VIII-84	28	VIII-132	18
VIII-27	13	VIII-85	11	VIII-133	43
VIII-28	72	VIII-86	13	VIII-134	14
VIII-29	77	VIII-87	6	VIII-135	28
VIII-32	32	VIII-88	12	VIII-136	53
VIII-35	24	VIII-89	25	VIII-137	78
VIII-40	9	VIII-90	9	VIII-139	32
VIII-41	14	VIII-91	24	VIII-140	30
VIII-42	24	VIII-92	29	VIII-141	46
VIII-44	28	VIII-93	38	VIII-142	31
VIII-45	13	VIII-94	26	VIII-143	24
VIII-46	12	VIII-95	25	VIII-145	21
VIII-47	4	VIII-96	30	VIII-146	45
VIII-48	28	VIII-97	11	VIII-147	25
VIII-49	28	VIII-98	65	VIII-148	26
VIII-50	27	VIII-99	24	VIII-149	28

Composto Nº	BT-474 (nM)	Composto Nº	BT-474 (nM)	Composto Nº	BT-474 (nM)
VIII-51	9	VIII-100	16	VIII-150	30
VIII-52	9	VIII-101	12	VIII-151	47
VIII-53	12	VIII-102	7	VIII-152	22
VIII-55	25	VIII-103	11	VIII-153	21
VIII-56	14	VIII-104	60	VIII-154	31
VIII-57	15	VIII-105	10	VIII-155	28
VIII-58	37	VIII-106	16	VIII-156	24
VIII-59	11	VIII-107	23	VIII-157	25
VIII-60	14	VIII-108	31	VIII-158	27
VIII-61	11	VIII-109	40	VIII-159	15
VIII-62	12	VIII-110	21	VIII-160	47
VIII-63	13	VIII-111	15	VIII-161	49
VIII-64	22	VIII-112	8	VIII-162	42
VIII-65	30	VIII-113	13	VIII-163	38
VIII-66	8	VIII-114	37	VIII-164	31
VIII-67	32	VIII-116	50	VIII-165	23
VIII-68	41	VIII-117	20	VIII-167	21
VIII-69	16	VIII-118	22	VIII-168	44
VIII-70	7	VIII-119	31	VIII-169	35
VIII-71	17	VIII-120	32	VIII-170	19
VIII-72	21	VIII-121	10	VIII-171	52
VIII-73	12	VIII-122	14	VIII-172	70
VIII-74	28	VIII-123	31	VIII-173	40

Tabela 53

Composto Nº	BT-474 (nM)	Composto Nº	BT-474 (nM)	Composto Nº	BT-474 (nM)
VIII-174	14	VIII-190	14	VIII-209	19

Composto Nº	BT-474 (nM)	Composto Nº	BT-474 (nM)	Composto Nº	BT-474 (nM)
VIII-176	26	VIII-191	33	VIII-210	31
VIII-177	79	VIII-192	24	VIII-211	16
VIII-178	36	VIII-193	25	VIII-213	33
VIII-179	48	VIII-194	25	VIII-214	25
VIII-180	5	VIII-195	29	VIII-216	32
VIII-181	13	VIII-196	28	VIII-218	41
VIII-182	20	VIII-197	14	VIII-219	45
VIII-183	10	VIII-198	10	VIII-220	23
VIII-184	9	VIII-199	33	VIII-221	15
VIII-185	12	VIII-200	8	VIII-223	6
VIII-186	29	VIII-205	31	VIII-224	1,2
VIII-187	24	VIII-207	68	VIII-225	7
VIII-188	40	VIII-208	27	VIII-226	5
VIII-189	25				

Exemplo de teste 3 - Teste de avaliação de antitumor in vivo do composto de teste

[0262] Células NCI-N87 (cepa de células de câncer de estômago humano) foram transplantadas em uma massa de gordura mamária de um camundongo fêmea nu (BALB/cA Jcl-nu/nu, CLEA Japan, Inc.) a 5×10^6 células/camundongo (dia 0). No dia 5, um diâmetro comprido e um diâmetro curto de um tumor foram medidos com um compasso, e os camundongos foram divididos em grupo (N = 6) de modo que o tamanho do tumor entre os grupos fosse o mesmo. Um composto de teste (20, 80 mg/kg) suspendido em uma solução de metilcelulose (MC) foi administrado por via oral a partir do dia 5 por 15 dias consecutivos, e o efeito antitumor foi expresso pela proporção (T/C%) de um valor médio do tamanho de tumor entre um grupo medicado com composto (T) e um grupo de controle (C; 0,5% MC) no dia 20.

[0263] Os resultados da avaliação antitumor in vivo de um composto VIII-11 estão mostrados na Tabela 54 e os resultados de uma avaliação antitumor in vivo de um composto VIII-66 estão mostrados na Tabela 55.

Tabela 54

Média do tamanho do tumor (mm^3)	Grupo de controle	Grupo que recebeu 20 mg/kg	Grupo que recebeu 80 mg/kg
Dia 5	192	197	197
Dia 20	655	356	193
T/C%	100%	54%	29%

Tabela 55

Média do tamanho do tumor (mm^3)	Grupo de controle	Grupo que recebeu 20 mg/kg	Grupo que recebeu 80 mg/kg
Dia 5	150	134	150
Dia 20	483	154	17
T/C%	100%	32%	4%

Exemplos de preparação

Exemplo de preparação 1

[0264] É preparado um grânulo contendo os seguintes ingredientes.

Ingrediente Composto representado pela fórmula (I) 10 mg

Lactose 700 mg

Amido de milho 274 mg

HPC-L 16 mg

1000 mg

[0265] O composto representado pela fórmula (I) e lactose são passados por uma peneira de 60 mesh. O amido de milho é passado por uma peneira de 120 mesh. Estes são misturados com uma máquina de misturação tipo V. Uma solução aquosa de HPC-L (hidroxipropilcelulose de baixa viscosidade) é adicionada a um pó da

mistura, e este é amassado, granulado (granulação por extrusão, diâmetro de poro 0,5 a 1 mm), e secado. O grânulo seco resultante é peneirado com uma peneira vibratória (12/60 mesh) para obter um grânulo.

Exemplo de preparação 2

[0266] É preparado um pó para encher uma cápsula contendo os seguintes ingredientes.

Ingrediente	Composto representado pela fórmula (I)	10 mg
	Lactose	79 mg
	Amido de milho	10 mg
	Estearato de magnésio	1 mg
		100 mg

[0267] O composto representado pela fórmula (I), e lactose são passados por uma peneira de 60 mesh. O amido de milho é passado por uma peneira de 120 mesh. Estes e o estearato de magnésio são misturados com uma máquina de misturação tipo V. 10 trituração 100 mg são introduzidos em uma cápsula de gelatina dura N° 5.

Exemplo de preparação 3

[0268] É preparado um grânulo para encher uma cápsula contendo os seguintes ingredientes.

Ingrediente	Composto representado pela fórmula (I)	15 mg
	Lactose	90 mg
	Amido de milho	42 mg
	HPC-L	3 mg
		150 mg

[0269] O composto representado pela fórmula (I), e lactose são passados por uma peneira de 60 mesh. O amido de milho é passado por uma peneira de 120 mesh. Estes são misturados, uma solução de HPL-L é adicionada a um pó da mistura, e este é amassado, granulado, e secado. O grânulo seco resultante tem o tamanho ajustado, dos quais

150 mg são introduzidos em uma cápsula de gelatina dura N° 4.

Exemplo de preparação 4

[0270] É preparado um comprimido contendo os seguintes ingredientes.

Ingrediente	Composto representado pela fórmula (I)	10 mg
	Lactose	90 mg
	Celulose microcristalina	30 mg
	CMC-Na	15 mg
	Estearato de magnésio	5 mg
		150 mg

[0271] O composto representado pela fórmula (I), lactose, celulose microcristalina, CMC-Na (sal sódico de carboximetilcelulose) são passados por uma peneira de 60 mesh e misturados. O estearato de magnésio é misturado em um pó da mistura para obter um pó da mistura para formação de comprimido. O presente pó misturado é diretamente comprimido para obter um comprimido de 150 mg.

Exemplo de preparação 5

[0272] Uma preparação intravenosa é preparada da seguinte maneira:

Composto representado pela fórmula (I)	100 mg
Glicerídeo de ácidos graxos saturados	1000 ml

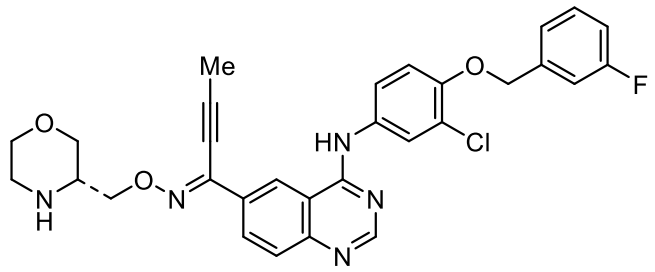
[0273] Uma solução dos ingredientes acima é administrada por via intravenosa a um paciente a uma taxa de 1 ml por minuto.

Aplicabilidade Industrial

[0274] Como o presente composto possui a excelente ação de inibir um receptor de EGF e HER2, e é bastante seguro, ele é útila como medicamento, entre outras coisas, como um produto terapêutico para um câncer.

REIVINDICAÇÕES

1. Composto, caracterizado pelo fato de que é representado pela fórmula:



ou um sal farmaceuticamente aceitável do mesmo.

2. Composição farmacêutica, caracterizada pelo fato de que compreende o composto como definido na reivindicação 1, ou um sal farmaceuticamente aceitável do mesmo, como um ingrediente ativo, e um aditivo farmacêutico.

3. Composição farmacêutica útil para tratar câncer, caracterizada pelo fato de que compreende o composto como definido na reivindicação 1, ou um sal farmaceuticamente aceitável do mesmo, como um ingrediente ativo.