(11) Número de Publicação: **PT 1255738 E**

(51) Classificação Internacional:
C07D 239/54 (2011.01) ***C07D 401/12*** (2011.01)
C07D 401/14 (2011.01) ***C07D 403/04*** (2011.01)
C07D 403/06 (2011.01) ***C07D 405/04*** (2011.01)
C07D 405/12 (2011.01) ***C07D 405/14*** (2011.01)
C07D 409/04 (2011.01) ***C07D 409/14*** (2011.01)
C07D 413/04 (2011.01) ***C07D 413/14*** (2011.01)
C07D 417/04 (2011.01) ***C07D 471/04*** (2011.01)
C07D 491/08 (2011.01) ***C07D 513/04*** (2011.01)

(12) **FASCÍCULO DE PATENTE DE INVENÇÃO**

(22) Data de pedido: **2001.01.25**

(30) Prioridade(s): **2000.01.25 US 177933 P**
2000.10.11 US 239683 P

(43) Data de publicação do pedido: **2002.11.13**

(45) Data e BPI da concessão: **2012.03.07**
116/2012

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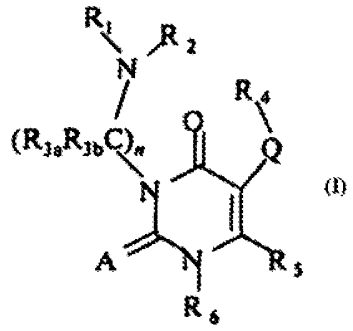
(54) Epígrafe: **ANTAGONISTAS DO RECEPTOR DA HORMONA DE LIBERTAÇÃO DA GONADOTROFINA E MÉTODOS RELACIONADOS COM OS MESMOS**

(57) Resumo:
ESTA INVENÇÃO REFERE-SE A ANTAGONISTAS RECEPTORES DA GNRH QUE TÊM UTILIDADE NO TRATAMENTO DE UMA VARIEDADE DE SITUAÇÕES RELACIONADOS COM A HORMONA SEXUAL, TANTO EM HOMENS COMO EM MULHERES. OS COMPOSTOS DESTA INVENÇÃO TÊM A ESTRUTURA DE FÓRMULA (I), EM QUE A, Q, R1, R2, R3A, R3B, R4, R5, R6 E N SÃO COMO AQUI DEFINIDOS, INCLUINDO ESTEREOISÓMEROS, PRÓ-FÁRMACOS, E SAIS FARMACEUTICAMENTE ACEITÁVEIS DOS MESMOS. TAMBÉM SÃO AQUI REVELADAS COMPOSIÇÕES CONTENDO UM COMPOSTO DESTA INVENÇÃO, EM COMBINAÇÃO COM UM VEÍCULO FARMACEUTICAMENTE ACEITÁVEL, BEM ASSIM COMO OS MÉTODOS RELACIONADOS COM O USO DOS MESMOS PARA ANTAGONIZAR A HORMONA DE LIBERTAÇÃO DA GONADOTROPINA NUM SUJEITO COM NECESSIDADE DA MESMA.

RESUMO

EPÍGRAFE:	"ANTAGONISTAS DO RECEPTOR DA HORMONA DE LIBERTAÇÃO DA GONADOTROFINA E MÉTODOS RELACIONADOS COM OS MESMOS"

Esta invenção refere-se a antagonistas receptores da GnRH que têm utilidade no tratamento de uma variedade de situações relacionados com a hormona sexual, tanto em homens como em mulheres. Os compostos desta invenção têm a estrutura de fórmula (I), em que A, Q, R1, R2, R3a, R3b, R4, R5, R6 e *n* são como aqui definidos, incluindo estereoisómeros, pró-fármacos, e sais farmaceuticamente aceitáveis dos mesmos. Também são aqui reveladas composições contendo um composto desta invenção, em combinação com um veículo farmaceuticamente aceitável, bem assim como os métodos relacionados com o uso dos mesmos para antagonizar a hormona de libertação da gonadotropina num sujeito com necessidade da mesma.



(I)

DESCRIÇÃO

EPÍGRAFE:	**"ANTAGONISTAS DO RECEPTOR DA HORMONA DE LIBERTAÇÃO DA GONADOTROFINA E MÉTODOS RELACIONADOS COM OS MESMOS"**

DECLARAÇÃO DE INTERESSE DO GOVERNO

O trabalho aqui descrito foi parcialmente financiado pelo Governo dos EUA sob a Subvenção No. R43-HD38625 concedida pelos Institutos Nacionais de Saúde. O Governo dos EUA pode ter certos direitos na presente invenção.

CAMPO TÉCNICO

Esta invenção refere-se, em geral, aos antagonistas do receptor da hormona de libertação de gonadotrofina (GnRH), e aos métodos de tratamento de perturbações por administração de tais antagonistas a um animal de sangue quente com necessidade dos mesmos.

ANTECEDENTES DA INVENÇÃO

A hormona de libertação de gonadotrofina (GnRH), também conhecida como hormona libertadora da hormona luteinizante (LHRH), é um decapéptido (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2) que desempenha um papel importante na reprodução humana. A GnRH é libertada a partir do hipotálamo e actua sobre a glândula pituitária para estimular a biossíntese e a libertação da hormona luteinizante (LH) e hormona folículo-estimulante (FSH). A LH libertada pela glândula pituitária é responsável pela regulação da produção de esteróides gonadais

em machos e fêmeas, enquanto a FSH regula a espermatogénese em machos e desenvolvimento folicular em fêmeas.

Devido à sua importância biológica, os antagonistas e agonistas sintéticos da GnRH têm sido o foco de atenção considerável, particularmente no contexto do cancro da próstata, cancro da mama, endometriose, leiomioma uterino, e puberdade precoce. Por exemplo, agonistas da GnRH peptídicos, tais como leuprorelina (pGlu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NHEt), têm sido usados para tratar essas situações. Tais agonistas parecem funcionar por meio de ligação ao receptor de GnRH nas gonadotrofinas hipofisárias, induzindo assim a síntese e libertação de gonadotrofinas. A administração crónica de agonistas de GnRH consome as gonadotrofinas e subsequentemente reduz a actividade do receptor, resultando na supressão de hormonas esteróides ao fim de algum tempo (por exemplo, na ordem de 2-3 semanas após o início da administração crónica).

Em contraste, crê-se que os antagonistas de GnRH suprimem as gonadotrofinas desde o início, e, por isso, têm recebido mais atenção ao longo das duas últimas décadas. Até à data, alguns dos principais obstáculos para o uso clínico de tais antagonistas têm sido a sua biodisponibilidade relativamente baixa e os efeitos colaterais adversos causados pela libertação de histamina. No entanto, vários antagonistas peptídicos com propriedades de libertação de histamina reduzida têm sido relatados, embora ainda devam ser administrados através de vias de administração sustentada (tais como injecção subcutânea ou pulverização intranasal) devido a biodisponibilidade limitada.

Tendo em vista as limitações associadas com antagonistas de GnRH peptídicos, tem sido proposto um conjunto de compostos não peptídicos. Por exemplo, Cho et al. (J. Med. Chem. 41:4190-4195, 1998) divulga tieno[2,3-b]piridin-4-onas para o

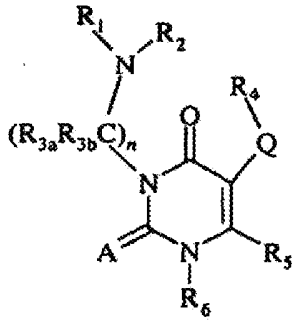
uso como antagonistas do receptor da GnRH; Patentes dos EUA Nos 5,780,437 e 5,849,764 ensinam indoles substituidos como antagonistas do receptor GnRH (tal como os PCTs publicados WO 97/21704, 98/55479, 98/55470, 98/55116, 98/55119, 97/21707, 97/21703 e 97/21435); PCT publicado WO 96/38438 divulga diazepinas tricíclicas como antagonistas do receptor da GnRH; Os PCTs publicados W097/14682, 97/14697 e 99/09033 divulgam derivados de quinolina e tienopiridínicos como antagonistas de GnRH; Os PCTs publicados WO 97/44037, 97/44041, 97/44321 e 97/44339 ensinam quinolin-2-onas substituidas como antagonistas do receptor da GnRH; e o PCT publicado WO 99/33831 revela certos compostos bicíclicos fundidos fenil-substituídos contendo átomos de azoto como antagonistas do receptor de GnRH.

A Patente US 5,859,014 refere-se a derivados de pirimidinadiona, pirimidinatriona, triazinadiona e tetrahidroquinazolinadiona como antagonista do receptor α_1-adrenérgico. A Patente WO 96/24597 descreve derivados de tienopirimidina. A Patente WO 00/69833 refere-se a arilo policiclico e uracilos heteroarilo substituidos como agentes anti-coagulantes. A Patente WO 00/29386 revela derivados da pirimidinadiona para uso como antagonista adrenoceptor alfa la.

Embora tenha havido avanços significativos neste campo, continua a existir uma necessidade na arte de pequenas moléculas eficazes como antagonistas dos receptores de GnRH. Existe também uma necessidade de composições farmacêuticas que contenham tais antagonistas do receptor de GnRH, bem como métodos relacionados com a sua utilização para tratar, por exemplo, situações relacionadas com a hormona sexual. A presente invenção atende a essas necessidades, e oferece outras vantagens relacionadas.

SUMÁRIO DA INVENÇÃO

Em resumo, esta invenção é geralmente dirigida aos antagonistas do receptor da hormona de libertação da gonadotrofina (GnRH), bem como aos métodos para a sua preparação e utilização, e a composições farmacêuticas contendo os mesmos. Mais especificamente, os antagonistas dos receptores de GnRH da presente invenção são compostos que possuem a seguinte estrutura geral (I):



(I)

incluindo estereoisómeros, pró-fármacos e os sais farmaceuticamente aceitáveis, em que A, Q, R_1, R_2, R_{3a}, R_{3b}, R_4, R_5, R_6, e n são como definido abaixo.

Os antagonistas dos receptores de GnRH da presente invenção têm utilidade numa vasta gama de aplicações terapêuticas, e podem ser usados para tratar uma variedade de situações relacionadas com a hormona sexual tanto nos homens como nas mulheres, bem como num mamífero, em geral, (também aqui referido como um "sujeito"). Por exemplo, tais situações incluem a endometriose, miomas uterinos, síndrome dos ovários policísticos, hirsutismo, puberdade precoce, neoplasia dependente do esteróide gonadal, tais como cancros da próstata, mama e ovário, adenomas gonadotróficos da pituitária, apneia do sono, síndrome do intestino irritável, síndrome pré-menstrual, hipertrofia prostática benigna, contracepção e infertilidade (por exemplo, a terapia de

reprodução assistida, tais como a fertilização *in vitro*). Os compostos da presente invenção também são úteis como um adjuvante no tratamento da deficiência de hormona de crescimento e baixa estatura, e para o tratamento de lúpus eritematoso sistémico. Os compostos são também úteis em combinação com androgénios, estrogénios, progesteronas, e anti-estrogénios e antiprogestinas para o tratamento de endometriose, miomas, e na contracepção, bem como em combinação com um inibidor da enzima conversora de angiotensina, um antagonista receptor da angiotensina II, ou um inibidor de renina para o tratamento de miomas uterinos. Além disso, os compostos podem ser usados em combinação com bisfosfonatos e outros agentes para o tratamento e/ou prevenção de perturbações do metabolismo do cálcio, fosfato e ósseo, e em combinação com estrogénios, progesteronas e/ou androgénios para a prevenção ou tratamento da perda de osso ou sintomas hipogonadais como ondas de calor durante o tratamento com um antagonista de GnRH.

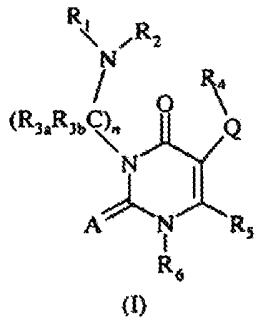
Os métodos da presente invenção incluem a administração de uma quantidade eficaz de um antagonista do receptor da GnRH, de preferência sob a forma de uma composição farmacêutica, a um mamífero com necessidade da mesma. Assim, numa outra forma de realização, são divulgadas composições farmacêuticas contendo um ou mais antagonistas do receptor da GnRH da presente invenção, em combinação com um transportador e/ou diluente farmaceuticamente aceitável.

Estes e outros aspectos da invenção serão evidentes mediante referência à descrição detalhada seguinte. Para este fim, diversas referências são aqui apresentadas as quais descrevem mais pormenorizadamente certa informação, procedimentos, compostos e/ou composições de fundo.

O problema da presente invenção é resolvido com base nas Reivindicações N°1 a N°.48.

DESCRIÇÃO DETALHADA DO INVENTO

Como mencionado acima, a presente invenção é dirigida geralmente a compostos úteis como antagonistas do receptor da hormona de libertação de gonadotrofina (GnRH). Os compostos da presente invenção têm a seguinte estrutura (I):



(I)

incluindo estereoisómeros, pró-fármacos e sais farmaceuticamente aceitáveis dos mesmos,

em que:

Q é uma ligação directa;

A é O, S, ou NR_7;

n é 2, 3 ou 4;

R_1 e R_2 são o mesmo ou diferente e, independentemente, hidrogénio, alquilo, alquilo substituído, arilo, arilo substituído, arilalquilo, arilalquilo substituido, heterociclilo, heterociclilo substituído, heterocicloalquilo, heterocicloalquilo substituído, $-C(R_{1a})(=NR_{1b})$ ou $-C(NR_{1a}R_{1c})(=NR_{1b})$;

ou R_1 e R_2 tomados em conjunto com o átomo de azoto ao qual estão ligados formam um anel heterocíclico ou um anel heterocíclico substituído;

R_{3a} e R_{3b} são o mesmo ou diferente e, em cada ocorrência, independentemente, hidrogénio, alquilo, alquilo substituído, alcoxi, alquiltio, alquilamino, arilo, arilo substituído, arilalquilo, arilalquilo substituido, heterociclilo,

heterociclilo substituído, heterocicloalquilo, heterocicloalquilo substituído, $-COOR_{14}$ ou $-CONR_{14}R_{15}$;

ou R_{3a} e R_{3b} tomados em conjunto com o átomo de carbono ao qual estão ligados formam um anel homocíclico, um anel homocíclico substituído, um anel heterocíclico ou um anel heterocíclico substituído;

ou R_{3a} e R_{3b} em conjunto formam $=NR_{3c}$;

ou R_{3a} e o átomo de carbono ao qual está ligado, em conjunto com R_1 e o átomo de azoto ao qual está ligado formam um anel heterociclico ou um anel heterocíclico substituido;

R_4 é arilo ou heterociclilo substituído;

R_5 é hidrogénio, halogéneo, alquilo inferior, alquilo inferior substituído, arilo, arilo substituído, arilalquilo, arilalquilo substituído, alcoxi, alquiltio, alquilamino, ciano ou nitro;

R_6 é alquilo superior, alquilo substituído, arilo, arilo substituído, arilalquilo, arilalquilo substituído, heteroarilo, heteroarilo substituído, heteroarilalquilo ou heteroarilalquilo substituído;

R_7 é hidrogénio, $-SO_2R_{11}$, ciano, alquilo, alquilo substituído, arilo, arilo substituído, arilalquilo, arilalquilo substituído, heteroarilo, heteroarilo substituído, heteroarilalquilo ou heteroarilalquilo substituído; e

R_{1a}, R_{1b}, R_{1c}, R_{3c}, R_{8a}, R_{8b}, R_9, R_{9a}, R_{10a}, R_{10b}, R_{11}, R_{12}, R_{13}, R_{14} e R_{15} são o mesmo ou diferente e, em cada ocorrência, independentemente, hidrogénio, acilo, alquilo, alquilo substituído, arilo, arilo substituído, arilalquilo, arilalquilo substituído, heterociclilo, heterociclilo substituído, heterocicloalquilo ou heterocicloalquilo substituído;

ou R_{1a} e R_{1b}, R_{8a} e R_{8b}, R_{10a} e R_{10b}, R_{12} e R_{13}, ou R_{14} e R_{15} tomados em conjunto com o átomo ou átomos aos quais estão ligados formam um anel homocíclico, um anel homocíclico

substituído, um anel heterocíclico ou um anel heterocíclico substituído.

Como aqui utilizado, os termos acima têm o seguinte significado:

"Alquilo" significa um hidrocarboneto alifático de cadeia linear ou ramificada, não cíclico ou cíclico, insaturado ou saturado, contendo de 1 a 10 átomos de carbono, enquanto que o termo "alquilo inferior" tem o mesmo significado que alquilo, mas contém de 1 a 6 átomos de carbono. O termo "alquilo superior" tem o mesmo significado que alquilo, mas contém de 2 a 10 átomos de carbono. Alquilos de cadeia linear saturados representativos incluem metilo, etilo, n-propilo, n-butilo, n-pentilo, e n-hexilo; enquanto os alquilos saturados ramificados incluem isopropilo, *sec*-butilo, isobutilo, *terc*-butilo, e isopentilo. Alquilos cíclicos saturados representativos incluem ciclopropilo, ciclobutilo, ciclopentilo, e ciclo-hexilo; enquanto os alquilos insaturados cíclicos incluem ciclopentenilo e ciclo-hexenilo. Os alquilos cíclicos são também aqui referidos como um "homociclos" ou "anéis homocíclicos." Os alquilos insaturados contêm, pelo menos, uma ligação dupla ou tripla entre átomos de carbono adjacentes (referidos como um "alcenilo" ou "alcinilo", respectivamente). Os alcenilos de cadeia linear ou ramificada representativos incluem etilenilo, propilenilo, 1-butenilo, 2-butenilo, isobutilenilo, 1-pentenilo, 2-pentenilo, 3-metil-1-butenilo, 2-metil-2-butenilo, 2,3-dimetil-2-butenilo; enquanto os alcinilos de cadeia linear ou ramificada representativos incluem acetilenilo, propinilo, 1-butinilo, 2-butinilo, 1-pentinilo, 2-pentinilo, 3-metil-1-butinilo.

"Arilo" significa uma porção carbocíclica aromática tal como fenilo ou naftilo.

"Arilalquilo" significa um alquilo tendo pelo menos um átomo de hidrogénio do alquilo substituído por um radical arilo, tal como benzilo, $-(CH_2)_2$fenilo, $-(CH_2)_3$fenilo, $-CH(fenil)_2$.

"Heteroarilo" significa um anel heterocíclico aromático de 5 a 10 membros e tendo pelo menos um heteroátomo seleccionado de entre azoto, oxigénio e enxofre, e contendo pelo menos 1 átomo de carbono, incluindo ambos sistemas de anel mono- e bicíclico. Heteroarilos representativos são o benzofuranilo, furilo, tiofenilo, benzotiofenilo, pirrolilo, indolilo, isoindolilo, azaindolilo, piridilo, quinolinilo, isoquinolinilo, oxazolilo, isooxazolilo, benzoxazolilo, pirazolilo, imidazolilo, benzimidazolilo, tiazolilo, benzotiazolilo, isotiazolilo, piridazinilo, pirimidinilo, pirazinilo, triazinilo, cinolinilo, ftalazinilo, e quinazolinilo.

"Heteroarilalquilo" significa um alquilo tendo pelo menos um átomo de hidrogénio do alquilo substituído por um radical heteroarilo, tal como $-CH_2$piridinilo, $-CH_3$pirimidinilo.

"Heterociclo" (também aqui referido como um "anel heterocíclico") significa um anel monocíclico de 4- a 7-membros, ou bicíclico de 7- a 10 membros, um anel heterocíclico que é ou saturado, insaturado, ou aromático, e que contém desde 1 a 4 heteroátomos independentemente seleccionados de entre azoto, oxigénio e enxofre, e em que os heteroátomos de azoto e de enxofre podem ser opcionalmente oxidados, e o heteroátomo de azoto pode ser opcionalmente quaternizado, incluindo anéis bicíclicos em que qualquer um dos heterociclos acima referidos são fundidos com um anel de benzeno. O heterociclo pode estar ligado através de qualquer heteroátomo ou átomo de carbono. Os heterociclos incluem heteroarilos, tal como definidos acima. Assim, para além dos heteroarilos listados acima, os heterociclos também incluem morfolinilo, pirrolidinonilo, pirrolidinilo, piperidinilo,

hidantoinilo, valerolactamilo, oxiranilo, oxetanilo, tetra-hidrofuranilo, tetra-hidropiranilo, tetrahidropiridinil, tetrahidroprimidinilo, tetrahidrotiofenilo, tetrahidrothiopiranilo, tetrahidropirimidinilo, tetrahidrotiofenilo, tetrahidrotiopiranilo.

"Heterocicloalquilo" significa um alquilo tendo pelo menos um átomo de hidrogénio do alquilo substituído por um heterociclo, tal como $-CH_2$morfolinilo.

"Homociclo" (também aqui referido como "anel homocíclico") significa um anel carbocíclico saturado ou insaturado (mas não aromático) contendo desde 3-7 átomos de carbono, tais como ciclopropano ciclobutano, ciclopentano, ciclohexano, cicloheptano, ciclohexeno, e semelhantes.

O termo "substituído", tal como aqui utilizado, significa qualquer dos grupos acima (isto é, alquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, homociclo, heterociclo e/ou heterocicloalquilo), em que pelo menos um átomo de hidrogénio é substituído por um substituinte. No caso de um substituinte ceto ("-C(=O)-") são substituídos dois átomos de hidrogénio. Quando um ou mais dos grupos acima referidos são substituídos, os "substituintes", no contexto da presente invenção, incluem halogéneo, hidroxi, ciano, nitro, amino, alquilamino, dialquilamino, alquilo, alcoxi, alquiltio, haloalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo e heterocicloalquilo, bem como $-NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aC(=O)NR_aNR_b$, $-NR_aC(=O)OR_b$-$NR_aSO_2R_b$. $-C(=O)R_a$, $-C(=O)OR_a$, $-C(=O)NR_aR_b$, $-OC(=O)NR_aR_b$, $-OR_a$, $-SR_a$, $-SOR_a$, $-S(=O)_2R_a$, $-OS(=O)_2R_a$ e $-S(=O)_2R_a$.

Além disso, os substituintes acima referidos podem ser ainda substituídos com um ou mais dos substituintes acima mencionados, de tal modo que o substituinte alquilo substituído, arilo substituído, arilalquilo substituído,

heterociclilo, heterociclilo substituído, heterocicloalquilo ou heterocicloalquilo substituído.
R_a e R_b, neste contexto, podem ser o mesmo ou diferentes e, independentemente, hidrogénio, alquilo, haloalquilo, alquilo substituído, arilo, arilo substituído, arilalquilo, arilalquilo substituído, heterociclilo, heterociclilo substituído, heterocicloalquilo ou heterocicloalquilo substituído.

"Halogéneo" significa flúor, cloro, bromo e iodo.

"Haloalquilo" significa um alquilo tendo pelo menos um átomo de hidrogénio substituído por halogéneo, tal como trifluorometilo.

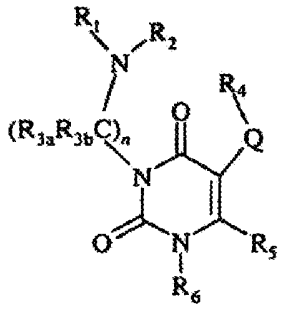
"Alcoxi" significa um radical alquilo ligado através de uma ponte de oxigénio (isto é, -O-alquilo), tal como metoxi, etoxi.

"Alquiltio" significa um radical alquilo ligado através de uma ponte de enzofre (isto é, -S-alquilo), tais como metiltio, etiltio.

"Alquilsulfonilo" significa um radical alquilo ligado através de uma ponte de sulfonilo (ie, $-SO_2$-alquilo), tal como metilsulfonilo, etilsulfonilo.

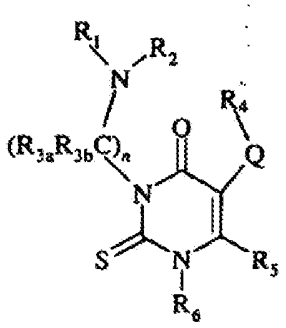
"Alquilamino" e "dialquilamino" significa um ou dois radicais alquilo ligados através de uma ponte de azoto (isto é, -N-alquilo) tal como metilamino, etilamino, dimetilamino, dietilamino, e semelhantes.

Numa forma de realização da presente invenção, A é O e os antagonistas do receptor da GnRH representativos da presente invenção incluem compostos que têm a seguinte estrutura (II):



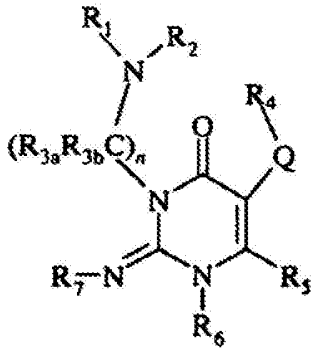
(II)

Noutra forma de realização, A é S, tal como representado pela seguinte estrutura (IV):



(IV)

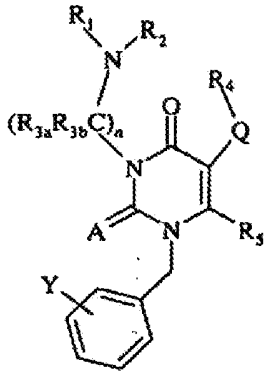
Do mesmo modo, numa outra forma de realização, A é NR_7, como representado pela seguinte estrutura (V):



(V)

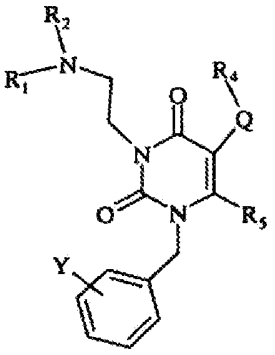
Noutras formas de realização da presente invenção, R_6 é benzilo substituído ou não substituído, tal como representado

pela seguinte estrutura (VI) (em que Y representa um ou mais substituintes opcionais tal como definidos acima):



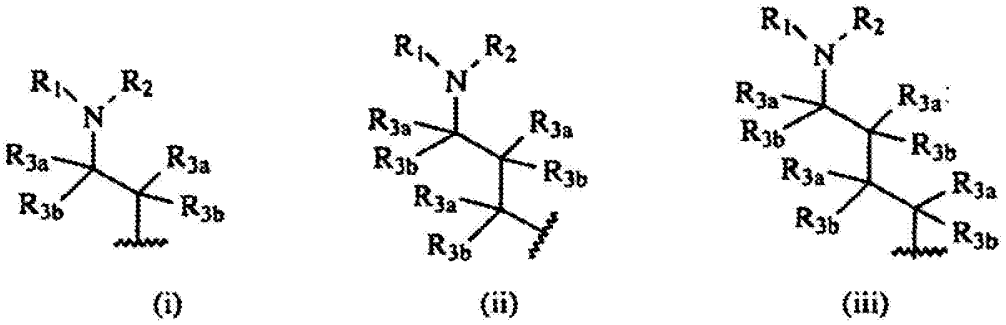
(VI)

Numa forma de realização mais específica da estrutura (VI), A é O, *n* é 2, e cada ocorrência de R_{3a} e R_{3b} é H, tal como representado pela seguinte estrutura (VII):



(VII)

No que respeita ao radical "$R_1R_2N(CR_{3a}R_{3b})_n$-" de estrutura (I), *n* pode ser 2, 3 ou 4. Assim, este radical pode ser representado pela seguinte estrutura (i) quando *n* é 2, pela estrutura (ii) quando n é 3, e pela estrutura (iii) quando n é 3:

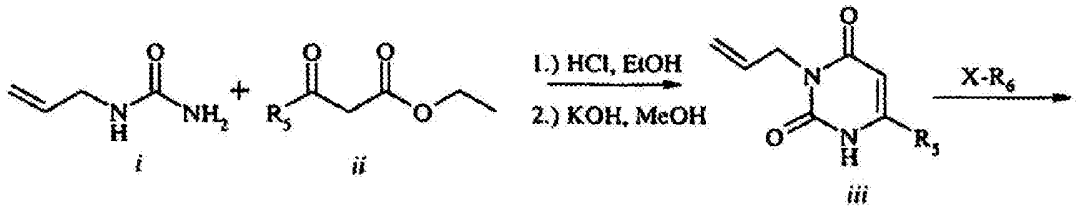


(i) (ii) (iii)

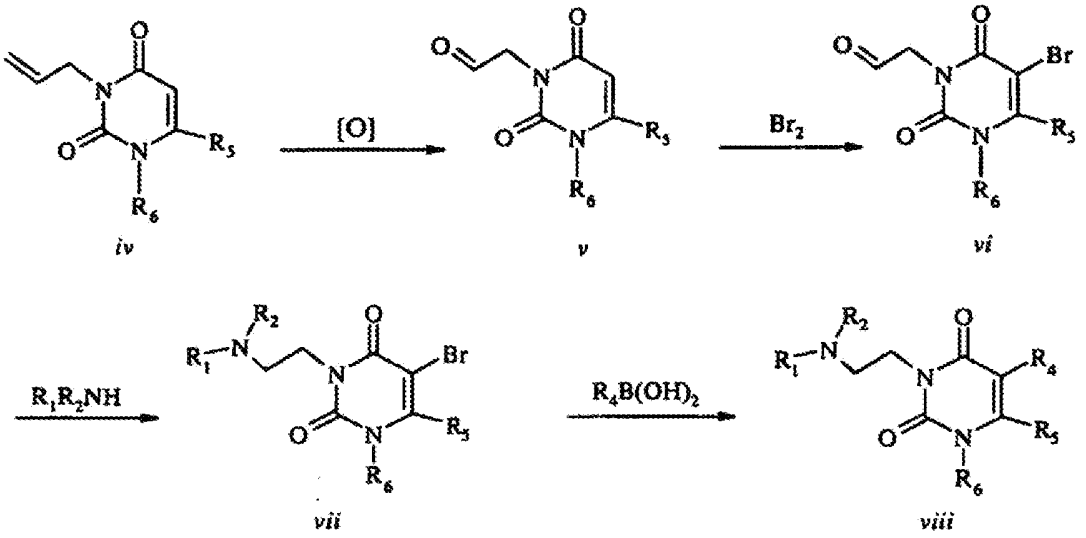
em que cada ocorrência de R_{3a} e R_{3b} acima pode ser a mesma ou diferente, e são como definidas acima. Por exemplo, quando cada ocorrência de R_{3a} e R_{3b} nas estruturas (i), (ii) e (iii) é hidrogénio, o radical "$R_1R_2N(CR_{3a}R_{3b})_n$-" tem a estrutura $R_1R_2N(CH_2)_2$-, $R_1R_2N(CH_2)_3$- e $R_1R_2N(CH_2)_4$-, respectivamente.

Os compostos da presente invenção podem ser preparados por técnicas conhecidas de síntese orgânica, incluindo os métodos descritos em mais pormenor nos Exemplos. No entanto, em geral, os compostos de estrutura (I) acima podem ser feitos pelos seguintes Esquemas de Reacção. Especificamente, os compostos de estrutura (I) em que A é oxigénio podem ser feitos pelos Esquemas de Reacção A a E. Os Esquemas de Reacção F a K são adequados para os compostos de estrutura (I) em que A é enxofre ou NR_7, bem como A é oxigénio. O Esquema de Reacção L mostra as condições para a conversão de tiouracilose (em que A é enzofre) em formas de realização em que A é NR_7. Todos os substituintes nos seguintes Esquemas de Reacção são como definidos acima, a menos que indicado em contrário.

Esquema de Reacção A



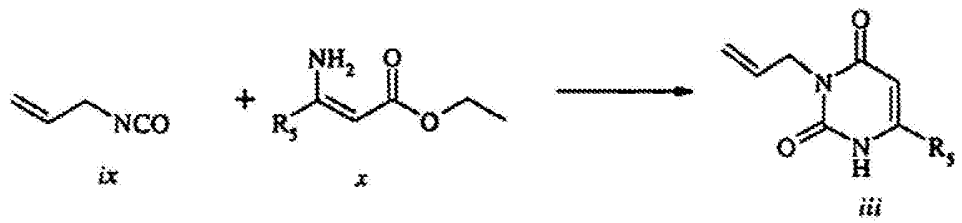
i *ii* *iii*



Alilureia (i) e acetoacetato substituído (ii) são condensados sob condições ácidas num solvente tal como etanol ou DMF a 25 a 100°C e, em seguida, ciclizados em condições fortemente básicas para dar 3-alil-2,4-pirimidinadiona (iii) substituída. O composto (iii) pode então ser modificado por alquilação com um halogeneto de alquilo apropriado (em que X é halogéneo) num solvente tal como DMF ou etanol durante 1 hora a 2 dias, na presença de uma base tal como hidreto de sódio ou fluoreto de tetrabutilamónio para dar (iv). A oxidação da funcionalidade alilo, utilizando tetróxido de ósmio e/ou periodato de sódio num solvente tal como THF e/ou água durante 1-24 horas, dá o aldeído (V). Bromação de (v) usando bromo ou N-bromossuccinimida num solvente tal como ácido acético ou clorofórmio durante 1-24 horas resultou no composto bromado (vi). A aminação redutiva de (VI) com uma amina apropriada utilizando um agente redutor tal como triacetoxiboro-hidreto de sódio num solvente tal como dicloroetano, a 0 até 100°C durante 1-24 horas dá (vii), que quando acoplado com um ácido borónico apropriado num solvente tal como o etanol ou tolueno a 25 a 150°C durante 1-24 horas, na presença de um catalisador de Pd(0) dá (viii).

Os dois últimos passos da síntese acima podem também ser invertidos, sendo, nesse caso, o acoplamento de Suzuki a penúltima etapa e aminação redutora o passo final. Alternativamente, o composto (iii) pode ser sintetizado pelo procedimento do Exemplo 2.

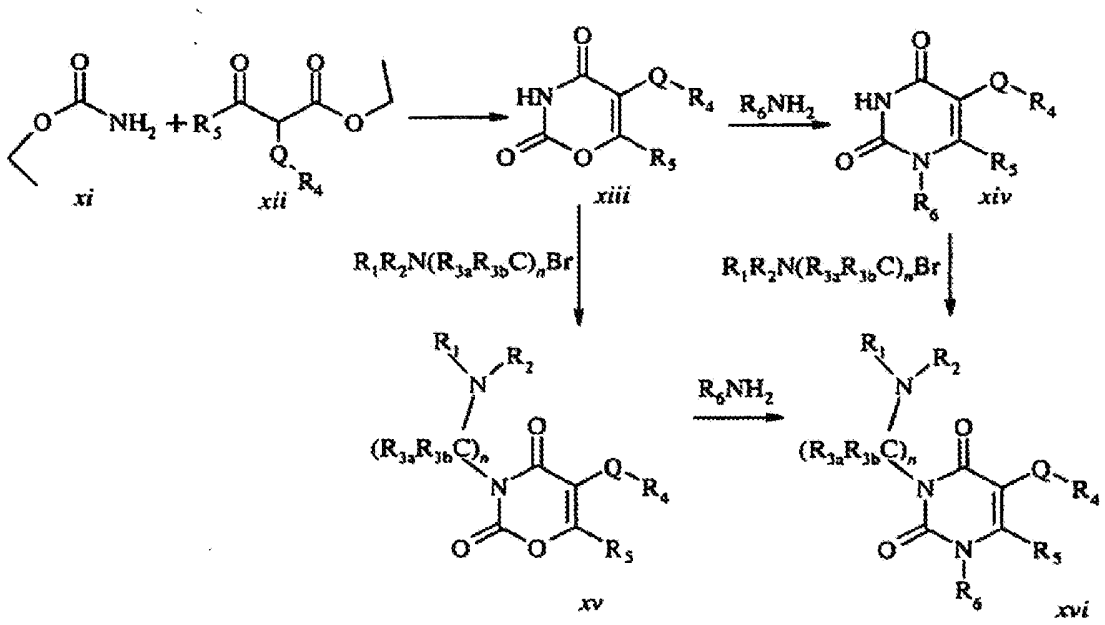
Esquema de Reacção B



ix *x* *iii*

O composto (iii) do Esquema de Reacção A1 também pode ser sintetizado por condensação e ciclização de isocianato de alilo (viii) e éster do aminoalceno apropriado (ix), tal como 3-aminocrotonato de etilo num solvente tal como tolueno ou DMF a 25 a 100°C durante 1-24 horas.

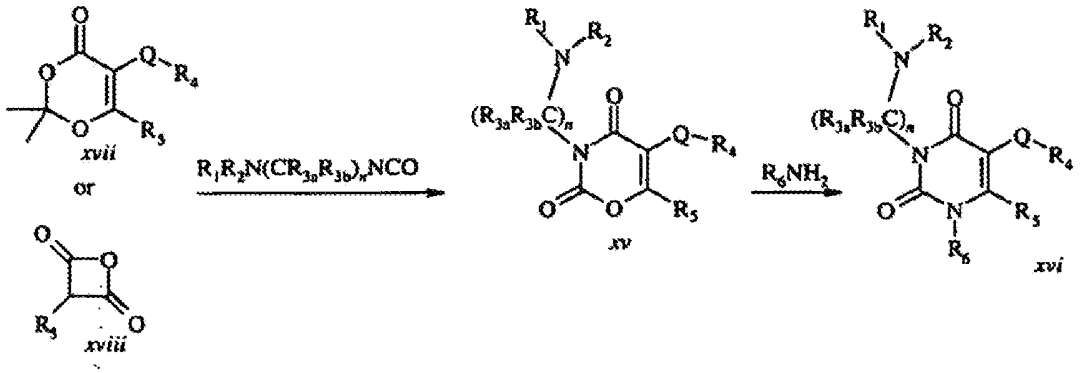
Esquema de Reacção C



xi *xii* *xiii* *xiv* *xv* *xvi*

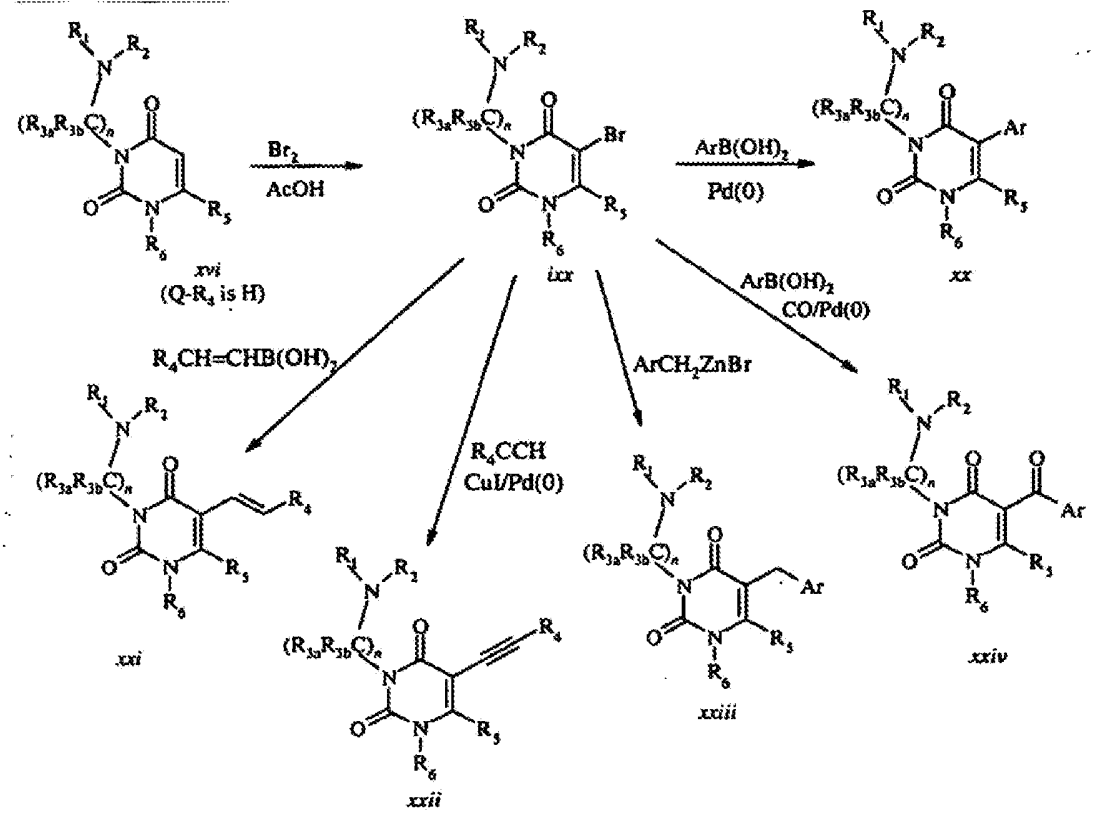
A ciclização de (XI) e (xii) num solvente tal como etanol ou DMF a 25 a 150° C, durante 1 a 24 horas, dá oxazina (xiii). A aminação de (xiii) num solvente, tal como DMF ou etanol a 25 a 150 °C durante 1-24 horas rendeu derivado de uracilo (xiv). A alquilação de (xiv) por um brometo de alquilo apropriado, na presença de uma base tal como hidreto de sódio ou hidróxido de sódio, num solvente tal como THF ou DMF, a 0 até 100°C durante 1-24 horas dá uracilo substituído (xvi). A ordem do esquema de reacção pode ser alterada permitindo que a oxazina (xiii) seja alquilada primeiro, sob as condições acima referidas, para (xv), seguindo-se a aminação para o produto (xvi).

Esquema de Reacção D



O composto (XVII) ou (XVIII) reage com um isocianato apropriadamente substituído, num solvente tal como tolueno ou clorofórmio, à temperatura ambiente a 100° C durante 1-24 horas, como uma síntese alternativa para oxazina intermédia (xv). A aminação com uma amina substituída num solvente tal como DMF ou etanol, a uma temperatura de 25 a 100° C durante um período de 1-24 horas, resulta num produto uracilo (xvi).

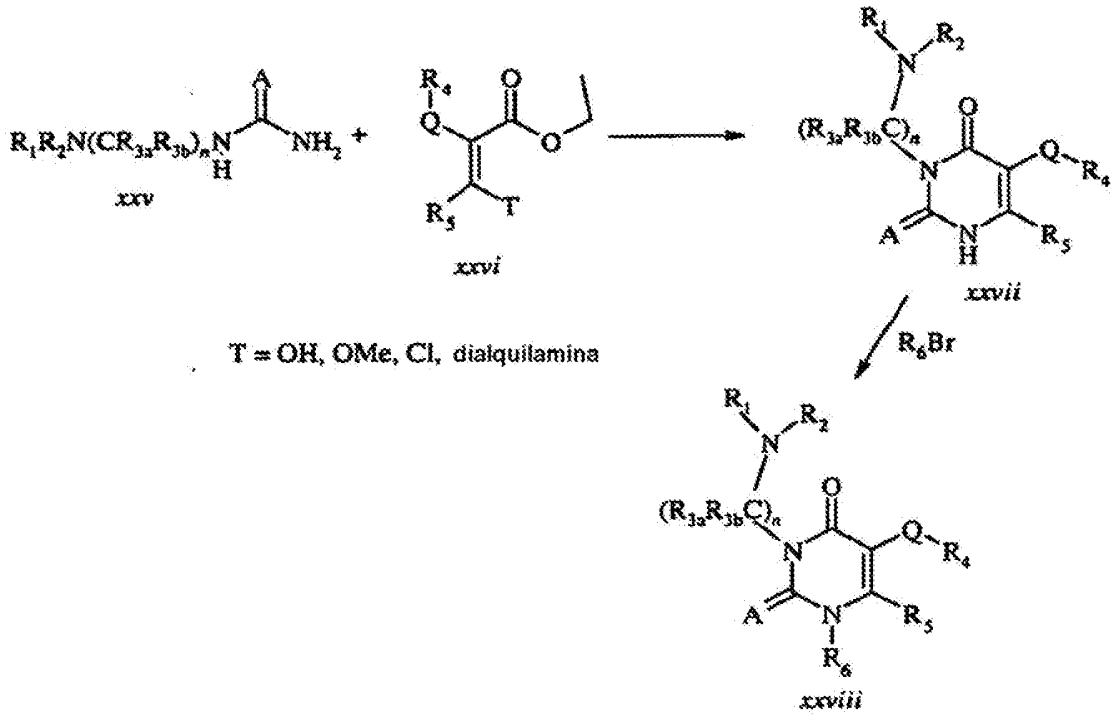
Esquema de Reacção E



O intermediário (xvi) pode ser bromado utilizando um agente de bromação tal como N-bromossuccinimida ou bromo num solvente tal como ácido acético ou o clorofórmio, a 0 até 100°C durante um período de 1-24 horas para produzir o composto bromo (IXX). O composto de bromo pode ser submetido a várias reacções de acoplamento cruzado catalisadas por paládio. Pode fazer-se reagir o composto (IXX) tomado no solvente, tal como etanol ou THF sob atmosfera de azoto usando um catalisador Pd(0) apropriado, tal como tetraquis (trifenilfosfina)Pd(0), durante 1-24 horas a 25 até 150°C, quer com ácido borónico arilo ($ARB(OH)_2$, em que Ar é arilo ou heteroarilo substituído), para dar o produto (xx), ou com um ácido vinil borónico substituido para dar o composto (XXI). O composto (IXX) tomado no solvente tal como etanol ou THF usando um catalisador Pd(0) apropriado, na presença de

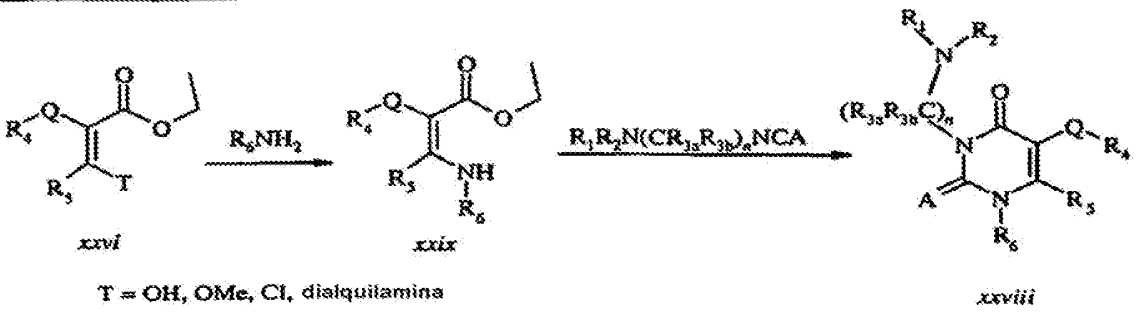
monóxido de carbono e ácido borónico produz (XXIV) após 1-24 horas a 0 a 150°C. Mais uma vez, utilizando a química de Pd(0), o composto (XXIII) é sintetizado num solvente tal como THF ou dioxano a partir da alquilação de (IXX) com um reagente de haleto de metal apropriado durante 1-24 horas a 0 até 150°C. O composto (IXX) na presença de um acetileno substituído, do catalisador de Pd(0), de haleto de metal tal como CuI, e uma base tal como trietilamina, num solvente apropriado, tal como acetonitrilo ou DMF a 25 a 150°C durante 1-24 horas dá alcino (xxii). O uracilo de alcinilo (XXII) pode ser selectivamente reduzido para o alceno usando um catalisador tal como paládio/$BaSO_4$ sob atmosfera de hidrogénio, num solvente tal como acetato de etilo ou metanol para dar (XXI).

Esquema de Reacção F



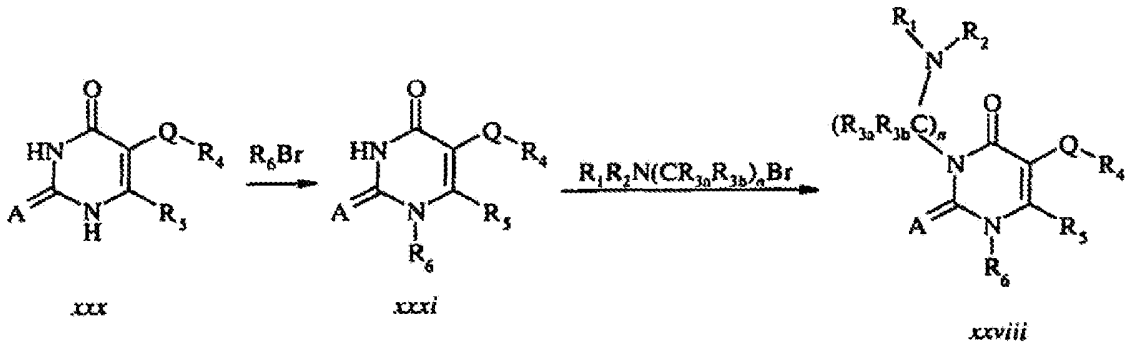
Éster de vinilo (xxvi) e (XXV) pode ser ciclizado num solvente tal como DMF ou EtOH a 25 a 150°C durante 1-24 horas, para dar (XXVII). A alquilação de (XXVII) com um halogeneto de alquilo ou arilo apropriado, num solvente tal como DMF ou THF na presença de uma base tal como hidreto de sódio ou hidróxido de sódio, durante 1-24 horas de 0 a 150°C, dá (XXVIII).

Esquema de Reacção G



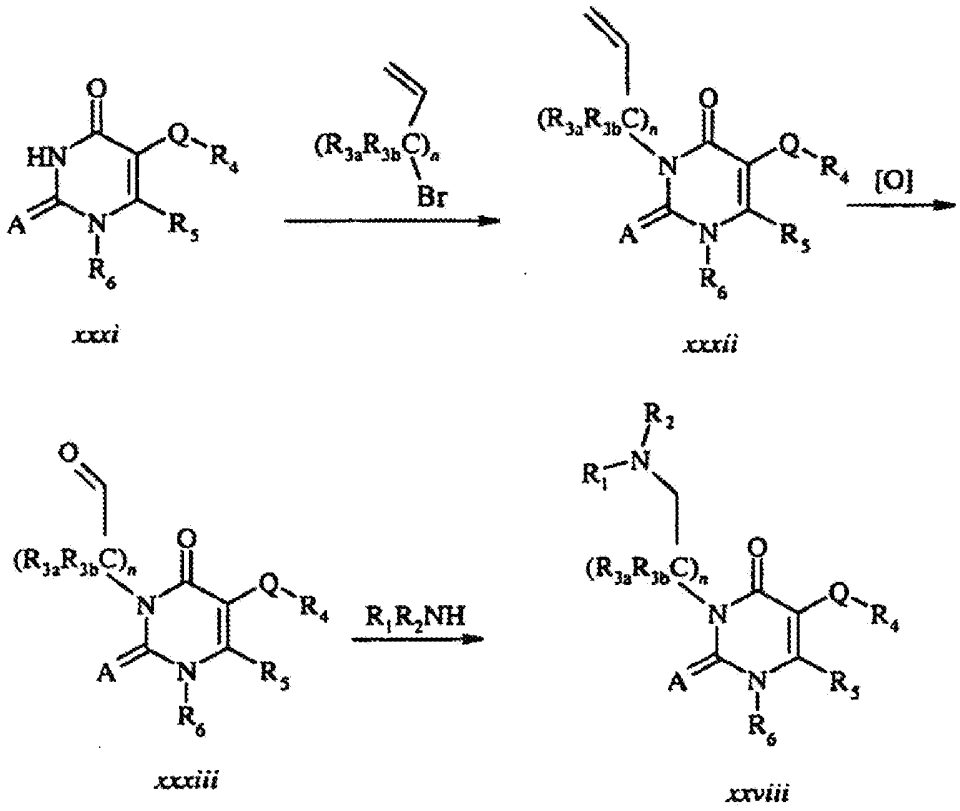
Éster de vinilo (*XXVI*) pode ser condensado com uma amina substituída num solvente tal como DMF ou etanol a 25 até 150 °C durante 1-24 horas para dar (*XXIX*). A ciclização de (*XXIX*) com um isocianato, isotiocianato, ou outro composto apropriado num solvente tal como DMF, THF ou dioxano, com ou sem uma base tal como etóxido de sódio ou hidreto de sódio a 0 até 100 °C, durante 1-24 horas, dá o produto (XXVIII).

Esquema de Reacção H



O composto (*XXX*) pode ser alquilado por um halogeneto de alquilo apropriado na presença de uma base tal como hidreto de sódio ou hidróxido de sódio, num solvente tal como THF ou DMF a 0 a 50 °C durante 1-24 horas, para dar (*XXXI*), que sob alquilação adicional por um segundo halogeneto de alquilo dá o produto (*XXVIII*).

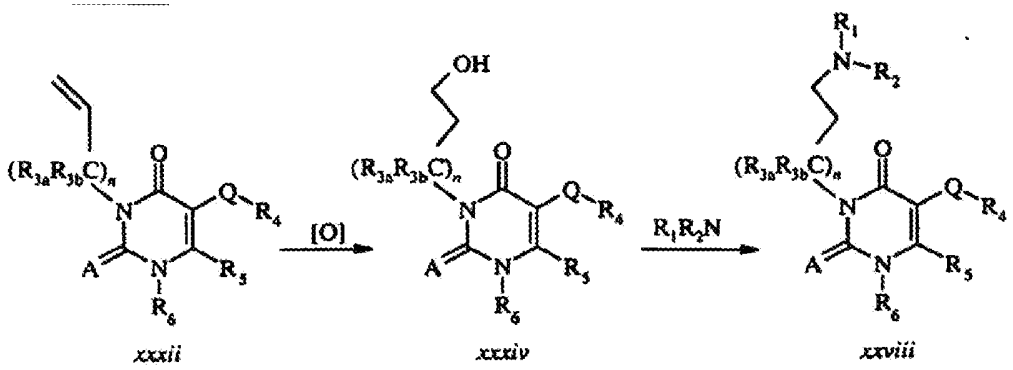
Esquema de Reacção I



O composto (*XXXI*) pode ser alquilado por um halogeneto de alquilo apropriado na presença de uma base tal como hidreto de sódio ou hidróxido de sódio, num solvente tal como THF ou DMF a 0 a 100°C durante 1-24 horas, para dar (*XXXII*). A ligação dupla terminal é oxidada usando um reagente de oxidação apropriado tal como tetróxido de ósmio ou periodato de sódio num solvente tal como THF e/ou água durante 1-24 horas de 0 a 100 °C para dar o aldeído (*XXXIII*). A aminação redutiva de

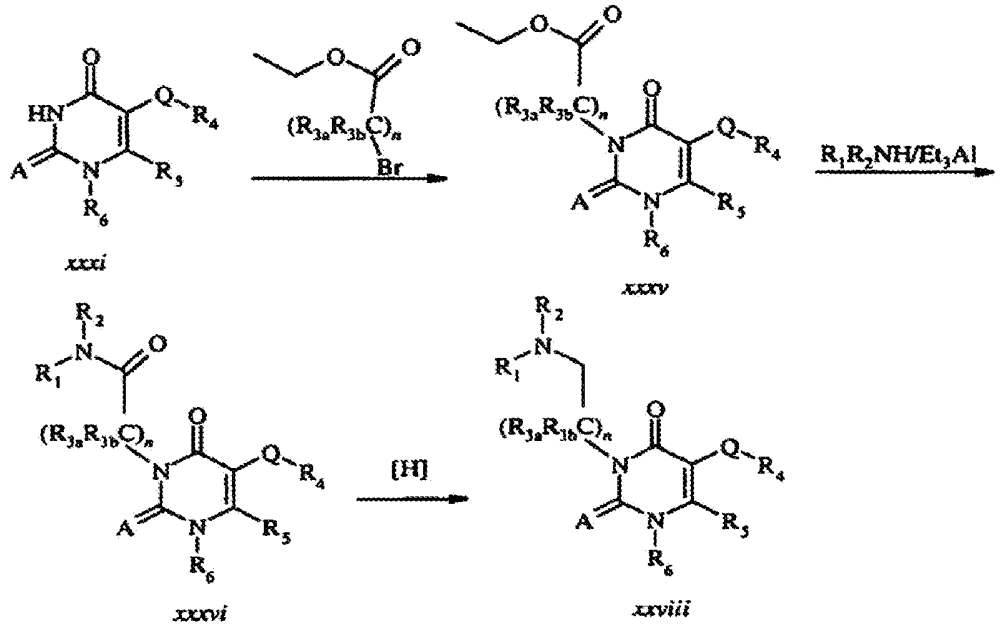
(*XXXIII*) com uma amina apropriada utilizando um agente redutor, tal como cianoboro-hidreto de sódio, num solvente tal como dicloroetano ou acetonitrilo a 0 até 100 °C, durante 1-24 horas, dá (*XXVIII*).

Esquema de Reacção J



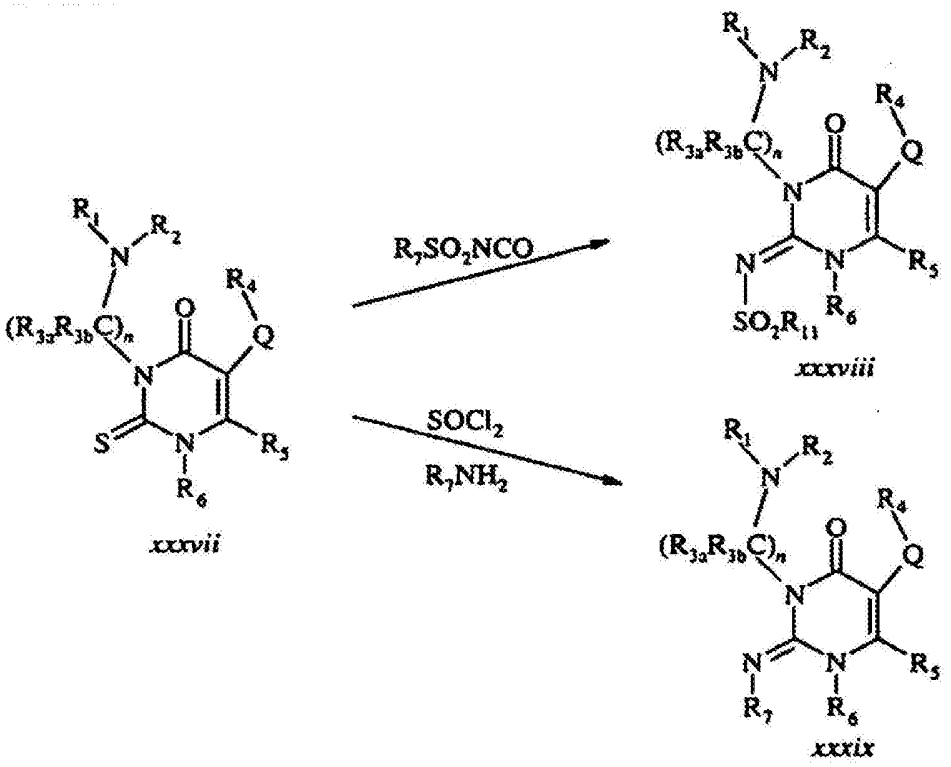
O composto (XXXII) pode ser oxidado para o álcool (*XXXIV*) primeiro por hidroboração com um complexo de borano num solvente tal como THF, seguido por oxidação com ozono ou peróxido de hidrogénio num solvente tal como metanol, etanol e/ou água a -25 para 100 °C, durante um período de 0,5-24 horas. O tratamento de (*XXXIV*) com cloreto de mesilo ou de tosilo em cloreto de metileno, com uma base tal como trietilamina ou piridina, a 0 até 100 °C durante 1-24 horas, seguida por reacção com uma amina num solvente tal como DMF ou tolueno, durante 0,5-12 horas a 25 a 100 °C dá (*XXVIII*).

Esquema de Reacção K



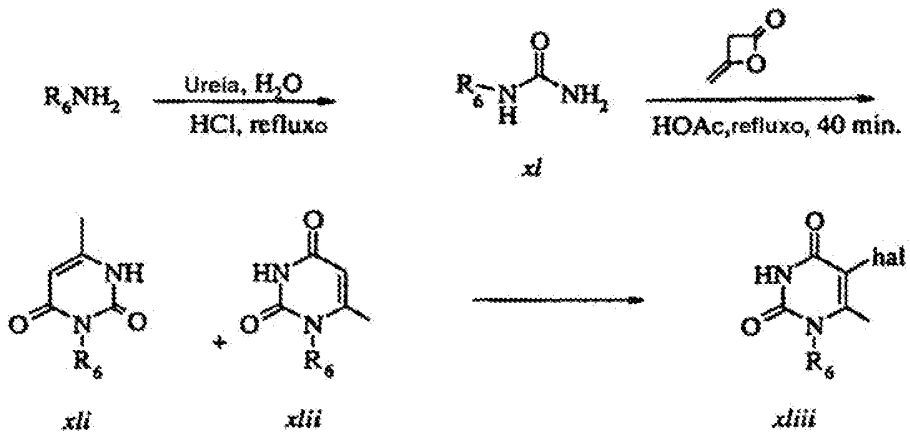
O composto (XXXI) pode ser alquilado com um éster apropriado num solvente tal como DMF ou etanol, na presença de uma base tal como hidreto de sódio ou etóxido de sódio, a uma temperatura de 25 a 150°C por um período de 1-24 horas, para dar (*XXXV*). O éster (*XXXV*) num solvente tal como clorofórmio ou benzeno com amina substituida e ácido de Lewis tal como trietilalumínio dá amida (*XXXVI*) após 1-24 horas de 0 a 100 °C. A redução de (*XXXVI*) com hidreto de alumínio e lítio ou complexo borano num solvente tal como THF ou éter a 0 a 100 °C durante 1-12 horas dá o produto (*XXVIII*).

Esquema de Reacção L



O composto tiouracilo (*XXXVII*) na presença de um sulfonilisocianato substituido no seio de um solvente tal como benzeno ou tolueno, por 1-48 horas de 25 a 125 °C dá sulfonamida (*XXXVIII*). Tiouracilo (*XXXVII*) clorado por cloreto de tionilo ou oxicloreto de fósforo a -25 a 100 °C, durante 1-24 horas, seguida por aminação com uma amina apropriada num solvente tal como benzeno ou tolueno, a 25 a 150 °C durante 1-24 horas, dá o composto (xxxix).

Esquema de Reacção M

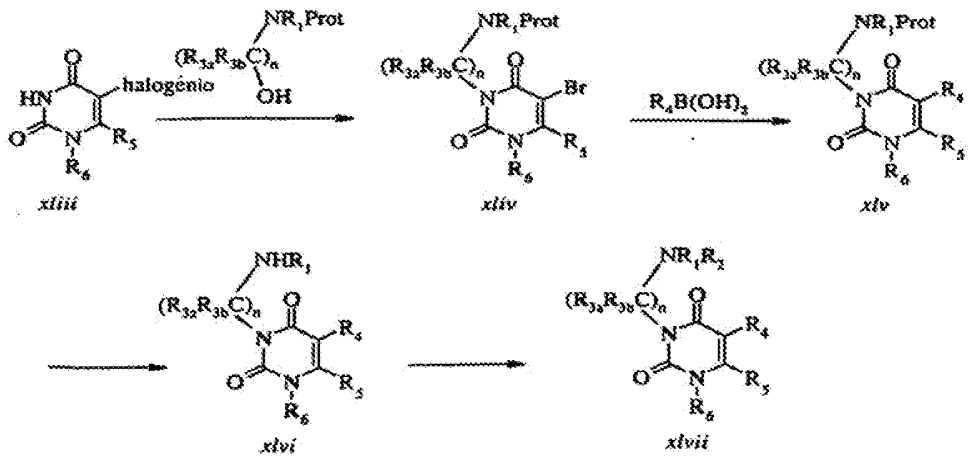


xl

xli xlii xliii

A amina substituida na presença de ureia ou tioureia é aquecida a uma temperatura de 50-125°C durante 0,5 a 12 horas para dar (xl). A ciclização de (xl) com diceteno em 50-150 °C em meios acídicos tais como ácido acético ou fórmico, durante 5 minutos a 4 horas, dá uma mistura de isómeros (xli) e (xlii). A halogenação de (xlii), utilizando um reagente de halogenação tal como N-halosuccinimida em clorofórmio ou bromo em ácido acético durante 5 minutos a 24 horas dá o produto halogenado (xliii).

Esquema de Reacção N

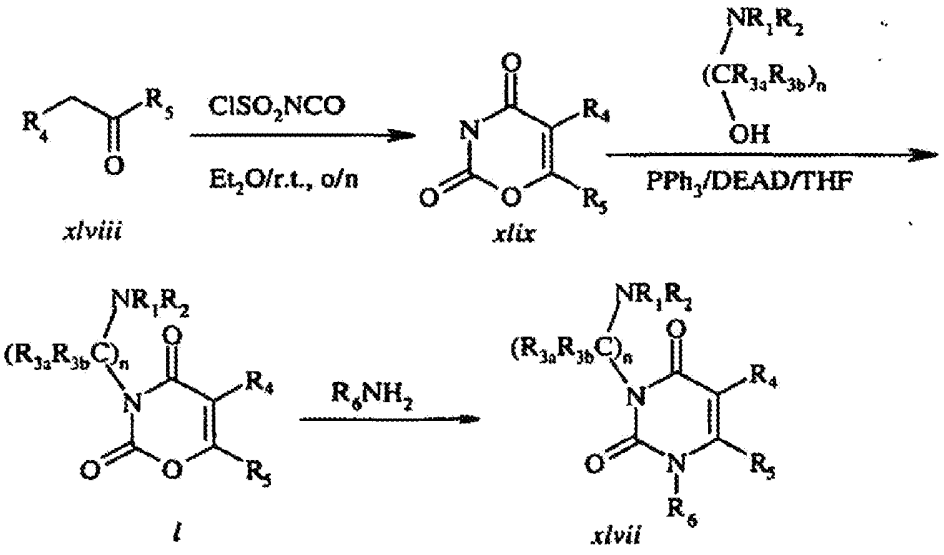


xliii xliv xlv

xlvi xlvii

O composto de uracilo (*xliii*) e um álcool adequadamente substituído são condensados sob condições de Mitsonobu, tais como axodicarboxilato de dietilo ou de dibutilo e trifenilfosfina num solvente tal como THF a 0 – 100 °C durante 0,5 a 10 horas para dar o composto (*xliv*). Um acoplamento de Suzuki de (*xliv*) e um ácido borónico ou éster de ácido borónico num solvente, tal como o etanol ou o tolueno a 25 a 150 °C durante 1-24 horas, na presença de um catalisador Pd(0) dá (*xlv*). A desprotecção da amina protegida dá (*xlvi*). A aminação redutiva de (*xlvi*) com um aldeído apropriado num solvente tal como cloreto de metileno ou acetonitrilo, utilizando um agente redutor tal como triacetoxiboro-hidreto de sódio ou boro-hidreto de sódio a 0 até 100 ° C durante 1-24 horas dá (*xlvii*).

Esquema de Reacção O



xlviii *xlix* *l* *xlvii*

Ceto ou aldeído *xlviii*, na presença de clorossulfonilisocianato ou clorocarbonilisocianato produz oxaz-2,4-diona *xlix* após agitação durante 1-24 horas a 0 °C a 75 °C, num solvente tal como THF ou éter. A condensação de Mitsonobu com um álcool apropriado dá *I* o qual, quando na

presença de amina R_6NH_2, à temperatura ambiente a 125 °C, com ou sem solvente tal como DMF ou um catalisador tal como ácido acético ou clorídrico, durante 1/2 a 24 horas, dá *xlvii*.

Os compostos da presente invenção podem geralmente ser utilizados como o ácido livre ou base livre. Alternativamente, os compostos da presente invenção podem ser utilizados sob a forma de sais de adição de ácidos ou de bases. Sais de adição de ácidos dos compostos amino livres da presente invenção podem ser preparados por métodos bem conhecidos na arte, e podem ser formados a partir de ácidos orgânicos e inorgânicos. Ácidos orgânicos adequados incluem os ácidos maleico, fumárico, benzóico, ascórbico, succínico, metanossulfónico, acético, trifluoroacético, oxálico, propiónico, tartárico, salicílico, cítrico, glucónico, láctico, mandélico, cinâmico, aspártico, esteárico, palmítico, glicólico, glutâmico, e benzenossulfónico. Ácidos inorgânicos adequados incluem ácido clorídrico, bromídrico, sulfúrico, fosfórico, e nítrico. Sais de adição de base incluídos os sais que formam com o anião carboxilato e incluem sais formados com catiões orgânicos e inorgânicos tais como os escolhidos de entre os metais alcalinos e alcalino-terrosos (por exemplo, lítio, sódio, potássio, magnésio, bário e cálcio), como bem como o ião amónio e seus derivados substituídos (por exemplo, dibenzilamónio, benzilamónio, 2-hidroxietilamónio). Assim, o termo "sal farmaceuticamente aceitável" de estrutura (I) destina-se a englobar qualquer e todas as formas de sal aceitáveis.

Além disso, os pró-fármacos também estão incluídos no âmbito da presente invenção. Os pró-fármacos são quaisquer transportadores ligados covalentemente que libertam um composto de estrutura (I) *in vivo* quando tal pró-fármaco é administrado a um paciente. Os pró-fármacos são geralmente preparados por modificação dos grupos funcionais de tal modo

que a modificação é clivada, quer por manipulação de rotina ou *in vivo*, produzindo o composto principal. Os pró-fármacos incluem, por exemplo, os compostos da presente invenção nos quais grupos hidroxi, amina ou sulfidrilo estão ligados a qualquer grupo que, quando administrado a um paciente, cliva para formar os grupos hidroxi, amina ou sulfidrilo. Assim, exemplos representativos de pró-fármacos incluem (mas não estão limitados a) derivados acetato, formato e benzoato de álcool e grupos amina funcionais dos compostos de estrutura (I). Além disso, no caso de um ácido carboxílico (-COOH), podem ser utilizados ésteres, tais como ésteres metílicos e ésteres etílicos.

No que respeita aos estereoisómeros, os compostos de estrutura (I) podem ter centros quirais e podem ocorrer como racematos, misturas racémicas e como enantiómeros individuais ou diastereómeros. Todas as formas isoméricas estão incluídas na presente invenção, incluindo as suas misturas. Os compostos de estrutura (I) podem também possuir quiralidade axial que pode resultar em atropisómeros. Além disso, algumas das formas cristalinas dos compostos de estrutura (I) podem existir como polimorfos, que estão incluídas na presente invenção. Além disso, alguns dos compostos de estrutura (I) podem também formar solvatos com água ou outros solventes orgânicos. Tais solvatos estão igualmente incluídos dentro do âmbito da presente invenção.

A eficácia de um composto como um antagonista do receptor de GnRH pode ser determinada por vários métodos de ensaio. Antagonistas adequados de GnRH da presente invenção são capazes de inibir a ligação específica de GnRH ao seu receptor e antagonizar as actividades associadas com a GnRH. Por exemplo, a inibição da libertação de LH estimulada pela GnRH, em ratos imaturos, podem ser medida de acordo com o método de Vilchez-Martinez (Endocrinology 96:1130-1134, 1975).

Resumidamente, ratos Spraque Dawley, machos, com 25 dias de idade, são administrados com um antagonista de GnRH em solução salina ou outro formulação adequada, por gavagem oral, injecção sub-cutânea ou intravenosa. Isto é seguido por injecção sub-cutânea de 200 ng de GnRH em 0,2 ml de solução salina. Trinta minutos após a última injecção, os animais são decapitados e o sangue do tronco recolhido. Após centrifugação, o plasma separado é armazenado a -20 °C até à determinação da LH e FSH por radioimunoensaio. Outras técnicas para a determinação da actividade dos antagonistas do receptor do GnRH são bem conhecidas no campo, tais como a utilização de culturas de células de pituitária para a medição da actividade do GnRH (Vale et al., Endocrinology 91:562-572, 1972), e uma técnica para medir a ligação do radioligando às membranas pituitárias do rato (Perrin et al., Mol. Pharmacol. 23:44-51, 1983).

Por exemplo, a eficácia de um composto como um antagonista do receptor do GnRH podem ser determinadas por um ou mais dos seguintes ensaios.

Ensaio de Cultura da Células Pituitárias Anteriores de Rato de Antagonistas de GnRH

As glândulas pituitárias anteriores são colectadas a partir de ratos Sprague Dawley fêmeas com 7 semanas de idade e as glândulas colhidas são digeridas com colagenase num balão de dispersão durante 1,5 hr a 37 °C. Após a digestão com colagenase, as glândulas são ainda digeridas com neuraminidase durante 9 min a 37 °C. O tecido digerido é então lavado com BSA 0,1%/meio McCoy's 5A, e as células lavadas suspensas em FBS 3%/BSA 0,1%/meio McCoy's 5A e plaqueadas em placas de 96 poços de cultura de tecidos a uma densidade celular de 40 000 células por poço em 200 µl de meio. As células são então incubadas a 37°C durante 3 dias. Uma glândula pituitária

normalmente dá para uma placa de 96 poços de células, que pode ser utilizada para ensaiar três compostos. Para o ensaio de um antagonista de GnRH, as células incubadas são primeiro lavadas uma vez com BSA 0,1%/ meio McCoy's 5A, seguido pela adição da amostra de ensaio mais GnRH 1nM em 200 µl BSA 0,1%/meio McCoy's 5A em poços em triplicado. Cada amostra é ensaiada em 5 níveis de dose para gerar uma curva de dose-resposta para a determinação da sua potência na inibição da libertação de FSH e/ou LH estimuladas pelo GnRH. Após 4 hr de incubação a 37°C, o meio é recolhido e o nível de LH e/ou FSH segregada para o meio determinado por RIA.

RIA de LH e FSH

Para a determinação dos níveis de LH, cada meio de amostra é ensaiado em duplicado e todas as diluições são feitas com tampão RIA (tampão fosfato de sódio 0,01M /NaCl 0,15M/BSA 1%/NaN3 0,01%, pH 7.5) e o kit de ensaio é obtido a partir do Nation Hormone and Pituitary Program suportado pelo NIDDK. Para um tubo de ensaio de polietileno de 12x75 milímetros é adicionado 100 µl da amostra do meio diluído a 1:5 ou padrão rLH em Tampão RIA e 100 µl de RLH marcado com [125I], (~30,000 cpm), mais 100 µl de anticorpo de coelho antirLH diluído a 1:187,500 e 100 µl de tampão RIA. A mistura é incubada à temperatura ambiente durante a noite. No dia seguinte, 100 µl de IgG de cabra anti-coelho diluída a 1:20 e 100 µl de soro normal de coelho diluido 1:1000 são adicionados e a mistura foi incubada por mais 3h à temperatura ambiente. Os tubos incubados são então centrifugados a 3000 rpm durante 30 min e o sobrenadante foi removido por sucção. O pellet restante nos tubos é contado num contador gama. A RIA da FSH é feita de uma forma semelhante ao ensaio para LH com substituição do

anticorpo LH pelo anticorpo FSH diluído a 1:30,000, e a RLH marcada pela rFSH rotulada.

Radio-iodação do Péptido de GnRH

O análogo de GnRH é marcado pelo método de cloramina-T. A 10 µg de péptido em 20 µl de tampão fosfato de sódio 0,5M, pH 7,6, é adicionado 1 mCi de Nal25I, seguido por 22,5 µg de cloramina-T e a mistura agitada em vórtex durante 20 segundos. A reacção é parada pela adição de 60 µg de metabissulfito de sódio e o iodo livre é removido por passagem da mistura iodinada através de um cartucho Sep-Pak C-8 (Millipore Corp, Milord, MA). O péptido é eluído com um pequeno volume de acetonitrilo 80%/água. O péptido marcado recuperado é ainda purificado por HPLC de fase reversa sobre uma coluna analítica Vydac C-18 (The Separations Group, Hesperia, CA) num sistema Beckman de HPLC de gradiente 334 utilizando um gradiente de acetonitrilo em TFA 0,1%. O péptido radioactivo purificado é armazenado em BSA 0,1%/acetonitrilo 20%/ TFA 0,1% a -80°C e pode ser usado até 4 semanas.

Ensaio de ligação da membrana do receptor de GnRH

São colhidas células transfectadas estável ou transitoriamente, com vectores de expressão de receptores de GnRH, ressuspensas em sacarose a 5% e homogeneizadas usando um homogeneizador politron (2x15 seg). Os núcleos são removidos por centrifugação (3000 x g durante 5 min.), e o sobrenadante centrifugado (20 000 x g durante 30 min, 4°C) para recolher a fracção da membrana. A preparação de membrana final é ressuspensa no tampão de ligação (10mm Hepes (pH 7.5), NaCl 150 mM, e BSA 0,1%) e armazenada a -70°C. As reacções de ligação são realizadas numa unidade de placa de filtração e uma MultiScreen Millipore de 96 poços com membranas GF/C revestidas com polietilenimina. A reacção é iniciada pela

adição de membranas (40 ug de proteína em 130 ul de tampão de ligação) para 50 ul de péptido de GnRH marcado com [^{125}I](~100 000 cpm), e 20 uL de competidor em concentrações variadas. A reacção é terminada após 90 minutos por aplicação de vácuo e lavagem (2X) com solução salina tamponada com fosfato. A radioactividade ligada é medida usando contagem de cintilação de 96-poços (Packard Topcount) ou através da remoção dos filtros da placa e da contagem gama directa. Os valores de K_i são calculados a partir dos dados de ligação de competição usando a regressão não-linear dos mínimos quadrados utilizando o pacote de software Prism (GraphPad Software).

A actividade dos antagonistas dos receptores de GnRH é tipicamente calculada a partir da IC_{50} o como a concentração de um composto necessária para deslocar 50% do ligando radiomarcado do receptor da GnRH, e é relatado como um valor calculado "k_i", através da seguinte equação:

$$K_i = \frac{IC_{50}}{1 + L / K_D}$$

Em que L = radioligando e K_D= afinidade do radioligando para o receptor (Cheng e Prusoff, Biochem. Pharmacol. 22: 3099, 1973). Antagonistas de receptores de GnRH da presente invenção têm um K_i de 100 μM ou menos. Numa forma de realização preferida da presente invenção, os antagonistas do receptor de GnRH têm um K_i inferior a 10 μM, e mais preferencialmente inferior a 1 μM, e ainda mais preferivelmente inferior a 0,1 μM (isto é, 100 nM). Para este fim, os antagonistas dos receptores de GnRH representativos da presente invenção, que têm um K_i inferior a 100 nM quando se utiliza o ensaio de ligação à membrana do receptor de GnRH, tal como descrito acima, incluem o seguinte Composto N°s

Tabela No.	Composto No.
1	3, 10, 11, 12, 13
3	1, 4
6	1, 2, 3, 8
7	2, 3, 4, 7, 9, 10, 11
8	2, 3, 4, 7, 12, 13, 14, 15, 16, 17, 19-21, 23, 25, 27-29, 31-36, 38-39, 42, 44, 51, 58, 59, 61, 63-66, 68, 70, 75, 77-97, 100, 106, 107, 109-113, 115-117, 124-135, 137-140
9	3, 4, 6, 7, 10, 14-16, 19, 24, 26, 32, 35, 37, 39, 40, 42, 46-49, 51-53, 55, 56, 58, 61, 63, 64, 66-68, 70, 72-78, 80-82, 85, 86, 89-93, 95, 96, 98-102, 107, 109, 110, 112, 138, 140, 142, 143, 145, 146, 149, 151- 155, 157-162, 164, 166-168, 170-176, 178-188, 191, 194-197, 199, 200, 202-207, 210-212, 214, 215, 219, 224, 225, 227, 229, 232-234, 237, 240, 242, 244, 245, 247, 249, 251-256, 258-261, 263, 265-267, 270, 275, 277-279, 281, 286, 287, 295-301, 304, 305, 307-309, 312, 318, 320, 321, 325-329, 331-336, 338-346, 348-355, 357-359, 361, 362, 364-385, 387-397, 399, 402, 406, 409, 410, 413, 415, 417, 419 424, 427-434, 437-439, 441, 443, 446, 448, 454, 455, 470, 473, 477, 480-487, 490-493, 495, 502, 503, 509, 512, 514, 517, 519-524, 547-552, 554-560, 565-568, 570, 581-584, 589, 595, 596, 602, 606-609, 612, 613, 618, 621, 622, 624-627, 634, 636, 642-648, 652, 653, 655-658, 660-662, 664, 665, 668-672, 677, 678, 680, 681, 688, 694, 696, 698-702, 704, 706-708,

	711, 712, 714, 718-726, 729-741, 745, 747-750, 755-756, 759-763, 774
10	1, 10, 14, 21-23, 25, 52, 54-56, 60, 61, 64, 65
12	1, 4, 5, 10, 20-22, 24, 27, 32
13	2, 4
15	1, 2

Como mencionado acima, os antagonistas do receptor de GnRH da presente invenção têm utilidade sobre uma vasta gama de aplicações terapêuticas, e podem ser usados para tratar uma variedade de situações relacionadas com as hormonas sexuais, tanto nos homens como nas mulheres, bem como nos mamíferos em geral. Por exemplo, essas condições incluem a endometriose, miomas uterinos, síndrome dos ovários policísticos, hirsutismo, puberdade precoce, neoplasias dependentes do esteróide gonadal, tais como cancro da próstata, mama e ovário, adenomas gonadotróficos da pituitária, apneia do sono, síndrome do intestino irritável, síndrome pré-menstrual, hipertrofia prostática benigna, contracepção e infertilidade (por exemplo, a terapia da reprodução assistida, tais como a fertilização *in vitro*).

Os compostos da presente invenção também são úteis como um adjuvante para o tratamento da deficiência da hormona de crescimento e baixa estatura, e para o tratamento de lúpus eritematoso sistémico.

Além disso, os compostos são úteis em combinação com androgénios, estrogénios, progesteronas, e anti-estrogénios e antiprogestinas para o tratamento da endometriose, miomas e na contracepção, bem como em combinação com um inibidor da enzima conversora da angiotensina, um antagonista do receptor da angiotensina II, ou um inibidor da renina, para o tratamento de miomas uterinos. Os compostos podem também ser usados em

combinação com bisfosfonatos e outros agentes para o tratamento e/ou prevenção de perturbações do metabolismo do cálcio, fosfato e ósseo, e em combinação com estrogénios, progesteronas e/ou androgénios, para a prevenção ou tratamento da perda óssea ou sintomas hipogonadais como ondas de calor durante a terapia com um antagonista de GnRH.

Noutra forma de realização da invenção, são reveladas composições farmacêuticas que contêm um ou mais antagonistas do receptor de GnRH. Para efeitos de administração, os compostos da presente invenção podem ser formulados como composições farmacêuticas. As composições farmacêuticas da presente invenção compreendem um antagonista do receptor de GnRH da presente invenção e um veículo farmaceuticamente aceitável e/ou diluente. O antagonista do receptor da GnRH está presente na composição numa quantidade que é eficaz para tratar um distúrbio particular - isto é, numa quantidade suficiente para atingir a actividade do antagonista do receptor de GnRH, e de preferência com toxicidade aceitável para o paciente. Tipicamente, as composições farmacêuticas da presente invenção podem incluir um antagonista do receptor de GnRH numa quantidade de 0,1 mg a 250 mg por dose, dependendo da via de administração, e mais tipicamente de 1 mg a 60 mg. As concentrações e dosagens apropriadas podem ser facilmente determinadas por um perito no ramo.

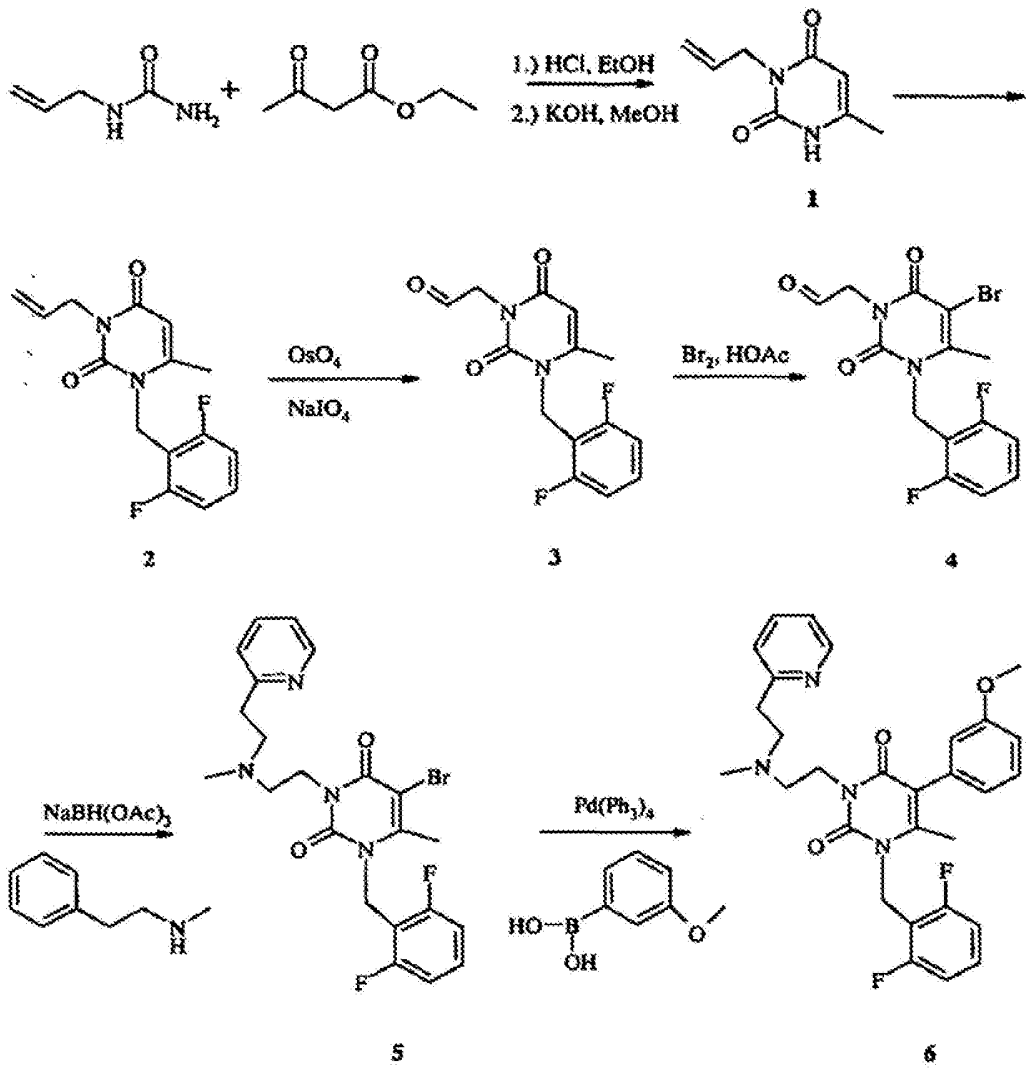
Um veículo e/ou diluentes farmaceuticamente aceitáveis são familiares para os peritos no ramo. Para composições formuladas como soluções líquidas, os veículos aceitáveis e/ou diluentes incluem solução salina e água esterilizada, e podem opcionalmente incluir antioxidantes, tampões, bacteriostatos e outros aditivos comuns. As composições podem também ser formuladas como pílulas, cápsulas, grânulos, ou comprimidos que contêm, para além de um antagonista do receptor de GnRH, diluentes, dispersantes e agentes tensoactivos, aglutinantes e

lubrificantes. Um perito neste ramo pode ainda formular o antagonista do receptor de GnRH de um modo adequado, e em conformidade, o uso de um composto ou de uma composição farmacêutica da presente invenção para a preparação de um medicamento para o tratamento de situações relacionadas com a hormona sexual, como discutido acima. Tais utilizações incluem a administração de um composto da presente invenção a um animal de sangue quente numa quantidade suficiente para tratar a situação. Neste contexto, "tratar" inclui a administração profilática. Tais utilizações incluem a administração sistémica de um antagonista do receptor de GnRH da presente invenção, de preferência sob a forma de uma composição farmacêutica, tal como discutido acima. Tal como aqui utilizado, a administração sistémica inclui métodos de administração oral e parentérica. Para a administração oral, composições farmacêuticas adequadas de antagonistas do receptor de GnRH incluem pós, grânulos, pílulas, comprimidos, e cápsulas, bem como líquidos, xaropes, suspensões, e emulsões. Estas composições também podem incluir aromatizantes, conservantes, agentes de suspensão, espessantes e emulsionantes e outros aditivos farmaceuticamente aceitáveis. Para a administração parentérica, os compostos da presente invenção podem ser preparados em soluções aquosas para injecção que podem conter, para além do antagonista do receptor de GnRH, tampões, antioxidantes, bacteriostatos, e outros aditivos vulgarmente utilizados em tais soluções.

O exemplo seguinte é fornecido para fins de ilustração. Em resumo, os antagonistas dos receptores de GnRH da presente invenção podem ser testados pelos métodos gerais divulgados acima, enquanto que os Exemplos que se seguem descrevem a síntese dos compostos representativos desta invenção.

EXEMPLO 1

Síntese de 1-(2,6-difluorobenzil)-5-(3-metoxifenil)-6-metil-3-[N-metil-N-(2-Piridiletil)aminoetil)uracilo



Passo 1A 3-Alil-6-metiluracilo

À alilureia (25g, 0,25 mol), em etanol (10 mL), foi adicionado de acetoacetato de etilo (31,86 mL, 0,25 mol) e 10 gotas de HCl conc. Após 12 dias à temperatura ambiente, a concentração da mistura deu um óleo que foi dissolvido em MeOH. Adicionou-se KOH (22,5g, 0,34 mol) e a solução deixada

em refluzo durante 1 hora. Após a neutralização, o sólido *1* resultante foi recolhido. Rendimento 2,7g (7%) .RMN($CDCl_3$)δ:2.16(3H,s), 4.52 (2H,d), 5.18(1H,d), 5.23(1H,d), 5.60 (1H,s), 5.82-5.93(1H,m), 10.3(1H,s).

Passo 1B 3-alil-1-(2,6-difluorobenzil)-6-metiluracilo

Ao sólido *1* (2,6 g, 15,7 mmol), em DMF (20 mL), foi adicionado fluoreto de tetrabutilamónio (25 mmol) e brometo de 2,6-difluorobenzilo (4,14 g, 20 mmol). Após 2 dias de agitação à temperatura ambiente, a cromatografia em coluna, utilizando acetato de etilo/hexano, deu 2,7 g (59% de rendimento) de 2. MS 293 $(MH)^+$.

Passo 1C 3-acetaldeído-1-(2,6-difluorobenzil)-6-metiluracilo

A uma solução de *2* (1,46 g, 5 mmol), em THF (20 mL) e H_2O (10 mL), foi adicionado tetróxido de ósmio (200 mg) e $NaIO_4$ (3,2 g, 15 mmol). Após 2 horas, foi adicionado mais 1g de $NaIO_4$. Foram adicionados acetato de etilo e H_2O e as camadas foram separadas. A evaporação da camada orgânica deu 3 como um sólido em bruto (1,0 g, 68%). MS 295 $(MH)^+$.

Passo 1D 3-Acetaldeído-5-bromo-1-(2,6-difluorobenzil)-6-metiluracilo

3 (294 mg, 1 mmol) foi dissolvido em ácido acético e foi adicionado bromo (1,2 equivalentes). A mistura de reacção foi agitada à temperatura ambiente durante 1 hora, evaporada e o resíduo foi dissolvido em EtOAc, lavada com uma solução de KOH 1N e concentrada para dar *4* como um óleo em bruto (295 mg, 79%). MS 373/375 $(MH)^+$. RMN ($CDCl_3$)δ:2.55 (3H,s), 4.87 (2H,d), 5.33 (2H,s), 7.26-7.33 (3H,2m), 9.59 (1h,d).

Passo 1E 5-bromo-1-(2,6-difluorobenzil)-6-metil-3-[N-metil-N-(2-piridiletil)aminoetil]uracilo

A *4* (295 mg, 0,8 mmol), em dicloroetano, foi adicionado 2-(metilaminoetil)piridina (200 mg, 1,5 mmol) e $NaBH(OAc)_3$ (636 mg, 3 mmol). Após agitação durante a noite, a mistura de reacção foi concentrada, dissolvida em EtOAc, lavada com H_2O, e purificada por TLC prep para dar 190 mg de 5 (48%).

Passo 1F 1-(2,6-Difluorobenzil)-5-(3-metoxifenil)-6-metil-3-[N-metil-N-(2-piridiletil)aminoetil]uracilo ("Comp. No.1")

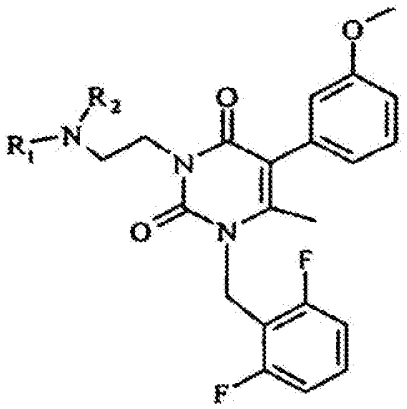
5 (150 mg, 0,3 mmol), ácido 3-metoxifenilborónico (92 mg, 0,6 mmol), K_2CO_3 (100 mg, 0,72 mmol), e $Pd(PPh_3)_4$ (20 mg) em H_2O (5 mL) e tolueno (10 mL) foi aquecida num tubo selado a 100°C durante 12 hr. A purificação por HPLC deu 40 mg de 6 ("Comp. No.1") como o sal de TFA (21% de rendimento). MS 521 $(MH)^+$RMN($CDCl_3$)δ:2.14(3H,s), 3.02(3H,s), 3.50(2H,m), 3.63 (2H,m), 3.71(2H,m), 3.81(3H,s), 4.37(2H,m), 5.25(2H,s), 6.81-6.83(2H,m), 6.88-6.95(3H,m), 7.28-7.34(2H, m), 7.63(1H,m), 7.89(1H,d), 8.13(1H,t), 8.62(1H, br s).

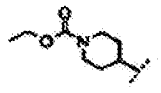
EXEMPLO 2

OS COMPOSTOS REPRESENTATIVOS

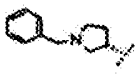
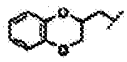
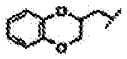
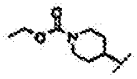
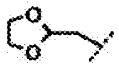
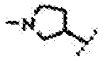
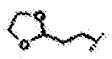
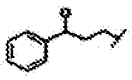
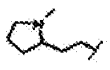
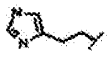
Seguindo os procedimentos como descrito no Exemplo 1 acima, foram preparados os compostos da Tabela 1 seguinte.

Tabela 1

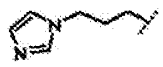
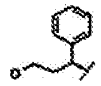
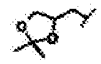
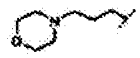
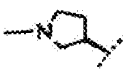
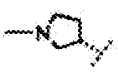
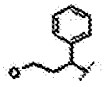


Comp. No.	R_1	R_2	MS (MH)$^+$
1-1	2-PyCH_2CH_2	H	507
1-2	2-PyCH_2	H	493
1-3	2-PyCH_2	Me	507
1-4	Bz	Me	506
1-5	PhCH_2CH_2	Me	520
1-6	2-PyCH_2CH_2	Pr	549
1-7	PhCHCH_3	Me	520
1-8	PhCHCH_3	Me	520
1-9	Bz	$(CH_3)_2N(CH_2)_2$	563
1-10	2-PyCH_2CH_2	Et	535
1-11	2-(6-Cl-Py)CH_2CH_2	Me	416,555
1-12	2-PyCH_2CH_2	CiclopropilCH_2	561
1-13	1-Et-3-pirrolidinil	Et	527
1-14		H	557
1-15		H	541
1-16	$(CH_3)_2CHOCH_2CH_2CH_2$	H	502
1-17	$Et_2NCH_2CH_2$	Me	515
1-18		H	513
1-19	$CH_3OCH_2CH_2CH_2$	H	474
1-20	$(EtO)_2CHCH_2CH_2$	H	532
1-21	$CH_3OCH_2CH_2$	Me	474
1-22		Me	575

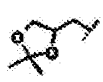
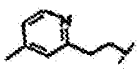
(continuação)

Comp. No.	R_1	R_2	MS $(MH)^+$
1-23		Me	575
1-24		H	550
1-25	$CH_3OCH_2CH_2CH_2$	Me	488
1-26	$(EtO)_2CHCH_2CH_2$	Me	546
1-27		Me	564
1-28		Me	571
1-29		Me	555
1-30	$(CH_3)_2CHOCH_2CH_2CH_2$	Me	516
1-31		Me	527
1-32		Me	513
1-33		Me	502
1-34	$Et_2NCH_2CH_2$	Me	487
1-35	$Me_2NCH_2CH_2CH_2$	Me	501
1-36	$Et_2NCH_2CH_2CH_2$	Me	529
1-37		Me	499
1-38	$EtOCH_2$	Me	474
1-39		Me	516
1-40		Me	550
1-41		H	513
1-42		H	496
1-43		H	529
1-44	$Me_2NCH_2CH_2CH_2$	H	487
1-45	$Et_2NCH_2CH_2CH_2$	H	515

(continuação)

Comp. No.	R_1	R_2	MS $(MH)^+$
1-46		H	510
1-47		H	541
1-48	$Me_2CHCH_2OCH_2CH_2CH_2$	H	516
1-49		H	502
1-50		H	471
1-51		H	471
1-52		H	536
1-53		H	516
1-54	$PyCH_2CH_2$	$HOCH_2CH_2$	551
1-55		Me	527
1-56		Me	510
1-57		Me	543
1-58	$Me_2CHN(Me)CH_2CH_2CH_2$	Me	529
1-59		Me	524
1-60		Me	555
1-61	$Me_2CHCH_2OCH_2CH_2CH_2$	Me	530
1-62	$BuOCH_2CH_2CH_2$	Me	530
1-63		Me	499
1-64		Me	499
1-65		Me	550

(continuação)

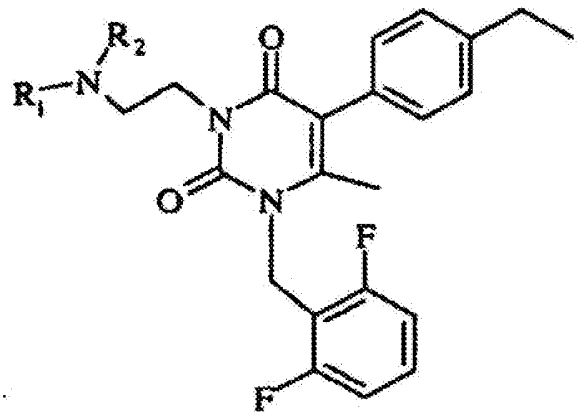
Comp. No.	R_1	R_2	MS $(MH)^+$
1-66		Me	530
1-67	$PhCH_2CH_2CH_2$	H	506
1-68		Me	535

EXEMPLOS 3

OUTROS COMPOSTOS REPRESENTATIVOS

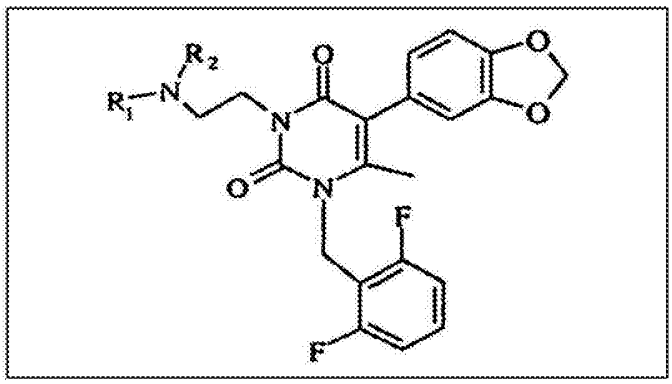
Ao inverter o Passo 1E e o Passo 1F no Exemplo 1, em que o acoplamento de ácido borónico é realizado seguido pela aminação redutiva, foram também preparados nos compostos das tabelas seguintes 2-7.

Tabela 2



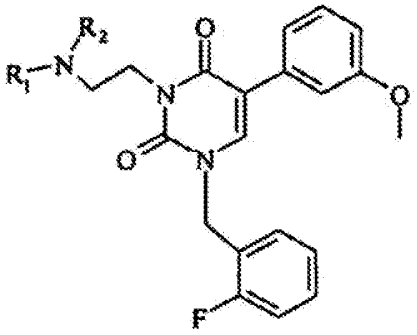
Comp. No.	R_1	R_2	MS $(MH)^+$
2-1	$2\text{-}PyCH_2CH_2$	Me	519
2-2	Bz	Me	504
2-3	$2\text{-}PyCH_2$	H	491
2-4	$2\text{-}PyCH_2CH_2$	H	505
2-5	$PhCH_2CH_2$	Me	518

Tabela 3



Comp. No.	R_1	R_2	MS (MH)$^+$
3-1	2-PyCH_2CH_2	Me	535
3-2	PhCH_2CH_2	Me	534
3-3	4-PyCH_2CH_2	Me	535
3-4	2-PyCH_2CH_2	Et	549

Tabela 4



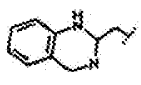
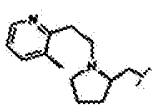
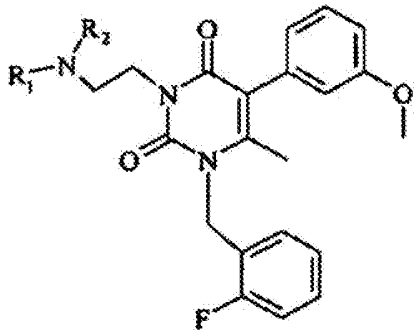
Comp. No.	R_1	R_2	MS (MH)$^+$
4-1	PhCH_2	Me	474
4-2	2-PyCH_2CH_2	Me	489
4-3			518
4-4			520
4-5			491
4-6			547

Tabela 5



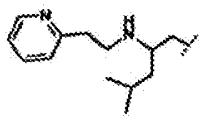
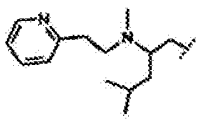
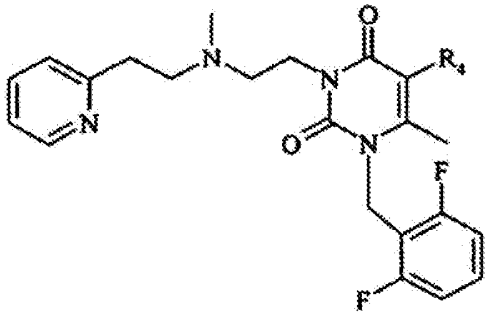
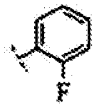
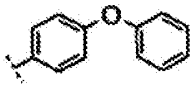
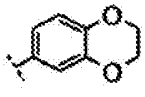
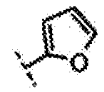
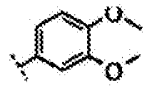
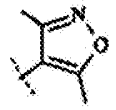
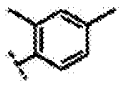
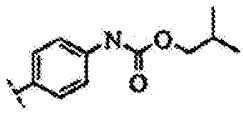
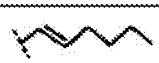
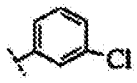
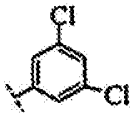
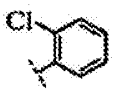
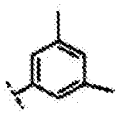
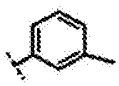
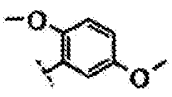
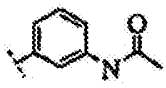
Comp. No.	R_1	R_2	MS (MH)+
5-1	$PhCH_2CH_2$	Me	488
5-2	2-$PyCH_2CH_2$	Me	503
5-3			545
5-4			559

Tabela 6

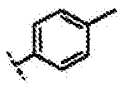
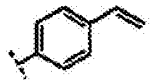
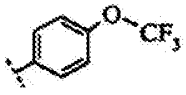
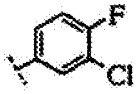
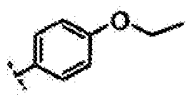
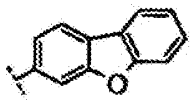
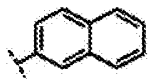
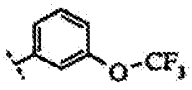
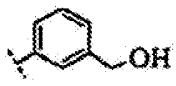
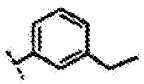
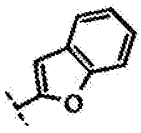
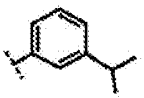
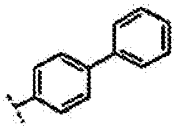


Comp. No.	R_4	MS (MH)+
6-1		509
6-2		583
6-3		549

(continuação)

Comp. No.	R_4	MS (MH)+
6-4		481
6-5		551
Referência 6-6		495
6-7		519
6-8		606
Referência 6-9		497
6-10		525
6-11		559/561
6-12		525
6-13		519
6-14		505
6-15		551
6-16		548
Referência 6-17		490

(continuação)

Comp. No.	R_4	MS $(MH)^+$
6-18		504
6-19		516
6-20		575
6-21		543
6-22		535
6-23		581
6-24		541
6-25		575
6-26		521
6-27		519
6-28		531
6-29		533
6-30		567

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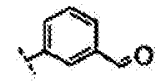
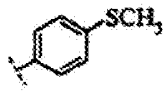
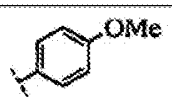
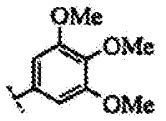
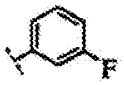
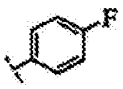
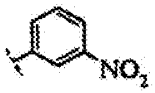
Comp. No.	R_4	MS (MH)$^+$
6-31		519
6-32		537
6-33		521
6-34		581
6-35		509
6-36		509
6-37		536
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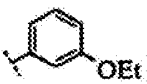
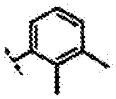
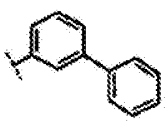
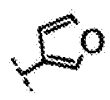
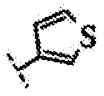
6-39		535
6-40		519
6-41		567
6-42		481
6-43		497

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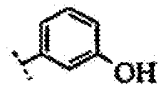
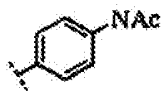
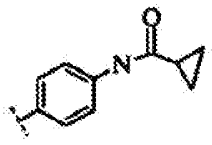
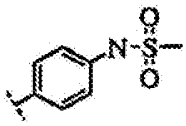
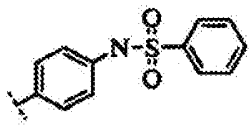
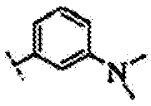
Comp. No.	R_4	MS $(MH)^+$
6-44		507
6-45		548
6-46		573
6-47		584
6-48		645
6-49		534
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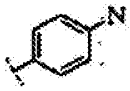
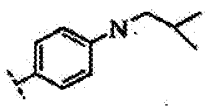
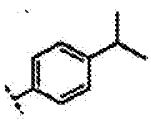
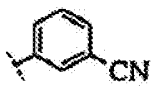
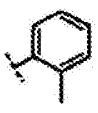
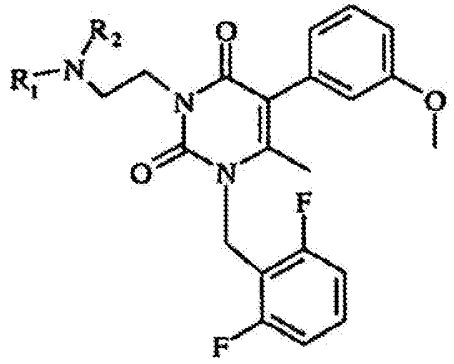
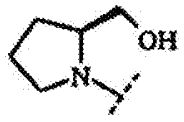
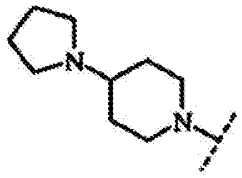
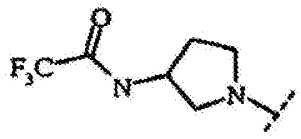
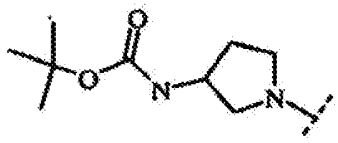
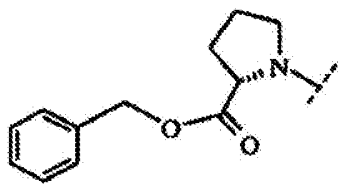
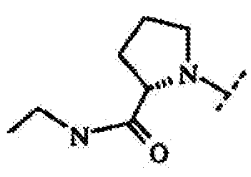
6-51		506
6-52		562
6-53		533
6-54		516
6-55		505

Tabela 7



Comp. No.	NR_1R_2	MS (MH)+
7-1		486
7-2		539
7-3		567
7-4		571
7-5		590
7-6		527

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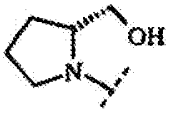
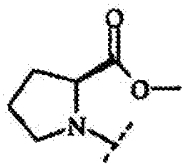
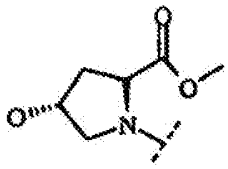
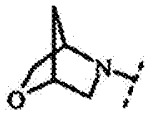
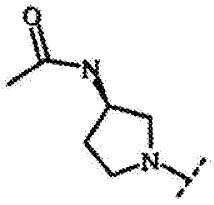
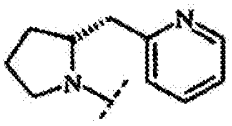
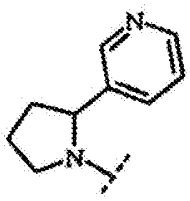
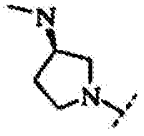
Comp. No.	NR_1R_2	MS (MH)+
7-7		486
7-8		514
7-9		530
7-10		484
7-11		513
7-12		546
7-13		553
7-14		485

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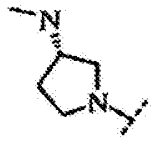
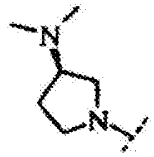
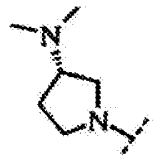
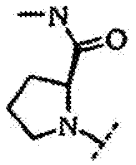
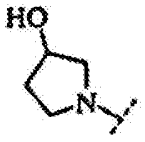
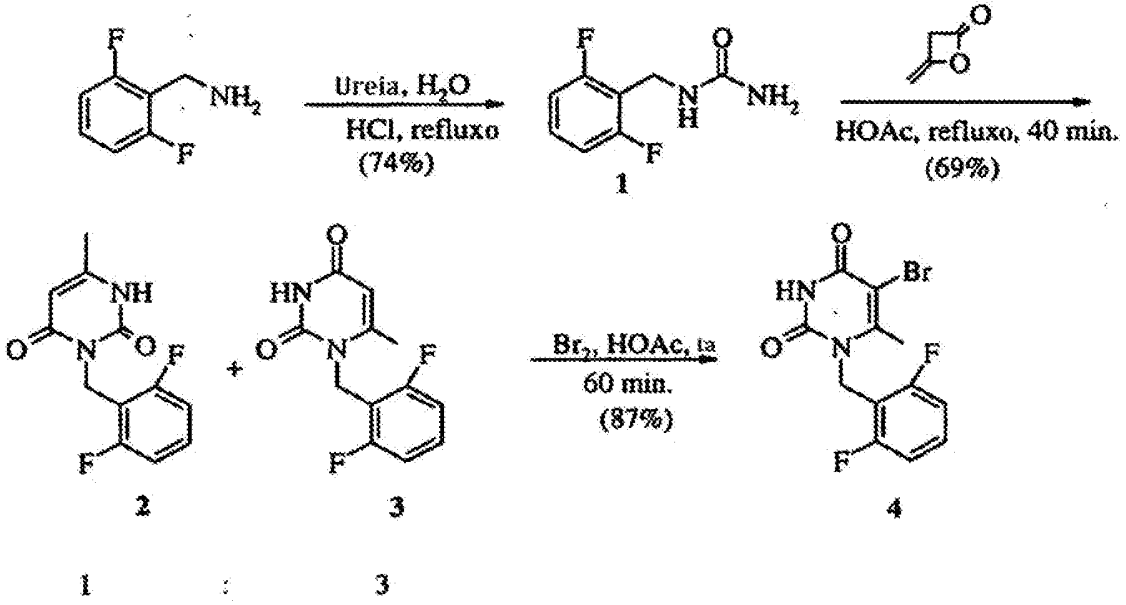
Comp. No.	NR_1R_2	MS $(MH)^+$
7-15		485
7-16		499
7-17		499
7-18		513
7-19		472
7-20		546

EXEMPLO 4

SÍNTESE DE 5-BROMO-1-(2,6-DIFLUOROBENZIL)-6-METIL-URACILO



Passo A 2,6-Difluorobenzil ureia

2,6-Difluorobenzilamina (25,0g, 0,175mol) foi adicionada gota a gota a uma solução com agitação de ureia (41,92g, 0,699 mol), em água (70 mL), e HCl concentrado (20,3 mL). A mistura resultante foi submetida a refluxo durante 2,5 horas, tempo após o qual foi arrefecida até à temperatura ambiente. Os sólidos que se formaram foram filtrados sob vácuo, e foram lavados cuidadosamente com água. Após a secagem sob vácuo, os sólidos foram recristalizados a partir de EtOAc para dar o produto 1, em forma de agulhas brancas leves (24,0g, 0,129 mol, 74%).

Passo B 1-(2,6-Difluorobenzil)-6-metil-uracilo

Diceteno (9,33 mL, 0,121 mol) foi adicionado numa porção a uma solução em refluxo de 2,6-difluorobenzil ureia **1** (20,46 g,

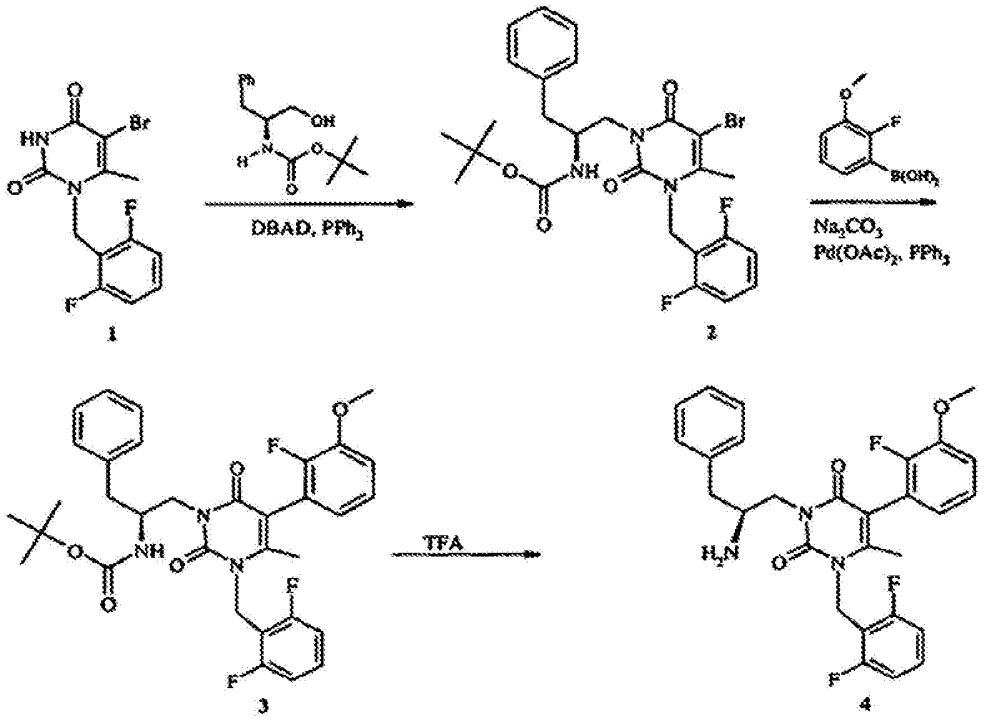
0,110 mol) e ácido acético glacial (110 mL). Depois de 40 minutos sob refluxo, a mistura foi arrefecida à temperatura ambiente e vertida sobre água (600 mL). O precipitado foi recolhido por filtração, lavado com água e seco sob vácuo para dar uma mistura 1:3 de isómeros **2** e **3**, respectivamente (19,07 g, 0,076 mol, 69%). A mistura foi recristalizada a partir de acetonitrilo (~600 mL) para dar o composto do título puro 3, como prismas brancos (1ª colheita - 7,85 g, 0,031 mol, 28%).

Passo C 5-bromo-1-(2,6-difluorobenzil)-6-metil-uracilo

1-(2,6-Difluorobenzil)-6-metil-uracilo **3** (7,56 g, 30 nmol) foi suspenso em ácido acético glacial (100 mL) e, a essa mistura, foi adicionado, gota a gota, bromo (1,93 mL, 37,5 mmol). A solução cor de laranja resultante transformou-se numa suspensão em cerca de 5 minutos. Após agitação durante 1 hora à temperatura ambiente, o precipitado foi filtrado sob vácuo e lavado com água. Os sólidos foram triturados com éter dietílico e seco sob vácuo para dar **4** (8,6g, 0,026 mmol, 87%).

EXEMPLO 5

OUTROS COMPOSTOS REPRESENTATIVOS



Passo A-1 3-(1-[2-BOC-(S)-amino-3-fenilpropil)-5-bromo-1-(2,6-difluorobenzil)-6-metil-uracilo

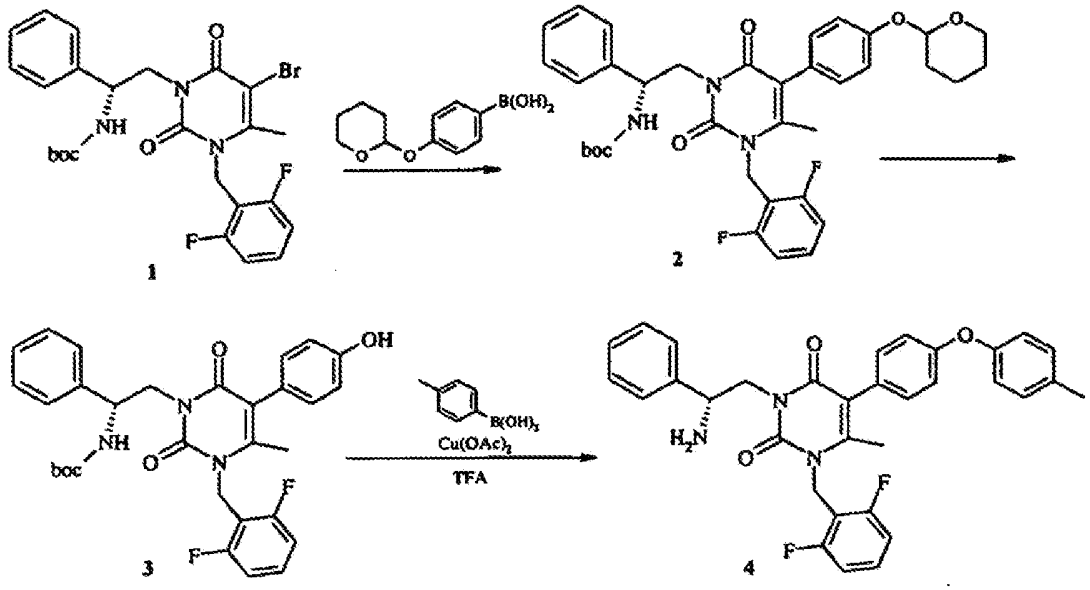
2-BOC-(S)-amino-3-fenil-1-propanol (2,51g, 10 mmol) e trifenilfosfina (3.14g, 12 mmol) foram adicionados a uma solução de 5-bromo-1-(2,6-difluorobenzil)-6-metil-uracilo **1** (3.31g, 10 mmol), em THF (50 mL). Azodicarboxilato de di-terc-butilo (2,76 g, 12 mmol) foi adicionado em várias porções ao longo de 5 minutos. Passados 5 minutos a mistura de reacção era clara. Após 1 hora, a mistura de reacção foi concentrada e o resíduo foi purificado por coluna (cartucho) de sílica (hexano/EtOAc como eluente). A concentração das fracções semelhantes deu 6,8g de um material oleoso que foi precipitado a partir de hexano para dar o produto **2** (4,95 g, 88%).

Passo B-1 3-(1-[2-BOC-(S)-amino-3-fenilpropil)-1-(2,6-difluorobenzil-5-(2-fluoro-3-metoxifenil)-6-metil-uracilo

O composto **2** (4,95g, 8,78 mmol) e carbonato de sódio (2,12g, 20 mmol) foram suspensos em tolueno (50 mL) e dimetoxietano (10 mL). Foi adicionada água (20 mL) e N_2 foi borbulhado através da mistura de reacção. Após 5 minutos ambas as camadas eram claras e $Pd(OAc)_2$ (394 mg, 0.2 eq) e trifenilfosfina ((921 mg, 0.4 eq) foram adicionados. O ácido borónico (1,7g, 10 mmol) foi adicionado e o recipiente de reacção foi selado e aquecido durante a noite a 100 °C. A camada orgânica foi separada, evaporada e purificada por cromatografia em sílica. As fracções contendo o produto foram combinadas e evaporadas para dar **3** como um óleo castanho (1,5g, rendimento 28%).

Passo C-1 3-(1-[2-(S)-Amino-3-fenilpropil)-1-(2,6-difluorobenzil)-5-(2-fluoro-3-metoxifenil)-6-metil-uracilo

O composto **3** (1,5g, 2.5 mmol) em ácido trifluoroacético/diclorometano (1:1, 50 mL) foi aquecido durante 4 horas. A evaporação deu um óleo vermelho que foi purificado por fase reversa HPLC preparativa utilizando água/CH_3CN com ácido trifluoroacético a 0,05% como eluente. As fracções contendo produto foram concentradas e liofilizadas para dar o produto **4** (0,56 g, 44%, MH^+ = 510).



Passo A-2 1-(2,6-Difluorobenzil-3-[(2R)-terc-butoxicarbonilamino-2-fenil]etil-6-metil-5-(4-[tetrahidropiran-2-iloxi]fenil)uracilo

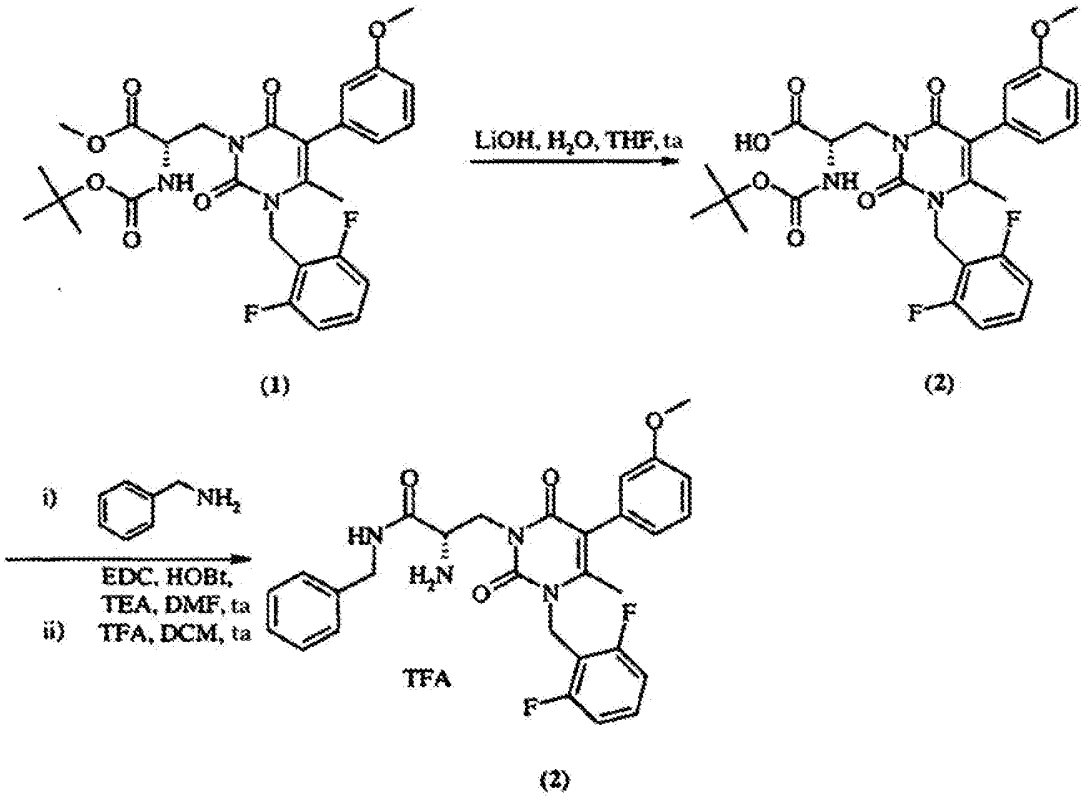
1-(2,6-Difluorobenzil-3-[(2R)-terc-butilcarbonilamino -2-fenil]etil-6-metil-5-bromouracilo **1** (2,58 g, 4,7 mmol), tetraquis(trifenilfosfina) paládio (0)(550 mg, 0,47 mmmol), éter tetrahidropirânico do ácido 4-hidroxifenil borónico (1,25 g, 5,7 mmol) e hidróxido de bário (38 mL de solução 0,14M, 5,2 mmol) numa solução de benzeno/etanol/dimetoxietano (10/1/11, 90 mL) foi aquecida a 90 °C num vaso de pressão sob atmosfera de N_2 durante a noite. A camada orgânica foi concentrada *in vacuo* e o resíduo foi purificado por cromatografia em sílica gel (hexanos/acetato de etilo como eluente) para dar 3,0 g de **2**, como uma espuma esbranquiçada.

Passo B-2 1-(2,6-Difluorobenzil-3-[(2R)-terc-butoxicarbonilamino-2-fenil]etil-6-metil-5-(4-hidroxifenil) uracilo

Uma mistura de **2** (3,0 g, 4,6 mmol) e de piridínio-p-toluenossulfonato (231 mg, 0,92 mmol), em etanol (92 mL), foi agitada a 45°C durante 5 horas. A mistura de reacção foi concentrada *in vacuo* e o resíduo foi dissolvido em cloreto de metileno e H_2O. A camada orgânica foi concentrada e o resíduo foi purificado por cromatografia em sílica gel usando hexanos/acetato de etilo como eluente para dar 2,1 g do composto **3** como uma espuma amarela.

Passo C-2 1-(2,6-Difluorobenzil-3-[(2R)-amino-2-fenil]etil-5-(4-[4-toliloxilfenil)uracilo

Uracilo substituído **3** (50 mg, 0,089 mmol), ácido p-tolilborónico (18 mg, 0,133 mmol), acetato de cobre (II) (16 mg, 0.089 mmol) e trietilamina (0,06 mL, 0,445 mmol), em CH_2Cl_2 (1 mL), foram agitados durante 3 dias à temperatura ambiente. A mistura de reacção foi purificada por cromatografia em sílica gel utilizando MeOH 1% em CH_2Cl_2 para dar 30 mg do produto protegido. Este material foi dissolvido em CH_2Cl_2 (1 mL) com 5 gotas de ácido trifluoroacético. A purificação HPLC/MS de fase reversa deu 5,0 mg do produto **4** m/z (Cl) 554 (MH^+).



Passo A-3 (S)-3-(ácido 1-N-*terc*-butoxicarbonilamino-1-carboxílico de etilo)-1-(2,6-difluorobenzil)-5-3-metoxifenil)-6-metiluracilo

A uma solução agitada de **1** (306 mg, 0,55 mmol), em tetrahidrofurano (15 mL) à temperatura ambiente, adicionou-se uma solução aquosa de hidróxido de lítio (15 mL de uma solução 1 M, 15 mmol). Após 2 h, a maior parte do tetrahidrofurano foi removido *in vacuo* e a solução resultante foi acidificada para um pH de 4 (com 10% de solução aquosa de ácido cítrico). O precipitado resultante foi extraído com acetato de etilo (2 x 15 mL) e a camada orgânica combinada foi lavada com água, salmoura e seca ($MgSO_4$). O solvente foi removido *in vacuo* para dar **2** (283 mg, 94%) como um óleo amarelo que não foi mais purificado, δ_H (300 MHz; $CDCl_3$) 7.26-7.34 (2 H, m, Ar), 6.73-6.95 (5H, m, Ar), 5.74 (1 H, brd, *J* 6, NH), 5.37 (1 H, d, *J*

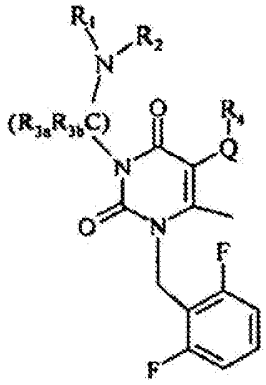
16, CH*H*Ar), 5.22 (1 H, d, *J* 16, CH*H*Ar), 4.62 (1 H, brs, CHN), 4.32-4.49 (2 H, m, CH_2N), 3.80 (3 H, s, OCH_3), 2.17 (3 H, s, CH_3) e 1.42 (9 H, s, 3 x CH_3), m/z (Cl) 446 (MH^+-Boc, 100%).

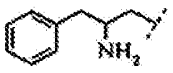
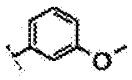
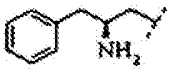
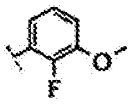
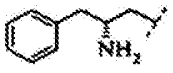
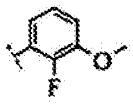
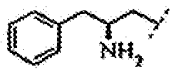
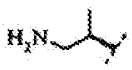
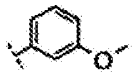
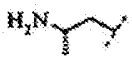
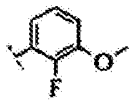
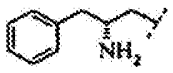
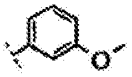
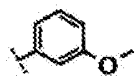
Passo B-3 (S)-3-(1-Amino-1-*NH*-benzilcarboxamida de etilo)-1-(2,6-difluorobenzil)-5-(3-metoxifenil)-6-metiluracilo, sal de ácido trifluoroacético

A uma solução agitada de **2** (20 mg, 0,037 mmol), benzilamina (15 µL, 0,14 mmol), 1-(hidroxi) hidrato de benzotriazole (9 mg, 0,066 mmol) e trietilamina (10 µL, 0,074 mmol) em *N*, *N*-dimetilformamida anidra (1 mL), à temperatura ambiente, adicionou-se 1-[3-(dimetilamino) propil]-3-etil carbodiimida cloridrato (11 mg, 0,056 mmol). Após 10 h, a mistura de reacção foi vertida em água (5 mL *ca.*) e o precipitado resultante foi extraído com acetato de etilo (5 mL *ca.*). A camada orgânica foi lavada com salmoura e seca ($MgSO_4$). O solvente foi removido *in vacuo* para dar um óleo amarelo, que foi redissolvido numa mistura de diclorometano (1 mL) e ácido trifluoroacético (0,5 mL, 6,5 mmol) e agitou-se à temperatura ambiente. Após 1 h, o solvente foi removido *in vácuo* para dar um óleo amarelo, o qual foi purificado por HPLC/MS de fase reversa para dar **3** (6 mg, 30%) como um sólido incolor, m/z (Cl) 535.2 (MH^+, 100%).

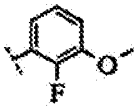
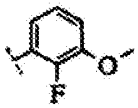
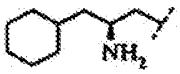
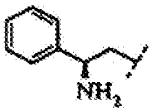
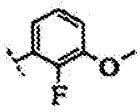
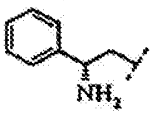
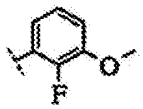
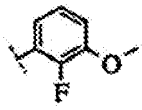
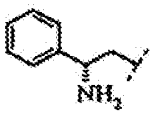
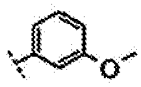
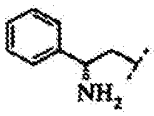
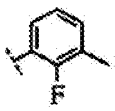
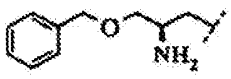
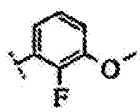
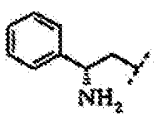
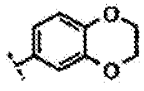
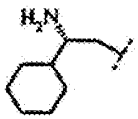
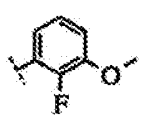
Os compostos da seguinte Tabela 8 foram também preparados pelo processo acima descrito.

Tabela 8

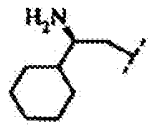
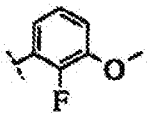
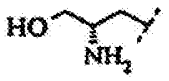
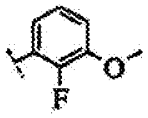
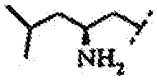
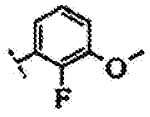
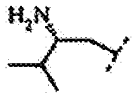
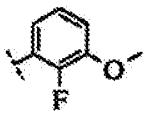
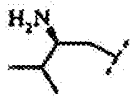
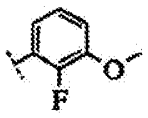
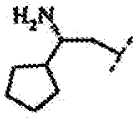
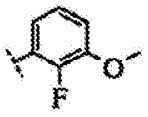
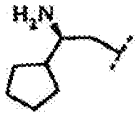
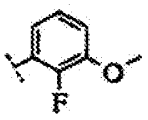
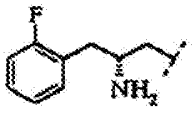
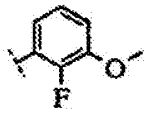
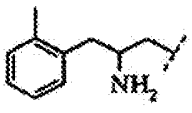
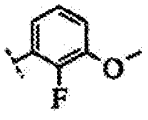
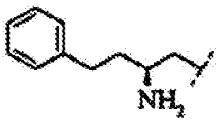
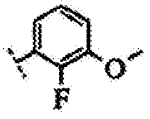


Comp. No.	$R_1R_2N(CR_{3a}R_{3b})_n$-	-Q-R_4	MS (calc)	MS Ion
8-1			491.5	492
8-2			509.5	510
8-3			509.5	510
Referência 8-4		H	385.4	386
8-5			415.4	416
8-6			433.4	434
Referência 8-7		H	385.4	386
8-8			415.4	416
8-9			415.4	416

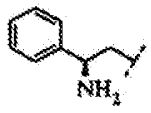
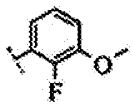
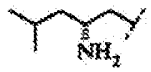
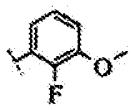
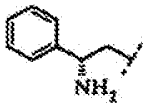
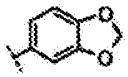
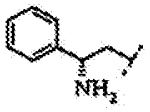
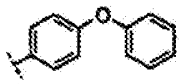
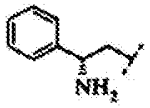
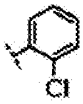
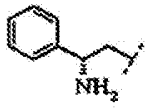
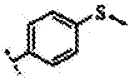
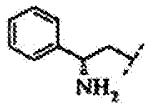
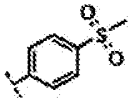
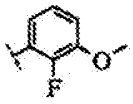
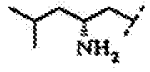
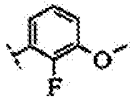
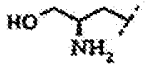
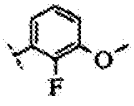
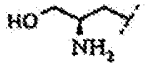
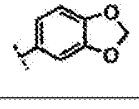
(continuação)

Comp. No.	$R_1R_2N(CR_{3a}R_{3b})_n$-	-Q-R_4	MS (calc)	MS Ion
8-10			433.4	434
8-11			515.6	516
Referência 8-12		H	391.5	392
8-13			495.5	496
8-14			495.5	496
8-15			539.6	540
8-16			477.5	478
8-17			479.5	480
8-18			539.6	540
8-19			505.5	506
8-20			501.5	502.2

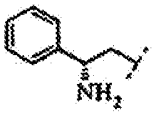
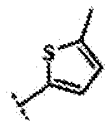
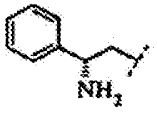
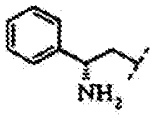
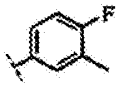
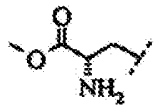
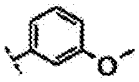
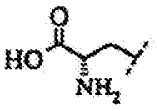
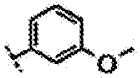
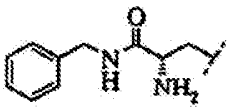
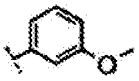
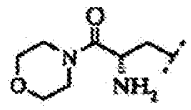
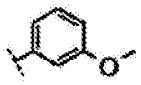
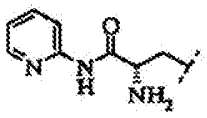
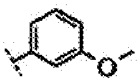
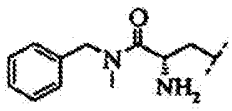
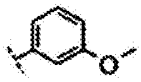
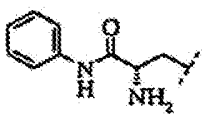
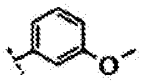
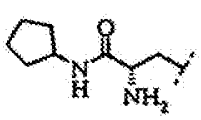
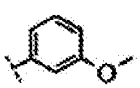
(continuação)

Comp. No.	$R_1R_2N(CR_{3a}R_{3b})_n$-	-Q-R_4	MS (calc)	MS Ion
8-21			501.5	502.2
8-22			465.5	450
8-23			475.5	476.2
8-24			461.5	462.2
8-25			461.5	462.2
8-26			487.5	488.2
8-27			487.5	488.2
8-28			527.5	528
8-29			523.6	524
8-30			523.6	524

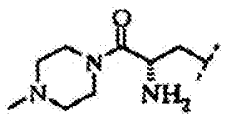
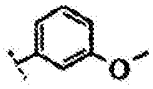
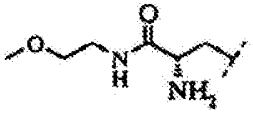
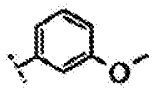
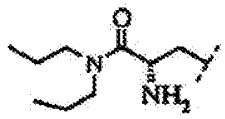
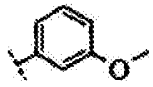
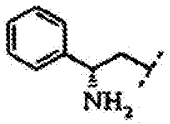
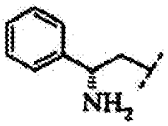
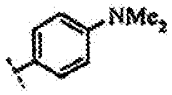
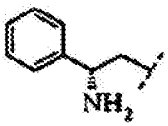
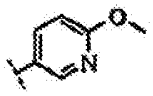
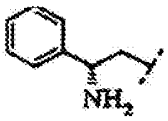
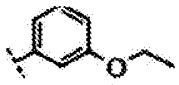
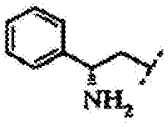
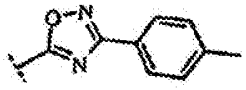
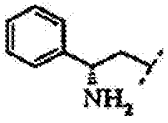
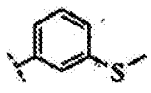
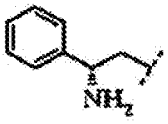
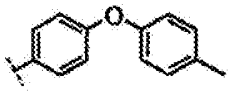
(continuação)

Comp. No.	$R_1R_2N(CR_{3a}R_{3b})_n$-	-Q-R_4	MS (calc)	MS Ion
8-31			495.5	496
8-32			475.5	476.2
8-33			491.5	492
8-34			539.6	540
8-35			481.9	482
8-36			493.6	494
8-37			525.6	526
8-38			489.5	490.2
8-39			475.5	476.2
8-40			449.4	450
8-41			445.4	446

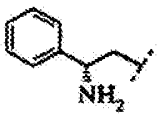
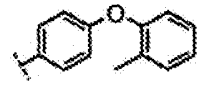
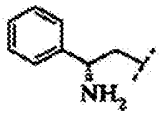
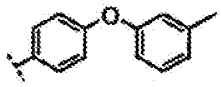
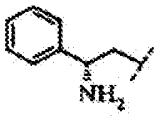
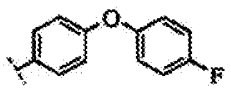
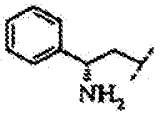
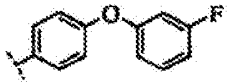
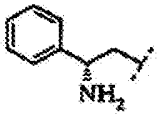
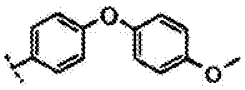
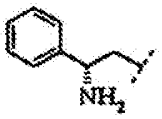
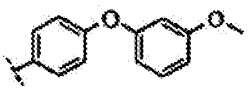
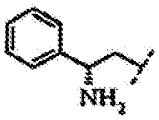
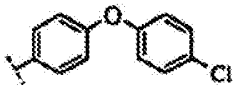
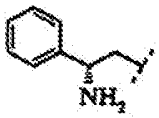
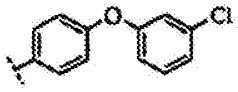
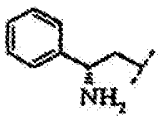
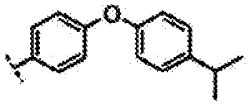
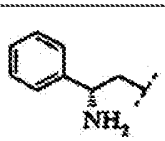
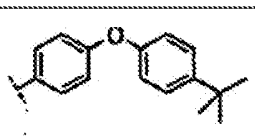
(Continuação)

Comp. No.	$R_1R_2N(CR_{3a}R_{3b})_n$-	-Q-R_4	MS (calc)	MS Ion
Referência 8-42			467.5	469
8-43			449.5	450
8-44			479.5	480
8-45			459.4	460.2
8-46			445.4	446.1
8-47			534.6	535.2
8-48			514.5	515.2
8-49			521.5	522.2
8-50			548.6	549.2
8-51			520.3	521.2
8-52			512.6	513.2

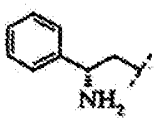
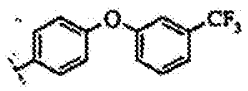
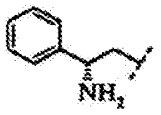
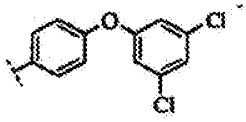
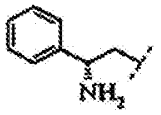
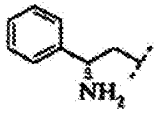
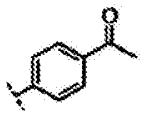
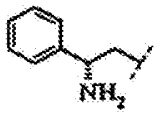
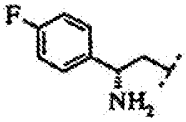
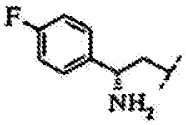
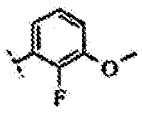
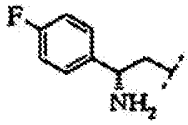
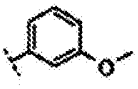
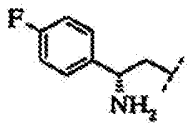
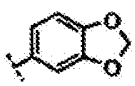
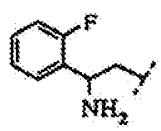
(Continuação)

Comp. No.	$R_1R_2N(CR_{3a}R_{3b})_n$-	-Q-R_4	MS (calc)	MS Ion
8-53			527.6	528.2
8-54			502.5	503.2
8-55			528.6	529.3
8-56		H	371.4	372.1
8-57			490.6	491.2
Referência 8-58			478.5	479.1
8-59			491.5	492.2
Referência 8-60			515.5	516.2
8-61			493.6	494.1
8-62			553.6	554.2

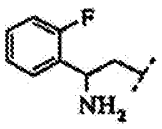
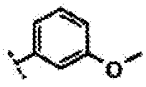
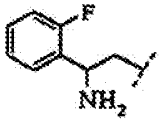
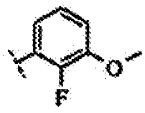
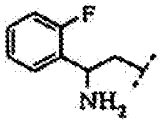
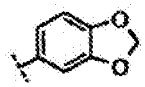
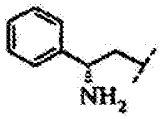
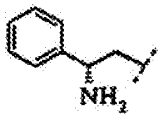
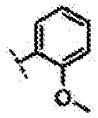
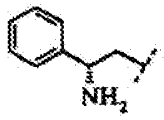
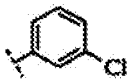
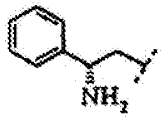
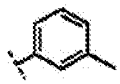
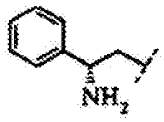
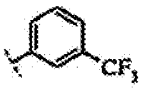
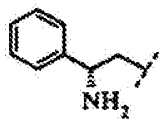
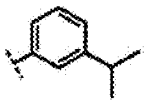
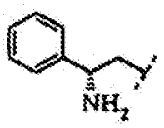
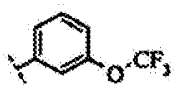
(Continuação)

Comp. No.	$R_1R_2N(CR_{3a}R_{3b})_n$-	-Q-R_4	MS (calc)	MS Ion
8-63			553.6	554.2
8-64			553.6	554.2
8-65			557.6	558.2
8-66			557.6	558.2
8-67			569.6	570.2
8-68			569.6	570.2
8-69			574.0	574.2
8-70			574	574.2
8-71			581.7	582.3
8-72			595.7	596.3

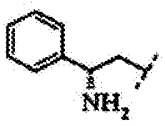
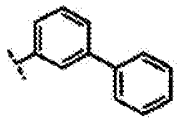
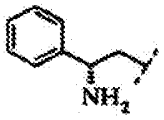
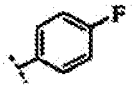
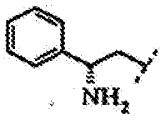
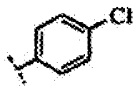
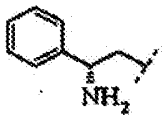
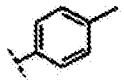
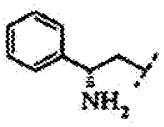
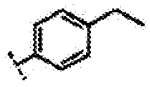
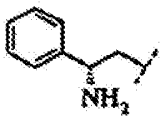
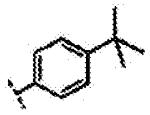
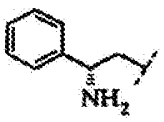
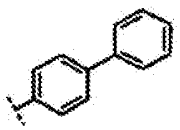
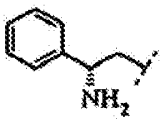
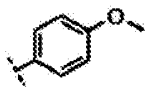
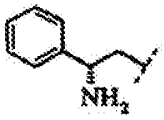
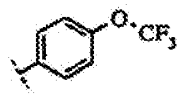
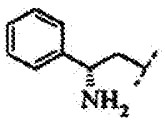
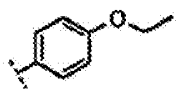
(Continuação)

Comp. No.	$R_1R_2N(CR_{3a}R_{3b})_n$-	-Q-R_4	MS (calc)	MS Ion
8-73			607.6	608.2
8-74			608.5	608.1
Referência 8-75			488	488.1
8-76			489.5	490.2
Referência 8-77			447.5	448.2
Referência 8-78			465.5	466.1
8-79			513.5	514.1
8-80			495.5	496.2
8-81			509.5	510.1
Referência 8-82			465.5	466.2

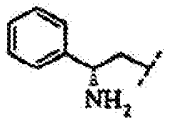
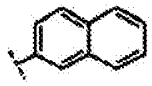
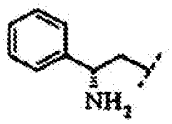
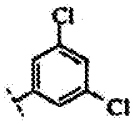
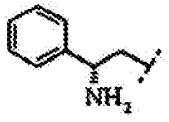
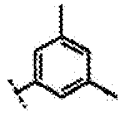
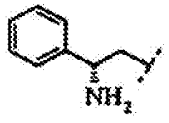
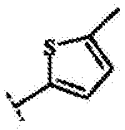
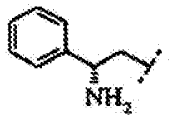
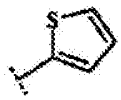
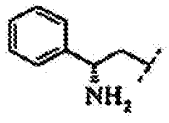
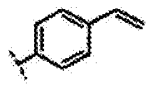
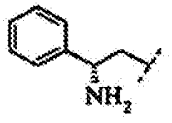
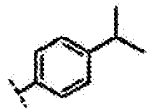
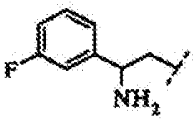
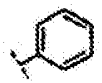
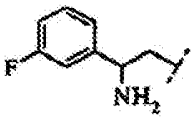
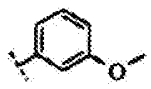
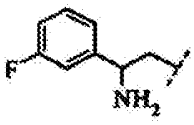
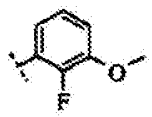
(Continuação)

Comp. No.	$R_1R_2N(CR_{3a}R_{3b})_n$-	-Q-R_4	MS (calc)	MS Ion
8-83			495.5	496.2
8-84			513.5	514.2
8-85			509.5	510.2
8-86			461.5	462
8-87			477.5	478
8-88			481.9	482
8-89			461.5	462
8-90			515.5	516
8-91			489.6	490
8-92			531.5	532

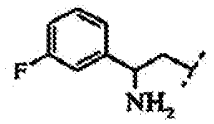
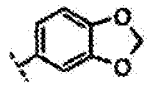
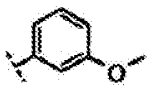
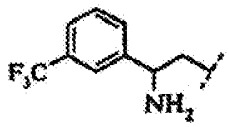
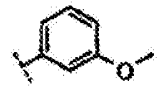
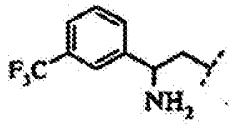
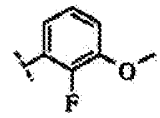
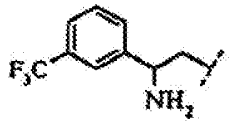
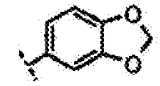
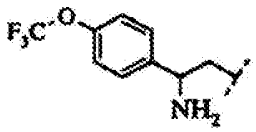
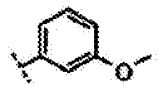
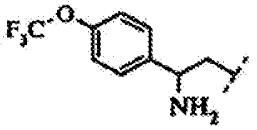
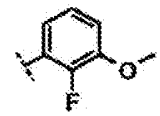
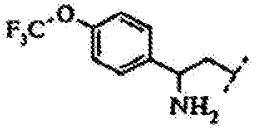
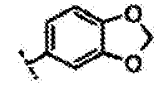
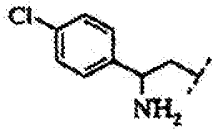
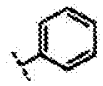
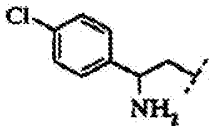
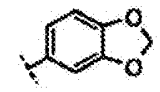
(Continuação)

Comp. No.	$R_1R_2N(CR_{3a}R_{3b})_n$-	-Q-R_4	MS (calc)	MS Ion
8-93			523.6	524
8-94			465.5	466
8-95			481.9	482
8-96			461.5	462
8-97			475.5	476
8-98			503.6	504
8-99			523.6	524
8-100			477.5	478
8-101			531.5	532
8-102			491.5	482

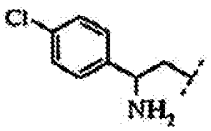
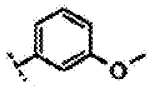
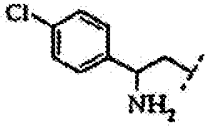
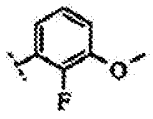
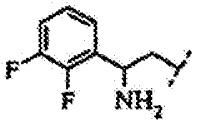
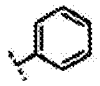
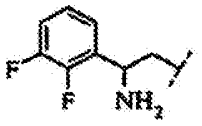
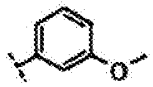
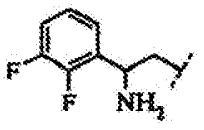
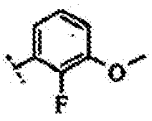
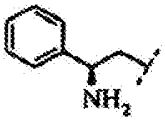
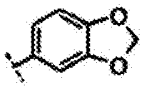
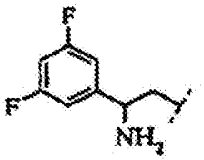
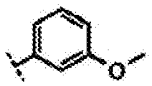
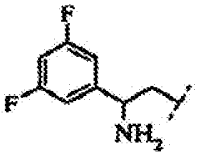
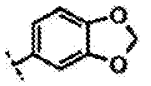
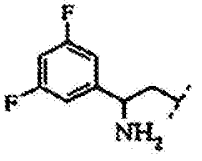
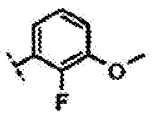
(Continuação)

Comp. No.	$R_1R_2N(CR_{3a}R_{3b})_n$-	-Q-R_4	MS (calc)	MS Ion
8-103			497.5	498
8-104			516.4	516
8-105			475.5	476
Referência 8-106			467.5	468
8-107			453.5	454
8-108			476.5	474
8-109			489.6	490
Referência 8-110			465.5	466.1
8-111			495.5	496.2
8-112			513.5	514.2

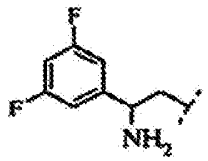
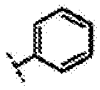
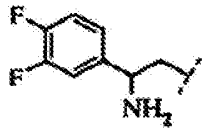
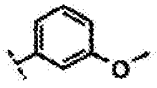
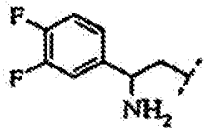
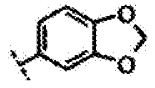
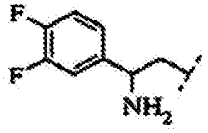
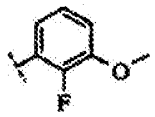
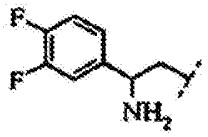
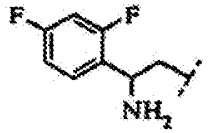
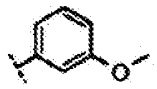
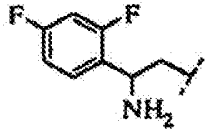
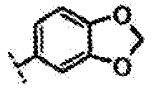
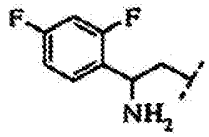
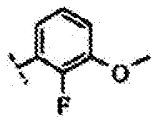
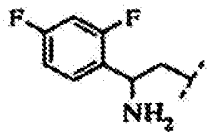
(Continuação)

Comp. No.	$R_1R_2N(CR_{3a}R_{3b})_n$-	-Q-R_4	MS (calc)	MS Ion
8-113			509.5	510.1
8-114			498.6	498
8-115			545.5	546.2
8-116			563.5	564.2
8-117			559.5	560.2
8-118			561.5	562.2
8-119			579.5	580.2
8-120			575.5	576.2
Referência 8-121			481.9	482.1
8-122			525.9	526.1

(continuação)

Comp. No.	$R_1R_2N(CR_{3a}R_{3b})_n$-	-Q-R_4	MS (calc)	MS Ion
8-123			512	512.1
8-124			529.9	530.1
Referência 8-125			483.5	484.1
8-126			513.5	496.2
8-127			531.5	532.1
8-128			491.5	492.2
8-129			513.5	514.2
8-130			527.5	528.1
8-131			531.5	532.2

(Continuação)

Comp. No.	$R_1R_2N(CR_{3a}R_{3b})_n$-	-Q-R_4	MS (calc)	MS Ion
Referência 8-132			483.5	484.1
8-133			513.5	514.2
8-134			527.5	528.2
8-135			531.5	532.2
Referência 8-136			483.5	484.1
8-137			513.5	514.1
8-138			527.5	528.2
8-139			531.5	532.2
Referência 8-140			483.5	484.1

EXEMPLO 6

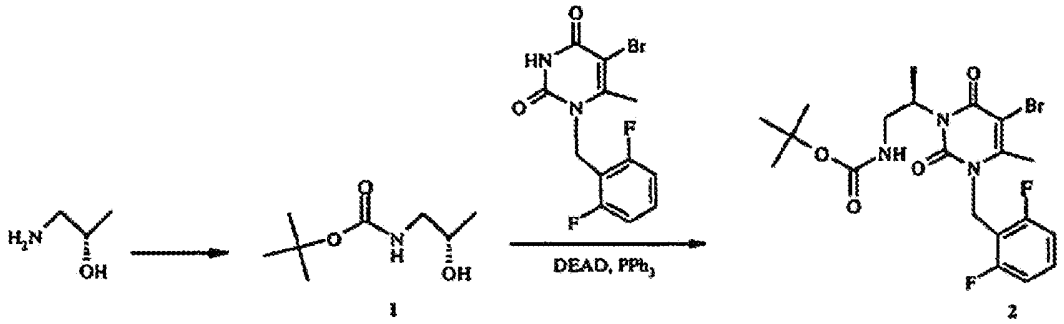
SÍNTESE DE ÁCIDOS BORÓNICOS

Passo A ácido 2-fluoro-3-metoxifenilborónico

n-Butil-lítio (20 mL, 2,5M) foi adicionado a uma solução de tetrametilpiperidina (8,44 mL, 50 mmol) em THF (125 mL) a -78°C. A mistura reaccional foi agitada a -78°C durante 1,5 horas. 2-fluoroanisole (6,31 g, 50 mmol) foi adicionado e a mistura foi agitada durante 8 horas a -78°C. Trimetilborato (6,17 mL, 55 mmol) foi adicionado e a mistura de reacção foi deixada aquecer lentamente até à temperatura ambiente durante a noite. A mistura foi vertida em HCl 1N (250 mL). A extracção com EtOAc seguida por evaporação deu um sólido pegajoso que foi triturado com hexanos para dar o produto (2,19 g, rendimento 26%).

EXEMPLO 7

SÍNTESE DOS COMPOSTOS REPRESENTATIVOS



Passo A BOC-(S)-1-amino-2-propanol

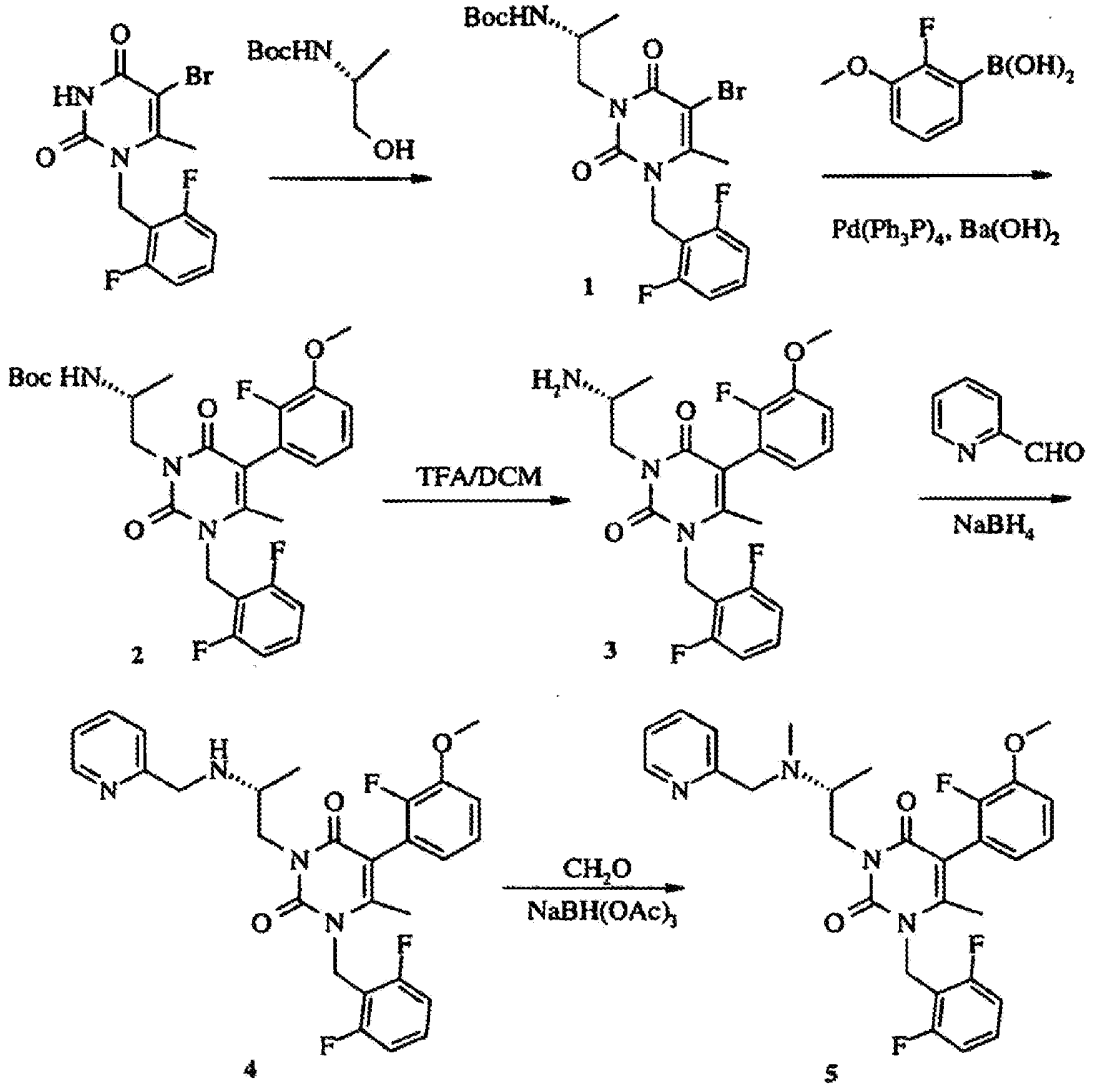
Di-t-butil dicarbonato (6,76 g, 31 mmol) foi adicionado em porções a uma solução agitada de (*S*)-1-amino-2-propanol e trietilamina (4,4 mL, 31,5 mmol) em CH_2Cl_2 (75 mL) a 0 °C. A mistura de reacção foi agitada durante 1 hora a 0 °C e durante 30 minutos à temperatura ambiente. A evaporação deu o produto **1** que foi utilizado sem purificação adicional.

Passo B 3-(2-BOC-(R)-1-aminopropil)-5-bromo-1-(2,6-difluoro-benzil)-6-metil-uracilo

5-Bromo-1-(2,6-difluorobenzil)-6-metiluracilo (3,31 g, 10 mmol) foi suspenso em THF (200 mL). O composto **1** (1,84 g, 10,5 mmol) e trifenilfosfina (3,93 g, 15 mmol) foram adicionados e a mistura foi agitada. DEAD (2,36 mL, 15 mmol) foi adicionado e a mistura de reacção tornou-se uma solução. Após agitação durante a noite, os voláteis foram removidos e o resíduo foi cromatografado em sílica utilizando EtOAc/hexanos como eluente para dar o sólido branco **2** (4,57 g, rendimento 94%).

EXEMPLO 8

SÍNTESE DOS COMPOSTOS REPRESENTATIVOS



Passo A

Uma solução de N-(t-butiloxicarbonil)-D-α-alaninol (1,75g, 10 mmol.), em THF anidro (15 mL), foi tratada com 5-bromo-1-(2,6-difluorobenzil)-6-metiluracilo (3,31 g, 10 mmol) e trifenilfosfina (3,15 g, 12 mmol), à temperatura ambiente, em seguida foi introduzido di-terc-butilazodicarboxilato (2,76 g, 12 mmol). A mistura de reacção foi agitada à temperatura ambiente durante 16 horas e os voláteis foram evaporados. O resíduo foi repartido entre $NaHCO_3$ saturado/H_2O e EtOAc. A camada orgânica foi seca (sulfato de sódio), evaporada e

purificada por cromatografia flash (sílica, 1:2 EtOAc/hexanos) para dar o composto **1** (4,69 g, 96.1%), MS (Cl) m/z 388.0, 390.0 (MH^+-Boc).

Passo B

Ao composto **1** (1,0 g, 2,05 mmol), em benzeno/EtOH/éter dimetílico de etileno glicol (20/2/22 mL), foi adicionado ácido 2-fluoro-3-metoxifenilborónico (435 mg, 2,56 mmol) e $Ba(OH)_2$ saturado/água (~0,5 M, 15 mL). A mistura de reacção foi desoxigenada com N_2 durante 10 min, foi adicionado tetraquis(trifenilfosfina) paládio (0) (242 mg, 0,21 mmol) e a mistura de reacção foi aquecida a 80 °C durante a noite sob a protecção de N_2. A mistura de reacção foi repartida entre solução salina e EtOAc. A camada orgânica foi seca (sulfato de sódio), evaporada, purificada por cromatografia flash (sílica, 40% EtOAc/hexanos) para dar o composto **2** (450 mg, 41,2%), MS (Cl) m/z 434.2 (MH^+-Boc).

Passo C

TFA (2 mL) foi adicionado a uma solução de **2** (267 mg, 0,5 mmol) em diclorometano (2 mL) e a mistura de reacção foi agitada à temperatura ambiente durante 1 hora. Os voláteis foram evaporados e o resíduo foi repartido entre $NaHCO_3$ saturado/água e EtOAc. A camada orgânica foi seca (sulfato de sódio), evaporada e purificada por HPLC de fase reversa (coluna C-18, 15-75% acetonitrilo/água) para dar o composto **3**, MS(Cl) m/z 434.2 (MH^+).

Passo D

Foi adicionado 2-Piridinacarboxialdeído (80 mg, 0,75 mmol) a uma solução de **3** (267 mg, 0,5 mmol) em MeOH (5 mL) e a

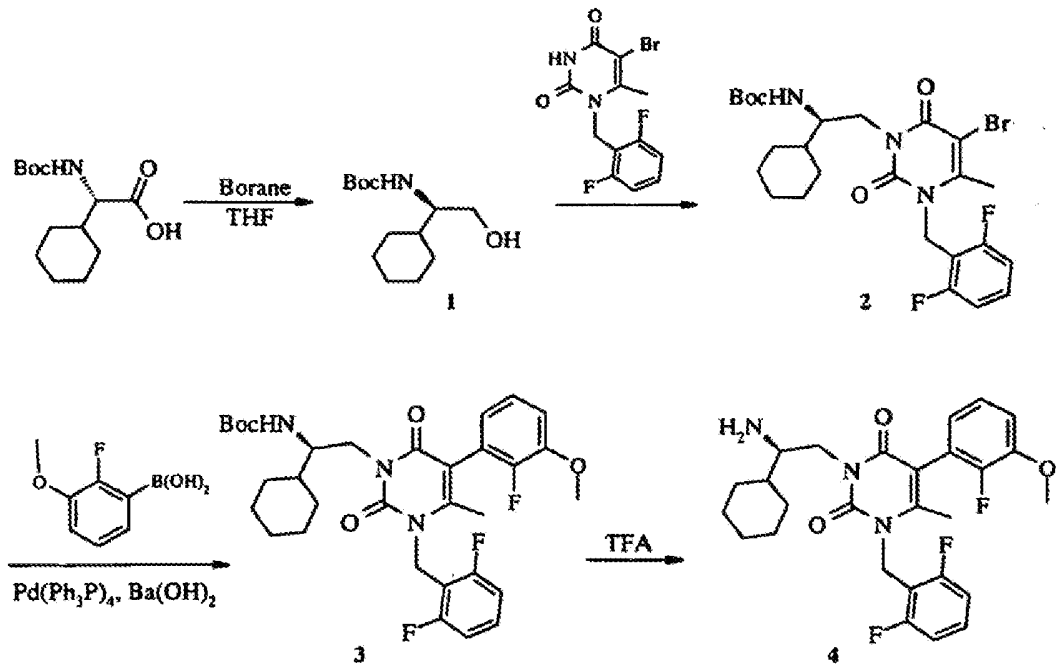
mistura de reacção foi agitada à temperatura ambiente durante 10 horas. Foi adicionado $NaBH_4$ (56 mg, 1,5 mmol) e a mistura de reacção foi mantida à temperatura ambiente durante 10 minutos. Os voláteis foram evaporados e o resíduo foi repartido entre $NaHCO_3$ saturado/água e diclorometano. A camada orgânica foi seca (sulfato de sódio), evaporada e purificada por HPLC de fase reversa (coluna C-18, 15-75% acetonitrilo/água) para dar o composto **4**, MS (Cl) m/z 525. 20 (MH^+).

Passo E

A uma solução de **4** (20 mg, 0,04 mmol), em dicloroetano (2 mL), foi adicionada 1 gota de formaldeído (solução a 37% em água) e $NaBH(OAc)_3$ (16 mg, 0,08 mmol). A mistura de reacção foi agitada à temperatura ambiente durante 2 horas, os voláteis foram evaporados e o resíduo foi repartido entre água e diclorometano. A camada orgânica foi seca (sulfato de sódio), evaporada e purificada por HPLC de fase reversa (coluna C-18, 15-75% acetonitrilo/água) para dar o composto **5**, MS (Cl) m/z 539.20 (MH^+).

EXEMPLO 9

SÍNTESE DOS COMPOSTOS REPRESENTATIVOS



Passo A

Uma solução de N^{α}-(t-butiloxicarbonil)-L-α-ciclohexilglicina (2,0 g, 7,77 mmol), em THF anidro, (10 mL) foi arrefecida até 0 °C. A solução de borano (1 M em THF, 15,5 mL, 15,5 mmol) foi adicionada lentamente e, em seguida, aquecida até à temperatura ambiente, e a mistura de reacção foi agitada à temperatura ambiente durante 2 h. A reacção foi interrompida com MeOH (5 mL), os voláteis foram evaporados e o resíduo foi repartido entre água e EtOAc. A camada orgânica foi lavada com $NaHCO_3$ saturado/água e salmoura e, em seguida foi seca (sulfato de sódio) e evaporada para dar o composto **1** (1,26g, 66,7%), MS (Cl) m/z 144.20 (MH^+-Boc).

Passo B

Uma solução de **1** (638 mg, 2,62 mmol), em THF (10 mL), foi tratada com 5-bromo-1-(2,6-difluorobenzil)-6-metiluracilo (869 mg, 2,62 mmol) e trifenilfosfina (1,03g, 3,93 mmol) à

temperatura ambiente e, em seguida, foi introduzido di-terc-butilazodicarboxilato (906 mg, 3,93 mmol). A mistura de reacção foi agitada à temperatura ambiente durante 16 horas e os voláteis foram evaporados. O resíduo foi repartido entre $NaHCO_3$ saturado/H_2O e EtOAc. A camada orgânica foi seca (sulfato de sódio), evaporada e purificada por cromatografia flash (sílica, 25% EtOAc/ hexanos) para dar o composto **2** (1,39 g, 95,4%), MS (Cl) m/z 456.10, 458.10 (MH^+-Boc).

Passo C

O composto **2** (1,0 g, 1,79 mmol), em benzeno/EtOH/éter dimetílico de etileno glicol (20/2/22 mL), foi adicionado 2-fluoro-3-metoxifenilborónico ácido (382 mg, 2,24 mmol) e $Ba(OH)_2$ saturado/água (~0,5 M, 15 mL). A mistura de reacção foi desoxigenada com N_2 durante 10 min, tetraquis(trifenilfosina) paládio(0) (208 mg, 0,18 mmol) foi adicionado e a mistura de reacção foi aquecida a 80° C durante a noite sob a protecção de N_2. A mistura de reacção foi repartida entre solução salina e EtOAc. A camada orgânica foi seca (sulfato de sódio), evaporada e purificada por cromatografia flash (sílica, 30% EtOAc/hexanos) para dar o composto **3** (348 mg, 32,3%), MS (Cl) m/z 502.20 (MH^+-Boc).

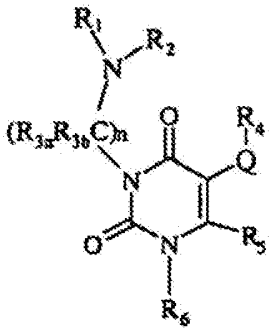
Passo D

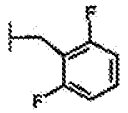
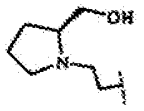
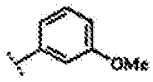
Uma solução de **3** (300 mg, 0,5 mmol), em diclorometano (2 mL), foi adicionado TFA (2 mL) e a mistura de reacção foi agitada à temperatura ambiente durante 1 h. Os voláteis foram evaporados e o resíduo foi repartido entre $NaHCO_3$ saturado/água e EtOAc. A camada orgânica foi seca (sulfato de sódio), evaporada e purificada por HPLC de fase reversa (coluna C-18,

15-75% ACN/água) para dar o composto **4**, MS (Cl) m/z 502.20 (MH^+).

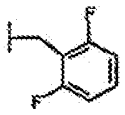
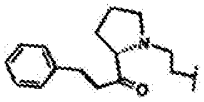
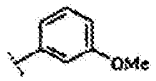
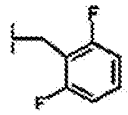
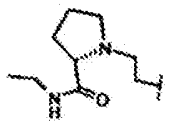
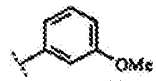
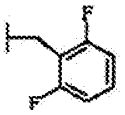
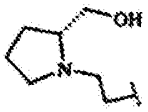
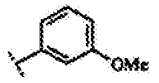
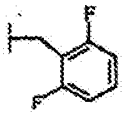
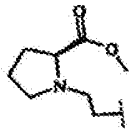
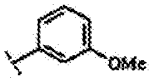
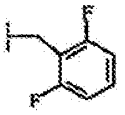
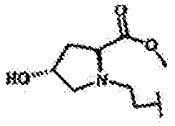
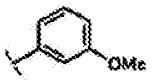
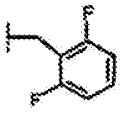
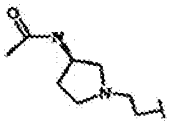
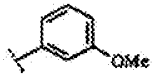
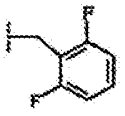
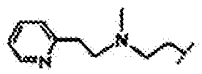
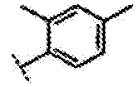
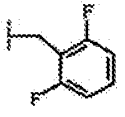
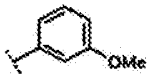
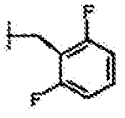
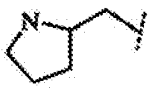
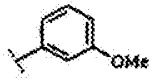
Os compostos da seguinte Tabela 9 foram também preparados pelo processo acima descrito.

Tabela 9

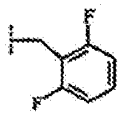
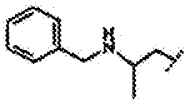
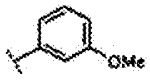
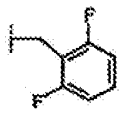
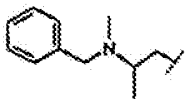
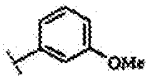
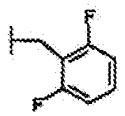
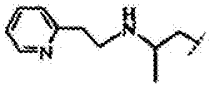
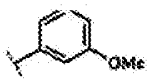
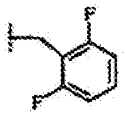
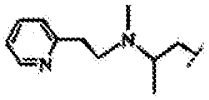
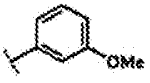
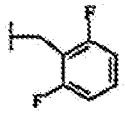
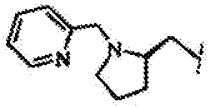
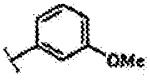
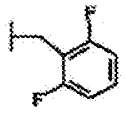
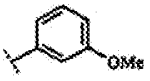
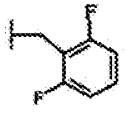
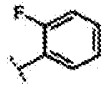
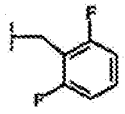
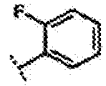
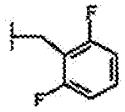
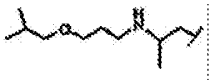
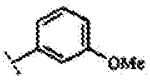


Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	MW (obs.)
9-1	Me				485.5	486

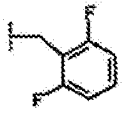
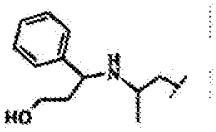
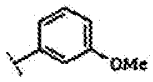
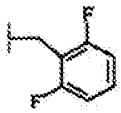
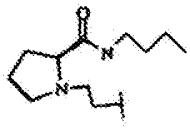
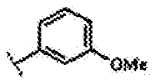
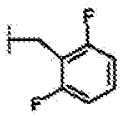
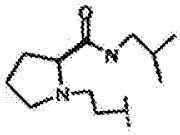
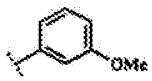
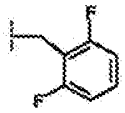
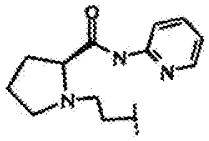
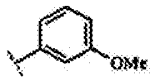
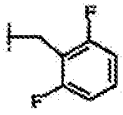
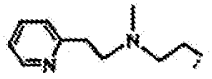
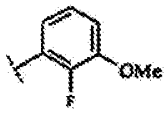
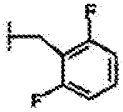
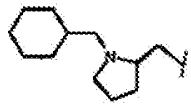
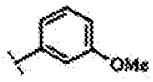
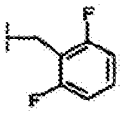
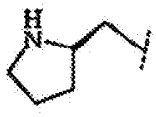
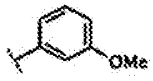
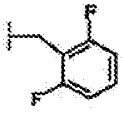
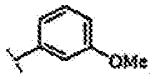
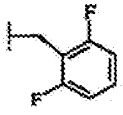
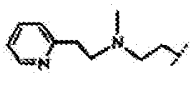
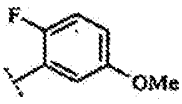
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-2	Me				569.6	590
9-3	Me				526.6	527
9-4	Me				485.5	486
9-5	Me				513.5	514
9-6	Me				529.5	530
9-7	Me				512.5	513
9-8	Me				518.6	519
9-9	Me				532.6	533
9-10	Me				427	428

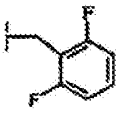
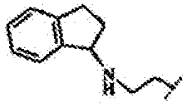
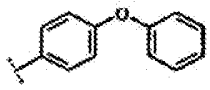
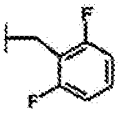
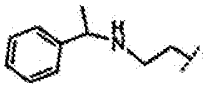
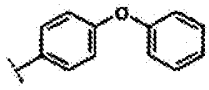
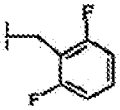
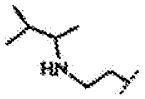
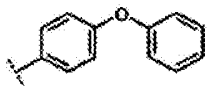
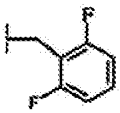
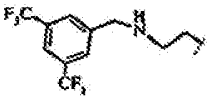
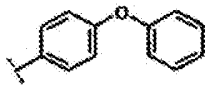
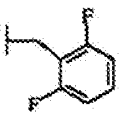
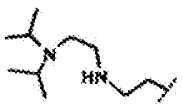
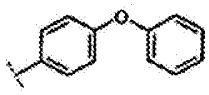
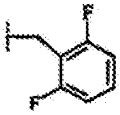
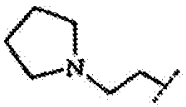
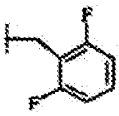
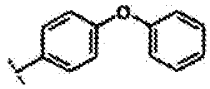
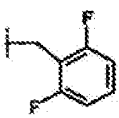
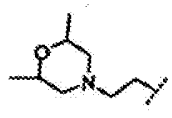
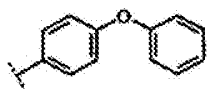
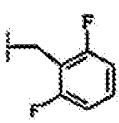
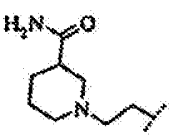
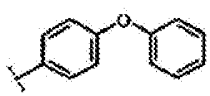
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-11	Me				505.6	506
9-12	Me				519.6	520
9-13	Me				520.6	521
9-14	Me				534.6	535
9-15	Me				532.6	533
9-16	Me				560.6	561
9-17	Me				534.6	535
9-18	Me				534.6	535
9-19	Me				529.6	530

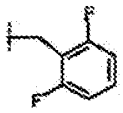
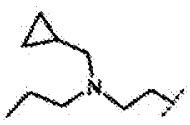
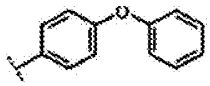
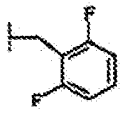
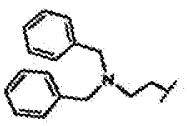
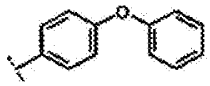
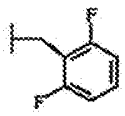
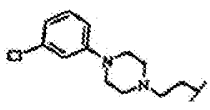
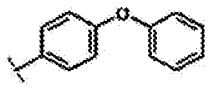
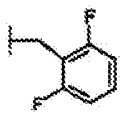
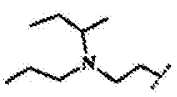
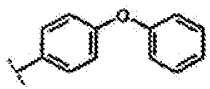
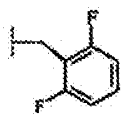
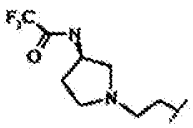
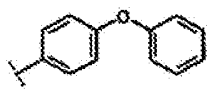
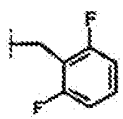
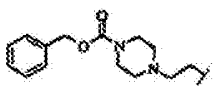
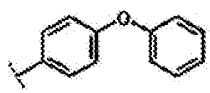
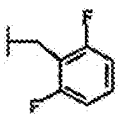
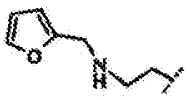
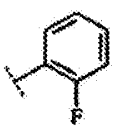
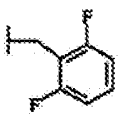
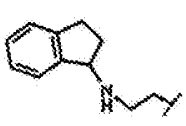
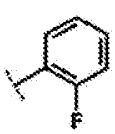
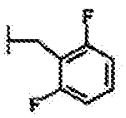
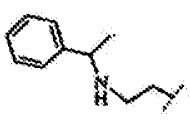
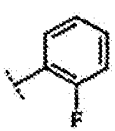
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-20	Me				549.6	550
9-21	Me				554.6	555
9-22	Me				554.6	555
9-23	Me				575.6	576
9-24	Me				538.6	539
9-25	Me				537.6	538
9-26	Me				441.5	442
9-27	Me				546.6	547
9-28	Me				538.6	539

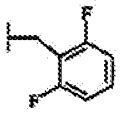
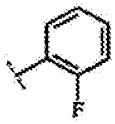
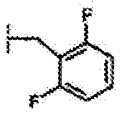
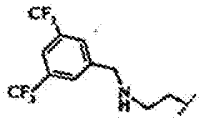
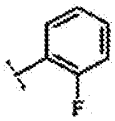
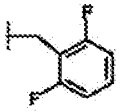
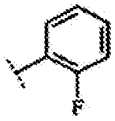
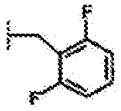
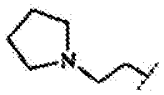
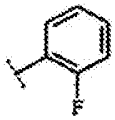
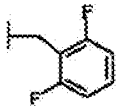
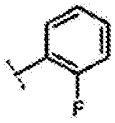
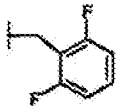
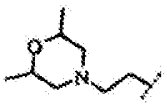
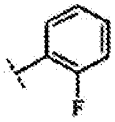
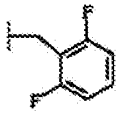
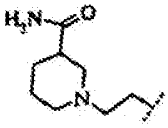
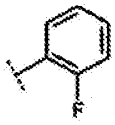
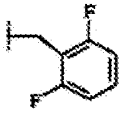
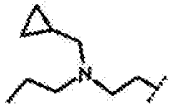
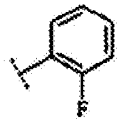
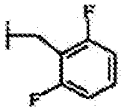
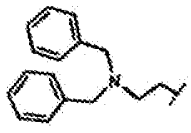
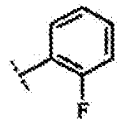
Continuação

Comp. No.	R_5	R_6	NR_1R_2 $(CR_{3a}CR_{3b})_n$	-Q-R_4	MW (calc.)	(obs.)
9-29	Me				579.6	447
9-30	Me				567.6	447
9-31	Me				533.6	534
9-32	Me				689.6	690
9-33	Me				590.7	591
9-34	Me				517.6	518
9-35	Me				666.7	667
9-36	Me				561.6	562
9-37	Me				574.6	575

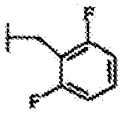
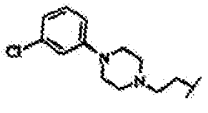
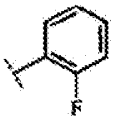
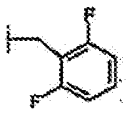
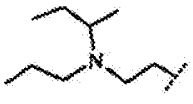
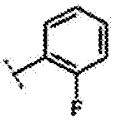
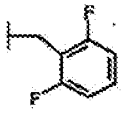
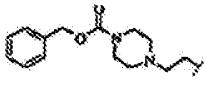
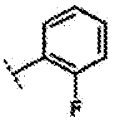
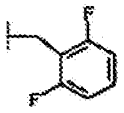
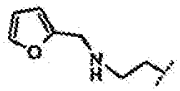
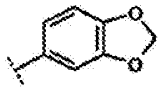
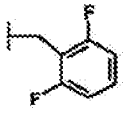
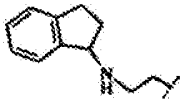
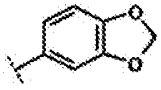
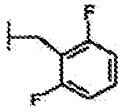
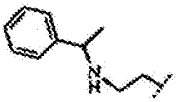
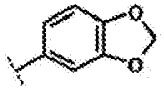
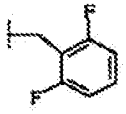
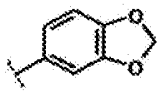
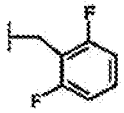
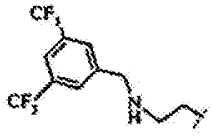
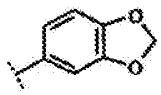
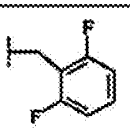
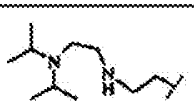
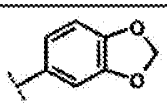
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-38	Me				559.6	560
9-39	Me				643.7	644
9-40	Me				643.1	643
9-41	Me				561.7	562
9-42	Me				628.6	629
9-43	Me				666.7	667
9-44	Me				469.5	373
9-45	Me				505.5	373
9-46	Me				493.5	373

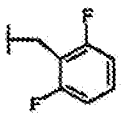
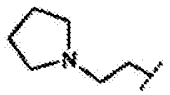
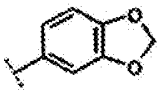
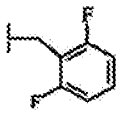
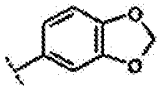
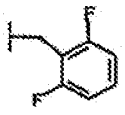
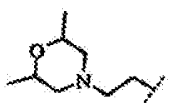
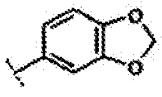
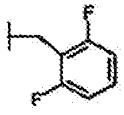
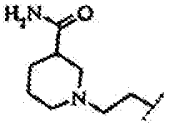
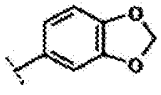
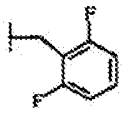
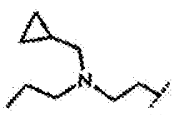
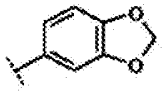
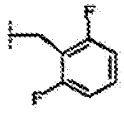
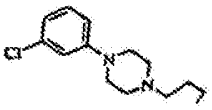
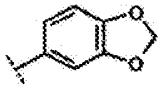
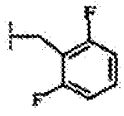
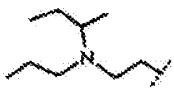
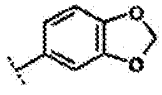
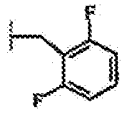
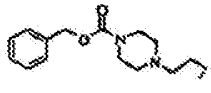
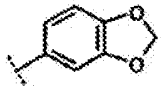
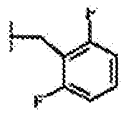
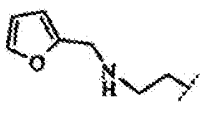
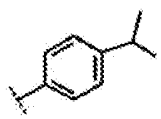
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-47	Me				459.5	373
9-48	Me				615.5	616
9-49	Me				516.6	517
9-50	Me				443.5	373
9-51	Me				592.6	593
9-52	Me				487.5	373
9-53	Me				500.5	501
9-54	Me				485.5	373
9-55	Me				569.6	372

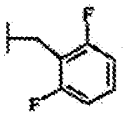
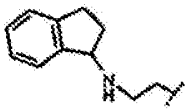
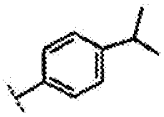
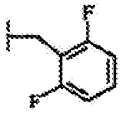
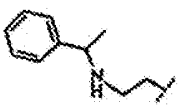
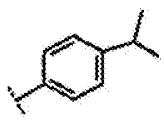
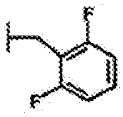
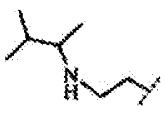
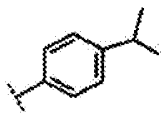
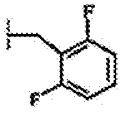
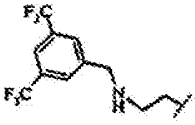
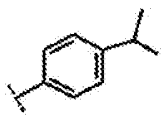
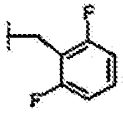
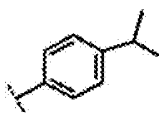
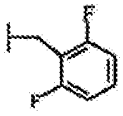
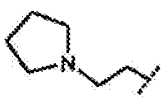
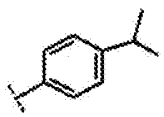
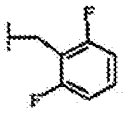
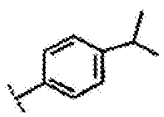
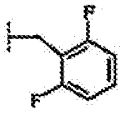
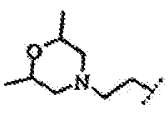
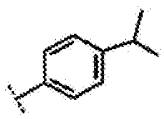
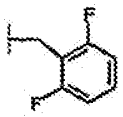
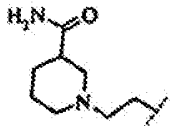
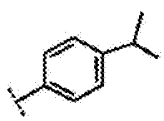
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-56	Me				569.0	569
9-57	Me				487.6	373
9-58	Me				592.6	593
9-59	Me				495.5	399
9-60	Me				531.6	532
9-61	Me				519.5	399
9-62	Me				485.5	399
9-63	Me				641.5	642
9-64	Me				542.6	543

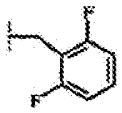
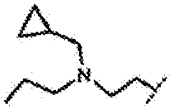
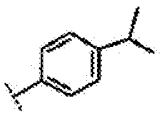
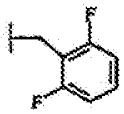
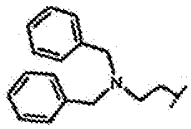
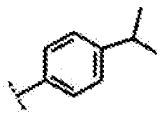
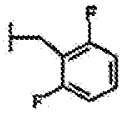
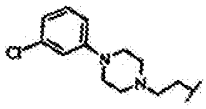
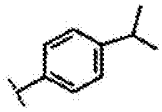
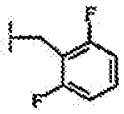
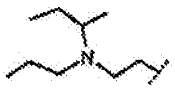
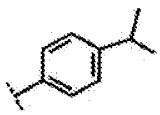
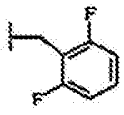
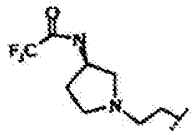
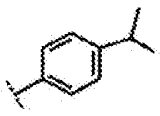
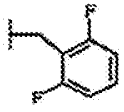
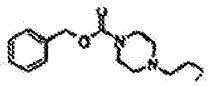
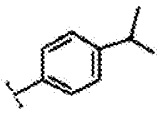
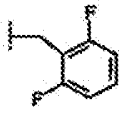
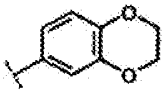
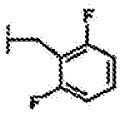
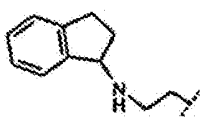
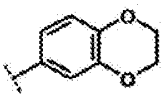
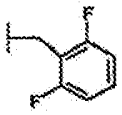
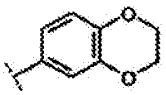
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-65	Me				469.5	470
9-66	Me				618.6	619
9-67	Me				513.5	514
9-68	Me				526.5	527
9-69	Me				511.6	512
9-70	Me				595.0	595
9-71	Me				513.6	399
9-72	Me				618.6	619
9-73	Me				493.6	397

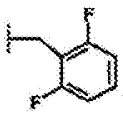
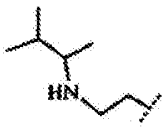
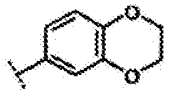
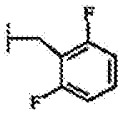
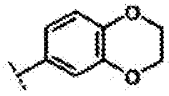
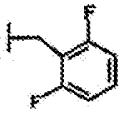
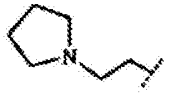
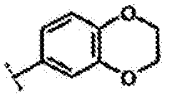
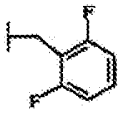
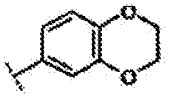
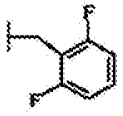
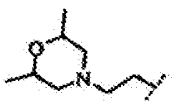
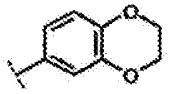
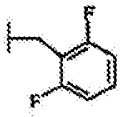
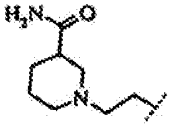
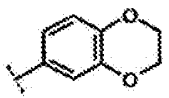
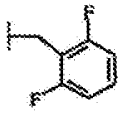
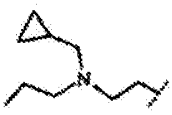
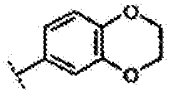
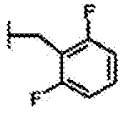
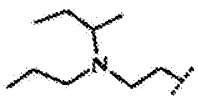
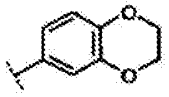
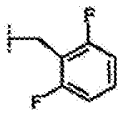
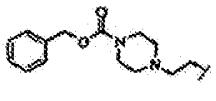
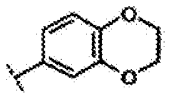
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	MW (obs.)
9-74	Me				529.6	397
9-75	Me				517.6	397
9-76	Me				483.6	397
9-77	Me				639.6	640
9-78	Me				540.7	541
9-79	Me				467.6	468
9-80	Me				616.7	617
9-81	Me				511.6	512
9-82	Me				524.6	525

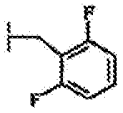
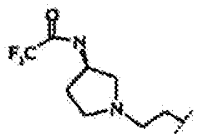
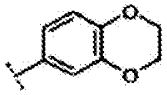
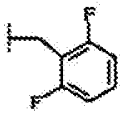
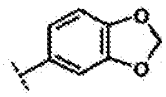
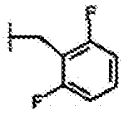
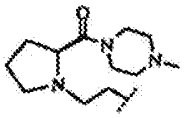
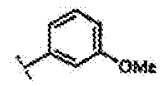
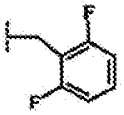
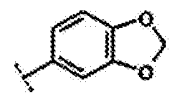
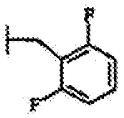
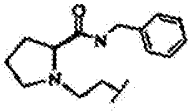
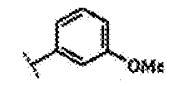
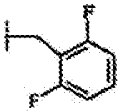
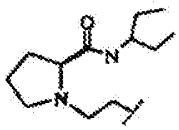
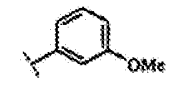
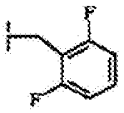
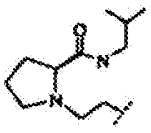
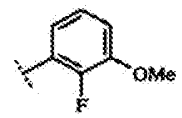
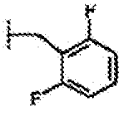
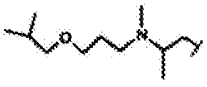
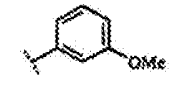
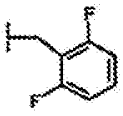
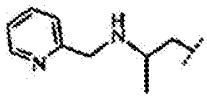
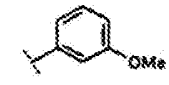
Continuação

Comp. No.	R_5	R_6	NR_1R_2- $(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	 (obs.)
9-83	Me				509.6	510
9-84	Me				593.7	594
9-85	Me				593.1	593
9-86	Me				511.7	512
9-87	Me				578.6	579
9-88	Me				616.7	617
9-89	Me				509.5	413
9-90	Me				545.6	413
9-91	Me				533.6	413

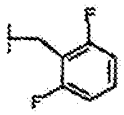
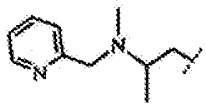
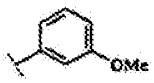
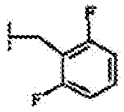
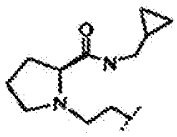
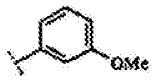
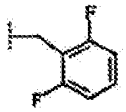
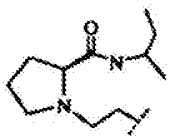
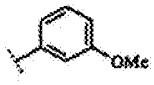
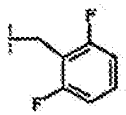
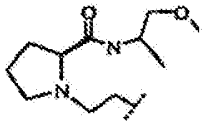
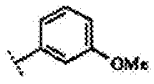
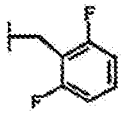
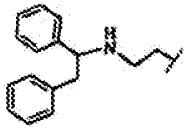
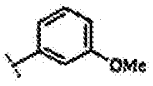
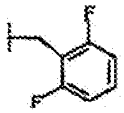
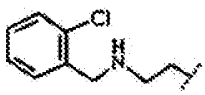
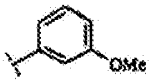
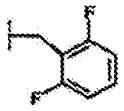
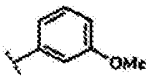
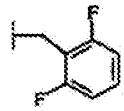
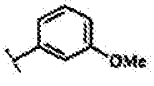
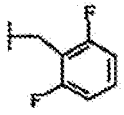
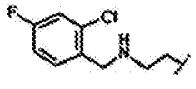
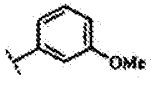
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-92	Me				499.6	500
9-93	Me				556.6	557
9-94	Me				483.5	484
9-95	Me				632.7	633
9-96	Me				527.6	528
9-97	Me				540.6	541
9-98	Me				525.6	526
9-99	Me				527.6	528
9-100	Me				632.7	633

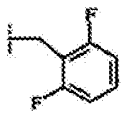
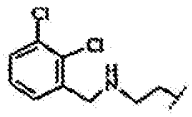
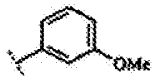
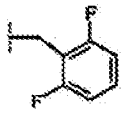
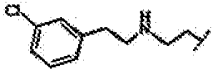
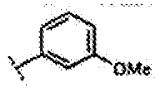
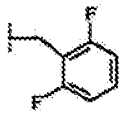
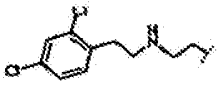
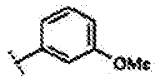
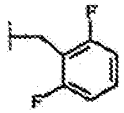
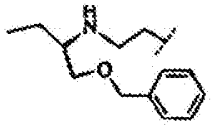
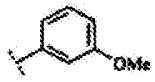
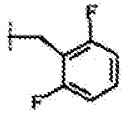
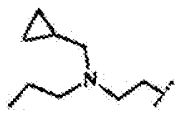
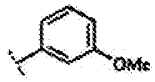
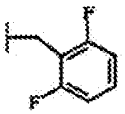
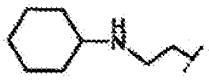
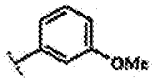
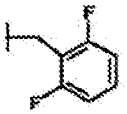
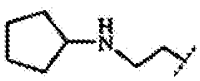
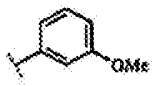
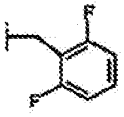
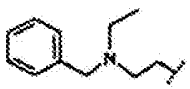
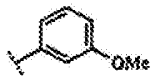
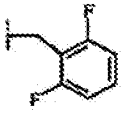
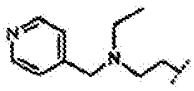
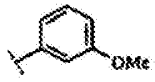
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-101	Me				554.5	555
9-102	Me				455.45	456
9-103	Me				581.66	
9-104	Me				545.58	546
9-105	Me				588.65	
9-106	Me				568.66	
9-107	Me				572.62	
9-108	Me				543.65	544.3
9-109	Me				506.55	507.2

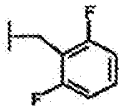
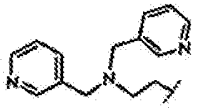
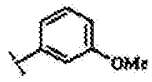
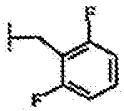
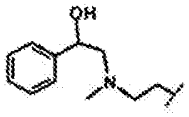
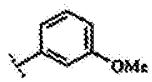
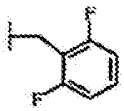
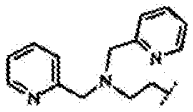
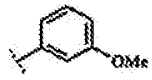
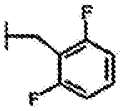
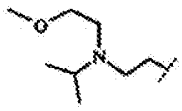
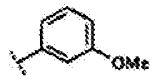
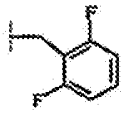
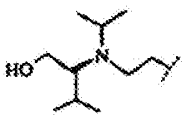
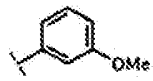
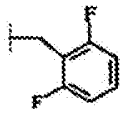
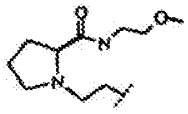
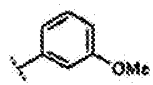
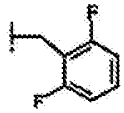
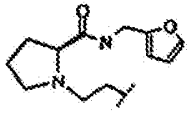
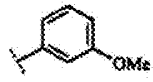
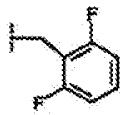
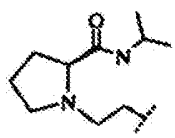
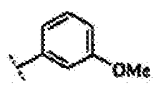
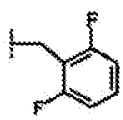
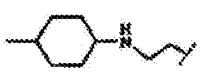
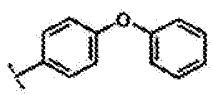
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-110	Me				520.57	521.2
9-111	Me				552.61	553.3
9-112	Me				554.63	555.3
9-113	Me				570.63	571.3
9-114	Me				581.66	582.2
9-115	Me				525.98	526.2
9-116	Me				540.00	540.2
9-117	Me				525.98	526.2
9-118	Me				543.97	544.2

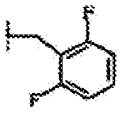
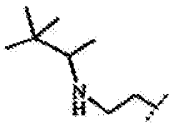
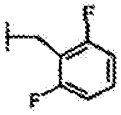
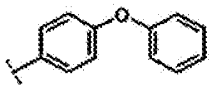
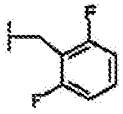
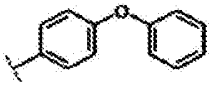
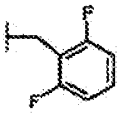
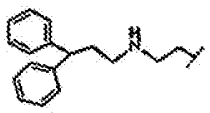
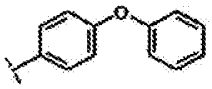
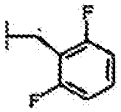
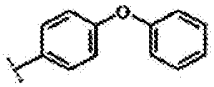
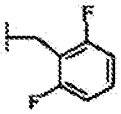
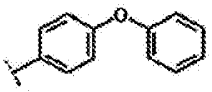
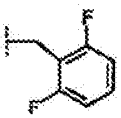
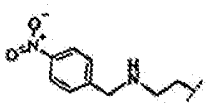
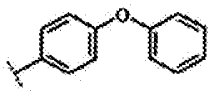
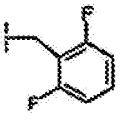
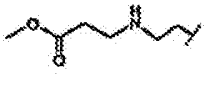
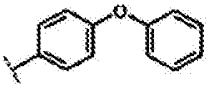
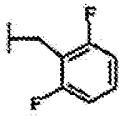
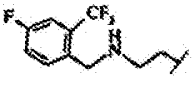
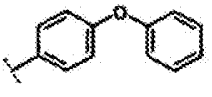
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-119	Me				560.42	561.1
9-120	Me				540.60	540.2
9-121	Me				574.45	574.0
9-122	Me				563.64	564.2
9-123	Me				497.58	498.2
9-124	Me				483.55	484.2
9-125	Me				469.52	470
9-126	Me				519.58	520.2
9-127	Me				520.57	521.2

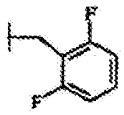
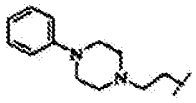
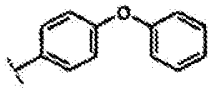
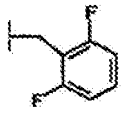
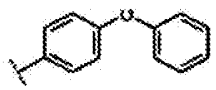
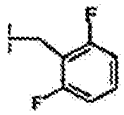
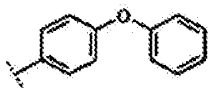
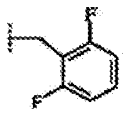
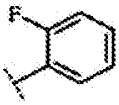
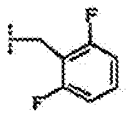
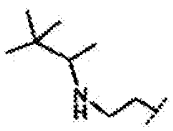
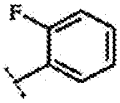
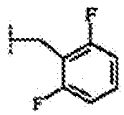
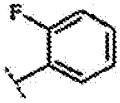
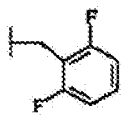
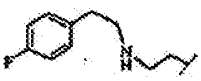
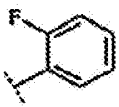
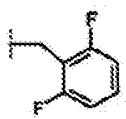
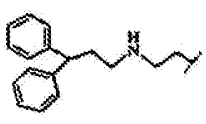
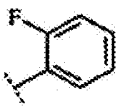
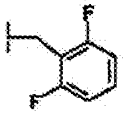
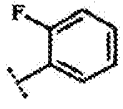
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-128	Me				583.63	584.2
9-129	Me				535.58	536.2
9-130	Me				583.63	584.2
9-131	Me				501.57	502.2
9-132	Me				529.62	528
9-133	Me				556.60	557
9-134	Me				578.61	578
9-135	Me				540.60	541
9-136	Me				559.65	560.4

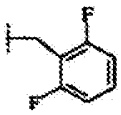
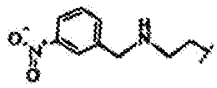
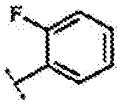
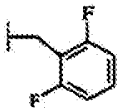
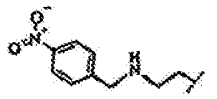
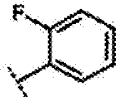
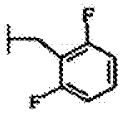
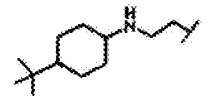
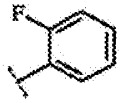
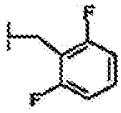
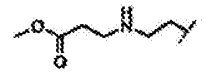
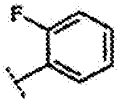
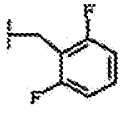
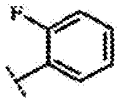
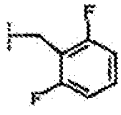
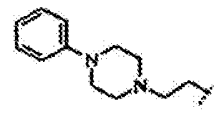
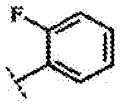
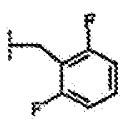
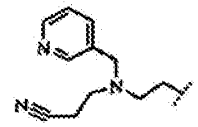
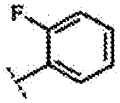
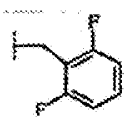
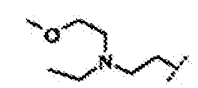
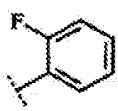
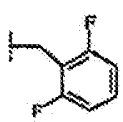
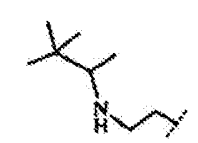
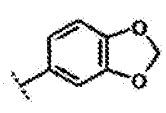
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-137	Me				547.64	548.5
9-138	Me				545.50	546.4
9-139	Me				585.62	586.4
9-140	Me				657.75	658.4
9-141	Me				561.66	562.6
9-142	Me				598.60	599.3
9-143	Me				598.60	599.3
9-144	Me				549.57	550.4
9-145	Me				639.59	640.4

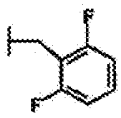
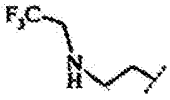
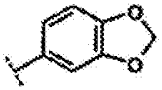
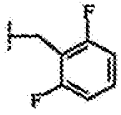
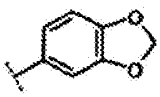
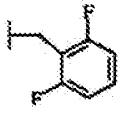
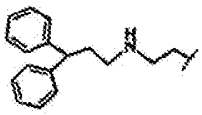
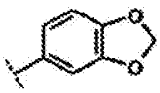
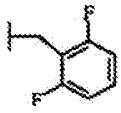
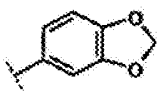
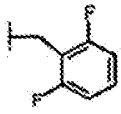
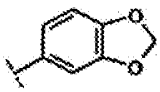
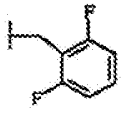
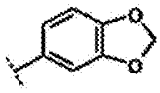
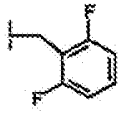
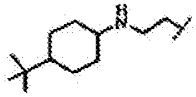
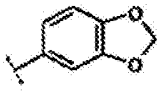
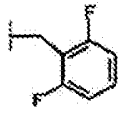
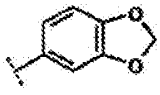
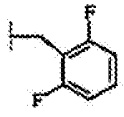
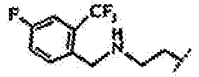
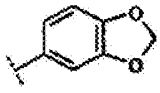
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-146	Me				608.68	609.4
9-147	Me				607.65	608.2
9-148	Me				549.61	550.4
9-149	Me				485.54	486.4
9-150	Me				473.53	474
9-151	Me				471.39	472.2
9-152	Me				511.51	512.4
9-153	Me				583.65	584.2
9-154	Me				487.56	488.2

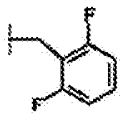
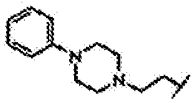
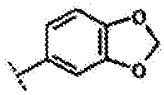
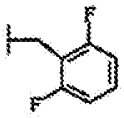
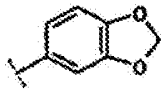
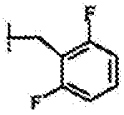
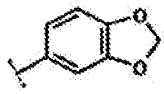
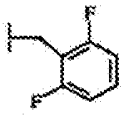
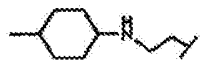
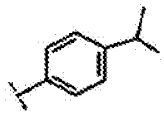
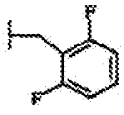
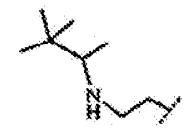
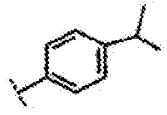
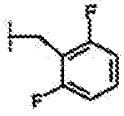
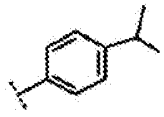
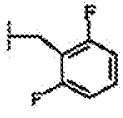
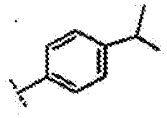
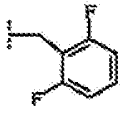
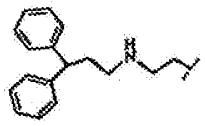
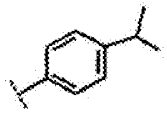
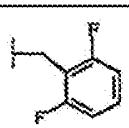
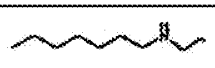
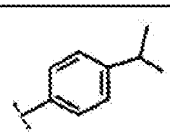
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-155	Me				524.49	525.4
9-156	Me				524.49	525.4
9-157	Me				527.62	528.4
9-158	Me				475.46	476.3
9-159	Me				565.48	566.4
9-160	Me				534.57	535.4
9-161	Me				533.55	534.5
9-162	Me				475.50	476.3
9-163	Me				499.55	500.4

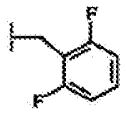
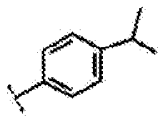
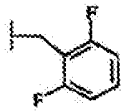
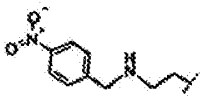
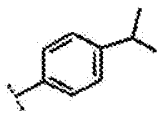
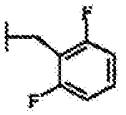
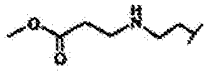
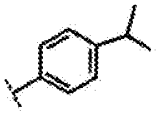
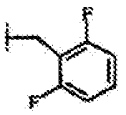
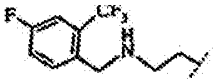
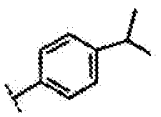
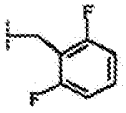
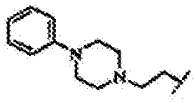
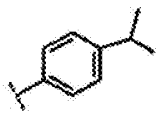
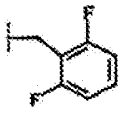
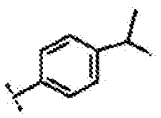
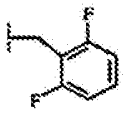
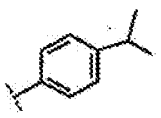
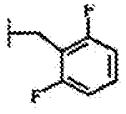
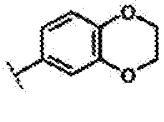
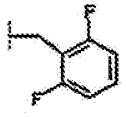
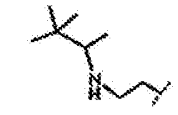
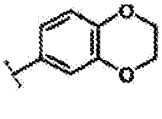
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-164	Me				497.41	498.3
9-165	Me				537.53	538.4
9-166	Me				609.67	610.3
9-167	Me				513.58	514.6
9-168	Me				550.51	551.3
9-169	Me				550.51	551.2
9-170	Me				553.64	554.3
9-171	Me				501.48	502.3
9-172	Me				591.50	592.4

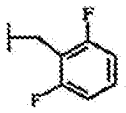
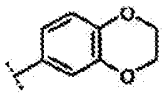
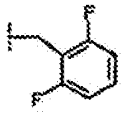
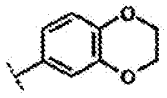
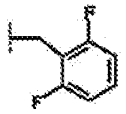
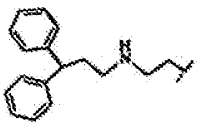
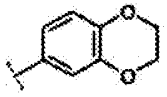
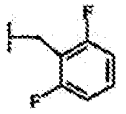
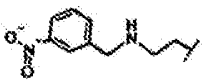
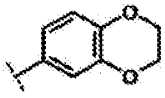
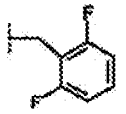
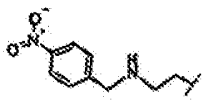
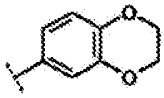
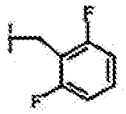
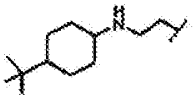
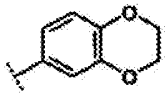
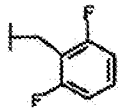
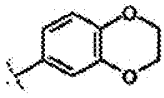
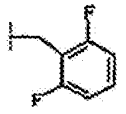
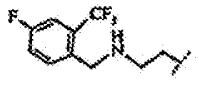
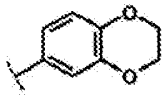
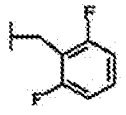
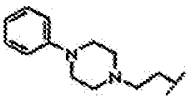
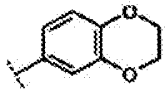
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-173	Me				560.59	561.3
9-174	Me				559.57	560.4
9-175	Me				501.52	502.3
9-176	Me				509.63	510.6
9-177	Me				497.62	498.5
9-178	Me				495.48	496.5
9-179	Me				535.60	536.6
9-180	Me				607.74	608.4
9-181	Me				511.65	512.5

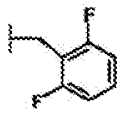
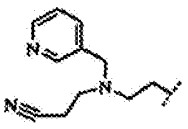
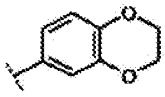
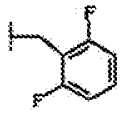
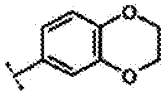
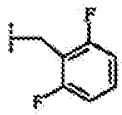
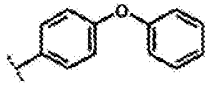
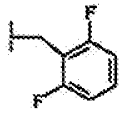
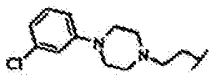
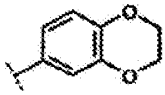
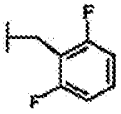
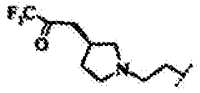
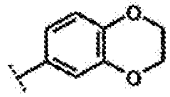
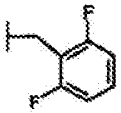
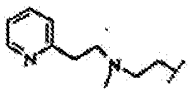
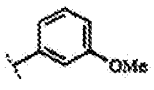
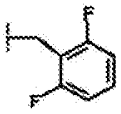
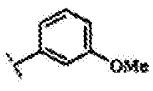
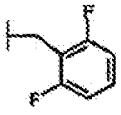
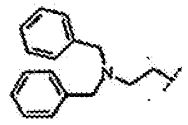
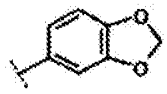
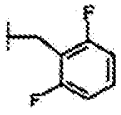
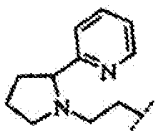
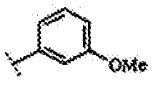
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-182	Me				548.58	549.4
9-183	Me				551.71	552.4
9-184	Me				499.55	500.4
9-185	Me				589.57	590.5
9-186	Me				558.66	559.3
9-187	Me				557.64	558.3
9-188	Me				499.59	500.4
9-189	Me				525.59	526.4
9-190	Me				513.58	514.2

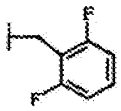
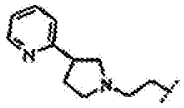
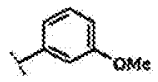
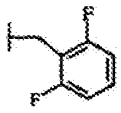
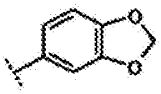
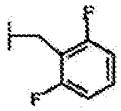
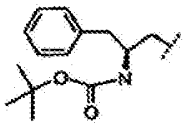
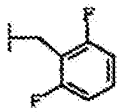
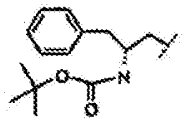
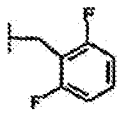
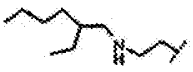
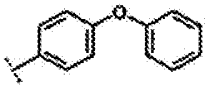
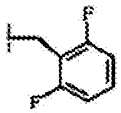
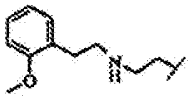
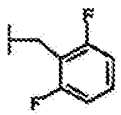
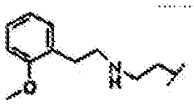
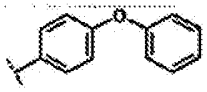
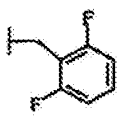
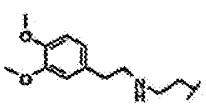
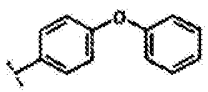
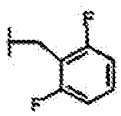
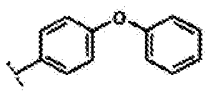
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-191	Me				511.44	512.5
9-192	Me				551.56	552.3
9-193	Me				623.69	624.4
9-194	Me				564.54	565.4
9-195	Me				564.54	565.4
9-196	Me				567.67	568.5
9-197	Me				515.51	516.3
9-198	Me				605.53	606.4
9-199	Me				574.6	575.4

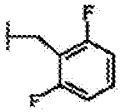
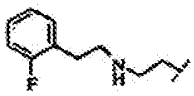
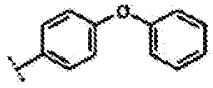
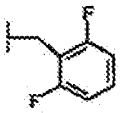
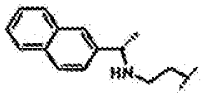
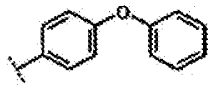
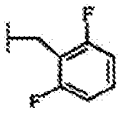
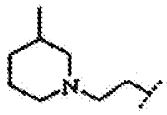
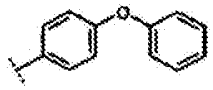
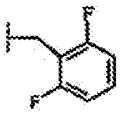
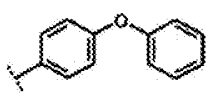
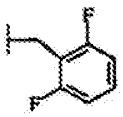
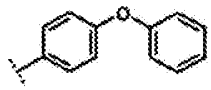
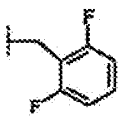
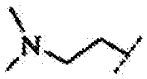
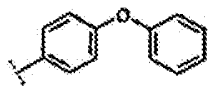
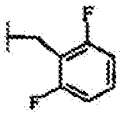
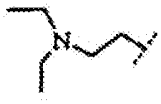
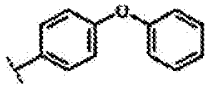
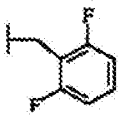
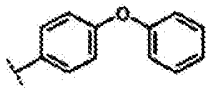
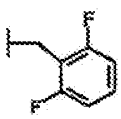
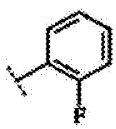
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-200	Me				573.6	574.3
9-201	Me				515.6	516.3
9-202	Me				543.56	544.2
9-203	Me				609.07	609.2
9-204	Me				593.54	595.2
9-205	Me				498.62	499.3
9-206	Me				484.59	485.2
9-207	Me				595.64	596.4
9-208	Me				532.58	533.2

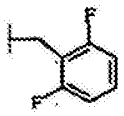
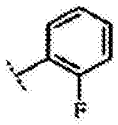
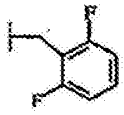
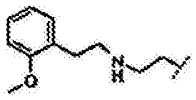
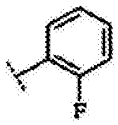
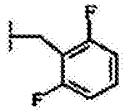
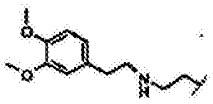
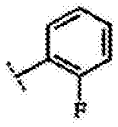
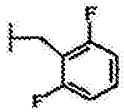
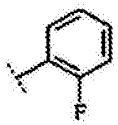
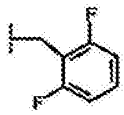
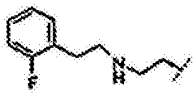
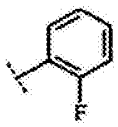
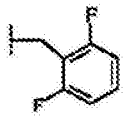
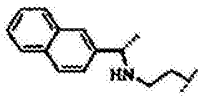
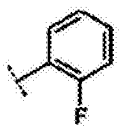
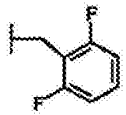
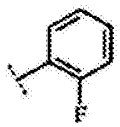
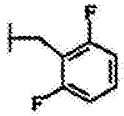
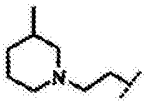
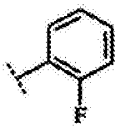
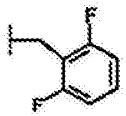
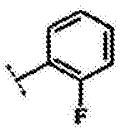
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-209	Me				532.58	533.2
9-210	Me				574.62	575
Referência 9-211	Me			**Br**	564.42	466/464
Referência 9-212	Me			**Br**	564.42	464/466
9-213	Me				575.69	576.3
9-214	Me				597.65	535.3
9-215	Me				597.65	598.2
9-216	Me				627.68	628.3
9-217	Me				517.57	518.2

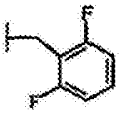
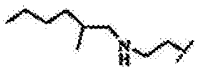
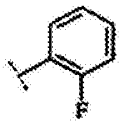
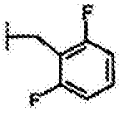
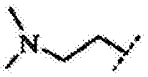
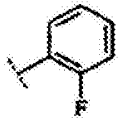
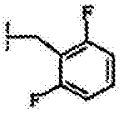
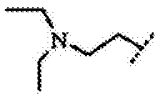
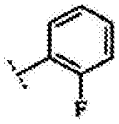
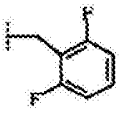
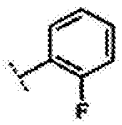
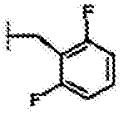
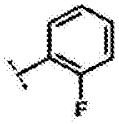
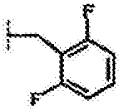
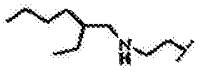
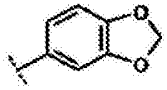
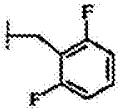
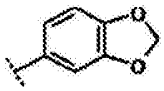
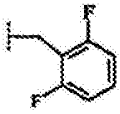
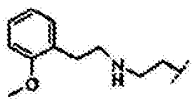
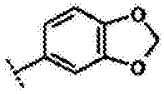
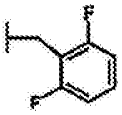
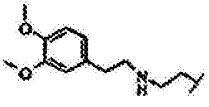
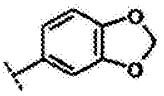
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-218	Me				585.62	586.2
9-219	Me				617.69	618.2
9-220	Me				545.62	546.2
9-221	Me				576.68	577.3
9-222	Me				533.61	534.2
9-223	Me				491.53	492.2
9-224	Me				519.58	520.2
9-225	Me				622.71	623.3
9-226	Me				501.59	502.3

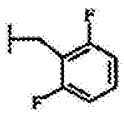
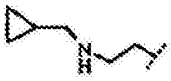
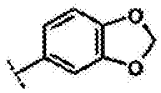
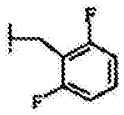
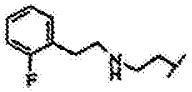
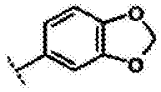
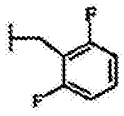
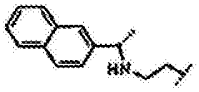
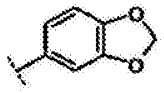
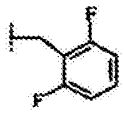
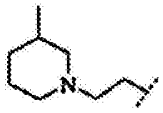
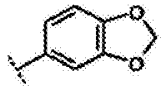
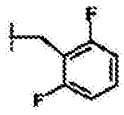
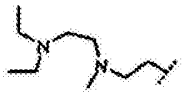
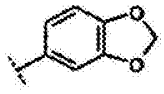
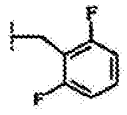
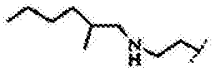
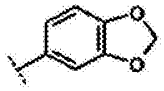
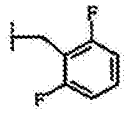
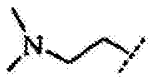
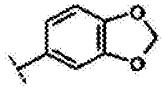
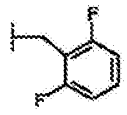
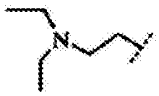
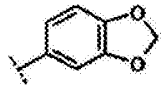
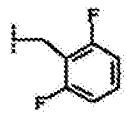
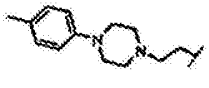
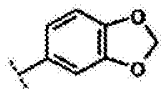
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-227	Me				460.49	461.2
9-228	Me				523.55	524.2
9-229	Me				553.57	554.2
9-230	Me				443.46	444.2
9-231	Me				511.51	512.2
9-232	Me				543.58	544.2
9-233	Me				429.44	430.1
9-234	Me				471.52	472.2
9-235	Me				502.57	503.3

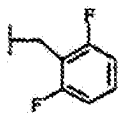
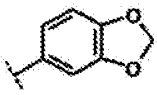
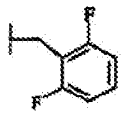
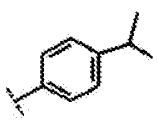
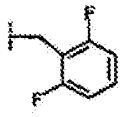
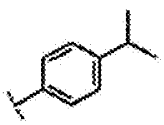
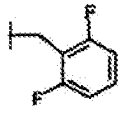
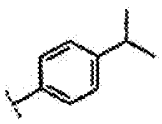
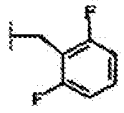
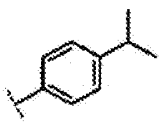
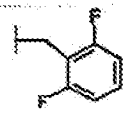
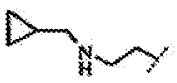
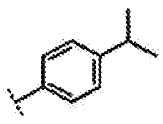
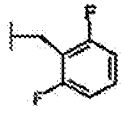
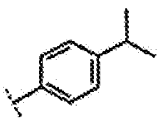
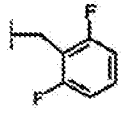
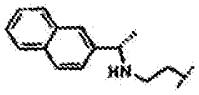
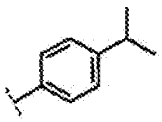
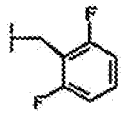
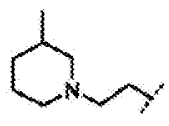
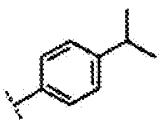
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-236	Me				459.50	460.2
9-237	Me				417.42	418.1
9-238	Me				445.46	446.1
9-239	Me				548.60	549.2
9-240	Me				500.56	501.2
9-241	Me				527.60	528.3
9-242	Me				486.51	487.2
9-243	Me				549.57	550.2
9-244	Me				579.59	580.2

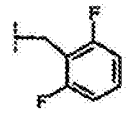
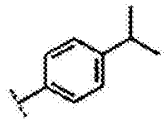
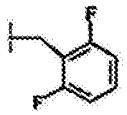
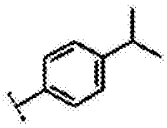
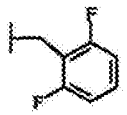
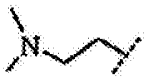
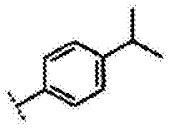
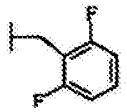
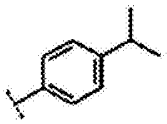
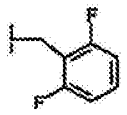
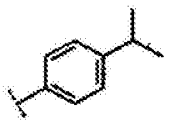
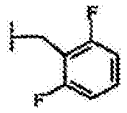
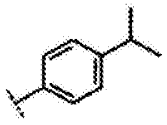
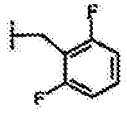
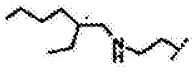
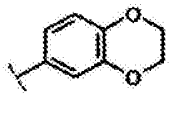
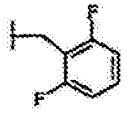
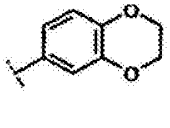
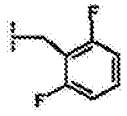
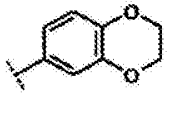
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-245	Me				469.48	470.2
9-246	Me				537.53	538.2
9-247	Me				569.60	570.2
9-248	Me				497.53	498.2
9-249	Me				528.59	529.2
9-250	Me				485.52	486.2
9-251	Me				443.44	444.1
9-252	Me				471.50	472.2
9-253	Me				574.62	575.2

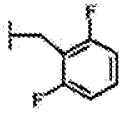
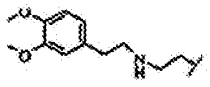
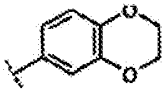
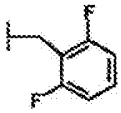
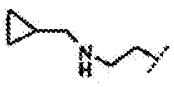
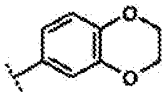
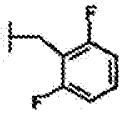
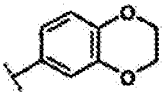
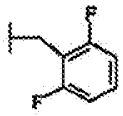
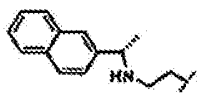
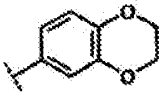
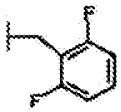
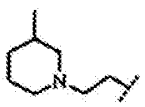
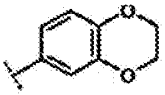
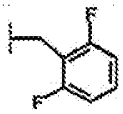
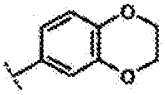
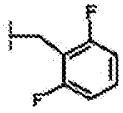
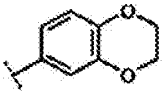
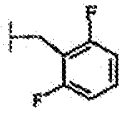
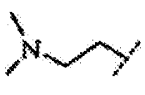
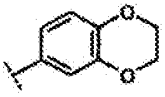
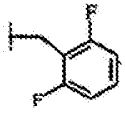
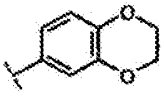
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-254	Me				526.58	527.2
9-255	Me				525.68	526.3
9-256	Me				484.58	485.2
9-257	Me				547.64	548.3
9-258	Me				577.66	578.3
9-259	Me				467.55	468.2
9-260	Me				535.60	536.2
9-261	Me				567.67	568.3
9-262	Me				495.61	496.2

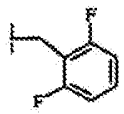
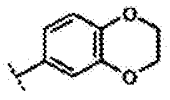
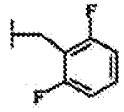
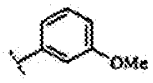
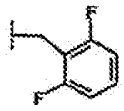
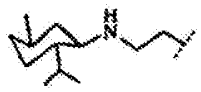
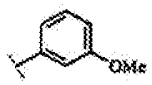
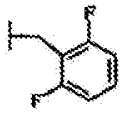
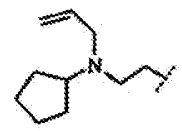
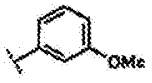
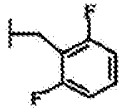
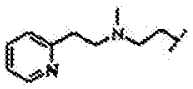
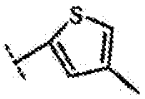
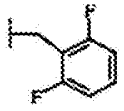
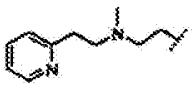
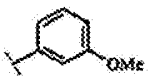
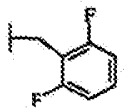
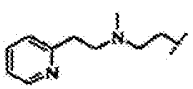
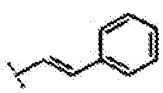
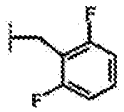
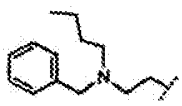
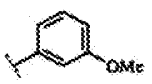
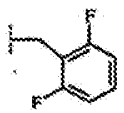
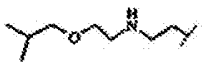
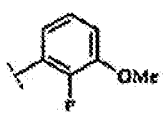
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-263	Me				526.66	527.3
9-264	Me				483.59	484.25
9-265	Me				441.51	442.2
9-266	Me				469.57	470.3
9-267	Me				572.69	573.3
9-268	Me				524.65	525.3
9-269	Me				541.63	542.3
9-270	Me				500.54	501.2
9-271	Me				563.59	564.2

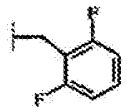
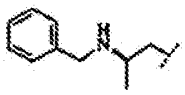
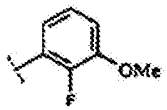
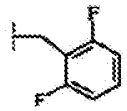
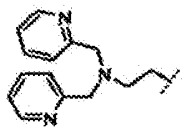
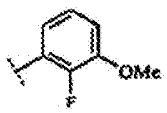
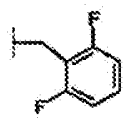
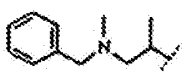
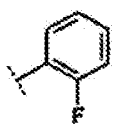
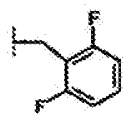
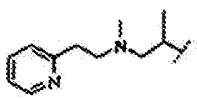
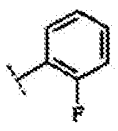
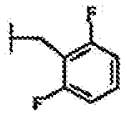
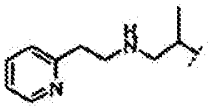
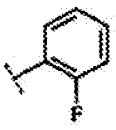
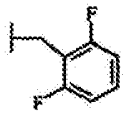
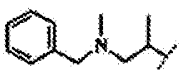
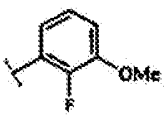
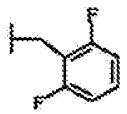
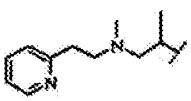
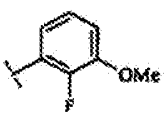
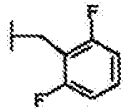
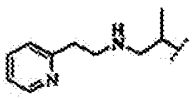
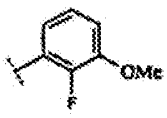
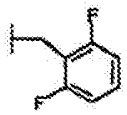
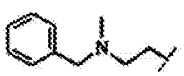
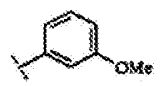
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-272	Me				593.62	594.2
9-273	Me				483.51	484.2
9-274	Me				551.56	552.2
9-275	Me				583.63	584.2
9-276	Me				511.56	512.2
9-277	Me				542.62	543.3
9-278	Me				499.55	500.3
9-279	Me				457.47	458.2
9-280	Me				485.52	486.2

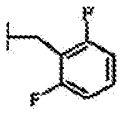
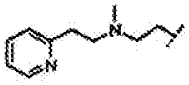
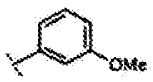
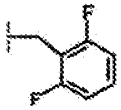
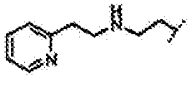
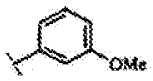
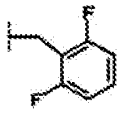
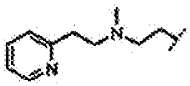
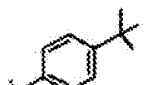
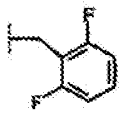
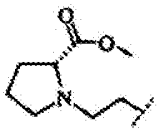
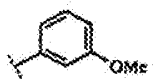
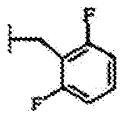
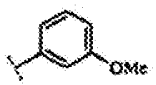
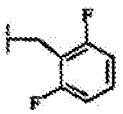
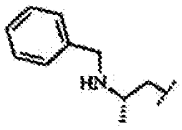
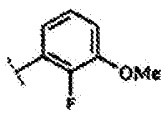
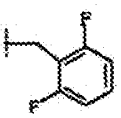
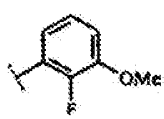
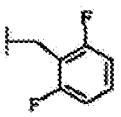
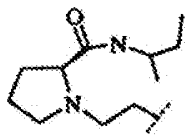
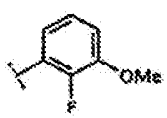
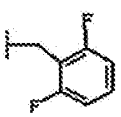
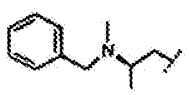
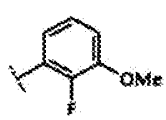
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-281	Me				588.65	589.3
9-282	Me				560.42	560
9-283	Me				539.66	540
9-284	Me				509.59	510
Referência 9-285	Me				510.60	511.5
9-286	Me				538.56	539.5
Referência 9-287	Me				516.58	517.4
9-288	Me				547.64	547
9-289	Me				519.56	534

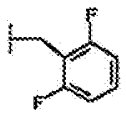
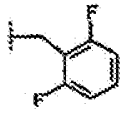
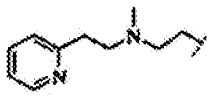
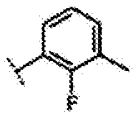
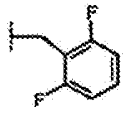
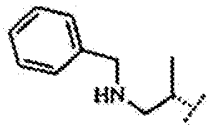
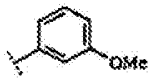
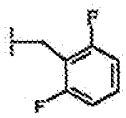
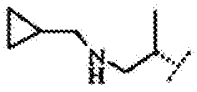
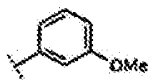
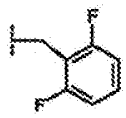
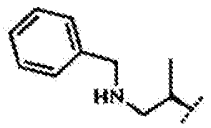
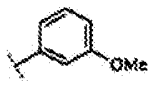
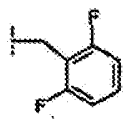
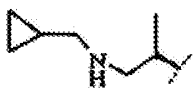
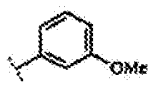
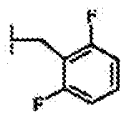
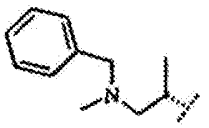
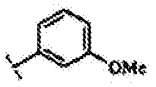
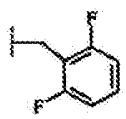
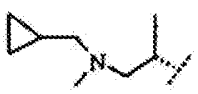
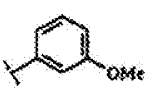
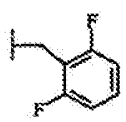
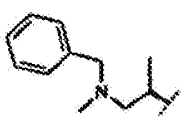
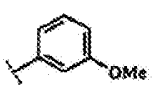
Continuação

Comp. No.	R_5	R_6	NR_1R_2 $(CR_{3a}CR_{3b})_n$	-Q-R_4	MW (calc.)	(obs.)
9-290	Me				523.55	524.2
9-291	Me				615.65	616.3
9-292	Me				507.55	508.2
9-293	Me				522.56	523.6
9-294	Me				508.54	509.5
9-295	Me				537.57	538.7
9-296	Me				552.59	553.2
9-297	Me				538.56	539.5
9-298	Me				469.58	470.3

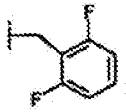
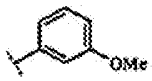
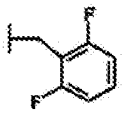
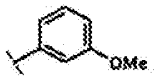
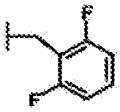
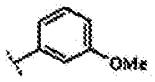
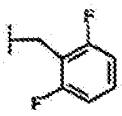
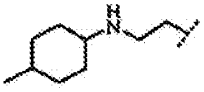
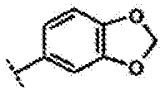
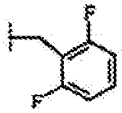
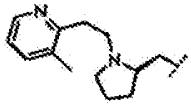
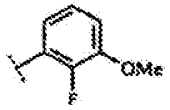
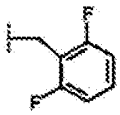
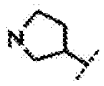
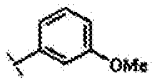
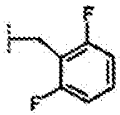
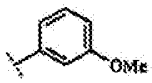
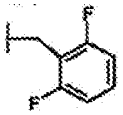
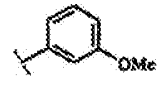
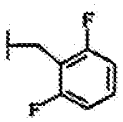
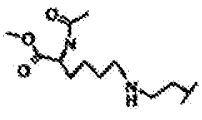
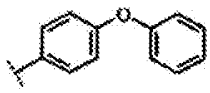
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-299	Me				484.59	485.3
9-300	Me				470.57	471.3
9-301	Me				546.65	547
9-302	Me				513.53	514
9-303	Me				495.56	496
9-304	Me				523.55	524
9-305	Me				537.57	538
9-306	Me				572.62	573
9-307	Me				537.57	538.3

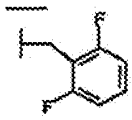
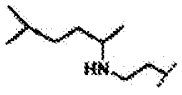
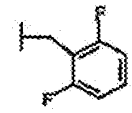
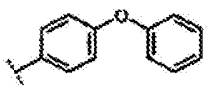
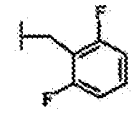
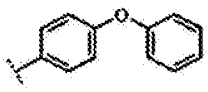
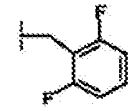
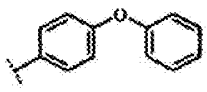
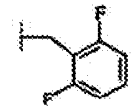
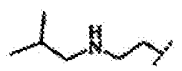
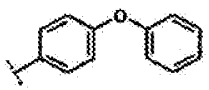
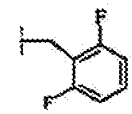
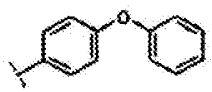
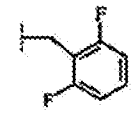
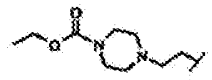
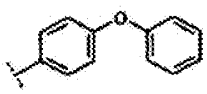
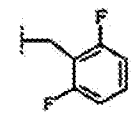
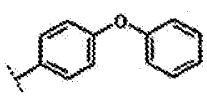
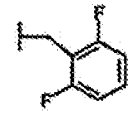
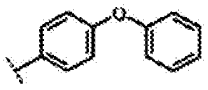
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	MW (obs.)
Referência 9-308	Me			Br	505.36	505/507
9-309	Me				522.56	523
9-310	Me				505.56	506
9-311	Me				469.52	470
9-312	Me				505.56	506
9-313	Me				469.52	470
9-314	Me				519.58	520
9-315	Me				483.55	484
9-316	Me				519.58	520

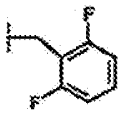
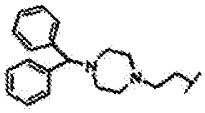
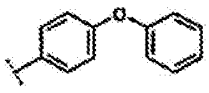
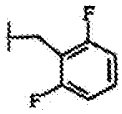
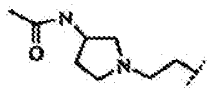
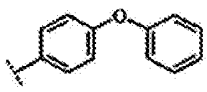
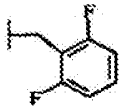
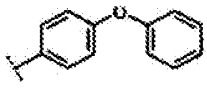
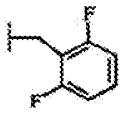
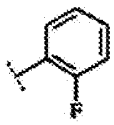
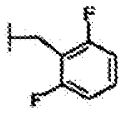
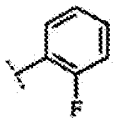
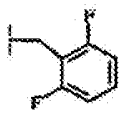
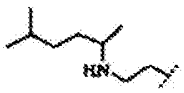
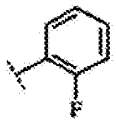
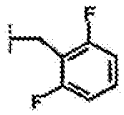
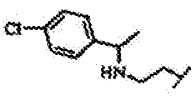
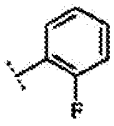
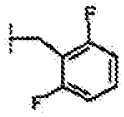
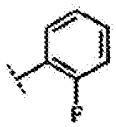
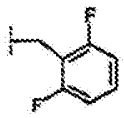
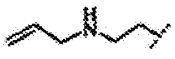
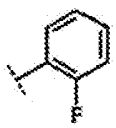
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-317	Me				483.55	484
9-318	Me				534.60	535.3
9-319	Me				534.60	535.3
9-320	Me				511.56	512.5
9-321	Me				578.63	598
9-322	Me				427.44	428.1
9-323	Me				517.57	518.2
9-324	Me				518.56	519.2
9-325	Me				648.70	649.5

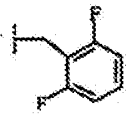
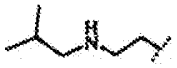
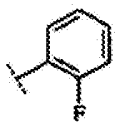
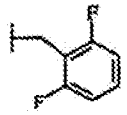
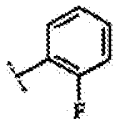
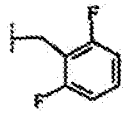
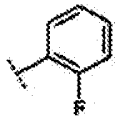
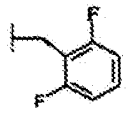
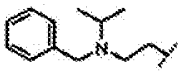
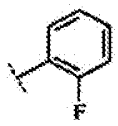
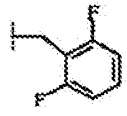
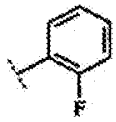
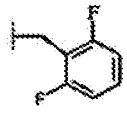
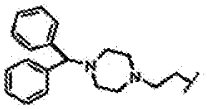
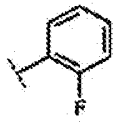
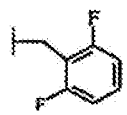
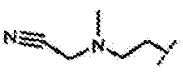
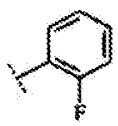
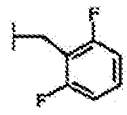
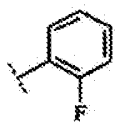
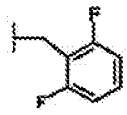
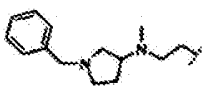
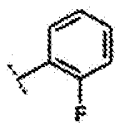
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-326	Me				561.66	562.5
9-327	Me				602.07	447.3
9-328	Me				491.53	447.4
9-329	Me				503.54	447.3
9-330	Me				519.58	447.2
9-331	Me				676.68	677.5
9-332	Me				604.65	605.3
9-333	Me				595.68	596.4
9-334	Me				632.70	633.4

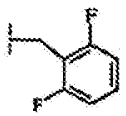
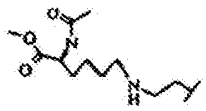
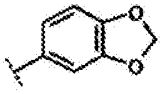
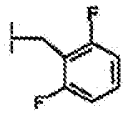
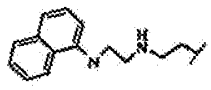
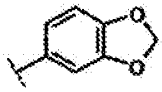
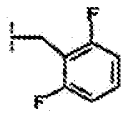
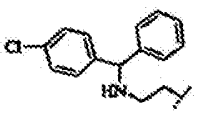
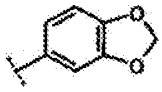
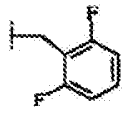
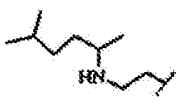
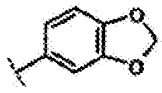
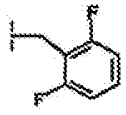
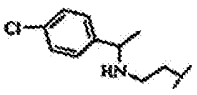
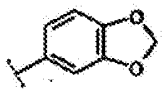
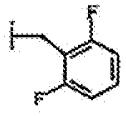
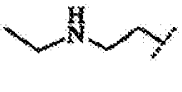
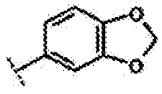
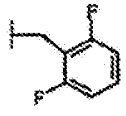
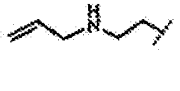
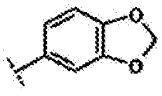
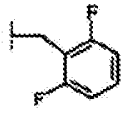
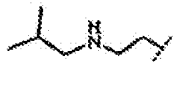
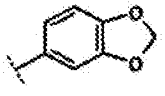
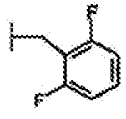
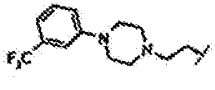
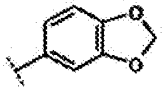
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-335	Me				698.81	699.5
9-336	Me				574.62	575.4
9-337	Me				636.73	637.5
9-338	Me				574.59	575.4
9-339	Me				558.60	559.3
9-340	Me				487.56	488.3
9-341	Me				527.97	373.3
9-342	Me				417.42	373.1
9-343	Me				429.44	373.3

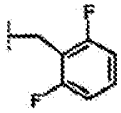
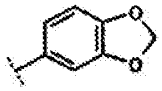
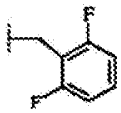
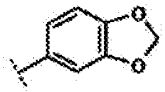
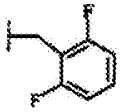
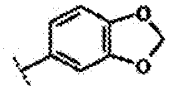
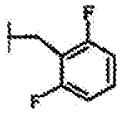
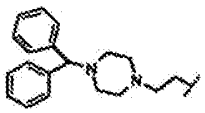
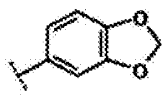
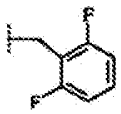
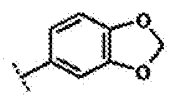
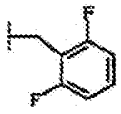
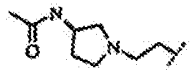
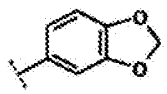
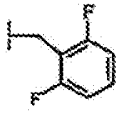
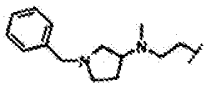
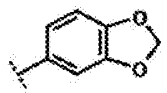
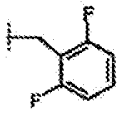
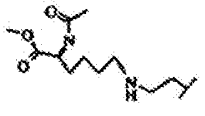
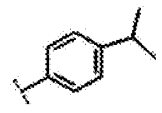
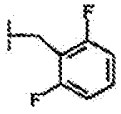
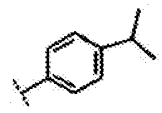
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-344	Me				445.48	373.2
9-345	Me				602.57	603.5
9-346	Me				530.54	531.3
9-347	Me				521.58	373.1
9-348	Me				558.60	559.3
9-349	Me				624.70	625.3
9-350	Me				442.43	373.3
9-351	Me				500.51	501.4
9-352	Me				562.63	563.4

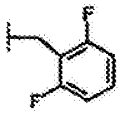
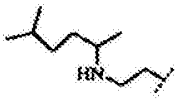
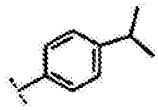
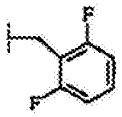
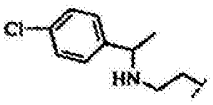
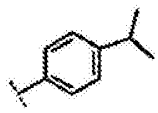
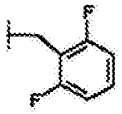
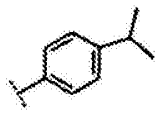
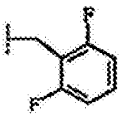
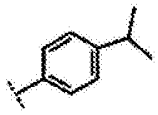
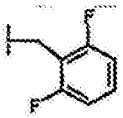
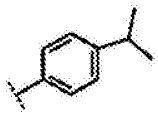
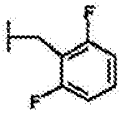
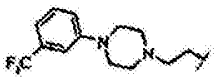
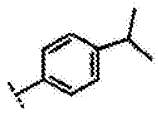
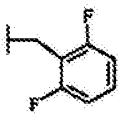
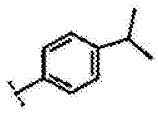
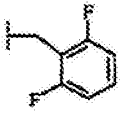
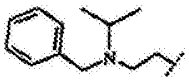
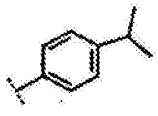
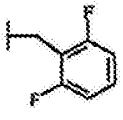
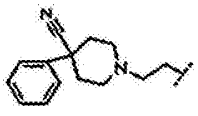
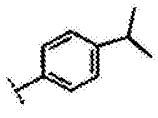
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-353	Me				600.61	601.3
9-354	Me				584.62	585.2
9-355	Me				616.06	201.3
9-356	Me				513.58	399.2
9-357	Me				553.99	399.2
9-358	Me				443.44	399.3
9-359	Me				455.45	399.2
9-360	Me				471.50	399.3
9-361	Me				628.59	629.6

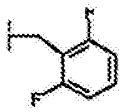
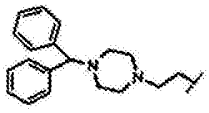
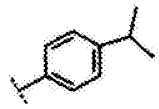
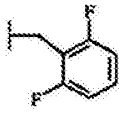
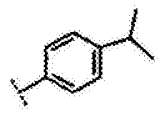
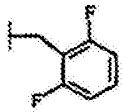
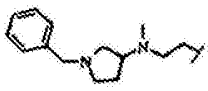
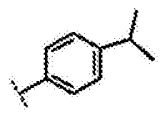
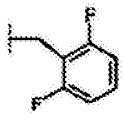
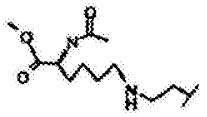
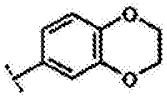
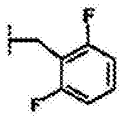
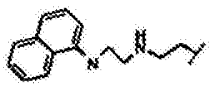
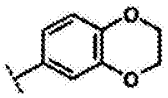
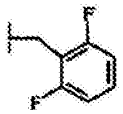
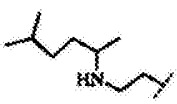
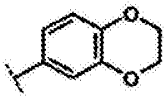
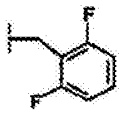
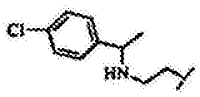
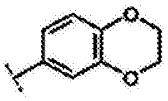
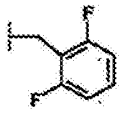
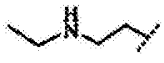
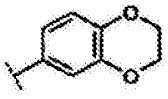
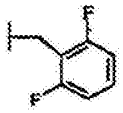
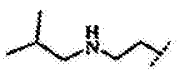
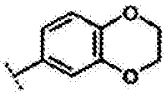
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-362	Me				556.56	557.3
9-363	Me				547.59	548.5
9-364	Me				584.62	585.2
9-365	Me				650.72	651.2
9-366	Me				468.45	399.1
9-367	Me				526.53	527.3
9-368	Me				588.65	589.5
9-369	Me				598.68	599.4
9-370	Me				582.69	583.4

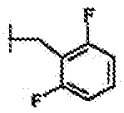
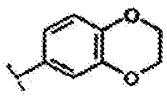
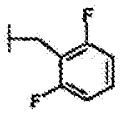
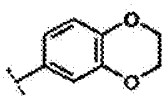
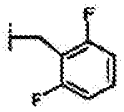
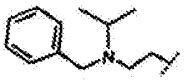
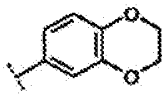
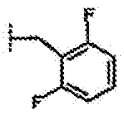
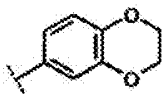
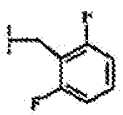
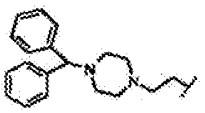
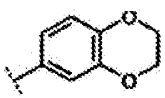
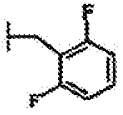
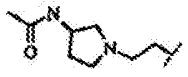
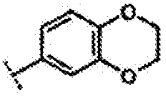
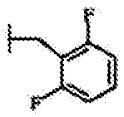
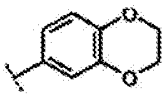
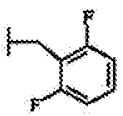
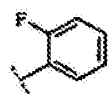
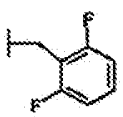
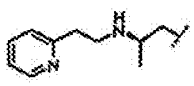
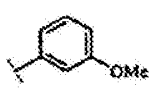
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-371	Me				511.65	512.5
9-372	Me				552.06	397
9-373	Me				441.51	397.1
9-374	Me				453.53	397
9-375	Me				469.57	397.1
9-376	Me				626.66	627.6
9-377	Me				554.63	555.5
9-378	Me				545.67	546.4
9-379	Me				582.69	583.3

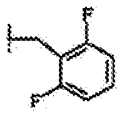
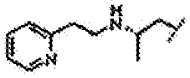
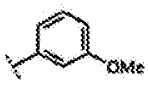
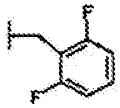
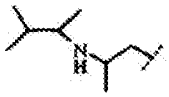
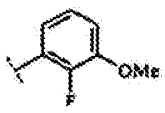
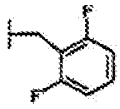
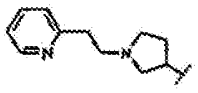
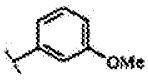
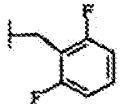
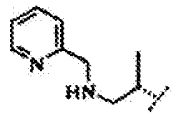
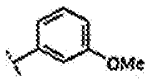
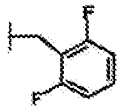
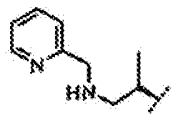
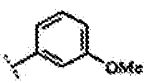
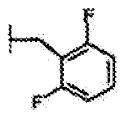
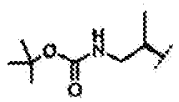
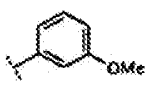
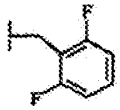
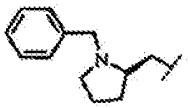
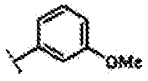
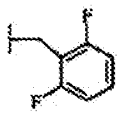
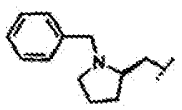
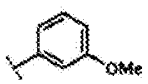
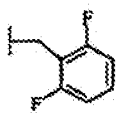
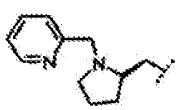
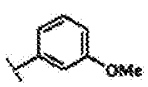
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-380	Me				648.79	649.6
9-381	Me				524.60	525.5
9-382	Me				586.72	587.5
9-383	Me				614.64	615.5
9-384	Me				598.64	599.4
9-385	Me				527.60	528.2
9-386	Me				568.01	568.5
9-387	Me				457.47	458
9-388	Me				485.52	486.3

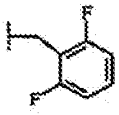
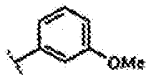
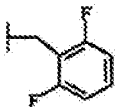
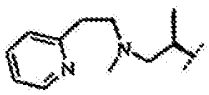
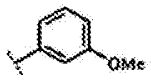
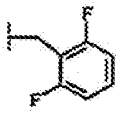
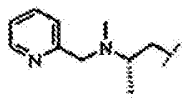
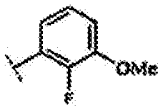
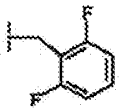
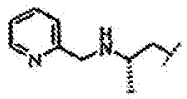
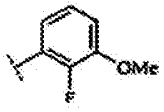
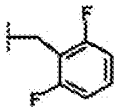
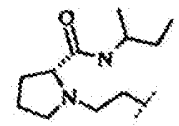
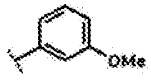
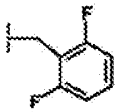
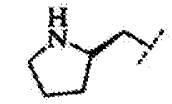
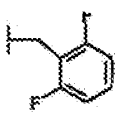
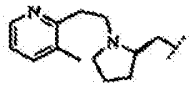
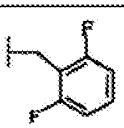
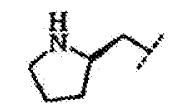
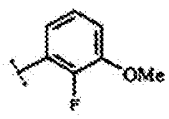
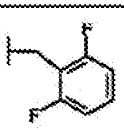
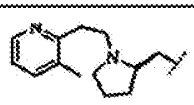
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-389	Me				642.62	643.7
9-390	Me				570.59	571
9-391	Me				561.62	562.5
9-392	Me				598.64	599.4
9-393	Me				664.74	665.5
9-394	Me				540.56	541.6
9-395	Me				602.67	603.6
9-396	Me				442.43	373.3
9-397	Me				520.57	521.3

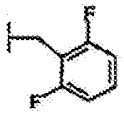
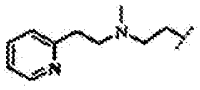
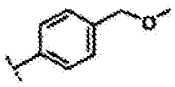
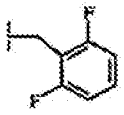
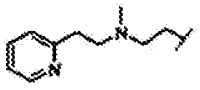
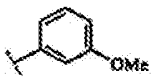
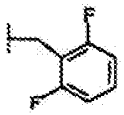
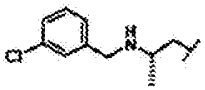
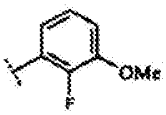
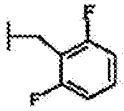
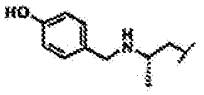
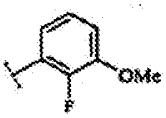
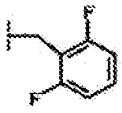
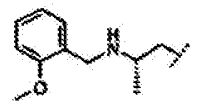
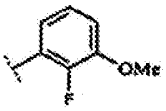
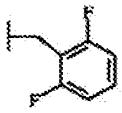
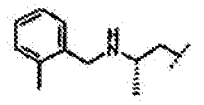
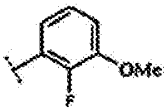
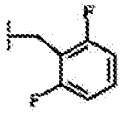
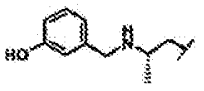
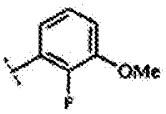
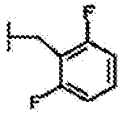
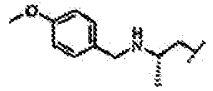
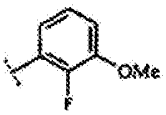
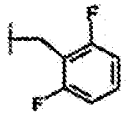
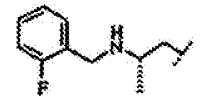
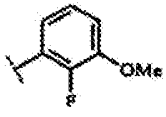
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-398	Me				520.57	521.2
9-399	Me				503.56	504.2
9-400	Me				532.58	533.2
9-401	Me				506.55	507
9-402	Me				506.55	507
9-403	Me				515.55	416
9-404	Me				531.6	532
9-405	Me				549.5	550
9-406	Me				550.57	550

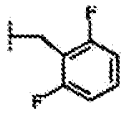
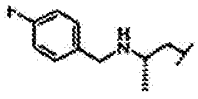
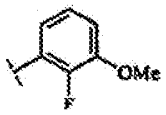
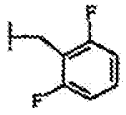
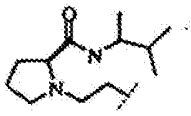
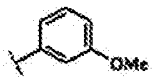
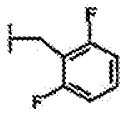
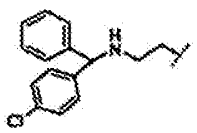
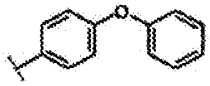
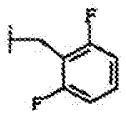
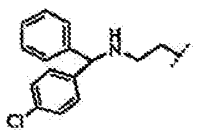
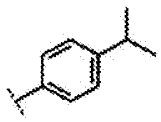
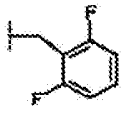
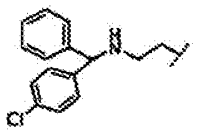
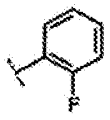
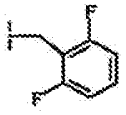
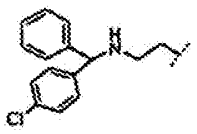
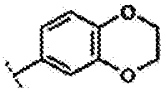
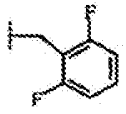
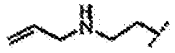
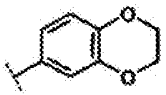
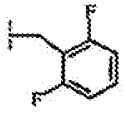
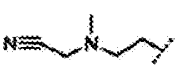
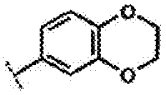
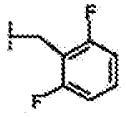
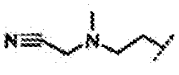
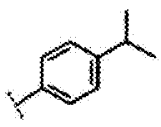
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-407	Me				534.60	535
9-408	Me				534.60	535
9-409	Me				538.56	539
9-410	Me				524.54	525
9-411	Me				554.63	555
Referência 9-412	Me			H	335.35	336
Referência 9-413	Me			Br	533.41	533/535
9-414	Me				459.46	460
Referência 9-415	Me			H	454.51	455

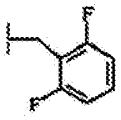
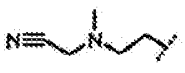
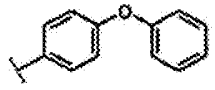
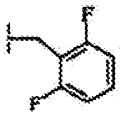
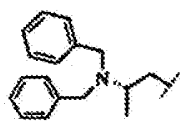
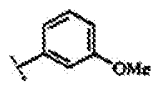
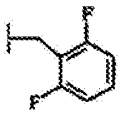
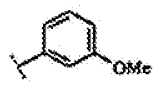
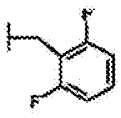
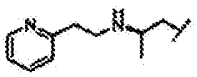
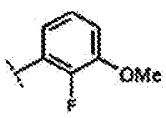
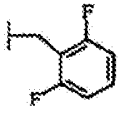
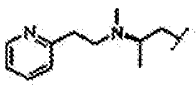
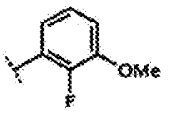
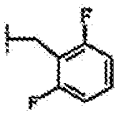
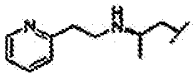
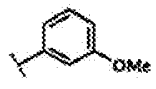
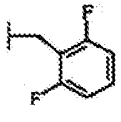
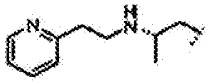
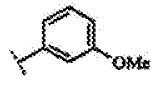
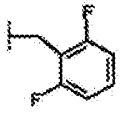
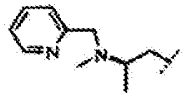
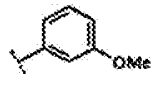
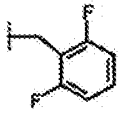
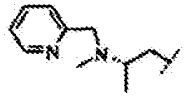
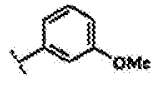
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-416	Me				534.60	535.5
9-417	Me				520.57	521.5
9-418	Me				557.99	558
9-419	Me				539.55	540
9-420	Me				553.57	554
9-421	Me				537.57	538
9-422	Me				539.55	540
9-423	Me				553.57	554
9-424	Me				541.54	542

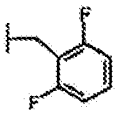
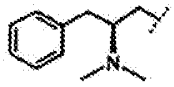
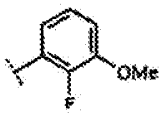
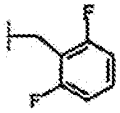
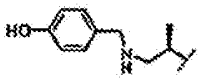
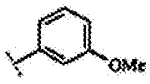
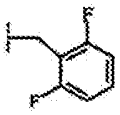
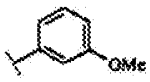
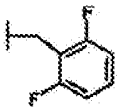
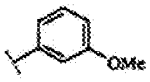
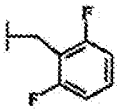
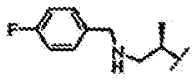
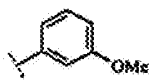
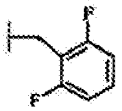
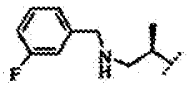
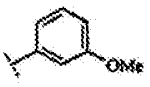
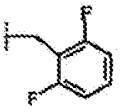
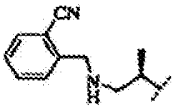
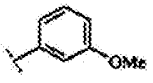
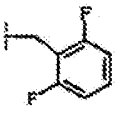
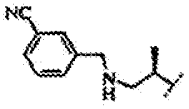
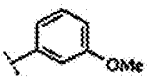
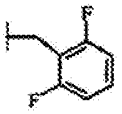
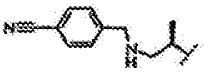
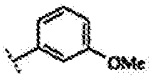
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-425	Me				541.54	542
9-426	Me				568.66	569
9-427	Me				664.14	664.2
9-428	Me				614.13	614.2
9-429	Me				590.04	590.2
9-430	Me				630.09	630.2
9-431	Me				469.48	470.2
9-432	Me				482.48	483.1
9-433	Me				466.52	467.2

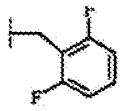
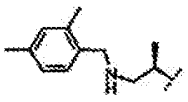
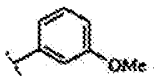
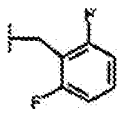
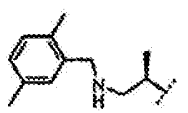
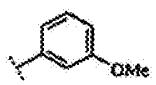
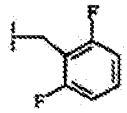
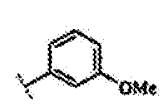
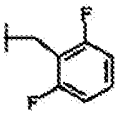
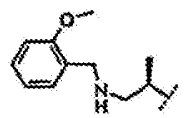
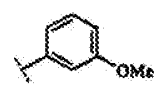
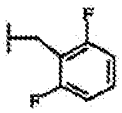
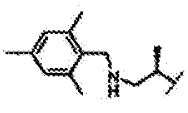
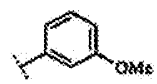
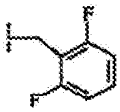
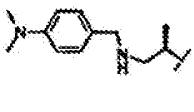
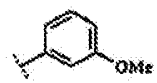
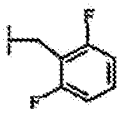
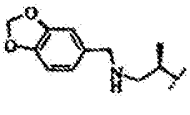
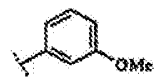
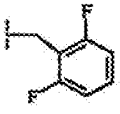
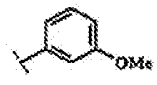
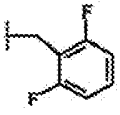
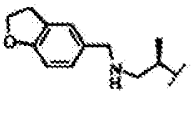
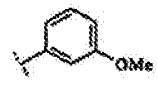
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-434	Me				516.54	517.2
9-435	Me				595.68	596.3
9-436	Me				595.68	596.3
9-437	Me				538.56	539.2
9-438	Me				552.59	553.3
9-439	Me				506.55	507.2
9-440	Me				506.55	507.2
9-441	Me				520.57	521.2
9-442	Me				520.57	521.2

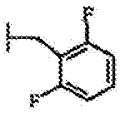
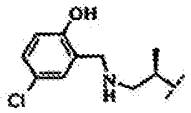
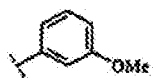
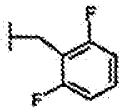
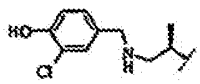
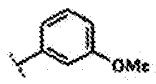
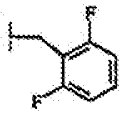
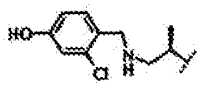
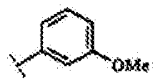
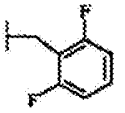
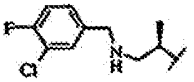
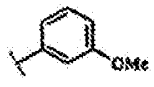
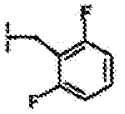
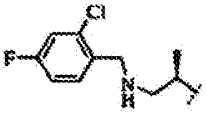
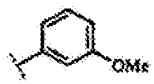
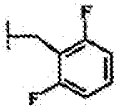
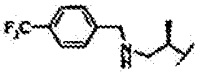
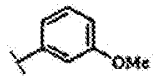
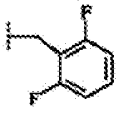
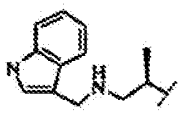
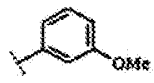
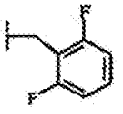
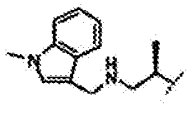
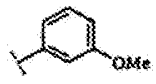
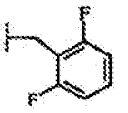
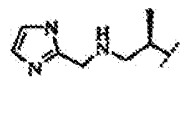
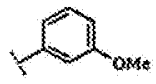
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-443	Me				537.57	538
9-444	Me				521.56	522.2
9-445	Me				521.56	522.2
9-446	Me				523.55	524.2
9-447	Me				523.55	524.2
9-448	Me				523.55	524.2
9-449	Me				530.57	531.2
9-450	Me				530.57	531.2
9-451	Me				530.57	531.2

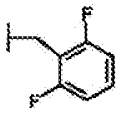
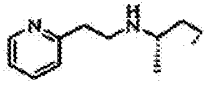
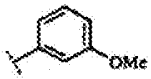
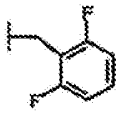
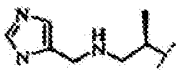
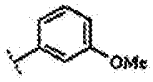
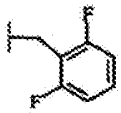
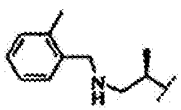
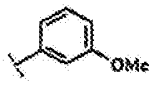
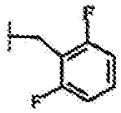
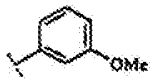
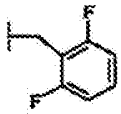
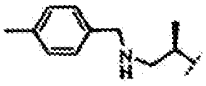
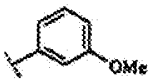
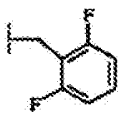
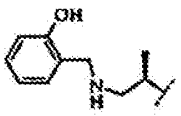
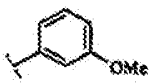
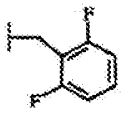
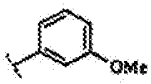
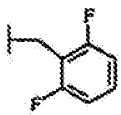
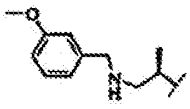
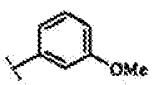
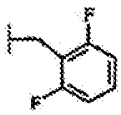
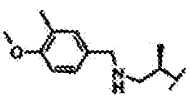
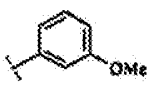
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-452	Me				533.61	534.3
9-453	Me				533.61	534.3
9-454	Me				533.61	534.2
9-455	Me				535.58	536.2
9-456	Me				547.64	548.3
9-457	Me				548.63	549.3
9-458	Me				549.57	550.2
9-459	Me				535.58	536.2
9-460	Me				547.59	548.3

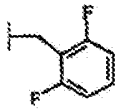
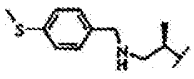
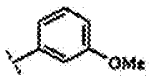
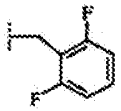
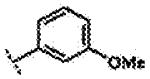
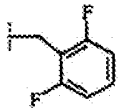
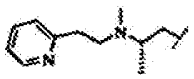
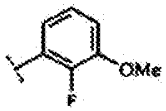
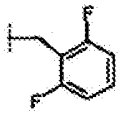
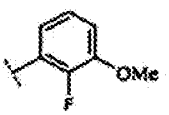
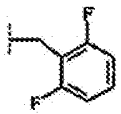
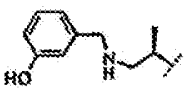
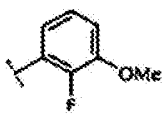
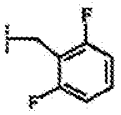
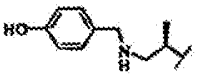
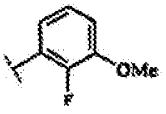
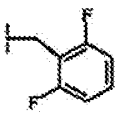
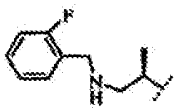
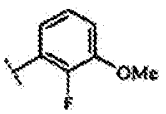
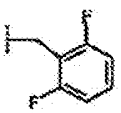
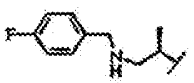
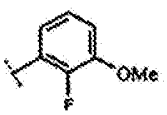
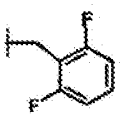
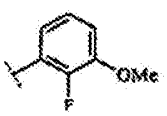
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-461	Me				556.00	556.2
9-462	Me				556.00	556.2
9-463	Me				556.00	556.2
9-464	Me				557.99	558.2
9-465	Me				557.99	558.2
9-466	Me				573.55	574.2
9-467	Me				544.59	545.2
9-468	Me				558.62	559.2
9-469	Me				495.52	496.2

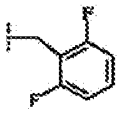
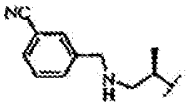
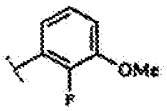
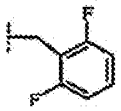
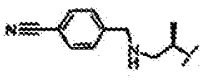
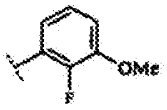
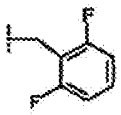
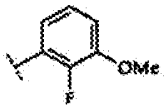
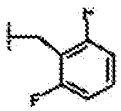
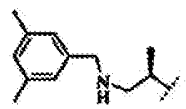
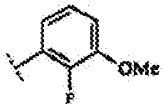
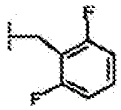
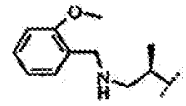
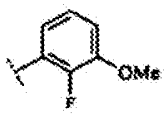
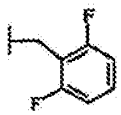
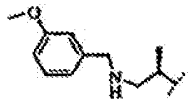
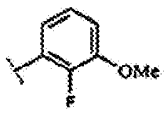
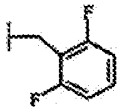
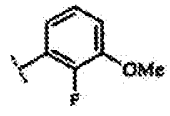
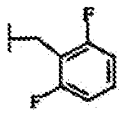
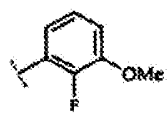
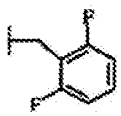
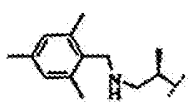
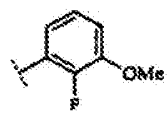
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-470	Me				538.56	539
9-471	Me				495.52	496.2
9-472	Me				519.58	520.2
9-473	Me				519.58	520.2
9-474	Me				519.58	520.2
9-475	Me				521.56	535.2
9-476	Me				533.61	534.2
9-477	Me				535.58	536.2
9-478	Me				549.61	550.2

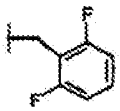
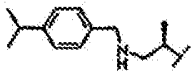
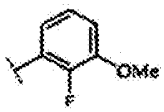
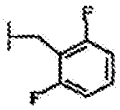
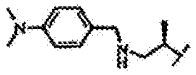
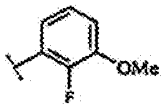
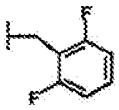
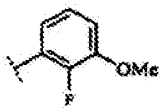
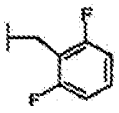
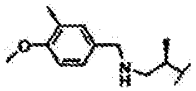
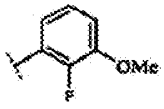
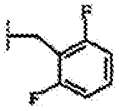
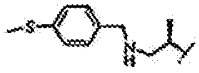
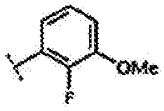
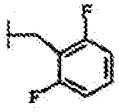
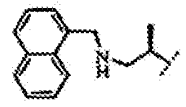
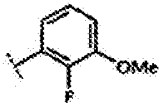
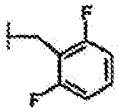
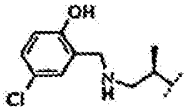
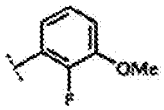
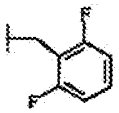
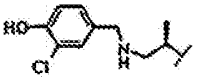
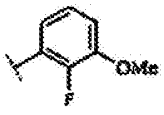
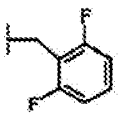
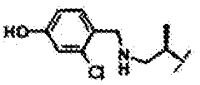
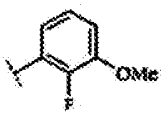
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-479	Me				551.65	552.2
9-480	Me				555.62	556.3
9-481	Me				552.59	553
9-482	Me				537.57	538.2
9-483	Me				539.55	540.2
9-484	Me				539.55	540.2
9-485	Me				541.54	542.2
9-486	Me				541.54	542.2
9-487	Me				541.54	542.2

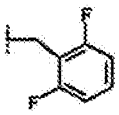
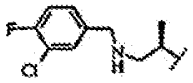
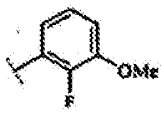
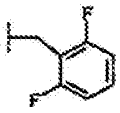
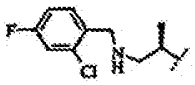
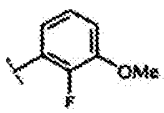
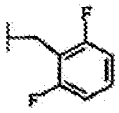
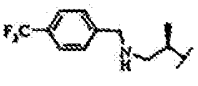
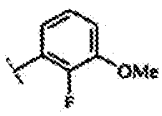
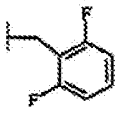
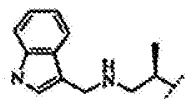
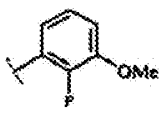
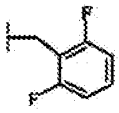
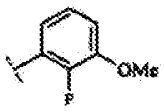
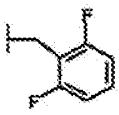
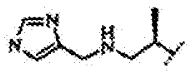
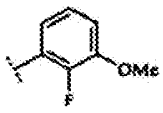
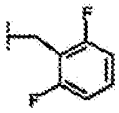
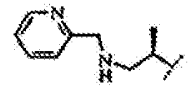
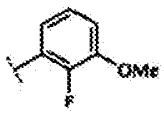
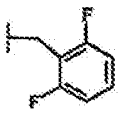
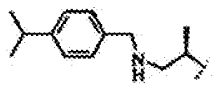
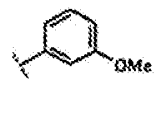
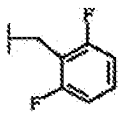
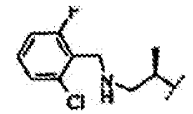
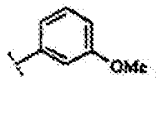
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-488	Me				548.56	549.2
9-489	Me				548.56	549.3
9-490	Me				551.60	552.3
9-491	Me				551.60	552.2
9-492	Me				553.57	554.2
9-493	Me				553.57	554.2
9-494	Me				553.57	554.2
9-495	Me				565.58	566.2
9-496	Me				565.63	566.3

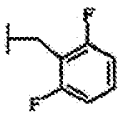
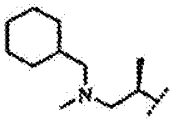
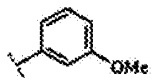
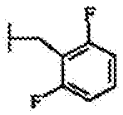
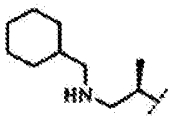
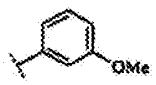
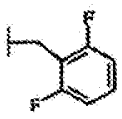
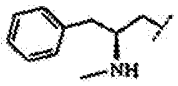
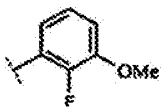
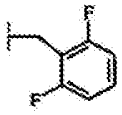
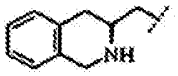
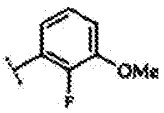
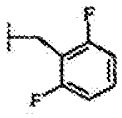
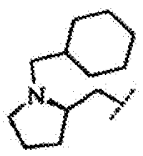
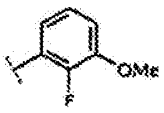
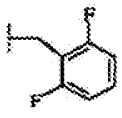
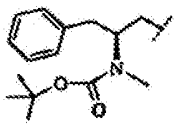
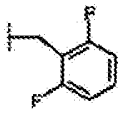
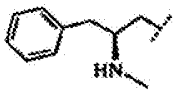
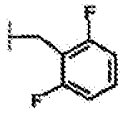
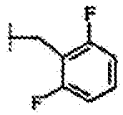
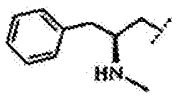
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-497	Me				565.63	566.3
9-498	Me				566.62	566.2
9-499	Me				567.56	567.3
9-500	Me				567.60	568.2
9-501	Me				569.64	568.2
9-502	Me				573.61	570.2
9-503	Me				573.99	574.2
9-504	Me				573.99	574.2
9-505	Me				573.99	574.2

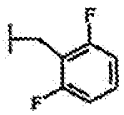
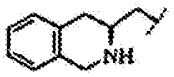
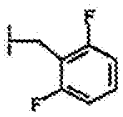
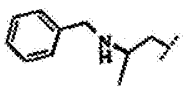
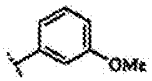
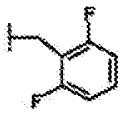
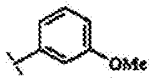
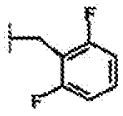
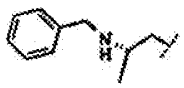
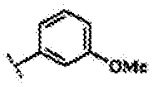
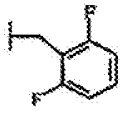
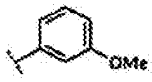
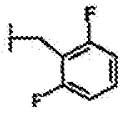
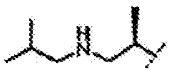
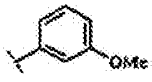
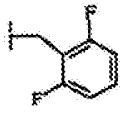
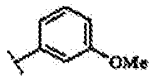
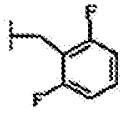
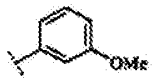
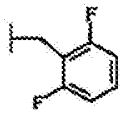
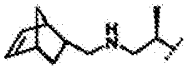
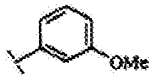
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-506	Me				575.98	574.2
9-507	Me				575.98	576.2
9-508	Me				591.54	592.2
9-509	Me				562.58	563.2
9-510	Me				513.51	514.2
9-511	Me				513.51	514.2
9-512	Me				524.54	525.2
9-513	Me				547.64	548.3
9-514	Me				557.99	558.2

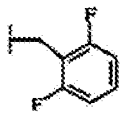
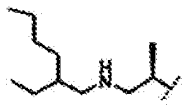
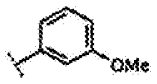
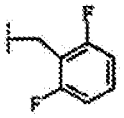
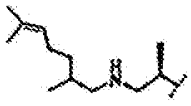
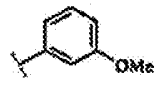
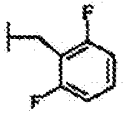
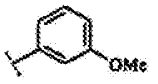
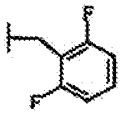
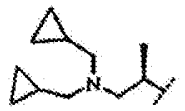
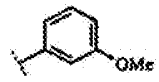
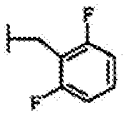
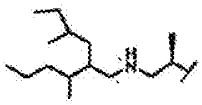
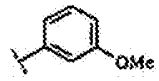
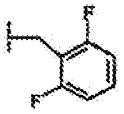
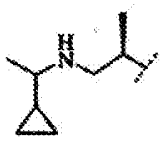
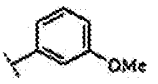
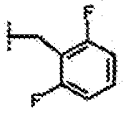
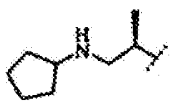
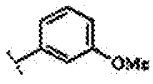
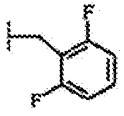
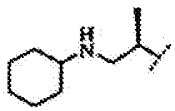
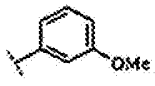
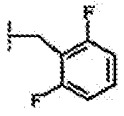
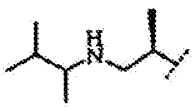
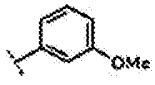
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-515	Me				525.63	526.3
9-516	Me				511.60	512.3
9-517	Me				523.55	524
9-518	Me				521.53	522
9-519	Me				555.63	556
Referência 9-520	Me			H	499.55	400 (MH-BOC)+
Referência 9-521	Me			H	399.43	400
Referência 9-522	Me			H	397.42	398
Referência 9-523	Me			Br	478.33	478/480

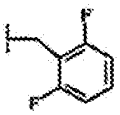
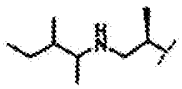
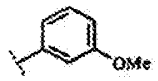
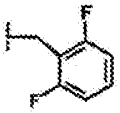
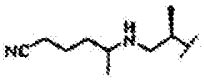
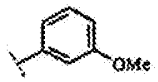
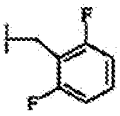
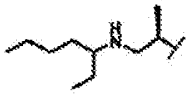
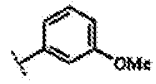
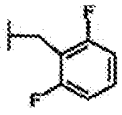
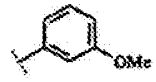
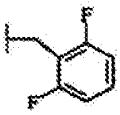
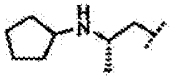
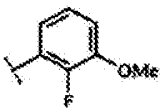
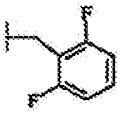
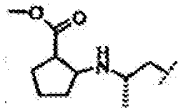
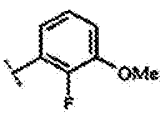
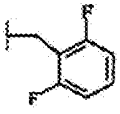
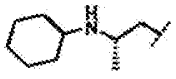
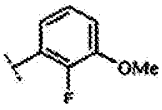
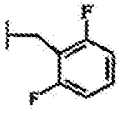
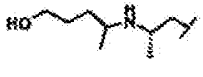
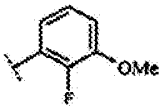
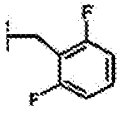
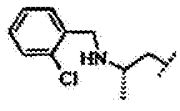
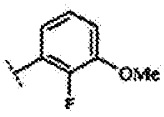
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
Referência 9-524	Me			Br	476.31	476/478
9-525	Me				505.56	506.3
9-526	Me				519.58	520.3
9-527	Me				505.56	506.2
9-528	Me				519.58	520.2
9-529	Me				471.54	472.2
9-530	Me				485.57	486.3
9-531	Me				499.59	500.3
9-532	Me				521.60	522.2

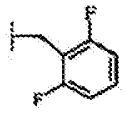
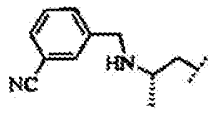
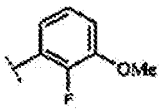
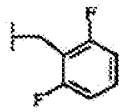
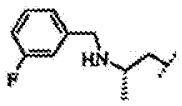
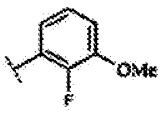
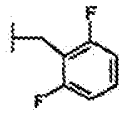
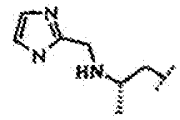
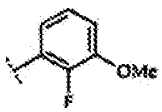
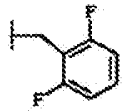
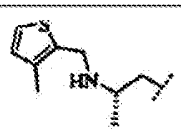
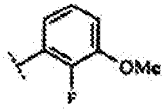
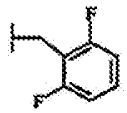
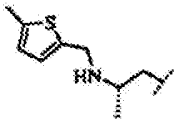
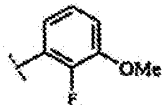
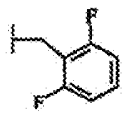
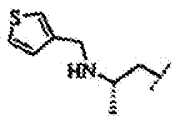
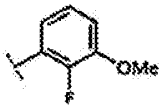
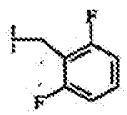
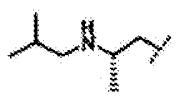
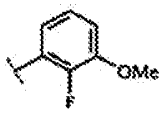
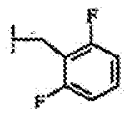
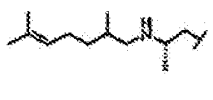
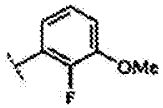
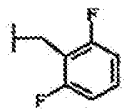
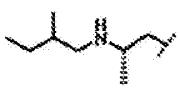
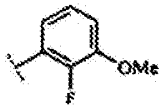
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-533	Me				527.65	528.3
9-534	Me				539.66	540.3
9-535	Me				583.75	584.4
9-536	Me				523.62	524.3
9-537	Me				555.70	556.3
9-538	Me				483.55	484.2
9-539	Me				483.55	484.2
9-540	Me				497.58	498.3
9-541	Me				485.57	486.3

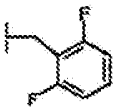
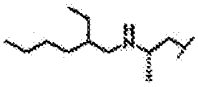
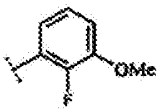
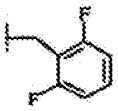
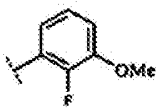
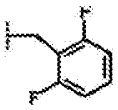
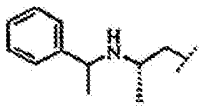
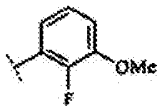
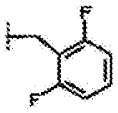
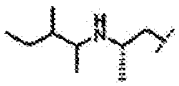
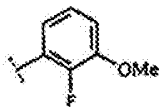
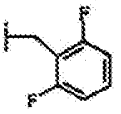
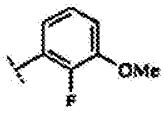
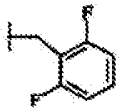
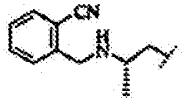
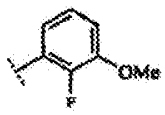
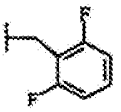
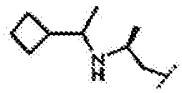
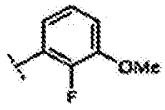
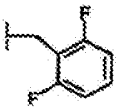
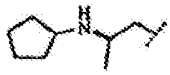
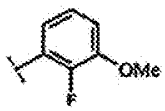
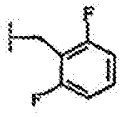
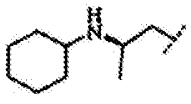
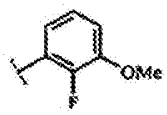
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-542	Me				499.59	500.3
9-543	Me				510.58	511.2
9-544	Me				513.62	514.3
9-545	Me				525.63	526.3
9-546	Me				501.54	502.2
9-547	Me				559.58	560.2
9-548	Me				515.57	516.2
9-549	Me				519.56	520.2
9-550	Me				557.99	558.2

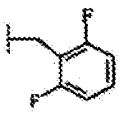
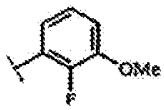
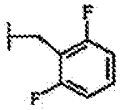
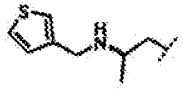
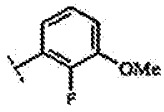
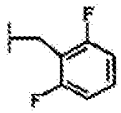
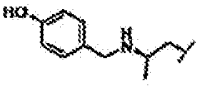
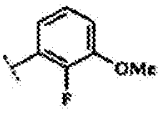
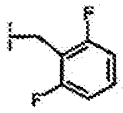
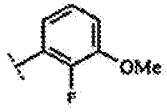
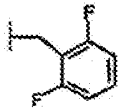
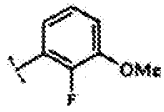
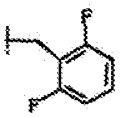
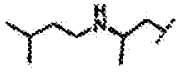
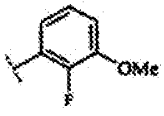
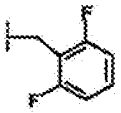
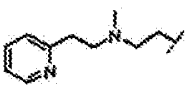
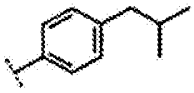
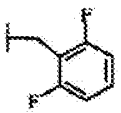
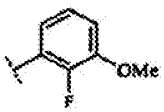
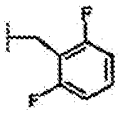
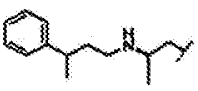
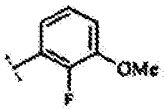
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-551	Me				548.56	549.2
9-552	Me				541.54	542.2
9-553	Me				513.51	514.2
9-554	Me				543.60	544.2
9-555	Me				543.60	544.2
9-556	Me				529.58	530.1
9-557	Me				489.53	490.2
9-558	Me				557.65	558.2
9-559	Me				503.56	504.2

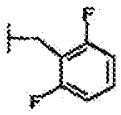
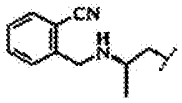
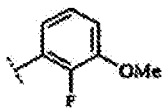
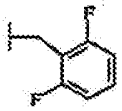
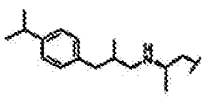
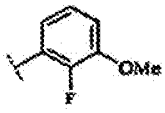
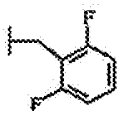
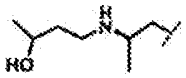
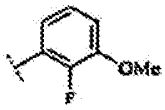
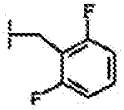
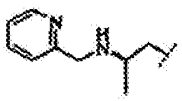
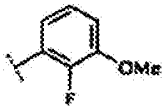
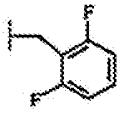
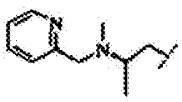
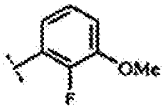
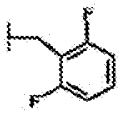
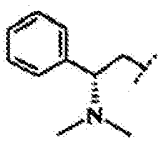
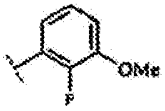
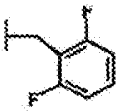
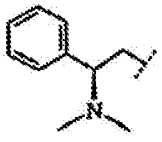
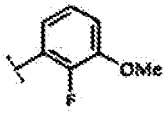
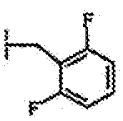
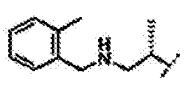
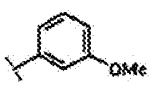
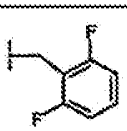
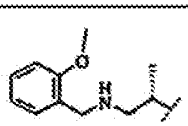
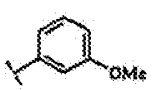
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-560	Me				545.64	546.2
9-561	Me				521.60	522.2
9-562	Me				537.57	538.2
9-563	Me				517.58	518.2
9-564	Me				559.66	560.2
9-565	Me				548.56	549.2
9-566	Me				515.57	516.2
9-567	Me				501.54	502.2
9-568	Me				515.57	516.2

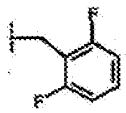
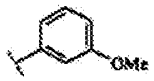
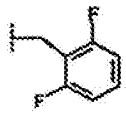
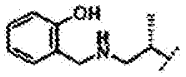
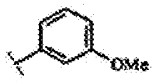
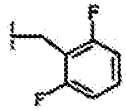
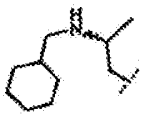
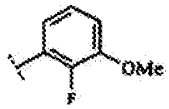
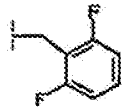
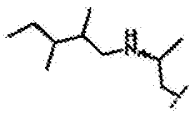
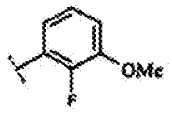
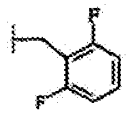
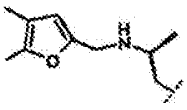
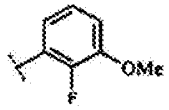
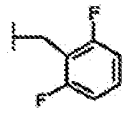
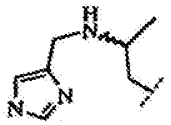
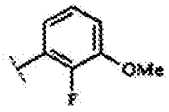
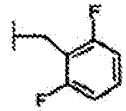
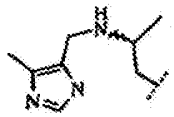
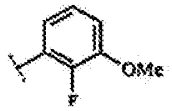
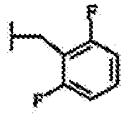
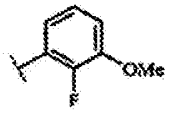
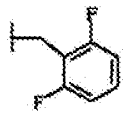
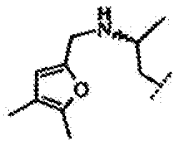
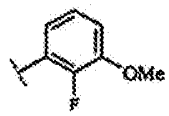
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-569	Me				513.51	514.2
9-570	Me				529.58	530.2
9-571	Me				539.55	540.2
9-572	Me				557.65	558.3
9-573	Me				545.64	546.3
9-574	Me				503.56	504.3
9-575	Me				546.65	547.3
9-576	Me				559.66	560.3
9-577	Me				565.63	566.3

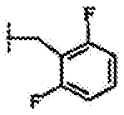
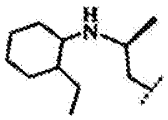
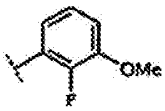
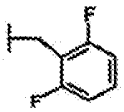
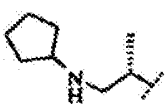
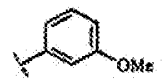
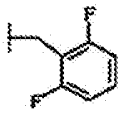
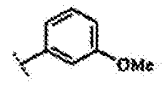
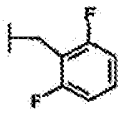
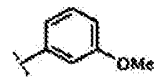
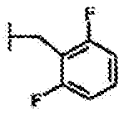
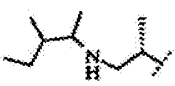
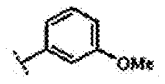
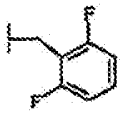
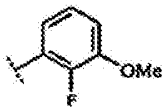
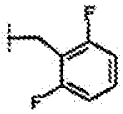
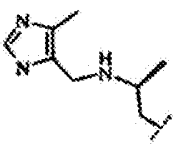
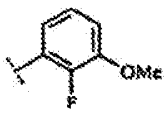
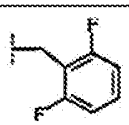
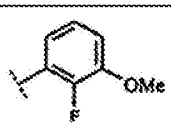
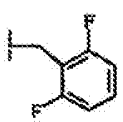
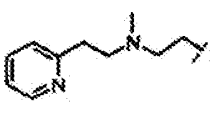
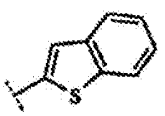
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-578	Me				548.56	549.2
9-579	Me				607.71	608.4
9-580	Me				505.53	506.2
9-581	Me				524.54	525.2
9-582	Me				538.56	539.2
9-583	Me				523.55	524.2
9-584	Me				523.55	524.2
9-585	Me				519.58	520.2
9-586	Me				535.58	536.2

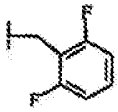
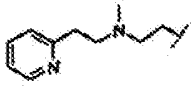
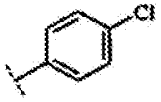
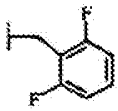
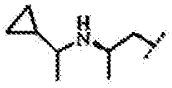
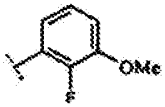
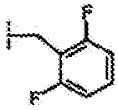
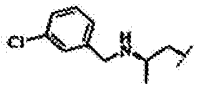
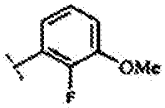
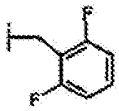
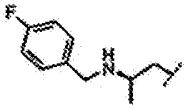
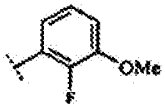
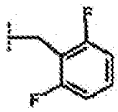
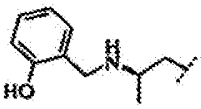
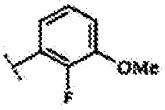
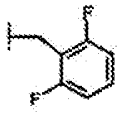
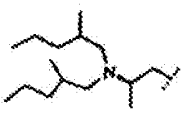
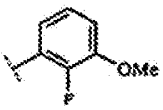
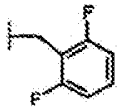
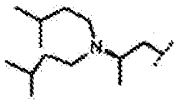
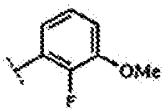
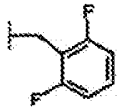
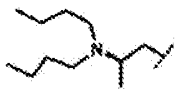
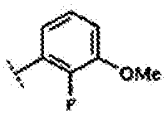
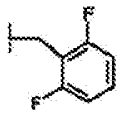
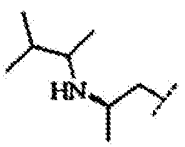
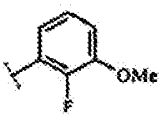
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-587	Me				523.55	524.2
9-588	Me				521.56	522.2
9-589	Me				529.6	530.2
9-590	Me				531.61	532.3
9-591	Me				541.56	542.3
9-592	Me				513.51	514.2
9-593	Me				527.54	528.2
9-594	Me				601.74	602.4
9-595	Me				541.56	542.2

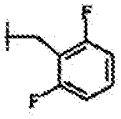
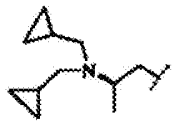
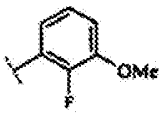
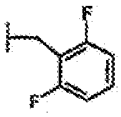
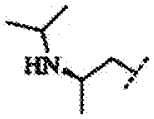
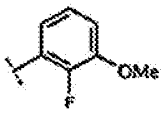
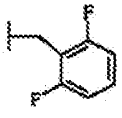
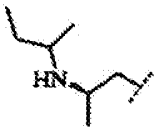
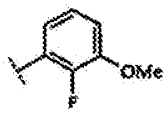
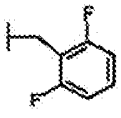
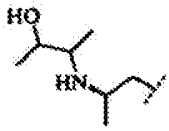
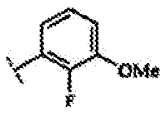
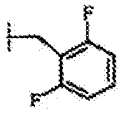
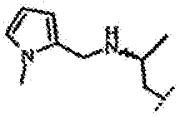
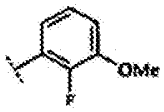
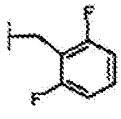
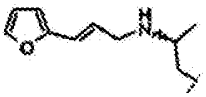
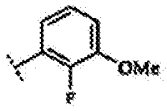
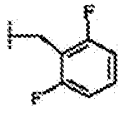
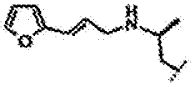
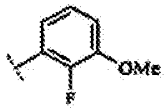
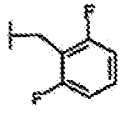
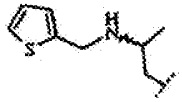
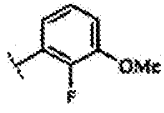
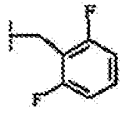
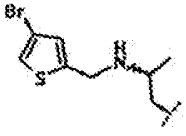
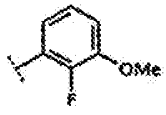
Continuação

Comp. No.	R_5	R_6	NR_1R_2- $(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	 (obs.)
9-596	Me				543.62	542.2
9-597	Me				483.55	484.2
9-598	Me				471.54	472.1
9-599	Me				485.57	486.3
9-600	Me				499.59	500.3
9-601	Me				601.74	602.4
9-602	Me				527.54	528.2
9-603	Me				513.51	514.2
9-604	Me				546.63	547

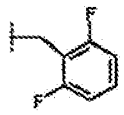
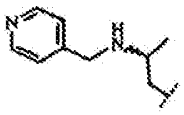
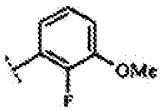
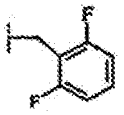
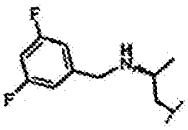
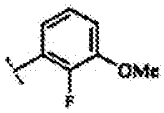
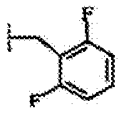
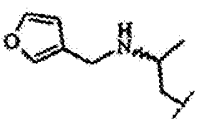
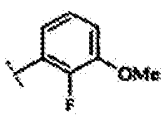
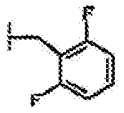
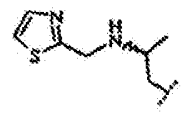
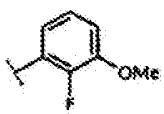
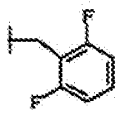
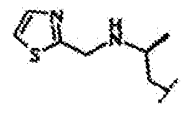
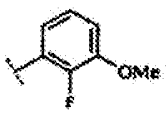
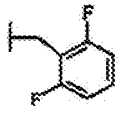
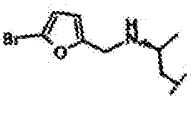
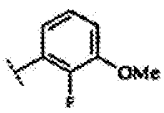
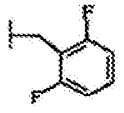
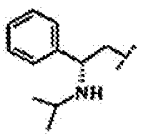
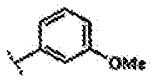
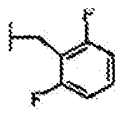
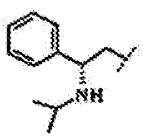
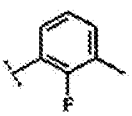
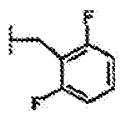
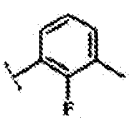
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-605	Me				524.99	525
9-606	Me				501.54	502.2
9-607	Me				557.99	558.2
9-608	Me				541.54	542.2
9-609	Me				539.55	540.3
9-610	Me				601.74	602.4
9-611	Me				573.69	574.3
9-612	Me				545.64	546.3
9-613	Me				503.56	504.2

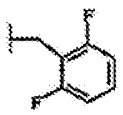
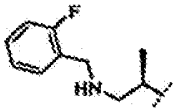
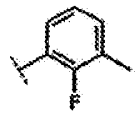
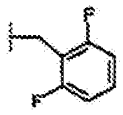
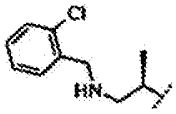
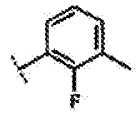
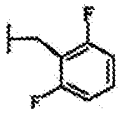
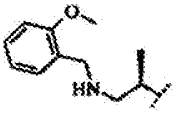
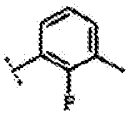
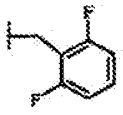
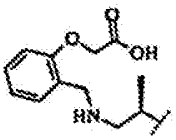
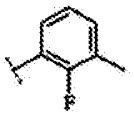
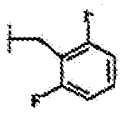
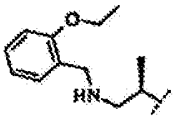
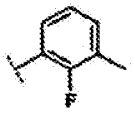
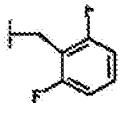
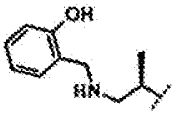
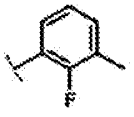
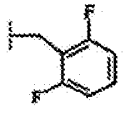
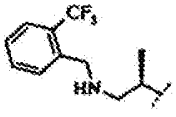
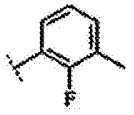
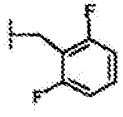
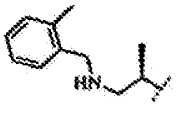
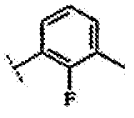
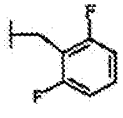
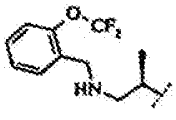
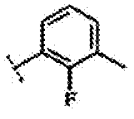
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-614	Me				541.61	542.3
9-615	Me				475.50	476.2
9-616	Me				489.53	490.3
9-617	Me				505.53	506.30
9-618	Me				526.55	527.2
9-619	Me				539.55	540.2
9-620	Me				539.55	540.2
9-621	Me				529.58	530.2
9-622	Me				608.47	608.1

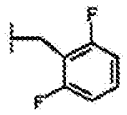
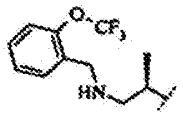
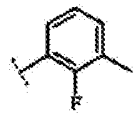
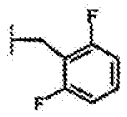
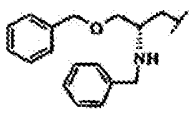
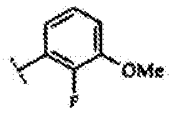
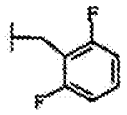
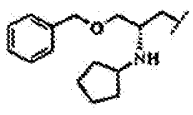
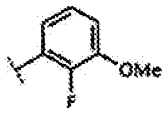
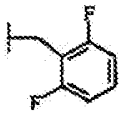
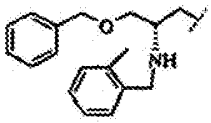
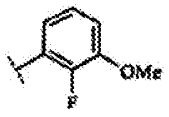
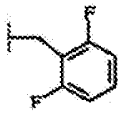
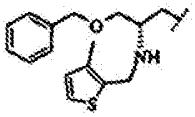
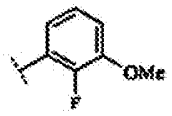
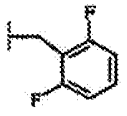
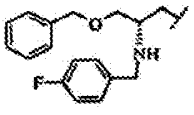
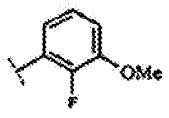
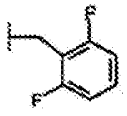
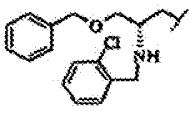
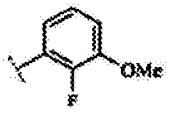
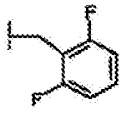
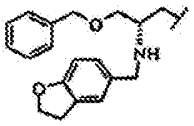
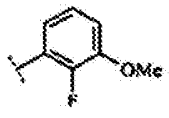
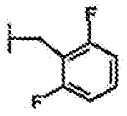
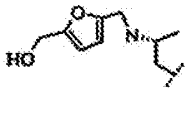
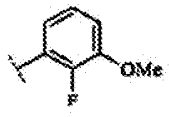
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-623	Me				524.54	525.2
9-624	Me				559.53	560.2
9-625	Me				513.51	514.2
9-626	Me				530.56	531.2
9-627	Me				530.56	531.2
9-628	Me				592.40	594.1
9-629	Me				519.58	520.2
9-630	Me				521.58	522.2
9-631	Me				507.55	508.3

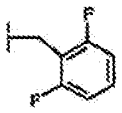
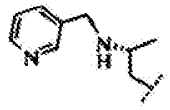
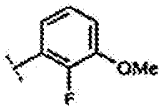
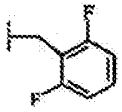
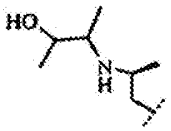
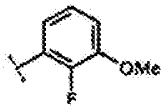
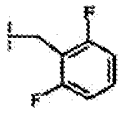
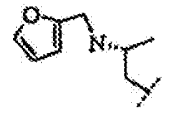
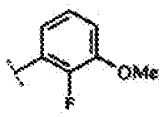
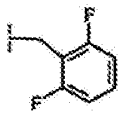
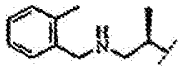
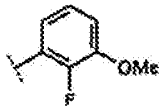
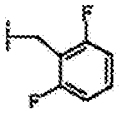
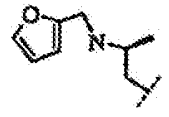
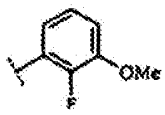
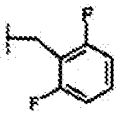
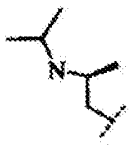
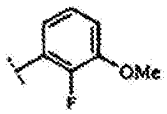
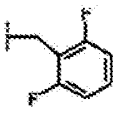
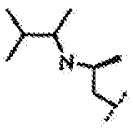
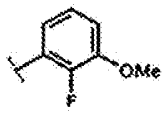
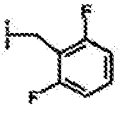
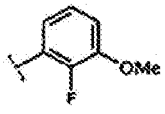
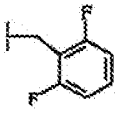
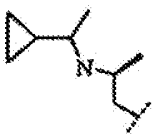
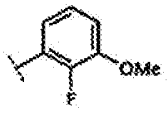
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-632	Me				525.54	526.2
9-633	Me				541.99	542.2
9-634	Me				537.57	538.3
9-635	Me				581.58	582.2
9-636	Me				551.60	552.3
9-637	Me				523.55	524.2
9-638	Me				575.55	576.2
9-639	Me				521.58	522.2
9-640	Me				573.55	574.2

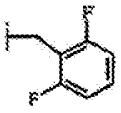
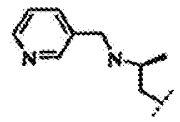
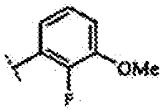
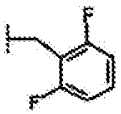
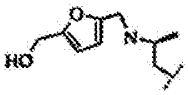
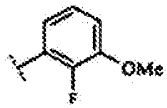
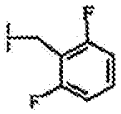
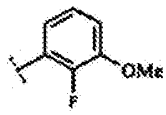
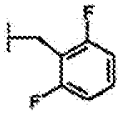
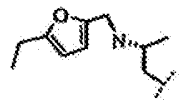
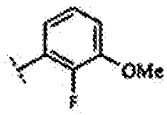
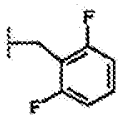
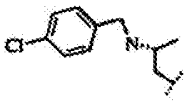
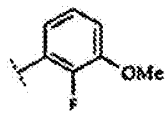
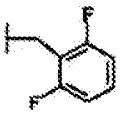
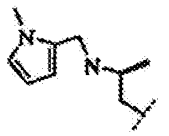
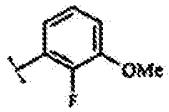
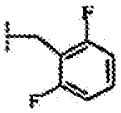
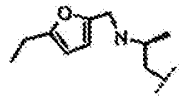
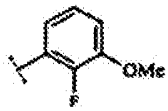
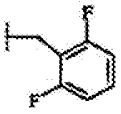
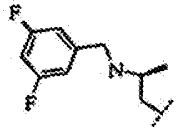
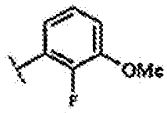
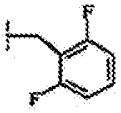
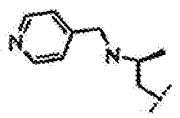
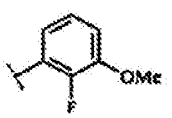
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-641	Me				591.54	592.2
9-642	Me				629.67	630
9-643	Me				607.66	608
9-644	Me				643.70	644
9-645	Me				649.73	650
9-646	Me				647.66	648
9-647	Me				664.12	664
9-648	Me				671.71	672
9-649	Me				543.53	544.2

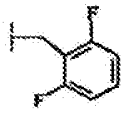
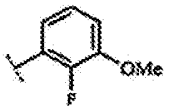
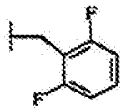
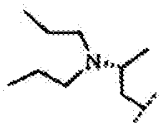
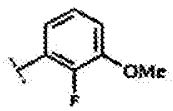
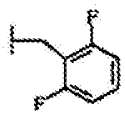
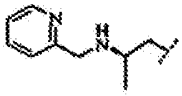
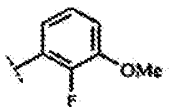
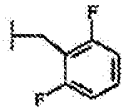
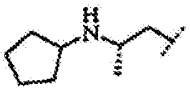
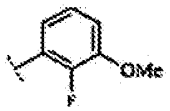
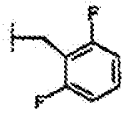
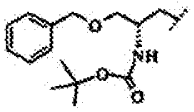
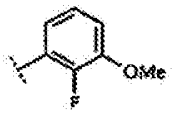
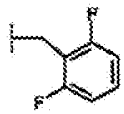
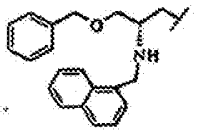
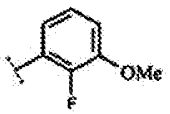
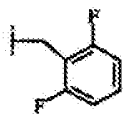
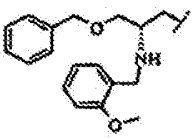
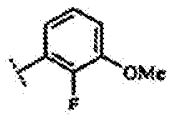
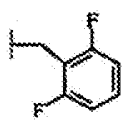
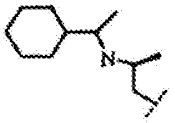
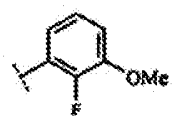
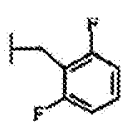
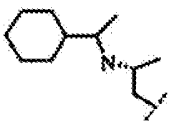
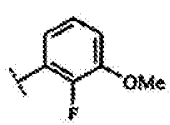
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-650	Me				524.54	525.2
9-651	Me				505.53	506.2
9-652	Me				513.51	514.2
9-653	Me				537.57	538.3
9-654	Me				513.51	514.2
9-655	Me				475.50	476.2
9-656	Me				503.56	504.3
9-657	Me				487.51	488.3
9-658	Me				501.54	502.2

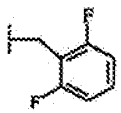
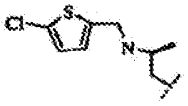
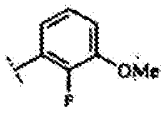
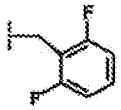
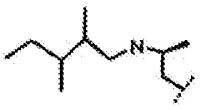
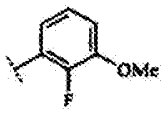
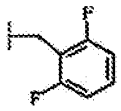
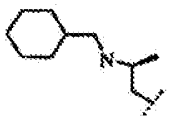
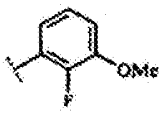
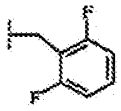
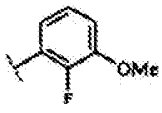
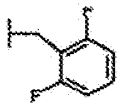
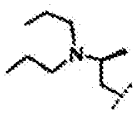
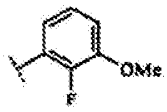
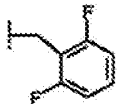
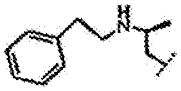
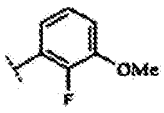
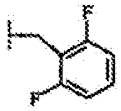
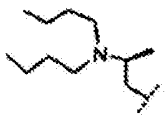
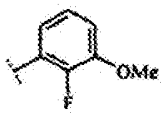
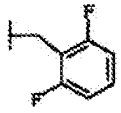
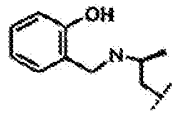
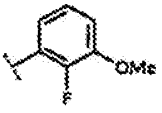
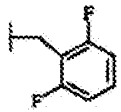
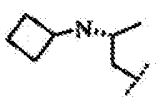
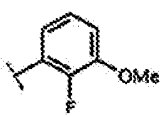
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-659	Me				524.54	525.2
9-660	Me				543.53	544.2
9-661	Me				489.53	490.3
9-662	Me				541.56	542.3
9-663	Me				557.99	558.2
9-664	Me				526.55	527.2
9-665	Me				541.56	542.3
9-666	Me				559.53	560.2
9-667	Me				524.54	525.2

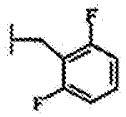
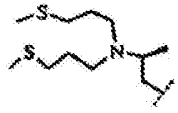
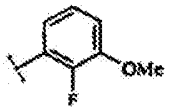
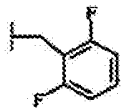
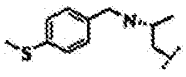
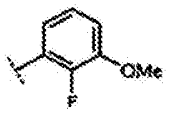
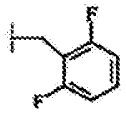
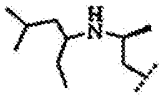
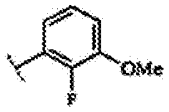
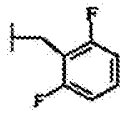
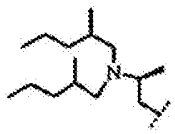
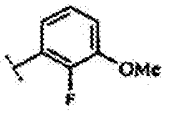
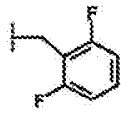
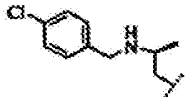
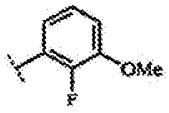
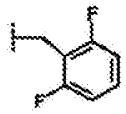
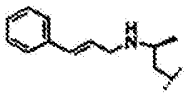
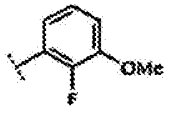
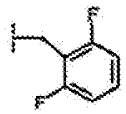
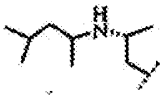
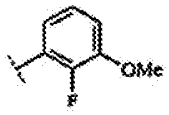
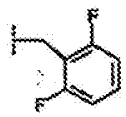
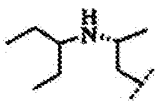
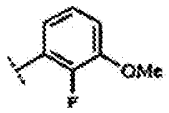
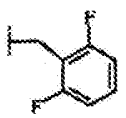
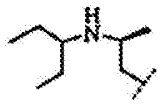
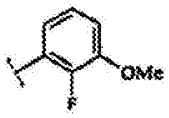
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-668	Me				513.51	514.2
9-669	Me				517.58	518.2
9-670	Me				524.54	525.2
9-671	Me				501.54	502
9-672	Me				639.66	540
9-673	Me				679.73	680
9-674	Me				659.70	660
9-675	Me				543.62	544.3
9-676	Me				543.62	544.3

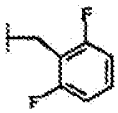
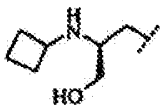
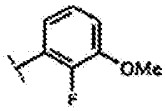
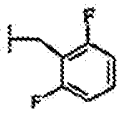
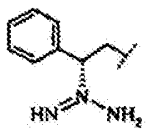
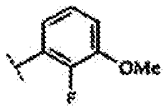
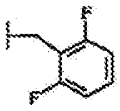
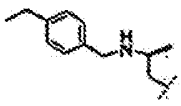
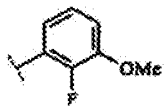
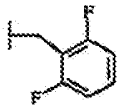
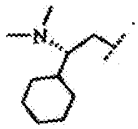
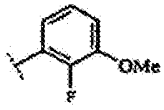
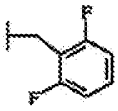
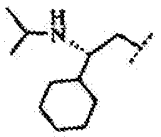
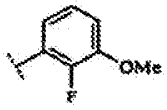
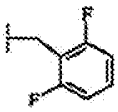
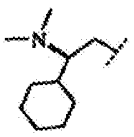
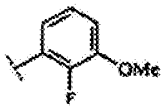
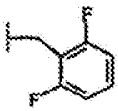
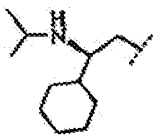
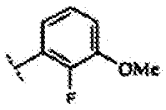
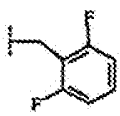
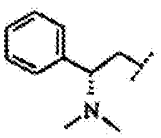
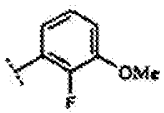
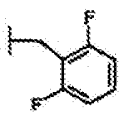
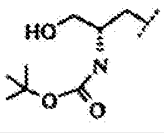
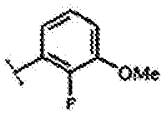
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-677	Me				564.02	564.2
9-678	Me				531.61	532.3
9-679	Me				529.6	530.2
9-680	Me				539.55	540.2
9-681	Me				517.58	518.3
9-682	Me				537.57	538.2
9-683	Me				545.64	544.3
9-684	Me				539.55	540.2
9-685	Me				487.51	488.2

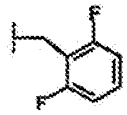
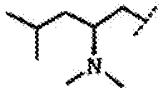
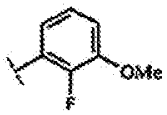
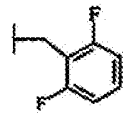
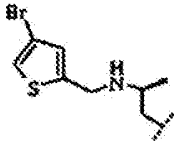
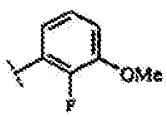
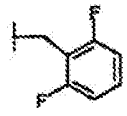
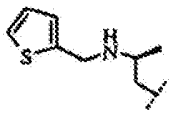
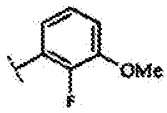
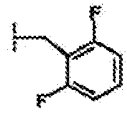
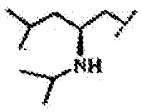
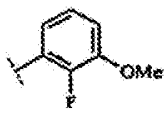
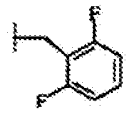
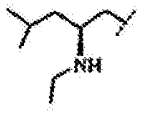
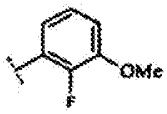
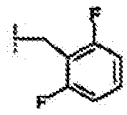
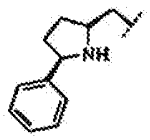
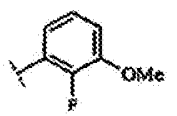
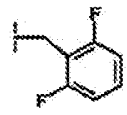
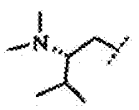
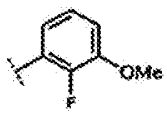
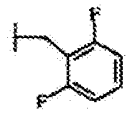
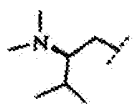
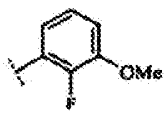
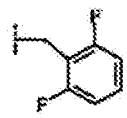
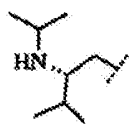
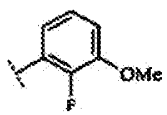
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-686	Me				609.77	610.3
9-687	Me				569.64	570.2
9-688	Me				531.61	532.3
9-689	Me				601.74	602.4
9-690	Me				557.99	558.2
9-691	Me				549.59	550.2
9-692	Me				517.58	518.2
9-693	Me				503.56	504.3
9-694	Me				503.56	504.3

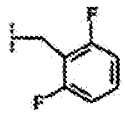
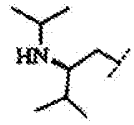
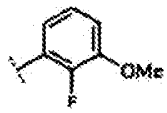
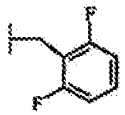
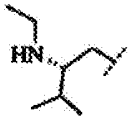
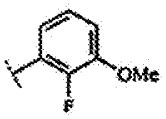
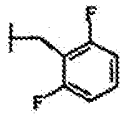
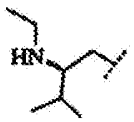
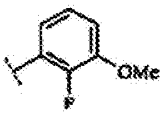
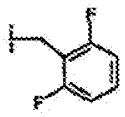
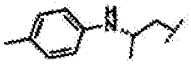
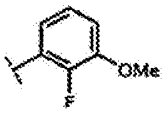
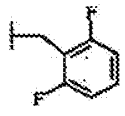
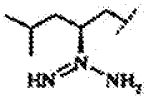
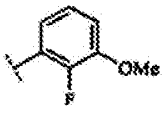
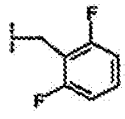
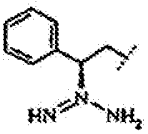
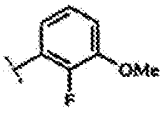
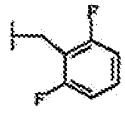
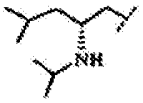
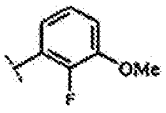
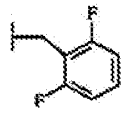
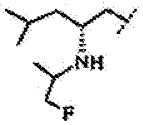
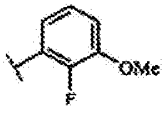
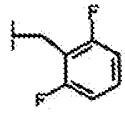
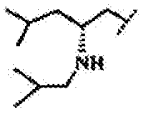
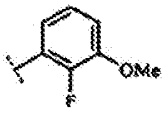
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-695	Me				503.51	504
9-696	Me				537.53	538.2
9-697	Me				551.60	552.3
9-698	Me				529.6	530.2
9-699	Me				543.62	544.3
9-700	Me				529.6	530.2
9-701	Me				543.62	544.3
9-702	Me				523.55	524.2
9-703	Me				549.54	450

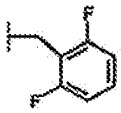
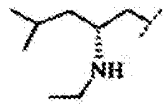
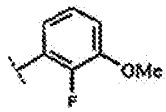
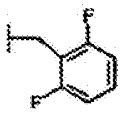
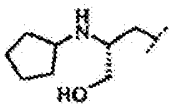
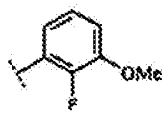
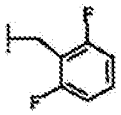
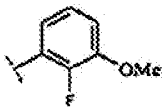
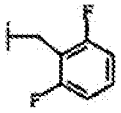
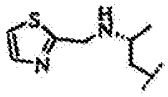
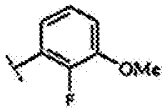
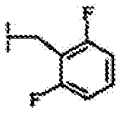
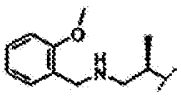
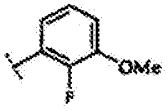
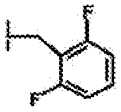
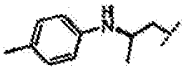
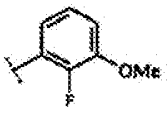
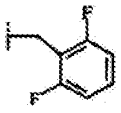
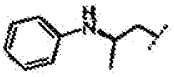
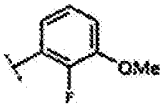
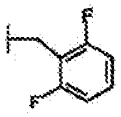
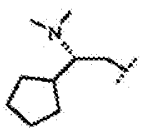
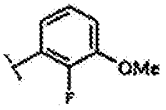
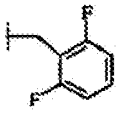
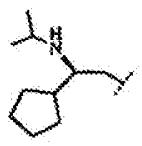
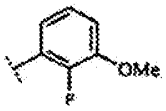
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-704	Me				503.56	504.3
9-705	Me				608.47	610.1
9-706	Me				529.58	530.2
9-707	Me				517.58	518.2
9-708	Me				503.56	504.3
9-709	Me				535.56	536.2
9-710	Me				489.53	490.2
9-711	Me				489.53	490.2
9-712	Me				503.56	504.2

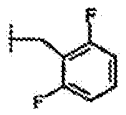
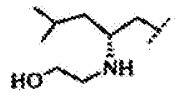
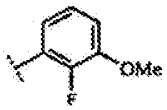
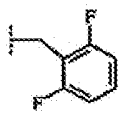
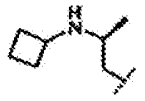
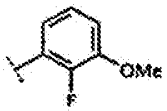
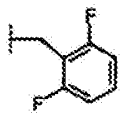
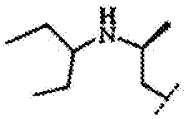
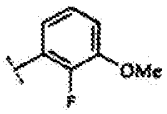
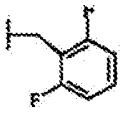
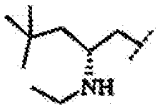
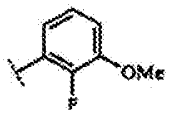
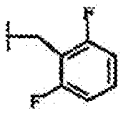
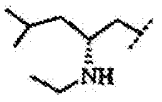
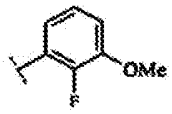
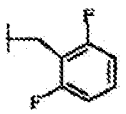
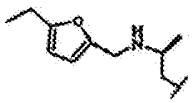
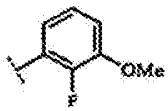
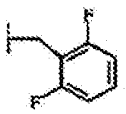
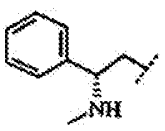
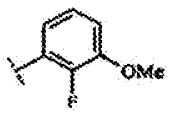
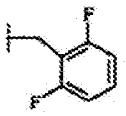
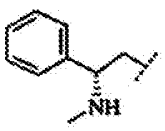
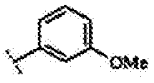
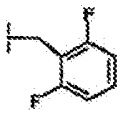
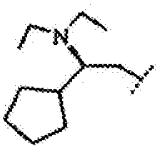
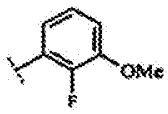
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-713	Me				503.56	504.2
9-714	Me				489.53	490.2
9-715	Me				489.53	490.2
9-716	Me				523.55	524.2
9-717	Me				517.54	518.2
9-718	Me				523.55	524
9-719	Me				517.58	518.3
9-720	Me				535.57	536.3
9-721	Me				531.61	532.3

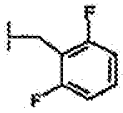
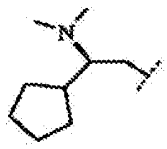
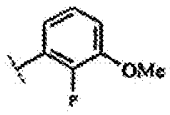
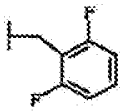
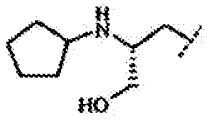
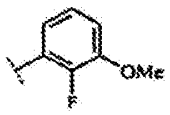
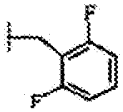
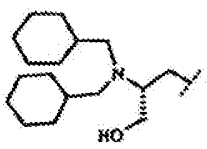
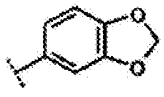
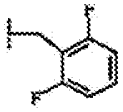
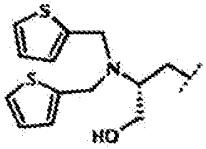
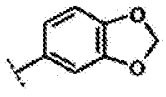
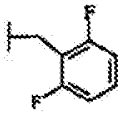
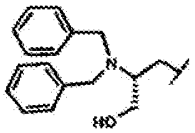
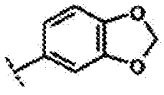
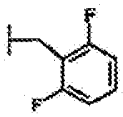
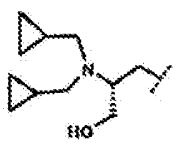
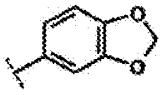
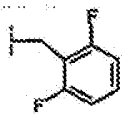
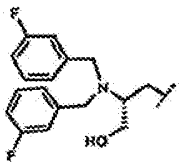
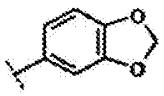
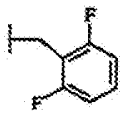
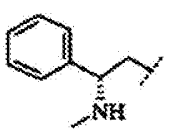
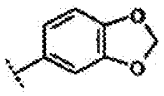
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-722	Me				503.56	504.3
9-723	Me				517.54	518
9-724	Me				543.60	544
9-725	Me				530.56	531
9-726	Me				553.57	554
9-727	Me				523.55	524.2
9-728	Me				509.52	510.2
9-729	Me				515.57	516.3
9-730	Me				529.6	530.3

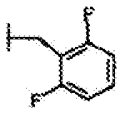
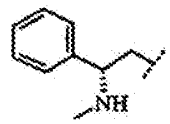
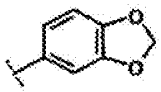
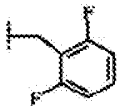
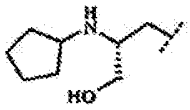
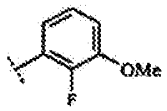
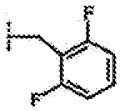
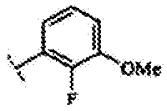
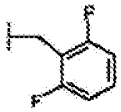
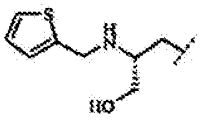
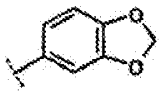
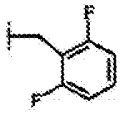
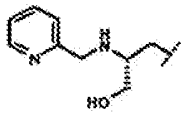
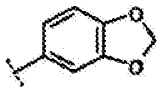
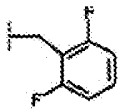
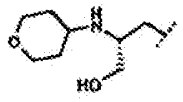
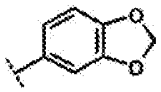
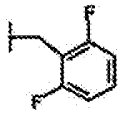
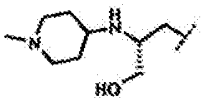
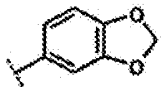
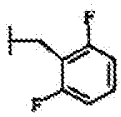
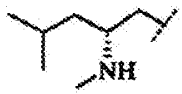
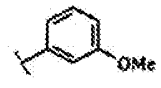
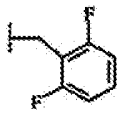
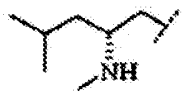
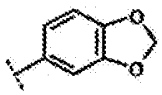
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-731	Me				519.56	520.2
9-732	Me				487.519	488
9-733	Me				503.562	504
9-734	Me				517.6	518.2
9-735	Me				485.6	486.2
9-736	Me				541.6	542
9-737	Me				509.5	510.2
9-738	Me				491.5	492.2
9-739	Me				543.6	544.3

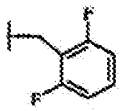
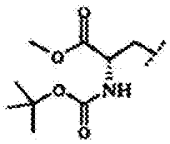
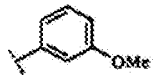
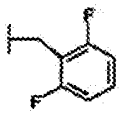
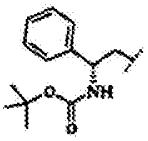
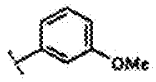
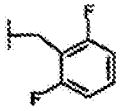
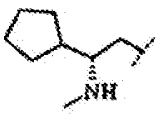
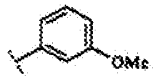
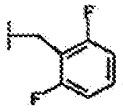
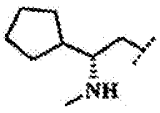
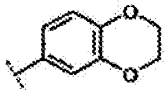
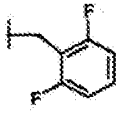
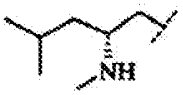
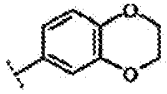
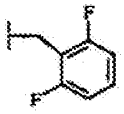
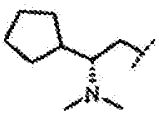
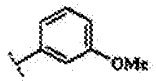
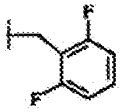
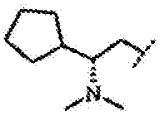
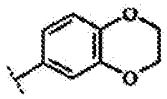
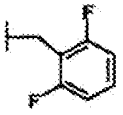
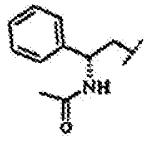
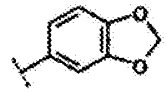
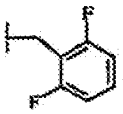
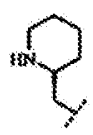
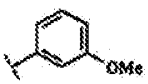
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-740	Me				515.6	516.3
9-741	Me				513.5	514
9-742	Me				637.8	638
9-743	Me				637.7	638
9-744	Me				625.7	626
9-745	Me				553.6	554
9-746	Me				661.6	662
9-747	Me				505.5	506.2

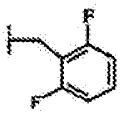
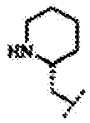
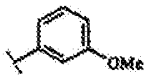
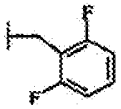
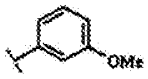
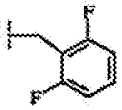
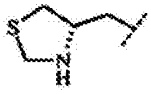
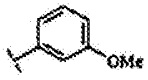
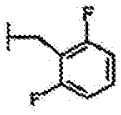
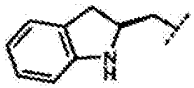
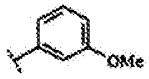
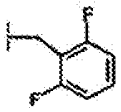
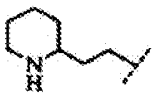
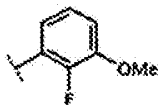
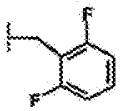
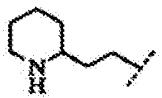
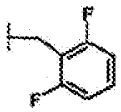
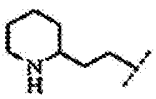
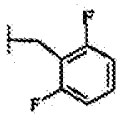
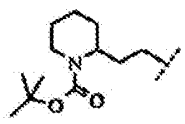
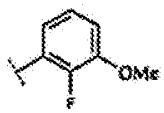
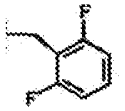
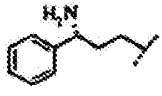
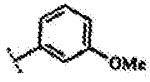
Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-748	Me				519.5	520.2
9-749	Me				517.5	518
9-750	Me				489.5	490.2
9-751	Me				541.6	542
9-752	Me				536.5	537
9-753	Me				529.5	530
9-754	Me				542.6	543
9-755	Me				471.5	472.2
9-756	Me				485.5	486.2

Continuação

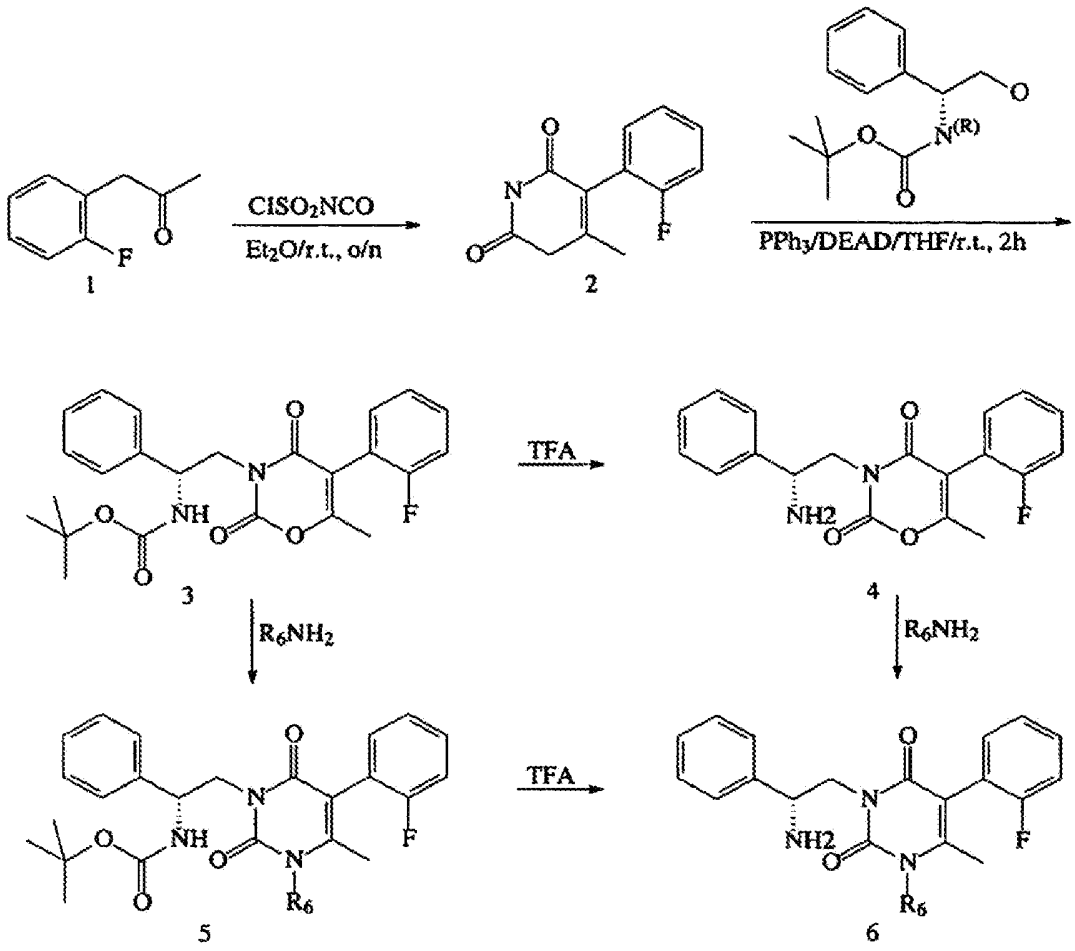
Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-757	Me				559.6	460.2
9-758	Me				527.6	428.2
9-759	Me				483.6	484.2
9-760	Me				511.6	512.2
9-761	Me				49.6	500.2
9-762	Me				497.6	498.2
9-763	Me				525.6	526.2
9-764	Me				533.5	534.2
9-765	Me				455.5	456.2

Continuação

Comp. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
9-766	Me				455.5	456.2
9-767	Me				459.5	460.1
9-768	Me				459.5	459
9-769	Me				489.5	489
9-770	Me				487.5	488
Referência 9-771	Me			Br	442.3	442
Referência 9-772	Me			H	363.4	364
9-773	Me				587.6	588
9-774	Me				491.5	491

EXEMPLO 10

SÍNTESE DE COMPOSTOS REPRESENTATIVOS



Passo A 6-Metil-5-(2-fluorofenil)-oxaz-2,4-diona

A uma solução agitada de 2'-fluorofenilacetona 1 (7,6g, 50 mmol), em éter (50 mL), foi adicionado, gota a gota, clorossulfonilisocianato (CSI, 16,2 g, 115 mmol), à temperatura ambiente. A solução amarela foi agitada durante a noite, vertida em gelo (100 g) e basificada com carbonato de sódio. O produto foi extraído com acetato de etilo (2x200 mL) e o extracto foi lavado com água e salmoura, seco sobre sulfato de magnésio e concentrado *in vacuo* para dar um resíduo

amarelo (9,5 g, RMN de protão, cerca de 70% de produto). O produto bruto foi cristalizado a partir de éter-hexanos para dar o composto **2** como um sólido amarelo (3,6 g, rendimento de 33%); ^{1}H RMN ($CDCl_3$): 2.14 (s, 3H), 7.16 (t, J = 9.0Hz, 1H), 7.24 (m, 2H), 7.41 (m, 1H), 9.20 (brs, 1H).

Passo B 6-Metil-5-(2-fluorofenil)-3-[2(R)-terc-butoxicarbonilamino-2-feniletiloxaz-2,4-diona

DEAD (348 mg, 1,2 mmol) foi adicionado a uma solução de oxazina **2** (221 mg, 1,0 mmol), trifenilfosfina (314 mg, 1,2 mmol) e N-Boc-(R)-fenilglisinol (249 mg, 1,05 mmol) em THF seco (5 mL). A mistura foi agitada à temperatura ambiente durante 2 horas, concentrada, e purificada por cromatografia em gel de sílica com 1:3 acetato de etilo/hexanos para dar o produto **3** (380 mg, 87%) como um sólido branco; ^{1}H RMN ($CDCl_3$): 1.39 (s, 9H), 2.14 (s, 3H), 4.02 (m, 1H), 4.28 (m, 1H), 5.21 (brs, 1H), 5.30 (m, 1H), 7.38 (m, 9H); MS (341, MH^+-BuOCO).

Passo C 6-Metil-5-(2-fluorofenil)-3-[2(R)-amino-2-feniletil]oxaz-2,4 diona sal de ácido trifluoroacético

6-Metil-5-(2-fluorofenil)-3-[2(R)-terc-butoxicarbonil-amino-2-feniletil]oxaz-2,4-diona 3 (30 mg) foi tratado com ácido trifluoroacético (1 mL), à temperatura ambiente, durante 30 minutos. A concentração *in vacuo* deu o composto do título **4** como um óleo incolor em rendimento quantitativo; ^{1}H RMN ($CDCl_3$): 2.05 e 2.08 (s, 3H), 4.10 (m, 1H), 4.45 (m, 1H), 4.62 (m, 1H), 7.15 (m, 3H), 7.40 (m, 6H), 8.20 (brs, 3H); MS: 341 (MH^+).

Passo D 6-Metil-5-(2-fluorofenil)-3-[2(R)-terc-butoxicarbonil-amino-2-feniletil]-1-(2-metoxibenzil)uracilo

Uma mistura de 6-metil-5-(2-fluorofenil)-3-[2(R)-terc--butoxicarbonilamino-2-feniletil]oxaz-2,4-diona, **3** (29 mg), e 2-metoxibenzilamina (0,15 mL), foi aquecida num vaso de reacção selado a 100 °C durante 1 hora. A cromatografia em gel de sílica com 1:2 de acetato de etilo-hexanos deu o composto **5** como um óleo incolor; ^{1}H RMN ($CDCl_3$): 1.40 (s, 9H), 2.04 (s, 3H), 3.87 (s, 3H), 4.18 (m, 1H), 4.44 (m, 1H), 5.22 (m, 2H), 5.65 (brs, 1H), 5.78 (m, 1H), 6.85-7.42 (m, 13H); MS: 460 (MH^+-BuOCO).

Os seguintes intermediários protegidos foram feitos usando o mesmo procedimento, mas substituindo 2-metoxibenzilamina por diferentes aminas. Pode ser utilizado ácido acético para catalisar a reacção.

6-Metil-5-(2-fluorofenil)-3-[2(R)-terc-butoxicarbonilamino-2-feniletil]-1-(2,6-difluorobenzil)uracilo

^{1}H RMN ($CDCl_3$): 1.39 (s, 9H), 2.18 (s, 3H), 4.10 (m, 1H), 4.38 (m, 1H), 4.90-5.80 (m, 4H), 6.92 (m, 2H), 7.10-7.42 (m, LOH), MS: 466 (MH^+-BuOCO).

6-Metil-5-(2-fluorofenil)-3-[2(R)-terc-butoxicarbonilamino-2-feniletil]-1-(2-clorobenzil)uracilo

^{1}H RMN ($CDCl_3$): 1.40 (s, 9H), 2.02 (s, 3H), 4.15 (m, 1H), 4.50 (m, 1H), 5.35 (m, 3H), 5.62 (m, 1H), 6.95 (m, 13H); MS: 464 (MH^+-BuOCO).

6-Metil-5-(2-fluorofenil)-3-[2(R)-terc-butoxicarbonilamino-2-feniletil]-1-(2-metilbenzil)uracilo

^{1}H RMN ($CDCl_3$): 1.40 (s, 9H), 2.02 (s, 3H), 2.37 (s, 3H), 4.15 (m, 1H), 4.42 (m, 1H), 5.72 (m, 1H), 6.80-7.42 (m, 13H); MS: 444 (MH^+-BuOCO).

Passo E 6-Metil-5-(2-fluorofenil)-3-[2(R)-amino-2-feniletil]-1-(2-metoxibenzil)uracilo, sal de ácido trifluoroacético

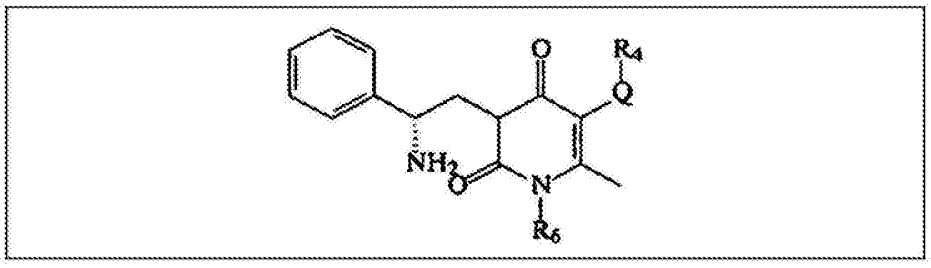
6-Metil-5-(2-fluorofenil)-3-[2(R)-terc-butoxicarbonil-amino-2-feniletil]-1-(2-metoxibenzil)uracilo 5 (20 mg) foi tratado com ácido trifluoroacético (1 mL), à temperatura ambiente durante 30 minutos. A concentração *in vacuo* deu o produto **6** como um óleo incolor em rendimento quantitativo; ^{1}H RMN ($CDCl_3$): 2.04 (s, 3H), 3.82 & 3.85 (s, 3H), 4.20 (m, 1H), 4.62 (m, 2H), 5.10 (m, 2H), 6.82-7.40 (m, 13H), 8.05 (brs, 3H); MS: 460 (MH^+).

Os produtos seguintes foram também preparados utilizando o mesmo procedimento.

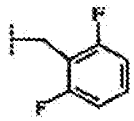
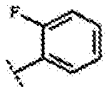
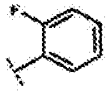
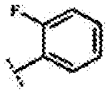
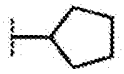
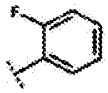
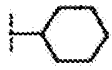
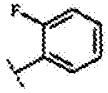
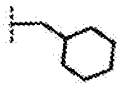
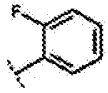
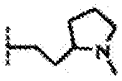
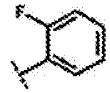
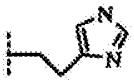
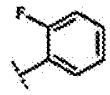
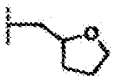
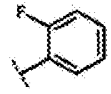
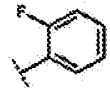
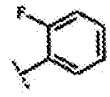
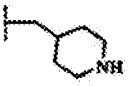
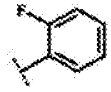
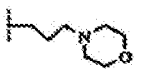
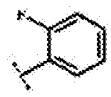
6-Metil-5-(2-fluorofenil)-3-[2(R)-amino-2-feniletil]-1-(2-clorobenzil)uracilo, sal de ácido trifluoroacético
^{1}H RMN ($CDCl_3$): 2.01 (s, 3H), 4.20 (m, 1H), 4.70 (m, 2H), 5.25 (m, 2H), 6.90-7.45 (m, 13H), 8. 20 (brs, 3H); MS: 464 (MH^+).
6-Metil-5-(2-fluorofenil)-3-[2(R)-amino-2-feniletil]-1-(2-metilbenzil)uracilo, sal de ácido trifluoroacético
^{1}H RMN ($CDCl_3$): 2.00 (s, 3H), 2.27 e 2.34 (s, 3H), 4.15 (m, 4H), 4.62 (m, 2H), 5.15 (m, 2H), 6.80-7.40 (m, 13H); MS: 444 (MH^+).
6-Metil-5-(2-fluorofenil)-3-[2(R)-amino-2-feniletil]-1-(2,6-difluorobenzil)uracilo, sal de ácido trifluoroacético
^{1}H RMN ($CDCl_3$): 2.14 (s, 3H), 4.18 (m, 1H), 4.62 (m, 2H), 5. 20 (m, 2H), 5. 62 (brs, 3H), 6.85-7.40 (m, 13H); MS: 466 (MH^+).

Os compostos da seguinte Tabela 10 foram também preparados pelo processo acima descrito.

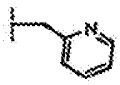
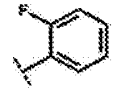
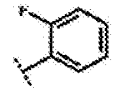
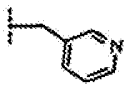
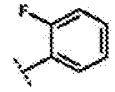
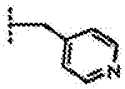
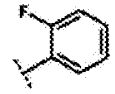
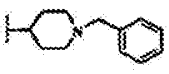
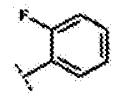
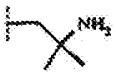
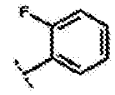
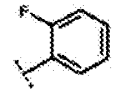
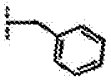
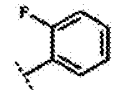
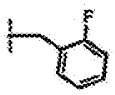
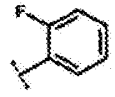
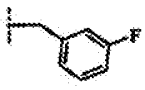
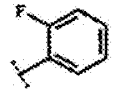
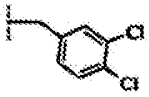
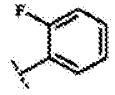
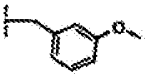
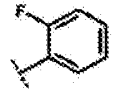
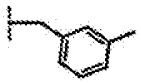
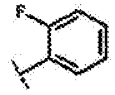
Tabela 10



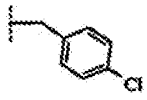
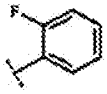
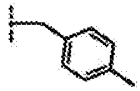
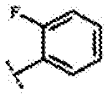
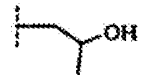
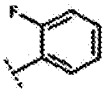
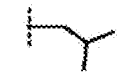
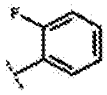
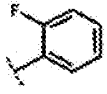
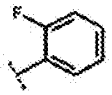
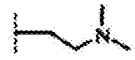
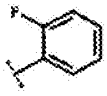
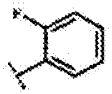
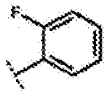
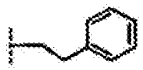
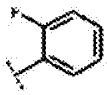
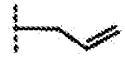
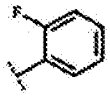
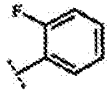
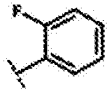
Continuação

Comp. No.	R_6	-Q-R_4	MW (calc.)	(obs.)
10-1			465.5	466
10-2			393.5	394.2
10-3			379.4	363
10-4			407.5	323.3
10-5			421.5	405.4
10-6			435.5	436.2
Referência 10-7			450.6	451.3
10-8			433.5	417.3
Referência 10-9			423.5	407.2
10-10			435.5	419.2
Referência 10-11			451.5	452.3
Referência 10-12			436.5	323.3
Referência 10-13			466.6	450.3

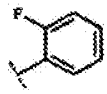
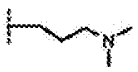
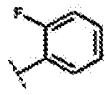
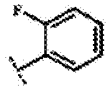
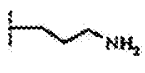
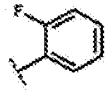
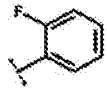
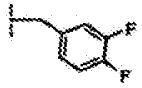
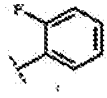
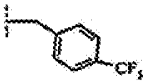
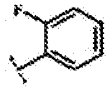
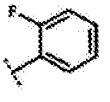
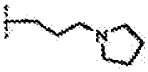
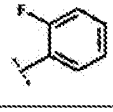
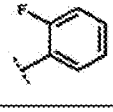
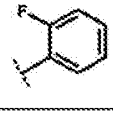
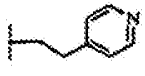
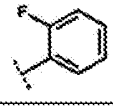
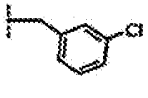
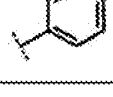
Continuação

Comp. No.	R_6	-Q-R_4	MW (calc.)	(obs.)
10-14			430.5	414.4
10-15			444.5	428.4
10-16			430.5	414.4
10-17			430.5	414.4
Referência 10-18			512.6	513.3
10-19			410.5	323.3
10-20			381.4	382.2
10-21			429.5	413.2
10-22			447.5	431.4
10-23			447.5	431.3
10-24			498.4	481.4
10-25			459.5	443.3
10-26			443.5	427.2

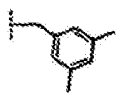
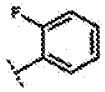
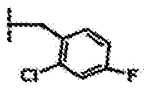
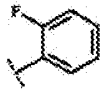
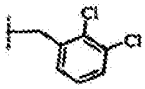
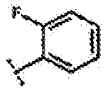
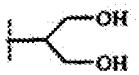
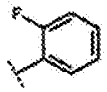
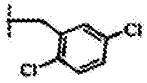
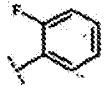
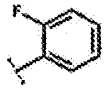
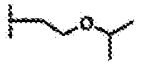
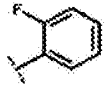
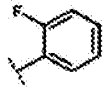
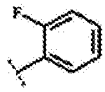
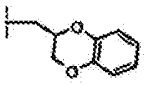
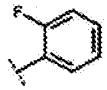
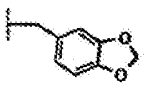
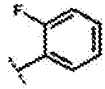
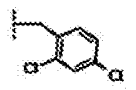
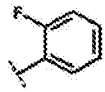
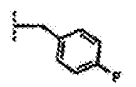
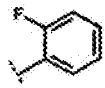
Continuação

Comp. No.	R_6	-Q-R_4	MW (calc.)	(obs.)
10-27			463.9	447.1
10-28			443.5	427.2
10-29			397.4	398.2
10-30			395.5	379.2
10-31			409.5	393.3
10-32			396.5	380.3
10-33			410.5	394.1
10-34			397.4	381.2
10-35			383.4	367.1
10-36			443.5	427.2
10-37			379.4	363.3
10-38			409.5	393.3
10-39			382.4	366.2

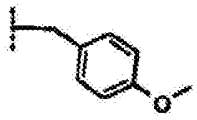
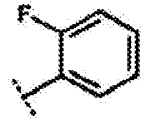
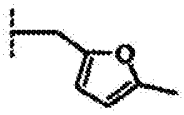
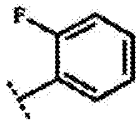
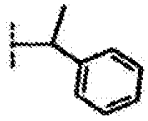
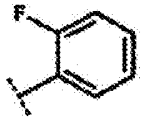
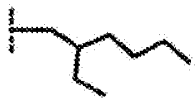
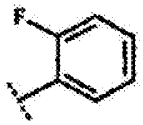
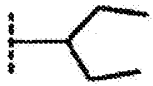
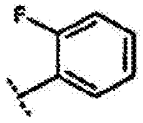
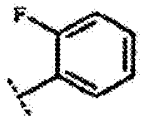
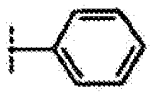
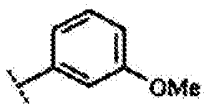
Continuação

Comp. No.	R_6	-Q-R_4	MW (calc.)	(obs.)
10-40			381.4	365.2
10-41			424.5	408.5
10-42			397.4	381.2
10-43			396.5	380.3
10-44			409.5	393.3
10-45			465.5	449.4
10-46			497.5	481.4
10-47			395.5	379.3
Referência 10-48			450.6	451.3
10-49			411.5	395.2
10-50			393.5	377.3
10-51			444.5	428.4
10-52			463.9	447.1

Continuação

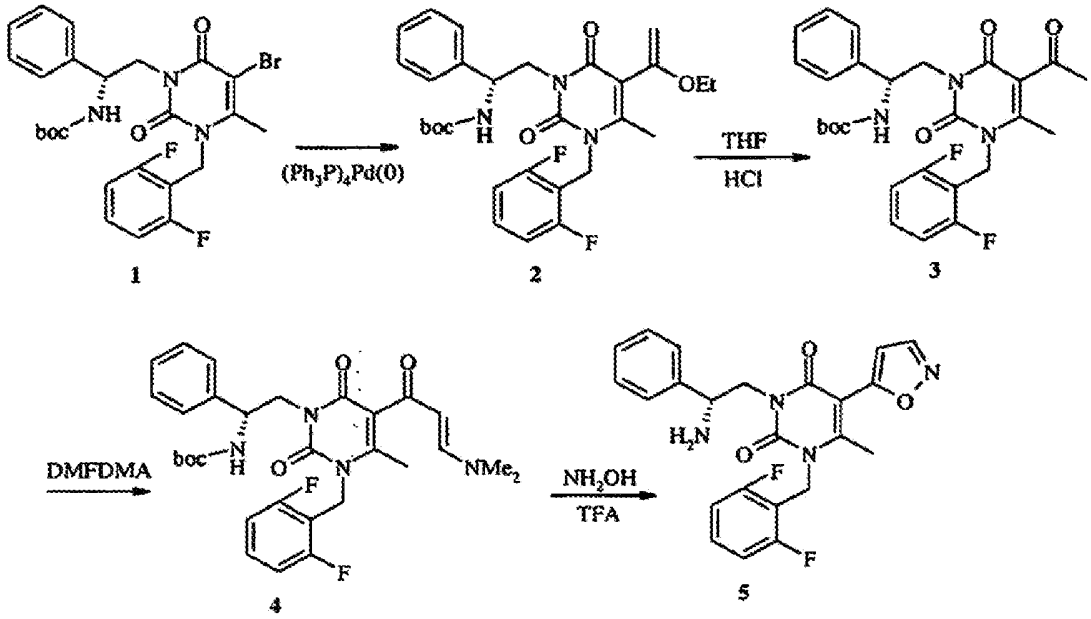
Comp. No.	R_6	-Q-R_4	MW (calc.)	(obs.)
10-53			457.5	441.3
10-54			481.9	465.4
10-55			498.4	481.2
10-56			413.4	397.1
10-57			498.4	481.2
Referência 10-58			408.5	409.2
10-59			425.5	409.2
10-60			444.5	428.4
Referência 10-61			422.5	323.4
10-62			487.5	471.3
10-63			473.5	474.2
10-64			498.4	498.1
10-65			447.5	448.2

Continuação

Comp. No.	R_6	-Q-R_4	MW (calc.)	(obs.)
10-66			459.5	460.2
10-67			443.5	434.2
10-68			443.5	444.2
10-69			451.6	452.3
10-70			409.5	410.2
10-71			409.5	410.2
10-72			427.5	428.2

EXEMPLO 11

SINTESE DOS COMPOSTOS REPRESENTATIVOS



Passo A 1-(2,6-difluorobenzil-3-[(2R)-terc-butilcarbonilamino-2-fenil]etil-5-(1-etoxivinil)-6-metiluracilo

Uma solução de 1-(2,6-difluorobenzil-3-[(2R)-terc-butilcarbonilamino-2-fenil]etil-5-bromo-6-metiluracilo **1** (500 mg, 0,91 mmol), tributil (etoxivinil)estanho (0,39 mL) e $(Ph_3P)_4Pd(0)$ (105 mg), em dioxano (5 mL), foi aquecida a 100 °C sob azoto durante 2 horas. A mistura de reacção foi concentrada *in vacuo* e o produto em bruto **2** foi utilizado para o passo seguinte. MS: 442 (MH^+-Boc).

Passo B 1-(2,6-Difluorobenzil-3-[(2R)-terc-butiloxicarbonil-amino-2-fenil]etil-5-acetil-6-metiluracil

Uma solução de 1-(2,6-difluorobenzil-3-[(2R)-terc-butilcarbonilamino-2-fenil]etil-5-(1-etoxivinil)-6-metiluracilo **2** (490 mg), em THF (10 mL), foi tratada com HCl aquoso 2,5M (3 mL) e agitada à temperatura ambiente durante uma hora. A mistura de reacção foi neutralizada com $NaHCO_3$ e concentrada *in vacuo* para remover o THF. O produto foi

extraído com acetato de etilo. O extracto foi lavado com água e salmoura, seco sobre $MgSO_4$ e concentrado *in vacuo* para dar um sólido castanho. A cromatografia em gel de sílica com 1:2 a 1:1 de acetato de etilo/hexanos deu o composto **3** como um sólido branco (227 mg, 50% de rendimento); 1H RMN: 1.37 (s, 9H), 2.38 (s, 3H), 2.58 (s, 3H), 4.12 (dd, J = 4.2, 10.0Hz, 1H), 4. 65 (dd, J = 6.5, 10.0Hz, 1H), 5.20 (m, 1H), 5.40 (d, J = 12.0Hz, 1H), 5. 49 (d, J = 12.0Hz, 1H), 5. 58 (d, J = 6.0Hz, 1H), 6.92 (t, J = 8.0Hz, 2H), 7.38 (m, 6H); MS: 414 (MH^+-Boc).

Passo C 1-(2,6-Difluorobenzil-3-[(2R-terc-butoxicarbonilamino-2-fenil]etil-5-(3-dimetilamino-1-oxopropenil)-6-metiluracilo

1-(2,6-Difluorobenzil-3-[(2R)-terc-butilcarbonilamino-2-fenil]etil-5-acetil-6-metiluracilo, **3**, (44 mg) foi suspenso em DMFDMA (1,0 mL) e aquecido a 50 °C durante 1 hora. O produto foi purificado em gel de sílica com 1:1 acetato de etilo/hexanos para dar o composto **4** como um óleo amarelo; 1H RMN: 1.39 (s, 9H), 2.36 (s, 3H), 2.84 (s, 6H), 4.05 (m, 1H), 4.30 (m, 1H), 4.66 (d, J = 12.0Hz 1H), 5.03 (m, 1H), 5.20 (d, J = 12Hz, 1H), 5.46 (d, J = 12Hz, 1H), 5.84 (d, J = 7Hz, 1H), 6.64 (d, J = 12.0Hz, 1H), 6.87 (t, J = 8.0Hz, 2H), 7.20-7.40 (m, 6H); MS: 596 (MH^+).

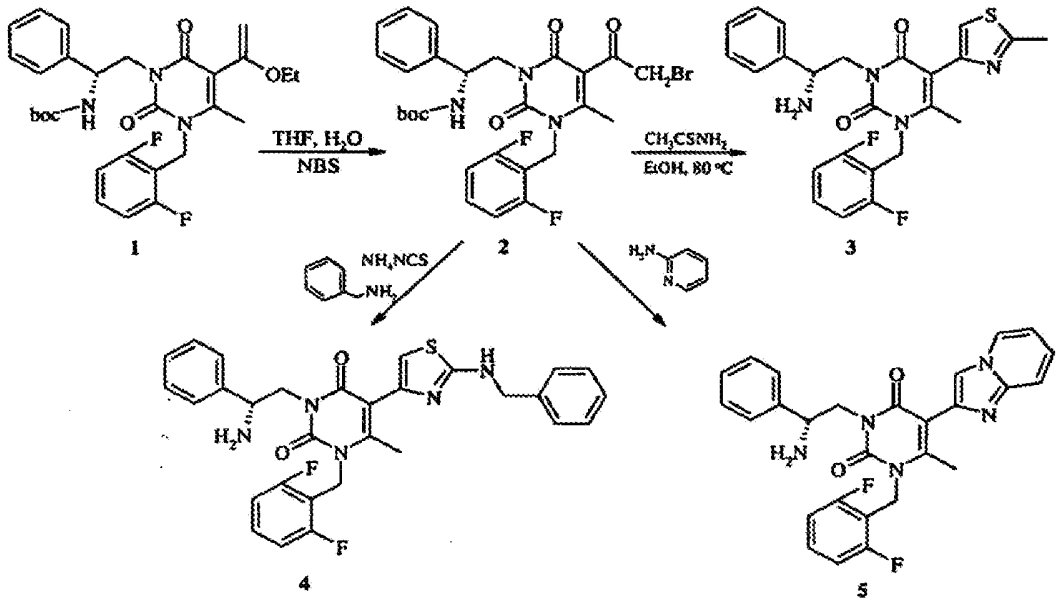
Passo D 1-(2,6-difluorobenzil-3-[(2R)-amino-2-fenil]etil-5-(isozazol-5-il)- 6-metiluracilo

Uma mistura de 1-(2,6-difluorobenzil-3-[(2R)-terc-butoxicarbonilamino-2-fenil]-etil-5-(3-dimetilamino-1-oxopropenil)-6-metiluracilo **4** (95 mg), cloridrato de hidroxilamina (150 mg), carbonato de sódio (18 mg), em metanol (5 mL), foi acidificada com ácido acético até pH-4. A mistura foi então aquecida a 120 °C durante 1,5 horas, arrefecida para

até à temperatura ambiente, filtrada, e concentrada *in vacuo* para dar o produto protegido. MS: 539 (MH+). O produto protegido foi dissolvido em diclorometano (2 mL), tratado com TFA (1 mL), e agitou-se à temperatura ambiente durante 1 hora. A concentração *in vácuo*, seguida de purificação em gel de sílica eluindo com NH_4OH 1% aq. em acetato de etilo deu o produto **5**; MS: 439 (MH+); 1H RMN (CD_3OD): 3.05 (s, 3H), 4.70 (m, 1H), 4.55 (m, 2H), 5.48 (d, J = 12.0Hz, 1H), 5.60 (d, J = 12.0Hz, 1H), 7.00 (t, J = 8.0Hz, 2H), 7.30-7.65 (m, 7H), 8.50 (d, J = 6.0Hz, 1H).

EXEMPLO 12

SÍNTESE DOS COMPOSTOS REPRESENTATIVOS



Passo A <u>1-(2,6-Difluorobenzil-3-[(2R)-terc-butilcarbonilamino-2-fenil]-etil-5-bromoacetil-6-metiluracilo</u>

Uma solução de 1-(2,6-difluorobenzil-3-[(2R)-terc-butilcarbonilamino-2-fenil]etil-5-(1-etoxivinil)-6-

metiluracilo, **1**, (3,68g, 6,8 mmol), em THF (120 mL) e água (120 mL), foi tratada com N-bromossuccinimida (2,3 g) à temperatura ambiente e a mistura foi agitada durante 4 horas. O THF foi removido *in vacuo* e o produto que precipitou em repouso foi recolhido por filtração e foi lavado com éter para dar o sólido branco **2** (1,6 g, 40%); 1H RMN: 1.39 (s, 9H), 2.40 (s, 3H), 4.04 (dd, J = 2.0, 7.0Hz, 1H), 4.36 (d, J = 7.0Hz, 1H), 4.10 (d, J = 5.5Hz, 1H), 4.6 (d, J = 5.5Hz, 1H), 55.50 (m, 1H), 5.24 (d, J = 12.0Hz, 1H), 5.40 (brs, 1H), 5.50 (d, J = 12.0Hz, 1H), 6.94 (t, J = 8.0Hz, 1H), 7.36 (m, 6H); MS: 492 (MH+).

Passo B 1-(2,6-Difluorobenzil-3-[(2R)-amino-2-fenil]-etil-5-(5-metiltiazol-4-il)-6-metiluracilo

Uma solução de 1-(2,6-difluorobenzil-3-[(2R)-terc-butilcarbonilamino-2-fenil]etil-5-bromoacetil-6-metiluracilo (100 mg, 0,17 mmol) e tioacetamida (30 mg, 0,4 mmol), em etanol (2 mL), foi aquecida a 80 °C num vaso de reacção selado, durante 3 horas. A mistura de reacção foi então concentrada *in vacuo* para dar um óleo e LCMS indicou o produto protegido; MS: 569 (MH+). O produto protegido foi dissolvido em diclorometano (2 mL) e tratado com TFA (1 mL) à temperatura ambiente durante 1 hora, e concentrada *in vacuo*. O produto foi purificado em gel de sílica eluindo com NH_4OH aq. 5% em acetato de etilo para dar o sólido amarelo **3**; 1H RMN: 2.12 (s, 3H), 2.71 (s, 3H), 4.15-4.70 (m, 3H), 5.66 (s, 2H), 7.00 (t, J = 8.0Hz, 2H), 7.30 (m, 7H); MS: 469 (MH+).

Passo C 1-(2,6-difluorobenzil-3-[(2R)-amino-2-fenil]etil-5-(5-benzilaminoltiazol-4-il)-6-metiluracilo

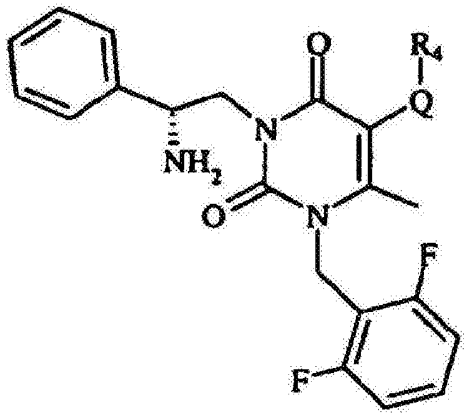
Uma solução de 1-(2,6-difluorobenzil-3-[(2R)-terc-butilcarbonilamino-2-fenil]etil-5-bromoacetil-6-metiluracilo 2

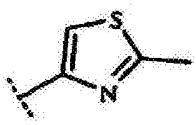
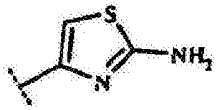
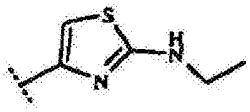
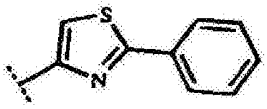
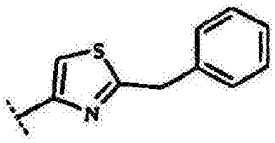
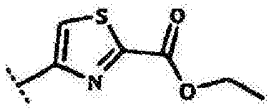
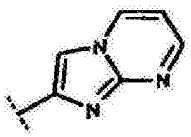
(35 mg) e tioisocianato de amónio (10 mg), em etanol (1 mL), foi aquecida a 80 °C num vaso de reacção selado durante 1 hora. Foi adicionada benzilamina (0,2 mL) e a mistura foi aquecida a 80 °C durante a noite. A mistura de reacção foi então concentrada *in vacuo*, e o produto protegido foi dissolvido em diclorometano (1 mL) e tratado com TFA (1 mL) à temperatura ambiente durante 1 hora. A mistura foi concentrada *in vacuo* e o resíduo foi purificado em gel de sílica com NH_4OH aq. 5% em acetato de etilo para dar o produto **4** como um sólido amarelo; ^{1}H RMN: 2.25 (s, 3H), 4.05 (dd, J = 3.0, 7.5Hz, 1H), 4.28 (dd, J = 6.5, 7.5Hz, 1H), 4.42 (m, 1H), 4.44 (s, 2H), 5.32 (d, J = 12.0Hz, 1H), 5.36 (d, J = 12.0Hz, 1H), 6.54 (s, 1H), 6.92 (t, J = 8.0Hz, 2H), 7.20-7.50 (m, 11H); MS: 560 (MH +).

Passo D <u>1-(2,6-Difluorobenzil-3-[(2R)-amino-2-fenil]etil-5-(imidazolo[1,2-a]pirid-2-il)-6-metiluracilo</u>

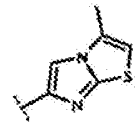
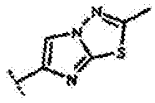
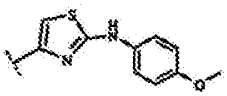
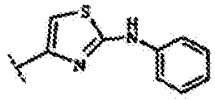
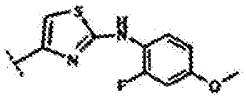
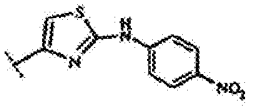
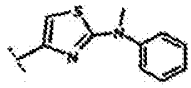
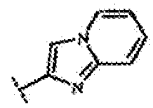
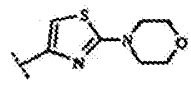
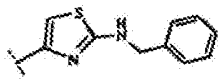
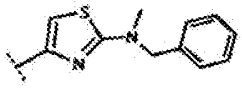
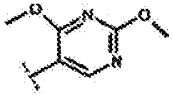
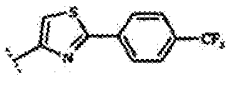
Uma mistura de 1-(2,6-difluorobenzil-3-[(2R)-terc-butilcarbonilamino-2-fenil]etil-5-bromoacetil-6-metil uracilo, **2** (35 mg), e 2-aminopiridina (7 mg), em etanol, foi aquecida na 80 °C durante a noite. A mistura de reacção foi então concentrada *in vacuo*, e o produto protegido foi dissolvido em diclorometano (1 mL) e tratado com TFA (1 mL) à temperatura ambiente durante 1 hora. Após concentração *in vacuo*, o produto **5** foi purificado em HPLC preparativa; 1H RMN: 2.32 (s, 3H), 4.04 (m, 1H), 4.67 (m, 2H), 5.17 (d, J = 16.2Hz, 1H), 5.41 (d, J = 16.2Hz, 1H), 6.92 (t, J = 8.1Hz, 2H), 7.24-7.40 (m, 7H), 7.73 (m, 1H), 7.80 (m, 1H), 8.03 (s, 1H), 8.30 (brs, 3H), 8.44 (d, J = 5.5Hz, 1H); MS: 488 (MH +).

Tabela 12

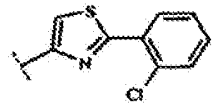
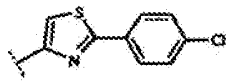
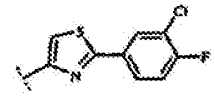
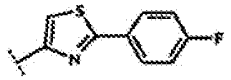
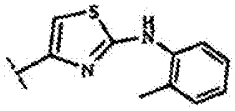
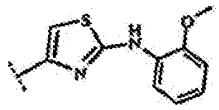
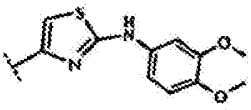
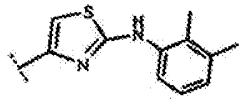
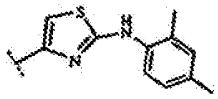
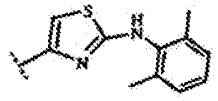
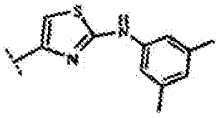
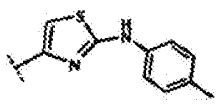


Comp. No.	-Q-R_4	MW (calc.)	MW (obs.)
Referência 12-1		468.5	469.1
Referência 12-2		469.5	470.1
Referência 12-3		497.6	498.2
Referência 12-4		530.6	531.1
Referência 12-5		544.6	545.2
Referência 12-6		526.6	527.2
12-7		488.5	489.2

Continuação

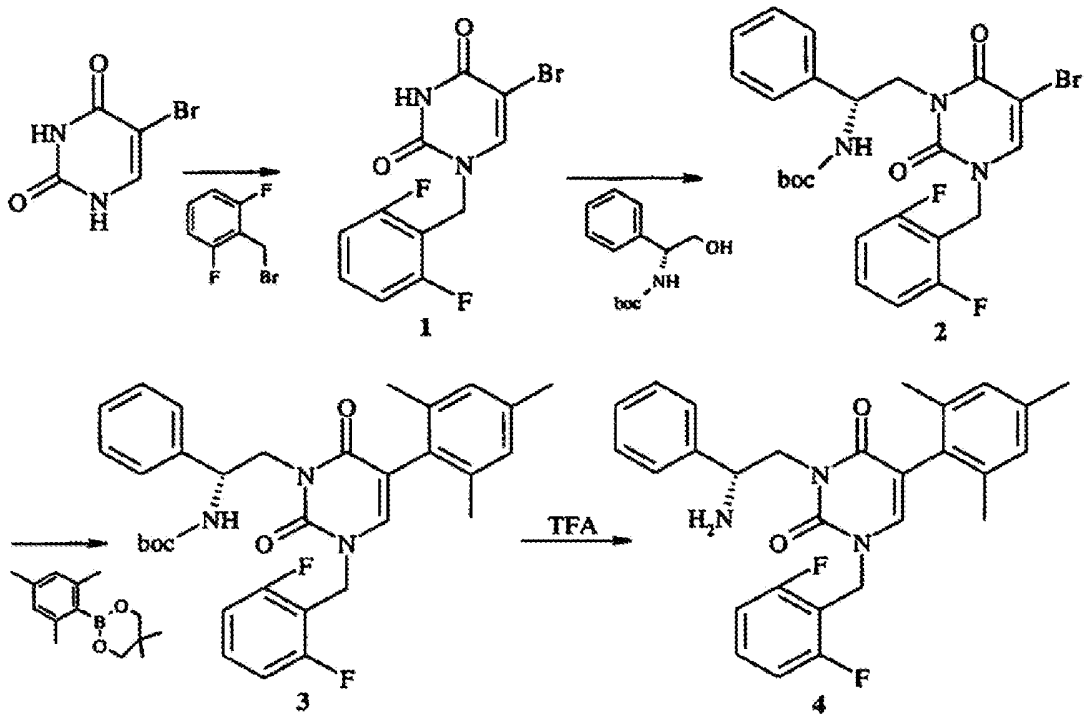
Comp. No.	-Q-R_4	MW	
		(calc.)	(obs.)
Referência 12-8		507.6	508.2
Referência 12-9		508.6	509.1
Referência 12-10		575.6	576.2
Referência 12-11		545.6	546.2
Referência 12-12		563.6	564.2
Referência 12-13		590.6	591.1
Referência 12-14		559.6	560.2
12-15		487.5	488.2
Referência 12-16		539.6	540.2
Referência 12-17		559.6	560.2
Referência 12-18		573.7	574.2
Referência 12-19		509.5	510
Referência 12-20		598.6	599.2

Continuação

Comp. No.	-Q-R_4	MW (calc.)	MW (obs.)
Referência 12-21		565.0	565.2
Referência 12-22		565.0	565.1
Referência 12-23		583.0	583.1
Referência 12-24		548.6	549.2
Referência 12-25		559.6	560.2
Referência 12-26		575.6	576.2
Referência 12-27		605.7	606.3
Referência 12-28		573.7	574.2
Referência 12-29		573.7	574.2
Referência 12-30		573.7	574.2
Referência 12-31		573.7	574.2
Referência 12-32		559.6	560.2

EXEMPLO 13

SÍNTESE DOS COMPOSTOS REPRESENTATIVOS



Passo A. 5-bromo-1-(2,6-difluorobenzil)uracil

Uma suspensão de 5-bromouracilo (18,45 g, 96,6 mmol), em 300 mL de dicloroetano, foi tratada com N,O-bis (trimetilsilil)acetamida (48 mL, 39,5 g, 194 mmol). A mistura de reacção foi aquecida a 80 °C durante 3 h sob o azoto. A solução foi arrefecida até à temperatura ambiente, foi adicionado brometo de 2,6-difluorobenzilo (25 g, 120 mmol) e a mistura de reacção foi aquecida a 80 °C durante a noite sob a protecção de azoto. A reacção foi arrefecida, interrompida com MeOH (15 mL), e repartida entre diclorometano (500 mL) e água (250 mL). A camada orgânica foi lavada com salmoura, seca (sulfato de sódio), e evaporada para dar um sólido. O produto bruto foi triturado com éter, filtrado, e lavado com éter três

vezes para dar o composto **1** como um sólido branco (15,2 g, 50%), MS (Cl) m/z 316.90, 318.90 (MH^+).

Passo B 1-(2,6-Difluorobenzil-3-[(2R-terc-butilcarbonilamino-2-fenil]etil-5-bromouracilo

Uma solução de *(R)-N-(terc*-butoxicarbonil)-2-fenilglicinol (14,97 g, 63,1 mmol), em THF anidro (300 mL), foi tratada com 5-bromo-1-(2,6-difluorobenzil)uracilo, **1** (20 g, 63,1 mmol), e trifenilfosfina (20,68 g, 78,8 mmol) à temperatura ambiente, em seguida, di-isopropilazodicarboxilato (15,52 mL, 15,94 g, 78,8 mmol), em THF (30 ml), foi introduzido através de uma ampola de adição gota-a-gota. A mistura de reacção foi agitada à temperatura ambiente durante 16 horas e os voláteis foram evaporados. O resíduo foi purificado por cromatografia flash (sílica, 25% EtOAc/hexanos) para dar o composto **2** (31,15 g, 92,1%) como um sólido branco, MS (Cl) m/z 436.0, 438.0 (MH^+-Boc).

Passo C 1-(2,6-Difluorobenzil-3-[(2R)-terc-butoxicarbonil-amino-2-fenil]etil-5-(2,4,6-trimetilfenil)uracilo

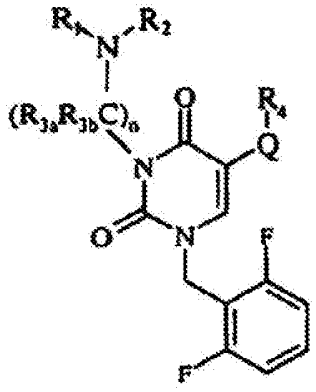
Ao composto **2** (134 mg, 0,25 mmol), em tolueno/H_2O/EtOH (6/3,75/0,75 mL), foi adicionado 2,4,6-trimetilfenil éster de ácido borónico (87 mg, 1,5 eq), K_2CO_3 (86 mg, 2,5 eq), e $Ba(OH)_2$ saturado/água (0,1 mL). A mistura de reacção foi desoxigenada com N_2 durante 10 min, foi adicionado tetraquis(trifenilfosfina)paládio(0) (29 mg, 0,1 eq) e a mistura de reacção foi aquecida a 100 °C durante a noite sob a protecção de N_2. A mistura de reacção foi repartida entre salmoura e EtOAc. A camada orgânica foi seca (sulfato de sódio), evaporada, purificada por cromatografia flash (sílica,

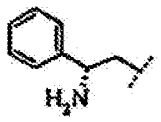
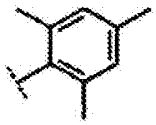
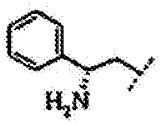
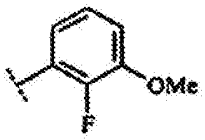
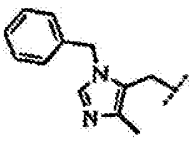
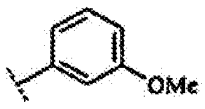
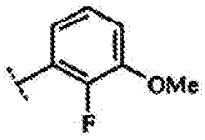
25% EtOAc/hexanos) para dar o composto **3** (130 mg) como um óleo amarelo pálido.

Passo D 1-(2,6-Difluorobenzil-3-[(2R)-amino-2-fenil]etil-5-(2,4,6-trimetilfenil)uracilo

TFA (3 ml) foi adicionado a uma solução de **3** (130 mg, 0,22 mmol), em diclorometano (3 mL), e a mistura de reacção foi agitada à temperatura ambiente durante 2 horas. Os voláteis foram evaporados e o resíduo foi repartido entre $NaHCO_3$ saturado/água e EtOAc. A camada orgânica foi seca (sulfato de sódio), evaporada e purificada por TLC prep eluindo com MeOH 5% em CH_2Cl_2 para dar o composto **4**, MS (CI) m/z 476.2 (MH^+).

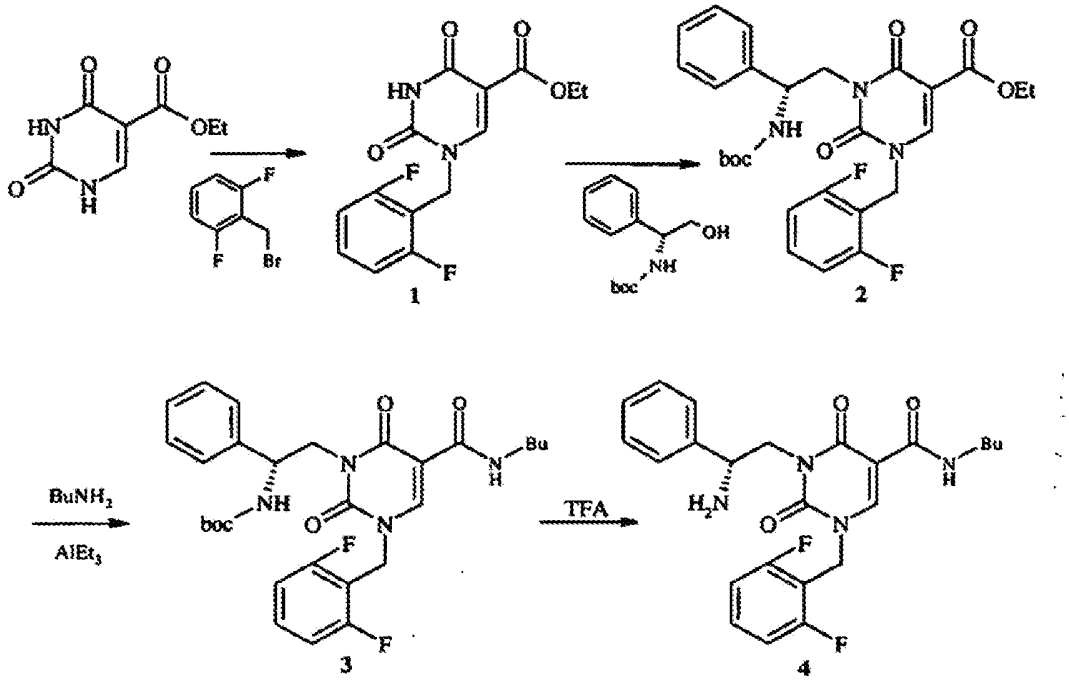
Tabela 13



Comp. No.	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	MW (obs.)
13-1			475.5	476.2
13-2			481.5	482
13-3			528.6	529
13-4			475.5	476.2

EXEMPLO 14

SÍNTESE DE COMPOSTOS REPRESENTATIVOS



Passo A 1-(2,6-difluorobenzil)-5-carbetoxiuracilo

5-Carbetoxiuracilo (5 g, 27,15 mmol) e N,O-bis (trimetilsilil)acetamida (13,4 mL, 2 eq), em dicloroetano (35 mL), foram aquecidos a 80°C durante 2 horas. Foi adicionado brometo de difluorobenzilo (8,4 g, 1,5 eq) e a mistura de reacção foi aquecida a 80 °C durante 16 horas. A reacção foi interrompida com metanol e repartida entre cloreto de metileno e solução de bicarbonato de sódio. A camada orgânica foi lavada com salmoura, seca e concentrada *in vacuo* e o resíduo foi triturado com éter para dar o composto **1** como um sólido branco (3,26 g).

Passo B 1-(2,6-Difluorobenzil-3-[(2R)-*tert*-butoxicarbonil-amino-2-fenil]etil-5-carbetoxiuracilo

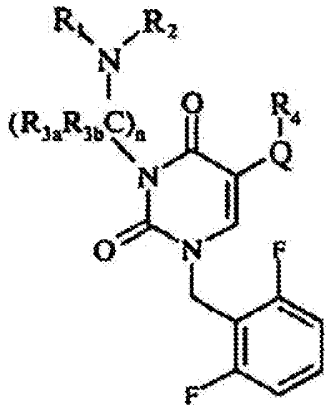
Uma solução de *(R)-N-(terc*-butoxicarbonil)-2-fenilglicinol (316 mg, 1,33 mmol), em THF anidro (30 mL), foi tratada com 1-(2,6-difluorobenzil)-5-carbetoxiuracil, **1** (413 mg, 1,33 mmol)

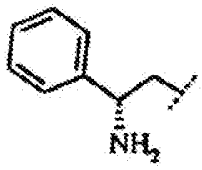
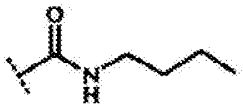
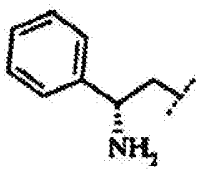
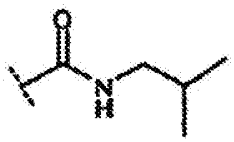
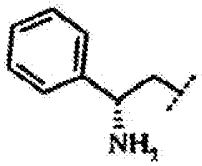
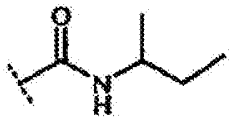
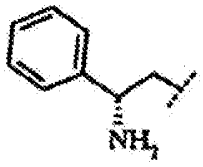
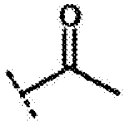
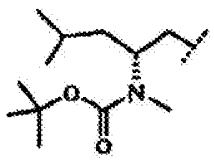
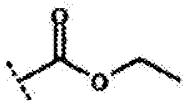
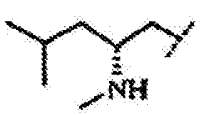
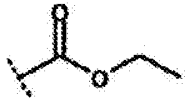
e trifenilfosfina (525 mg, 2 mmol) à temperatura ambiente, em seguida, diisopropilazodicarboxilato (460 mg, 2 mmol), em THF (5 mL), foi introduzido através de uma ampola de adição gota-a-gota. A mistura de reacção foi agitada à temperatura ambiente durante 5 h, e os voláteis foram evaporados. O resíduo foi purificado por cromatografia flash (sílica, 35% EtOAc/ hexanos) para dar o composto **2** (427 mg) como uma espuma branca.

Passo C 1-(2,6-Difluorobenzil-3-[(2R)-terc-butilcarbonilamino-2-fenil]etil-5-n-butilamidouracilo

Uma solução de trietilalumínio (1,9 M em tolueno, 0,26 mL, 0,5 mmol) foi adicionada a n-butilamina (0,1 mL, 1 mmol), em dicloroetano, e a mistura de reacção foi selada sob azoto e agitada durante ½ hora. Foi adicionado 1-(2,6-Difluorobenzil-3-[(2R)-terc-butilcarbonilamino-2-fenil]etil-5-carbetoxi-uracilo, **2**, e a mistura foi agitada a 70-80 °C durante 12 horas para dar **3**. Ácido trifluoroacético (1 mL) foi adicionado e a mistura de reacção foi agitada durante 1 hora. A mistura foi concentrada *in vacuo* e o resíduo foi repartido entre cloreto de metileno e solução de carbonato de sódio. A camada orgânica foi lavada com salmoura, seca e concentrada para dar um resíduo que foi purificado por HPLC preparativa para dar o composto **4** (56 mg, MH^+ 457).

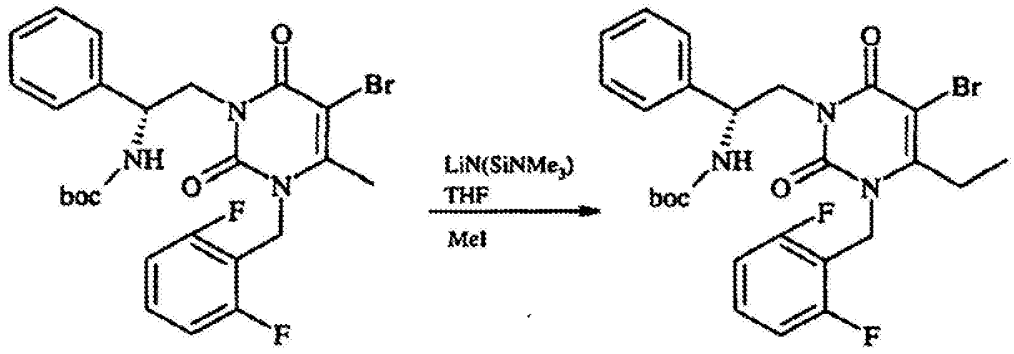
Tabela 14



Comp. No.	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	MW (obs.)
Referência 14-1			456.5	457.2
Referência 14-2			456.5	457.2
Referência 14-3			456.5	457.2
Referência 14-4			413.4	414.1
Referência 14-5			523.6	424.2
Referência 14-6			423.5	424.2

EXEMPLO 15

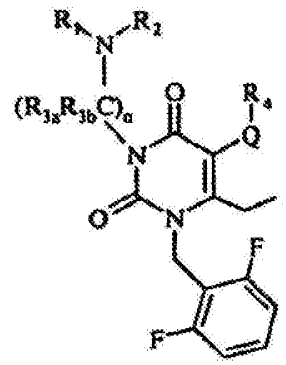
SÍNTESE DOS COMPOSTOS REPRESENTATIVOS

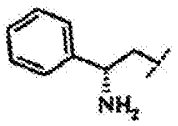
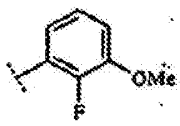
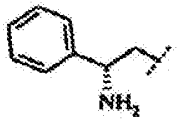
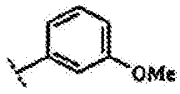
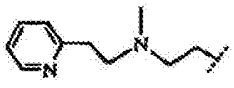
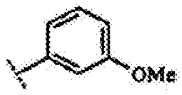
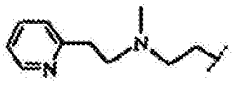


Passo A 1-(2,6-Difluorobenzil-3-[(2R)-terc-butoxicarbonil-amino-2-fenil]etil-5-bromo-6-etiluracilo

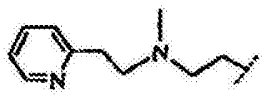
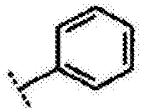
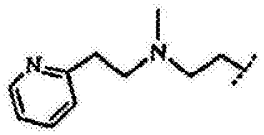
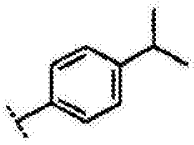
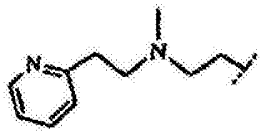
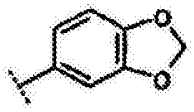
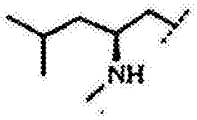
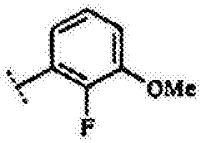
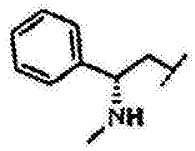
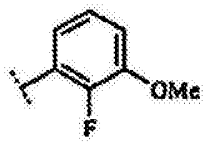
1-(2,6-Difluorobenzil-3-[(2R)-terc-butoxicarbonilamino-2-fenil]etil-5-bromo-6-metiluracilo **1** (550 mg, 1 mmol) foi dissolvido em THF (10 mL) e a solução foi arrefecida a 0°C. Lítio bis(trimetilsilil)amida (1,0 M em THF, 1,3 mL, 1,3 mmol) foi adicionado gota a gota e a reacção foi agitada durante 40 minutos a 0 °C. Foi adicionado iodometano (0,093 mL, 1,5 mmol), gota a gota, e depois de 30 minutos, foi adicionada água e a mistura foi extraída com acetato de etilo. Concentração *in vacuo* deu o composto **2** como uma espuma amarela.

Tabela 15



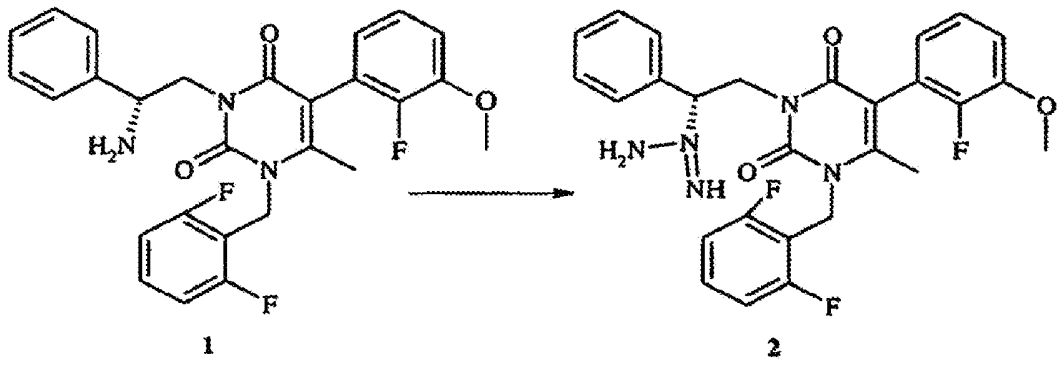
Comp. No.	NR_1R_2-($CR_{3a}CR_{3b}$)$_n$-	-Q-R_4	MW (calc.)	MW (obs.)
15-1			509.5	510.2
15-2			491.5	492
15-3			534.6	535
Referência 15-4		H	428.5	429

Continuação

Comp. No.	NR_1R_2-($CR_{3a}CR_{3b}$)$_n$-	-Q-R_4	MW (calc.)	(obs.)
Referência 15-5			504.6	505
15-6			546.65	
15-7			548.58	549.2
15-8			503.6	504.3
15-9			523.6	524

EXEMPLO 16

SÍNTESE DOS COMPOSTOS REPRESENTATIVOS



1 2

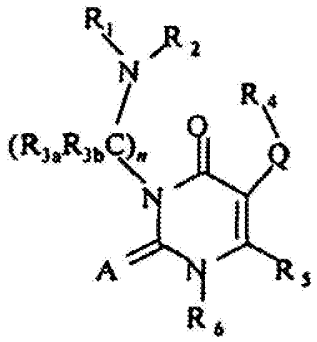
Passo A 1-(2,6-Difluorobenzil)-3-(4-metil-2R-guanidopentil) - 5-(2-fluoro-3-metoxifenil)-6-metiluracilo

Uma solução de 1-(2,6-difluorobenzil)-3-(4-metil-2R-aminopentil)-5-(2-fluoro-3-metoxifenil)-6-metiluracilo 1 (75 mg), (1H)-pirazol-1-carboxamidina cloridrato (23 mg) diisopropiletilamina (21 mg), em DMF anidro, foi aquecida a 40-50 °C durante a noite (0,5 mL). A mistura de reacção foi tratada com água e o produto foi extraído com acetato de etilo. O extracto foi seco sobre $MgSO_4$, filtrado e concentrado *in vacuo* e o resíduo foi purificado em gel de sílica (Et_3N/MeOH/$CHCl_3$ (2:5:93) como eluente) para dar o sólido branco **2**. MS: 518 (MH^+).

Lisboa, 6 de Junho de 2012

REIVINDICAÇÕES

1- Um composto tendo a seguinte estrutura:



ou um estereoisómero, pró-fármaco ou sal farmaceuticamente aceitável do mesmo,
caracterizado por:

Q ser uma ligação directa;
A é O, S ou NR_7;
n é 2, 3 ou 4;

R_1 e R_2 são o mesmo ou diferente e são, independentemente, hidrogénio, alquilo, alquilo substituído, arilo, arilo substituído, arilalquilo, arilalquilo substituído, heterociclilo, heterociclilo substituído, heterocicloalquilo, heterocicloalquilo substituído, $-C(R_{1a})(=NR_{,1b})$, ou $-C(NR_{1a}R_{1}c)(=NR_{1b})$;

ou R_1 e R_2 tomados em conjunto com o átomo de azoto ao qual estão ligados formam um anel heterocíclico ou um anel heterociclico substituído;

R_{3a} e R_{3b} são o mesmo ou diferente e, em cada ocorrência, independentemente hidrogénio, alquilo, alquilo substituído, alcoxi, alquiltio, alquilamino, arilo, arilo substituído,

arilalquilo, arilalquilo substituído, heterociclilo, heterociclilo substituído, heterocicloalquilo, heterocicloalquilo substituído, $-COOR_{14}$ ou $-CONR_{14}R_{15}$;

ou R_{3a} e R_{3b} tomados em conjunto com o átomo de carbono ao qual estão ligados formam um anel homocíclico, anel homociclico substituído, anel heterocíclico ou um anel heterocíclico substituído;

ou R_{3a} e R_{3b} tomados em conjunto formam $-NR_{3c}$;

ou R_{3a} e o átomo de carbono ao qual está ligado, tomados em conjunto com R_1 e o átomo de azoto ao qual está ligado, forma um anel heterocíclico ou um anel heterocíclico substituído;

R_4 é arilo ou heterociclilo substituído;

R_5 é hidrogénio, halogéneo, alquilo inferior, alquilo inferior substituído, arilo, arilo substituido, arilalquilo, arilalquilo substituído, alcoxi, alquiltio, alquilamino, ciano ou nitro;

R_6 é alquilo superior, alquilo substituído, arilo, arilo substituído, arilalquilo, arilalquilo substituído, heteroarilo, heteroarilo substituído, heteroarilalquilo ou heteroarilalquilo substituído;

R_7 é hidrogénio, $-SO_2R_{11}$, ciano, alquilo, alquilo substituído, arilo, arilo substituído, arilalquilo, arilalquilo substituído, heteroarilo, heteroarilo substituído, heteroarilalquilo ou heteroarilalquilo substituído; e

R_{1a}, R_{1b}, R_{1c}, R_{3c}, R_{8a}, R_{8b}, R_9, R_{9a}, R_{10a}, R_{10b}, R_{11}, R_{12}, R_{13}, R_{14} e R_{15} são o mesmo ou diferente e, em cada ocorrência, independentemente, hidrogénio, acilo, alquilo, alquilo substituído, arilo, arilo substituído, arilalquilo, arilalquilo substituído, heterociclilo, heterociclilo substituído, heterocicloalquilo ou heterocicloalquilo substituído;

ou R_{1a} e R_{1b}, R_{8a} e R_{8b}, R_{10a} e R_{10b}, R_{12} e R_{13}, ou R_{14} e R_{15} tomados em conjunto com o átomo ou átomos aos quais estão ligados formam um anel homocíclico, um anel homocíclico substituído, anel heterocíclico ou um anel heterocíclico substituído,

em que "alquilo" é uma cadeia de hidrocarboneto alifático linear ou ramificada, não cíclico ou cíclico, insaturado ou saturado contendo de 1 a 10 átomos de carbono,

em que alquilo consiste em 1 a 10 átomos de carbono, alquilo inferior consiste de 1 a 6 átomos de carbono e alquilo superior consiste de 2 a 10 átomos de carbono,

em que o pró-fármaco consiste em derivados acetato, formato e benzoato do álcool e grupos funcionais amina de estrutura (I) e ésteres de grupos funcionais de ácido carboxílico,

em que o termo "substituído", como aqui usado, significa cada um dos grupos acima, em que pelo menos um átomo de hidrogénio é substituído por um substituinte, e, no caso do substituinte ceto ("-C(=O)-"), são substituídos dois átomos de hidrogénio, em que os substituintes são seleccionados de entre halogéneo, hidroxi, ciano, nitro, amino, alquilamino, dialquilamino, alquilo, alcoxi, alquiltio, haloalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo e heterocicloalquilo, bem assim como $-NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aC(=O)R_b$, $-NR_aC(=O)R_b$, $-NR_aC(=O)NR_aNR_b$, $-NR_aC(=O)OR_b$, $-NR_aCO_2R_b$, $-C(=O)R_a$, $-C(=O)OR_a$, $-C(=O)NR_aR_b$, $-OC(=O)NR_aR_b$, $-SR_a$, $-SOR_a$, $-S(=O)_2R_a$, $-OS(=O)_2R_a$ e $-S(=O)_2Or_a$, em que os substituintes acima podem ser ainda substituídos por um ou mais dos substituintes acima, e em que R_a e R_b podem ser os mesmos ou diferentes e, independentemente, hidrogénio, alquilo, haloalquilo, alquilo substituído, arilo, arilo substituído, arilalquilo, arilalquilo substituído, heterociclilo,

heterociclilo substituído, heterocicloalquilo ou heterocicloalquilo substituído.

2- O composto, de acordo com a reivindicação N°.1, caracterizado por A ser O.

3- O composto, de acordo com a Reivindicação N°.1, caracterizado por R ser hidrogénio ou alquilo inferior.

4- O composto, de acordo com a Reivindicação N°1, caracterizado por R_2 ser hidrogénio, alquilo ou alquilo substituído.

5- O composto, de acordo com a Reivindicação N°.1, caracterizado por R_2 ser hidrogénio ou metilo.

6- O composto, de acordo com a reivindicação N°.1, caracterizado por R_{3a} ser hidrogénio, alquilo, arilo ou arilalquilo.

7- O composto, de acordo com a reivindicação N°.1, caracterizado por R_{3a} ser hidrogénio, metilo, isobutilo, ciclohexilo, fenilo ou benzilo.

8- O composto, de acordo com a reivindicação N°.1, caracterizado por R_{3b} ser, em cada ocorrência, hidrogénio.

9- O composto, de acordo com a reivindicação N°.1, caracterizado por n ser 2.

10- O composto, de acordo com a reivindicação N°.1, caracterizado por $(R_{3a}R_{3b}RC)_n$- ter a estrutura $-C(R_{3a})(R_{3b})CH_2-$.

11- O composto, de acordo com a reivindicação N°.10, caracterizado por R_{3a} ser alquilo.

12- O composto, de acordo com a reivindicação N°.11, caracterizado por R_{3a} ser isobutilo ou ciclohexilo.

13- O composto, de acordo com a reivindicação N°.10, caracterizado por R_{3b} ser hidrogénio ou metilo.

14- O composto, de acordo com a reivindicação N°.1, caracterizado por R_4 ser arilo substituído.

15- O composto, de acordo com a reivindicação N°.1, caracterizado por R_4 ser fenilo substituído.

16ª O composto, de acordo com a reivindicação N°.15, caracterizado por R_4 ser fenilo substituído com halogéneo, alcoxi, ou ambos, halogéneo e alcoxi.

17ª O composto, de acordo com a reivindicação N°.1, caracterizado por R_5 ser H, alquilo inferior ou alquilo inferior substituído.

18ª O composto, de acordo com a reivindicação N°.1, caracterizado por R_5 ser hidrogénio ou metilo.

19ª O composto, de acordo com a reivindicação N°.1, caracterizado por R_6 ser arilo, arilo substituído, arilalquilo, arilalquilo substituído, heteroarilo, heteroarilo substituído, heteroarilalquilo ou heteroarilalquilo substituído.

20ª O composto, de acordo com a reivindicação N°.1, caracterizado por R_6 ser arilalquilo, arilalquilo substituído, heteroarilalquilo ou heteroarilalquilo substituído.

21ª O composto, de acordo com a reivindicação N°.1, caracterizado por R_6 ser benzilo ou benzilo substituído.

22ª O composto, de acordo com a reivindicação N°.1, caracterizado por R_6 ser benzilo substituído com dois halogéneos.

23ª Uma composição farmacêutica, caracterizada por compreender um composto de acordo com reivindicação N°.1 e um transportador ou diluente farmaceuticamente aceitável.

24ª A utilização de uma quantidade eficaz de um composto, de acordo com a reivindicação N°.1 ou composição farmacêutica, de acordo com a reivindicação N°.23, caracterizada por se destinar à preparação de um medicamento para antagonizar a hormona libertadora de gonadotropina num sujeito com necessidade do mesmo.

25ª A utilização de uma quantidade eficaz de um composto, de acordo com a reivindicação N°.1 ou composição farmacêutica, de acordo com a reivindicação N°.23 para a preparação de um

medicamento para o tratamento de uma condição relacionada com hormona sexual de um sujeito em necessidade do mesmo.

26- A utilização, de acordo com a reivindicação N°.25, caracterizada por a condição relacionada com a hormona sexual ser o cancro, a hipertrofia prostática benigna ou o mioma do útero.

27- O uso, de acordo com a Reivindicação N°.26, caracterizado por o cancro ser o cancro da próstata, cancro do útero, cancro da mama ou adenomas gonadotróficos da glândula pituitária.

28- O uso, de acordo com a Reivindicação N°.25, caracterizado por a condição relacionada com a hormona sexual ser a endometriose, síndrome dos ovários policísticos, miomas uterinos ou puberdade precoce.

29- A utilização de uma quantidade eficaz de um composto, de acordo com a Reivindicação N°.1 ou composição farmacêutica, de acordo com a Reivindicação N°.23, para a preparação de um medicamento para prevenir a gravidez de um sujeito com necessidade deste, ou para o tratamento de lúpus eritematoso sistémico, síndrome do intestino irritável, síndrome pré-menstrual, hirsutismo, estatura baixa ou distúrbios do sono, num sujeito com necessidade do mesmo.

30- O composto, de acordo com a reivindicação N°.2, caracterizado por, tal como aplicado para R_1 e R_2, a cadeia linear ou a porção ramificada da porção alquilo ser saturada.

31- O composto, de acordo com a reivindicação N°.2, caracterizado por R_2 ser hidrogénio, cadeia linear ou alquilo ramificado, ou de cadeia linear substituída ou alquilo ramificado.

32- O composto, de acordo com a reivindicação N°.2, caracterizado por R_2 ser hidrogénio ou metilo.

33- O composto, de acordo com a reivindicação N°.2, caracterizado por R_{3a} ser hidrogénio, alquilo, arilo ou

arilalquilo.

34- O composto, de acordo com a reivindicação N°.2, caracterizado por R_{3a} ser hidrogénio, metilo, isobutilo, ciclohexilo, fenilo ou benzilo.

35- O composto, de acordo com a reivindicação N°.2, caracterizado por R_{3b} ser, em cada ocorrência, hidrogénio.

36- O composto, de acordo com a reivindicação N°.2, caracterizado por n ser 2.

37- O composto, de acordo com a reivindicação N°.36, caracterizado por $-(R_{3a}R_{3b}C)_n-$ ter a estrutura $-C(R_{3a})(R_{3b})CH_2-$.

38- O composto, de acordo com a reivindicação N°.37, caracterizado por R_{3a} ser isobutilo ou ciclo-hexilo.

39- O composto, de acordo com a reivindicação N°.37, caracterizado por R_{3b} ser hidrogénio ou metilo.

40- O composto, de acordo com a reivindicação N°.2, caracterizado por R_4 ser arilo substituído.

41- O composto, de acordo com a reivindicação N°.2, caracterizado por R_4 ser fenilo substituído.

42- O composto, de acordo com a reivindicação N°.2, caracterizado por R_4 ser fenilo substituído com halogéneo, alcoxi, ou ambos, halogéneo e alcoxi.

43- O composto, de acordo com a reivindicação N°.2, caracterizado por R_5 ser hidrogénio, alquilo inferior ou alquilo inferior substituído.

44- O composto, de acordo com a reivindicação N°.2, caracterizado por R_5 ser hidrogénio ou metilo.

45- O composto, de acordo com a reivindicação N°.2, caracterizado por R_6 ser arilo, arilo substituído, arilalquilo, arilalquilo substituído, heteroarilo, heteroarilo substituído, heteroarilalquilo ou heteroarilalquilo substituído.

46- O composto, de acordo com a reivindicação N°.2, caracterizado por R_6 ser arilalquilo, arilalquilo substituído, heteroarilalquilo ou heteroarilalquilo substituído.

47- O composto, de acordo com a reivindicação Nº.2, caracterizado por R_6 ser benzilo ou benzilo substituído.

48- O composto, de acordo com a reivindicação Nº.2, caracterizado por R_6 ser benzilo substituído com dois halogéneos.

Lisboa, 6 de Junho de 2012