06-129487

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL 06-129487

21 **EXPEDIENTE No** 06-129487

54 **TITULO** INHIBIDORES DE IAP

51 **CLASIFICACION INTERNACIONAL**

71 **SOLICITANTE** GENENTECH, INC

DOMICILIO SAN FRANCISCO, CALIFORNIA, ESTADOS UNIDOS DE AMERICA

74 **APODERADO** JUAN PABLO CADENA SARMIENTO

22 **SANTAFE DE BOGOTA, D C**

PETITORIO

AS: 102.630

Industria y Comercio
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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☒ Capítulo I. ☐ Capítulo II.

2 SOLICITANTE (71)	Nombre: **GENENTECH, INC.** Dirección: 1 DNA Way, South San Francisco, CA 94080-4990, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: JUAN PABLO CADENA SARMIENTO Dirección: Carrera 7 # 71 – 21 Torre B – Piso 4 Teléfono: 744-2200 Fax: 744-2700 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número 80.410.337 TP 57492
4 INVENTOR (ES) (72)	**Nombre: Frederick COHEN, Kurt DESHAYES, Wayne J. FAIRBROTHER, Bainian FENG, John FLYGARE, Lewis J. GAZZARD, Vickie Hsiao-Wei TSUI** **Dirección: 2001 McAllister Street, #143, San Francisco, CA 94118 (US); 138 Southwood Drive, San Francisco, CA 94112 (US); 1008 Toyon Drive, Burlingame, CA 94010 (US); 1018 Avalon Avenue, Foster City, CA 94404 (US); 1419 Vancouver Avenue, Burlingame, CA 94010 (US); 2552 Belmont Canyon Road, Belmont, CA 94002 (US); 650 Chestnut Street #108, San Francisco, CA 94133 (US), Respectivamente** **Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente)**	

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2020-F06 (01-11-15)

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10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $463.000
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. **Fotocopia Autenticada**
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] Otros: Tarjeta de Propietarios
  Listado de Secuencias
  Documentos PCT

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente,

NOMBRE: **JUAN PABLO CADENA SARMIENTO**

FIRMA: Juan Pablo Cadena

C.C. 80.410.337 de Usaquén TP 57492 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

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FECHA : NOVIEMBRE 8 DE 2006

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
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C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50003-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

PATENTE [X] PCT/US2005/023564 MODELO DE UTILIDAD [ ] DISEÑO INDUSTRIAL [ ]

SOLICITANTE/S. RAZON SOCIAL O APELLIDOS Y NOMBRES: GENENTECH, INC.

DOMICILIO: SAN FRANCISCO, CALIFORNIA, ESTADOS UNIDOS DE AMERICA

APODERADO: JUAN PABLO CADENA SARMIENTO

TITULO: INHIBIDORES DE IAP

CLASIFICACION:

EXPEDIENTE No.: FECHA DE SOLICITUD: ROLLO MICROFILM:

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PRORROGA: CAMBIO DE NOMBRE:

TRASPASO A:

INVENTOR (ES): FREDERICK COHEN, KURT DESHAYES, WAYNE J. FAIRBROTHER, BAINIAN FENG, JOHN

OTROS: FLYGARE, LEWIS J.GAZZARD, VICKIE HSIAO-WEI TSUI

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(72) Inventors; and

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(74) Agents: EVANS, David, W. et al.; Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080-4990 (US).

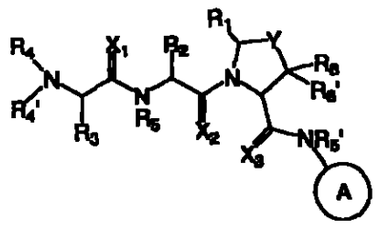
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(54) Title: INHIBITORS OF IAP



(I)

(57) Abstract: The invention provides novel inhibitors of IAP that are useful as therapeutic agents for treating malignancies where the compounds have the general formula I: wherein X, Y, A, R_1, R_2, R_3, R_4, R_4', R_5, R_5', R_6 and R_6' are as described herein.

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INHIBITORS OF IAP

FIELD OF THE INVENTION

The present invention relates to organic compounds useful for therapy and/or prophylaxis in a mammal, and in particular to inhibitors of IAP proteins useful for treating cancers.

BACKGROUND OF THE INVENTION

Apoptosis or programmed cell death is a genetically and biochemically regulated mechanism that plays an important role in development and homeostasis in invertebrates as well as vertebrates. Aberrancies in apoptosis that lead to premature cell death have been linked to a variety of developmental disorders. Deficiencies in apoptosis that result in the lack of cell death have been linked to cancer and chronic viral infections (Thompson et al., (1995) Science 267, 1456-1462).

One of the key effector molecules in apoptosis are the caspases (cysteine containing aspartate specific proteases). Caspases are strong proteases, cleaving after aspartic acid residues and once activated, digest vital cell proteins from within the cell. Since caspases are such strong proteases, tight control of this family of proteins is necessary to prevent premature cell death. In general, caspases are synthesized as largely inactive zymogens that require proteolytic processing in order to be active. This proteolytic processing is only one of the ways in which caspases are regulated. The second mechanism is through a family of proteins that bind and inhibit caspases.

A family of molecules that inhibit caspases are the Inhibitors of Apoptosis (IAP) (Deveraux et al., J Clin Immunol (1999), 19:388-398). IAPs were originally discovered in baculovirus by their functional ability to substitute for P35 protein, an anti-apoptotic gene (Crook et al. (1993) J Virology 67, 2168-2174). IAPs have been described in organisms ranging from *Drosophila* to human. Regardless of their origin, structurally, IAPs comprise one to three Baculovirus IAP repeat (BIR) domains, and most of them also possess a carboxyl-terminal RING finger motif. The BIR domain itself is a zinc binding domain of about 70 residues comprising 4 alpha-helices and 3 beta strands, with cysteine and histidine residues that coordinate the zinc ion (Hinds et al., (1999) Nat. Struct. Biol. 6, 648-651). It is the BIR domain that is believed to cause the anti-apoptotic effect by inhibiting the caspases and thus inhibiting apoptosis. As an example, human X-chromosome linked IAP (XIAP) inhibits caspase 3, caspase 7 and the Apaf-1-cytochrome C mediated activation of caspase 9 (Deveraux et al., (1998) EMBO J. 17, 2215-2223). Caspases 3 and 7 are inhibited by the BIR2 domain of XIAP, while the BIR3 domain of XIAP is responsible for the inhibition of

caspase 9 activity. XIAP is expressed ubiquitously in most adult and fetal tissues (Liston et al, Nature, 1996, 379(6563):349), and is overexpressed in a number of tumor cell lines of the NCI 60 cell line panel (Fong et al, Genomics, 2000, 70:113; Tamm et al, Clin. Cancer Res. 2000, 6(5):1796). Overexpression of XIAP in tumor cells has been demonstrated to confer protection against a variety of pro-apoptotic stimuli and promotes resistance to chemotherapy (LaCasse et al, Oncogene, 1998, 17(25):3247). Consistent with this, a strong correlation between XIAP protein levels and survival has been demonstrated for patients with acute myelogenous leukemia (Tamm et al, supra). Down-regulation of XIAP expression by antisense oligonucleotides has been shown to sensitize tumor cells to death induced by a wide range of pro-apoptotic agents, both *in vitro* and *in vivo* (Sasaki et al, Cancer Res., 2000, 60(20):5659; Lin et al, Biochem J., 2001, 353:299; Hu et al, Clin. Cancer Res., 2003, 9(7):2826). Smac/DIABLO-derived peptides have also been demonstrated to sensitize a number of different tumor cell lines to apoptosis induced by a variety of pro-apoptotic drugs (Arnt et al, J. Biol. Chem., 2002, 277(46):44236; Fulda et al, Nature Med., 2002, 8(8):808; Guo et al, Blood,2002, 99(9):3419; Vucic et al, J. Biol. Chem.,2002, 277(14):12275; Yang et al, Cancer Res., 2003, 63(4):831).

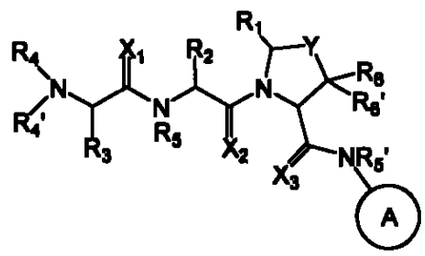
Melanoma IAP (ML-IAP) is an IAP not detectable in most normal adult tissues but is strongly upregulated in melanoma (Vucic et al., (2000) Current Bio 10:1359-1366). Determination of protein structure demonstrated significant homology of the ML-IAP BIR and RING finger domains to corresponding domains present in human XIAP, C-IAP1 and C-IAP2. The BIR domain of ML-IAP appears to have the most similarities to the BIR2 and BIR3 of XIAP, C-IAP1 and C-IAP2, and appears to be responsible for the inhibition of apoptosis, as determined by deletional analysis. Furthermore, Vucic et al., demonstrated that ML-IAP could inhibit chemotherapeutic agent induced apoptosis. Agents such as adriamycin and 4-tertiary butylphenol (4-TBP) were tested in a cell culture system of melanomas overexpressing ML-IAP and the chemotherapeutic agents were significantly less effective in killing the cells when compared to a normal melanocyte control. The mechanism by which ML-IAP produces an anti-apoptotic activity is in part through inhibition of caspase 3 and 9. ML-IAP did not effectively inhibit caspases 1, 2, 6, or 8.

Since apoptosis is a strictly controlled pathway with multiple interacting factors, the discovery that IAPs themselves are regulated was not unusual. In the fruit fly Drosophila, the Reaper (rpr), Head Involution Defective (hid) and GRIM proteins physically interact with and inhibit the anti-apoptotic activity of the Drosophila family of IAPs. In the mammal, the proteins SMAC/DIABLO act to block the IAPs and allow apoptosis to proceed. It was shown that during normal apoptosis, SMAC is processed into an active form and is released from the mitochondria into the cytoplasm where it physically binds to IAPs and prevents the IAP from binding to a caspase. This inhibition

of the IAP allows the caspase to remain active and thus proceed with apoptosis. Interestingly, sequence homology between the IAP inhibitors shows that there is a four amino acid motif in the N-terminus of the processed, active proteins. This tetrapeptide appears to bind into a hydrophobic pocket in the BIR domain and disrupts the BIR domain binding to caspases (Chai et al., (2000) Nature 406:855-862, Liu et al., (2000) Nature 408:1004-1008, Wu et al., (2000) Nature 408 1008-1012).

SUMMARY OF THE INVENTION

In one aspect of the present invention there is provided novel inhibitors of IAP proteins having the general formula (I)



I

wherein

X_1, X_2 and X_3 are independently O or S;

Y is $(CHR_7)_n$, O or S; wherein n is 1 or 2 and R_7 is H, halogen, alkyl, aryl, aralkyl, amino, arylamino, alkylamino, aralkylamino, alkoxy, aryloxy or aralkyloxy;

A is a 5-member heterocycle comprising 1 to 4 heteroatoms optionally substituted with amino, hydroxyl, mercapto, halogen, carboxyl, amidino, guanidino, alkyl, alkoxy, aryl, aryloxy, acyl, acyloxy, acylamino, alkoxycarbonylamino, cycloalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonylamino or a heterocycle; wherein each alkyl, alkoxy, aryl, aryloxy, acyl, acyloxy, acylamino, cycloalkyl and heterocycle substitution is optionally substituted with hydroxyl, halogen, mercapto, carboxyl, alkyl, alkoxy, haloalkyl, amino, nitro, cyano, cycloalkyl, aryl or a heterocycle;

R_1 is H or R_1 and R_2 together form a 5-8 member ring;

R_2 is alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, a heterocycle or heterocyclylalkyl; each optionally substituted with hydroxyl, mercapto, halogen, amino, carboxyl, alkyl, haloalkyl, alkoxy or alkylthio;

R_3 is H or alkyl;

R_4 and R_4' are independently H, hydroxyl, amino, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, or heteroarylalkyl wherein each alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl and heteroarylalkyl is optionally substituted with halogen, hydroxyl, mercapto, carboxyl, alkyl, alkoxy, amino and nitro;

R_5, and R_5' are each independently H or alkyl;

R_6, and R_6' are each independently H, alkyl, aryl or aralkyl;

and salts and solvates thereof.

In another aspect of the invention, there are provided compositions comprising compounds of formula I and a carrier, diluent or excipient.

In another aspect of the invention, there is provided a method of inducing apoptosis in a cell comprising introducing into said cell a compound of formula I.

In another aspect of the invention, there is provided a method of sensitizing a cell to an apoptotic signal comprising introducing into said cell a compound of formula I.

In another aspect of the invention, there is provided a method for inhibiting the binding of an IAP protein to a caspase protein comprising contacting said IAP protein with a compound of formula I.

In another aspect of the invention, there is provided a method for treating a disease or condition associated with the overexpression of an IAP protein in a mammal, comprising administering to said mammal an effective amount of a compound of formula I.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

"Alkyl" means a branched or unbranched, saturated or unsaturated (i.e. alkenyl, alkynyl) aliphatic hydrocarbon group, having up to 12 carbon atoms unless otherwise specified. When used as part of another term, for example "alkylamino", the alkyl portion is preferably a saturated hydrocarbon chain, however also includes unsaturated hydrocarbon carbon chains such as "alkenylamino" and "alkynylamino. Examples of preferred alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 2,2-dimethylbutyl, n-heptyl, 3-heptyl, 2-methylhexyl, and the like. The terms "lower

alkyl" "C_1-C_4 alkyl" and "alkyl of 1 to 4 carbon atoms" are synonymous and used interchangeably to mean methyl, ethyl, 1-propyl, isopropyl, cyclopropyl, 1-butyl, sec-butyl or t-butyl. Unless specified, substituted, alkyl groups may contain one (preferably), two, three or four substituents which may be the same or different. Examples of the above substituted alkyl groups include, but are not limited to; cyanomethyl, nitromethyl, hydroxymethyl, trityloxymethyl, propionyloxymethyl, aminomethyl, carboxymethyl, carboxyethyl, carboxypropyl, alkyloxycarbonylmethyl, allyloxycarbonylaminomethyl, carbamoyloxymethyl, methoxymethyl, ethoxymethyl, t-butoxymethyl, acetoxymethyl, chloromethyl, bromomethyl, iodomethyl, trifluoromethyl, 6-hydroxyhexyl, 2,4-dichloro(n-butyl), 2-amino(iso-propyl), 2-carbamoyloxyethyl and the like. The alkyl group may also be substituted with a carbocycle group. Examples include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, and cyclohexylmethyl groups, as well as the corresponding –ethyl, -propyl, -butyl, -pentyl, -hexyl groups, etc. Preferred substituted alkyls are substituted methyls e.g. a methyl group substituted by the same substituents as the "substituted C_n-C_m alkyl" group. Examples of the substituted methyl group include groups such as hydroxymethyl, protected hydroxymethyl (e.g. tetrahydropyranyloxymethyl), acetoxymethyl, carbamoyloxymethyl, trifluoromethyl, chloromethyl, carboxymethyl, bromomethyl and iodomethyl.

"Amidine" denotes the group -C(NH)-NHR wherein R is H or alkyl or aralkyl. A preferred amidine is the group -NH-C(NH)-NH_2.

"Amino" denotes primary (i.e. –NH_2) , secondary (i.e. –NRH) and tertiary (i.e. –NRR) amines. Preferred secondary and tertiary amines are alkylamine, dialkylamine, arylamine, diarylamine, aralkylamine and diaralkylamine. Particular preferred secondary and tertiary amines are methylamine, ethylamine, propylamine, isopropylamine, phenylamine, benzylamine dimethylamine, diethylamine, dipropylamine and disopropylamine.

"Amino-protecting group" as used herein refers to a derivative of the groups commonly employed to block or protect an amino group while reactions are carried out on other functional groups on the compound. Examples of such protecting groups include carbamates, amides, alkyl and aryl groups, imines, as well as many N-heteroatom derivatives which can be removed to regenerate the desired amine group. Preferred amino protecting groups are Boc, Fmoc and Cbz. Further examples of these groups are found in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley & Sons, Inc., New York, NY, 1991, chapter 7; E. Haslam, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, and T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and

Sons, New York, NY, 1981. The term "protected amino" refers to an amino group substituted with one of the above amino-protecting groups.

"Aryl" when used alone or as part of another term means a carbocyclic aromatic group whether or not fused having the number of carbon atoms designated or if no number is designated, up to 14 carbon atoms. Preferred aryl groups include phenyl, naphthyl, biphenyl, phenanthrenyl, naphthacenyl, and the like (see e.g. *Lang's Handbook of Chemistry* (Dean, J. A., ed) 13th ed. Table 7-2 [1985]) and most preferred phenyl. Substituted phenyl or substituted aryl denotes a phenyl group or aryl group substituted with one, two, three, four or five, preferably 1-2, 1-3 or 1-4 substituents chosen, unless otherwise specified, from halogen (F, Cl, Br, I), hydroxy, protected hydroxy, cyano, nitro, alkyl (preferably C_1-C_6 alkyl), alkoxy (preferably C_1-C_6 alkoxy), benzyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, aminomethyl, protected aminomethyl, trifluoromethyl, alkylsulfonylamino, arylsulfonylamino, heterocyclylsulfonylamino, heterocyclyl, aryl, or other groups specified. One or more methyne (CH) and/or methylene (CH_2) groups in these substituents may in turn be substituted with a similar group as those denoted above. Examples of the term "substituted phenyl" includes but is not limited to a mono- or di(halo)phenyl group such as 2-chlorophenyl, 2-bromophenyl, 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2-fluorophenyl and the like; a mono- or di(hydroxy)phenyl group such as 4-hydroxyphenyl, 3-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and the like; a nitrophenyl group such as 3- or 4-nitrophenyl; a cyanophenyl group, for example, 4-cyanophenyl; a mono- or di(lower alkyl)phenyl group such as 4-methylphenyl, 2,4-dimethylphenyl, 2-methylphenyl, 4-(iso-propyl)phenyl, 4-ethylphenyl, 3-(n-propyl)phenyl and the like; a mono or di(alkoxy)phenyl group, for example, 3,4-dimethoxyphenyl, 3-methoxy-4-benzyloxyphenyl, 3-methoxy-4-(1-chloromethyl)benzyloxy-phenyl, 3-ethoxyphenyl, 4-(isopropoxy)phenyl, 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and the like; 3- or 4-trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such 4-carboxyphenyl, ; a mono- or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 3-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl)phenyl or (protected aminomethyl)phenyl such as 2-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 3-(N-methylsulfonylamino))phenyl. Also, the term "substituted phenyl" represents disubstituted phenyl groups where the substituents are different, for example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy-4-chlorophenyl, and the like, as well as trisubstituted phenyl groups where

the substituents are different, for example 3-methoxy-4-benzyloxy-6-methyl sulfonylamino, 3-methoxy-4-benzyloxy-6-phenyl sulfonylamino, and tetrasubstituted phenyl groups where the substituents are different such as 3-methoxy-4-benzyloxy-5-methyl-6-phenyl sulfonylamino. Preferred substituted phenyl groups include the 2-chlorophenyl, 2-aminophenyl, 2-bromophenyl, 3-methoxyphenyl, 3-ethoxy-phenyl, 4-benzyloxyphenyl, 4-methoxyphenyl, 3-ethoxy-4-benzyloxyphenyl, 3,4-diethoxyphenyl, 3-methoxy-4-benzyloxyphenyl, 3-methoxy-4-(1-chloromethyl)benzyloxy-phenyl, 3-methoxy-4-(1-chloromethyl)benzyloxy -6- methyl sulfonyl aminophenyl groups. Fused aryl rings may also be substituted with any, preferably 1, 2 or 3, of the substituents specified herein in the same manner as substituted alkyl groups.

"Carbocyclyl", "carbocyclylic", "carbocycle" and "carbocyclo" alone and when used as a moiety in a complex group such as a carbocycloalkyl group, refers to a mono-, bi-, or tricyclic aliphatic ring having 3 to 14 carbon atoms and preferably 3 to 7 carbon atoms which may be saturated or unsaturated, aromatic or non-aromatic. Preferred saturated carbocyclic groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups and more preferred are cyclopropyl and cyclohexyl and most preferred is cyclohexyl. Preferred unsaturated carbocycles are aromatic e.g. aryl groups as previously defined, the most preferred being phenyl. The terms "substituted carbocyclyl", "carbocycle" and "carbocyclo" mean these groups substituted by the same substituents as the "substituted alkyl" group.

"Carboxy-protecting group" as used herein refers to one of the ester derivatives of the carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such carboxylic acid protecting groups include 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxybenzhydryl, 2,2',4,4'-tetramethoxybenzhydryl, alkyl such as t-butyl or t-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, 2-phenylprop-2-yl, trimethylsilyl, t-butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl, beta-(trimethylsilyl)ethyl, beta-(di(n-butyl)methylsilyl)ethyl, p-toluenesulfonylethyl, 4-nitrobenzylsulfonylethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)prop-1-en-3-yl, and like moieties. The species of carboxy-protecting group employed is not critical so long as the derivatized carboxylic acid is stable to the condition of subsequent reaction(s) on other positions of the molecule and can be removed at the appropriate point without disrupting the remainder of the molecule. In particular, it is important not to subject a carboxy-protected molecule to strong nucleophilic bases, such as lithium hydroxide or NaOH, or reductive conditions employing highly activated metal hydrides such as $LiAlH_4$. (Such harsh removal

conditions are also to be avoided when removing amino-protecting groups and hydroxy-protecting groups, discussed below.) Preferred carboxylic acid protecting groups are the alkyl (e.g. methyl, ethyl, t-butyl), allyl, benzyl and p-nitrobenzyl groups. Similar carboxy-protecting groups used in the cephalosporin, penicillin and peptide arts can also be used to protect a carboxy group substituents. Further examples of these groups are found in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley & Sons, Inc., New York, N.Y., 1991, chapter 5; E. Haslam, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, Chapter 5, and T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1981, Chapter 5. The term "protected carboxy" refers to a carboxy group substituted with one of the above carboxy-protecting groups.

"Guanidine" denotes the group -NH-C(NH)-NHR wherein R is H or alkyl or aralkyl. Preferred guanidine is the group -NH-C(NH)-NH_2.

"Hydroxy-protecting group" as used herein refers to a derivative of the hydroxy group commonly employed to block or protect the hydroxy group while reactions are carried out on other functional groups on the compound. Examples of such protecting groups include tetrahydropyranyloxy, benzoyl, acetoxy, carbamoyloxy, benzyl, and silylethers (e.g. TBS, TBDPS) groups. Further examples of these groups are found in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley & Sons, Inc., New York, NY, 1991, chapters 2-3; E. Haslam, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, and T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1981. The term "protected hydroxy" refers to a hydroxy group substituted with one of the above hydroxy-protecting groups.

"Heterocyclic group", "heterocyclic", "heterocycle", "heterocyclyl", or "heterocyclo" alone and when used as a moiety in a complex group such as a heterocycloalkyl group, are used interchangeably and refer to any mono-, bi-, or tricyclic, saturated or unsaturated, aromatic (heteroaryl) or non-aromatic ring having the number of atoms designated, generally from 5 to about 14 ring atoms, where the ring atoms are carbon and at least one heteroatom (nitrogen, sulfur or oxygen) and preferably 1 to 4 heteroatoms. Typically, a 5-membered ring has 0 to 2 double bonds and 6- or 7-membered ring has 0 to 3 double bonds and the nitrogen or sulfur heteroatoms may optionally be oxidized (e.g. SO, SO_2), and any nitrogen heteroatom may optionally be quaternized. Preferred non-aromatic heterocycles include morpholinyl (morpholino), pyrrolidinyl, oxiranyl, oxetanyl, tetrahydrofuranyl, 2,3-dihydrofuranyl, 2H-pyranyl, tetrahydropyranyl, thiiranyl, thietanyl, tetrahydrothietanyl, aziridinyl, azetidinyl, 1-methyl-2-

pyrrolyl, piperazinyl and piperidinyl. A "heterocycloalkyl" group is a heterocycle group as defined above covalently bonded to an alkyl group as defined above. Preferred 5-membered heterocycles containing a sulfur or oxygen atom and one to three nitrogen atoms include thiazolyl, in particular thiazol-2-yl and thiazol-2-yl N-oxide, thiadiazolyl, in particular 1,3,4-thiadiazol-5-yl and 1,2,4-thiadiazol-5-yl, oxazolyl, preferably oxazol-2-yl, and oxadiazolyl, such as 1,3,4-oxadiazol-5-yl, and 1,2,4-oxadiazol-5-yl. Preferred 5-membered ring heterocycles containing 2 to 4 nitrogen atoms include imidazolyl, preferably imidazol-2-yl; triazolyl, preferably 1,3,4-triazol-5-yl; 1,2,3-triazol-5-yl, 1,2,4-triazol-5-yl, and tetrazolyl, preferably 1H-tetrazol-5-yl. Preferred benzo-fused 5-membered heterocycles are benzoxazol-2-yl, benzthiazol-2-yl and benzimidazol-2-yl. Preferred 6-membered heterocycles contain one to three nitrogen atoms and optionally a sulfur or oxygen atom, for example pyridyl, such as pyrid-2-yl, pyrid-3-yl, and pyrid-4-yl; pyrimidyl, preferably pyrimid-2-yl and pyrimid-4-yl; triazinyl, preferably 1,3,4-triazin-2-yl and 1,3,5-triazin-4-yl; pyridazinyl, in particular pyridazin-3-yl, and pyrazinyl. The pyridine N-oxides and pyridazine N-oxides and the pyridyl, pyrimid-2-yl, pyrimid-4-yl, pyridazinyl and the 1,3,4-triazin-2-yl groups, are a preferred group. Substituents for optionally substituted heterocycles, and further examples of the 5- and 6-membered ring systems discussed above can be found in W. Druckheimer *et al.*, U.S. Patent No. 4,278,793.

"Heteroaryl" alone and when used as a moiety in a complex group such as a heteroaralkyl group, refers to any mono-, bi-, or tricyclic aromatic ring system having the number of atoms designated where at least one ring is a 5-, 6- or 7-membered ring containing from one to four heteroatoms selected from the group nitrogen, oxygen, and sulfur, and preferably at least one heteroatom is nitrogen (*Lang's Handbook of Chemistry, supra*). Included in the definition are any bicyclic groups where any of the above heteroaryl rings are fused to a benzene ring. Heteroaryls in which nitrogen or oxygen is the heteroatom are preferred. The following ring systems are examples of the heteroaryl (whether substituted or unsubstituted) groups denoted by the term "heteroaryl": thienyl, furyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, thiazinyl, oxazinyl, triazinyl, thiadiazinyl, oxadiazinyl, dithiazinyl, dioxazinyl, oxathiazinyl, tetrazinyl, thiatriazinyl, oxatriazinyl, dithiadiazinyl, imidazolinyl, dihydropyrimidyl, tetrahydropyrimidyl, tetrazolo[1,5-b]pyridazinyl and purinyl, as well as benzo-fused derivatives, for example benzoxazolyl, benzofuryl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl, benzoimidazolyl and indolyl. A particularly preferred group of "heteroaryl" include; 1,3-thiazol-2-yl, 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl, 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl sodium salt, 1,2,4-thiadiazol-5-yl, 3-methyl-1,2,4-thiadiazol-5-yl, 1,3,4-triazol-5-yl, 2-methyl-1,3,4-triazol-5-yl, 2-hydroxy-1,3,4-triazol-5-yl, 2-carboxy-4-methyl-1,3,4-triazol-5-yl sodium salt,

2-carboxy-4-methyl-1,3,4-triazol-5-yl, 1,3-oxazol-2-yl, 1,3,4-oxadiazol-5-yl, 2-methyl-1,3,4-oxadiazol-5-yl, 2-(hydroxymethyl)-1,3,4-oxadiazol-5-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-thiol-1,3,4-thiadiazol-5-yl, 2-(methylthio)-1,3,4-thiadiazol-5-yl, 2-amino-1,3,4-thiadiazol-5-yl, 1H-tetrazol-5-yl, 1-methyl-1H-tetrazol-5-yl, 1-(1-(dimethylamino)eth-2-yl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl sodium salt, 1-(methylsulfonic acid)-1H-tetrazol-5-yl, 1-(methylsulfonic acid)-1H-tetrazol-5-yl sodium salt, 2-methyl-1H-tetrazol-5-yl, 1,2,3-triazol-5-yl, 1-methyl-1,2,3-triazol-5-yl, 2-methyl-1,2,3-triazol-5-yl, 4-methyl-1,2,3-triazol-5-yl, pyrid-2-yl N-oxide, 6-methoxy-2-(n-oxide)-pyridaz-3-yl, 6-hydroxypyridaz-3-yl, 1-methylpyrid-2-yl, 1-methylpyrid-4-yl, 2-hydroxypyrimid-4-yl, 1,4,5,6-tetrahydro-5,6-dioxo-4-methyl-as-triazin-3-yl, 1,4,5,6-tetrahydro-4-(formylmethyl)-5,6-dioxo-as-triazin-3-yl, 2,5-dihydro-5-oxo-6-hydroxy-astriazin-3-yl, 2,5-dihydro-5-oxo-6-hydroxy-as-triazin-3-yl sodium salt, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-astriazin-3-yl sodium salt, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-as-triazin-3-yl, 2,5-dihydro-5-oxo-6-methoxy-2-methyl-as-triazin-3-yl, 2,5-dihydro-5-oxo-as-triazin-3-yl, 2,5-dihydro-5-oxo-2-methyl-as-triazin-3-yl, 2,5-dihydro-5-oxo-2,6-dimethyl-as-triazin-3-yl, tetrazolo[1,5-b]pyridazin-6-yl and 8-aminotetrazolo[1,5-b]-pyridazin-6-yl. An alternative group of "heteroaryl" includes; 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl, 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl sodium salt, 1,3,4-triazol-5-yl, 2-methyl-1,3,4-triazol-5-yl, 1H-tetrazol-5-yl, 1-methyl-1H-tetrazol-5-yl, 1-(1-(dimethylamino)eth-2-yl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl sodium salt, 1-(methylsulfonic acid)-1H-tetrazol-5-yl, 1-(methylsulfonic acid)-1H-tetrazol-5-yl sodium salt, 1,2,3-triazol-5-yl, 1,4,5,6-tetrahydro-5,6-dioxo-4-methyl-as-triazin-3-yl, 1,4,5,6-tetrahydro-4-(2-formylmethyl)-5,6-dioxo-as-triazin-3-yl, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-as-triazin-3-yl sodium salt, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-as-triazin-3-yl, tetrazolo[1,5-b]pyridazin-6-yl, and 8-aminotetrazolo[1,5-b]pyridazin-6-yl.

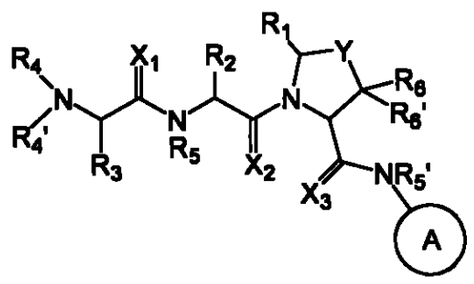
"Inhibitor" means a compound which reduces or prevents the binding of IAP proteins to caspase proteins or which reduces or prevents the inhibition of apoptosis by an IAP protein. Alternatively, "inhibitor" means a compound which prevents the binding interaction of X-IAP with caspases or the binding interaction of ML-IAP with SMAC.

"Pharmaceutically acceptable salts" include both acid and base addition salts. "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid and the like, and organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic

acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, maloneic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicyclic acid and the like.

"Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic non-toxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

The present invention provides novel compounds having the general formula I:



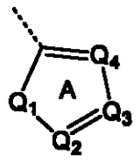
I

wherein X, Y, A, R_1, R_2, R_3, R_4, R_4', R_5, R_5', R_6 and R_6' are as described herein.

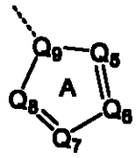
X_1 and X_2 are each independently O or S. In a preferred embodiment, X_1 and X_2 are both O. In another preferred embodiment X_1 and X_2 are both S. In another preferred embodiment, X_1 is S while X_2 is O. In another preferred embodiment, X_1 is O while X_2 is S.

Y is $(CHR_7)_n$, O or S; wherein n is 1 or 2 and R_7 is H, halogen, alkyl, aryl, aralkyl, amino, arylamino, alkylamino, aralkylamino, alkoxy, aryloxy or aralkyloxy. In a particular embodiment, Y is CH_2. In a particular embodiment n is 1. In a particular embodiment n is 1 and Y is CHR_7 wherein R_7 is aralkyloxy, for example benzyloxy. In a particular embodiment n is 1 and Y is CHR_7 wherein R_7 is F. In a particular embodiment n is 1 and Y is CHR_7 wherein R_7 is aralkylamino, for example benzylamino. In another particular embodiment Y is O. In another particular embodiment Y is S.

Ring 'A' is a 5-member heterocycle comprising 1 to 4 heteroatoms optionally substituted with amino, hydroxyl, mercapto, halogen, carboxyl, amidino, guanidino, alkyl, alkoxy, aryl, aryloxy, acyl, acyloxy, acylamino, alkoxycarbonylamino, cycloalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonylamino or a heterocycle; wherein each alkyl, alkoxy, aryl, aryloxy, acyl, acyloxy, acylamino, cycloalkyl and heterocycle substitution is optionally substituted with hydroxyl, halogen, mercapto, carboxyl, alkyl, alkoxy, haloalkyl, amino, nitro, cyano, cycloalkyl, aryl or a heterocycle. In an embodiment, the 5-member heterocycle ring A groups are optionally substituted with amino, hydroxyl, mercapto, halogen, carboxyl, amidino, guanidino, alkyl, alkoxy, aryl, aryloxy, acyl, acyloxy, acylamino, cycloalkyl or a heterocycle; wherein each alkyl, alkoxy, aryl, aryloxy, acyl, acyloxy, acylamino, cycloalkyl and heterocycle substitution is optionally substituted with hydroxyl, halogen, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, cycloalkyl, aryl or a heterocycle. In a particular embodiment ring A is aromatic. In a particular embodiment ring A has the formula IIa or IIb:



IIa

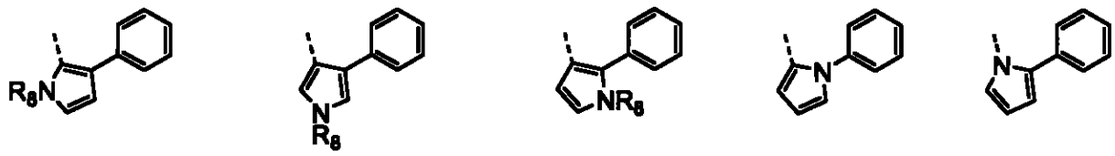


IIb

wherein Q_1 is NR_8, O or S; Q_2, Q_3, Q_4, Q_5, Q_6, Q_7, and Q_8, are independently CR_9 or N; wherein R_9 is H, amino, hydroxyl, mercapto, halogen, carboxyl, amidino, guanidino, alkyl, alkoxy, aryl, aryloxy, acyl, acyloxy, acylamino, cycloalkyl or a heterocycle; wherein each alkyl, alkoxy, aryl, aryloxy, acyl, acyloxy, acylamino, cycloalkyl and heterocycle substitution is optionally substituted with hydroxyl, halogen, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, cycloalkyl, aryl or a heterocycle; R_8 is H, alkyl, acyl, aryl, cycloalkyl or a heterocycle; wherein each alkyl, aryl, cycloalkyl and heterocycle is optionally substituted with hydroxyl, halogen, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, cycloalkyl, aryl or a heterocycle; and Q_9 is CH or N. In a particular

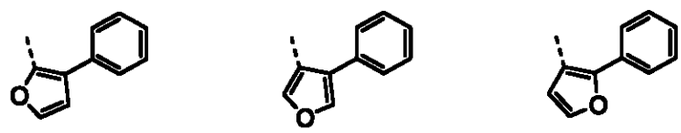
embodiment, ring A is a group of formula II. In a particular embodiment ring A is a group of formula II wherein Q_4 is CR_9 wherein R_9 is aryl or heteroaryl optionally substituted as described above. In a particular embodiment ring A is a group of formula II wherein Q_4 is CR_9 and R_9 is phenyl. In a particular embodiment, ring A is a group of formula II wherein Q_4 is CR_9 and R_9 is phenyl and Q_3 is CH or CF. In another embodiment, ring A is a group of formula II wherein Q_4 is CR_9 and R_9 is pyridin-2-yl. In another embodiment, ring A is a group of formula II wherein Q_4 is CR_9, R_9 is pyridin-2-yl and Q_3 is C-Me.

In another embodiment, ring A according to IIa or IIb is a pyrrole ring optionally substituted with alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, a heterocycle or a heterocycle-alkyl optionally substituted with halogen hydroxyl, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, aryl or heteroaryl. In an embodiment ring A is substituted with an aryl or heteroaryl group. In a particular embodiment, ring A is selected from the group consisting of:



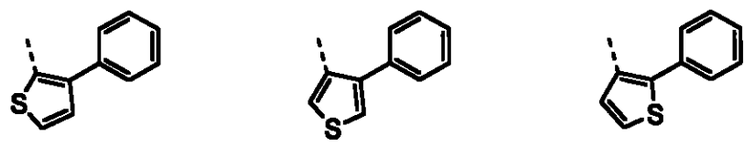
wherein R_8 is H, alkyl (for example methyl, ethyl or propyl) or acyl (for example acetyl). In a particular embodiment R_8 is H.

In another embodiment ring A is furan optionally substituted with alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, a heterocycle or a heterocycle-alkyl optionally substituted with halogen hydroxyl, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, aryl or heteroaryl. In an embodiment ring A is substituted with an aryl or heteroaryl group. In a particular embodiment, ring A is selected from the group consisting of:

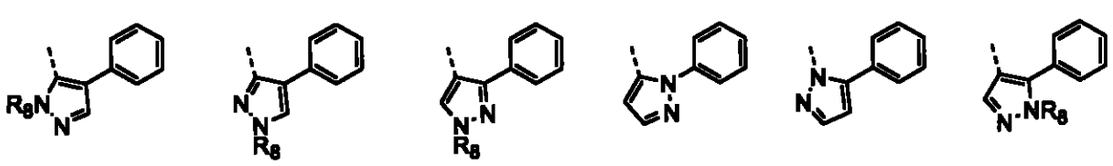


In another embodiment ring A is thiophene optionally substituted with alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, a heterocycle or a heterocycle-alkyl optionally substituted with halogen hydroxyl, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, aryl or heteroaryl. In an

embodiment ring A is substituted with an aryl or heteroaryl group. In a particular embodiment, ring A is selected from the group consisting of:

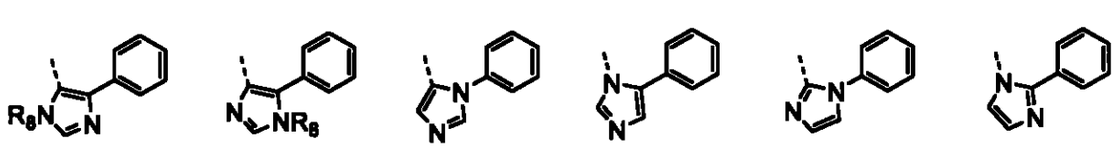


In another embodiment ring A is pyrazole optionally substituted with alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, a heterocycle or a heterocycle-alkyl optionally substituted with halogen hydroxyl, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, aryl or heteroaryl. In an embodiment ring A is substituted with an aryl or heteroaryl group. In a particular embodiment, ring A is selected from the group consisting of:



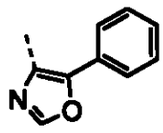
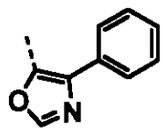
wherein R_8 is H, alkyl (for example methyl, ethyl or propyl) or acyl (for example acetyl). In a particular embodiment R_8 is H.

In another embodiment ring A is imidazole optionally substituted with alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, a heterocycle or a heterocycle-alkyl optionally substituted with halogen hydroxyl, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, aryl or heteroaryl. In an embodiment ring A is substituted with an aryl or heteroaryl group. In a particular embodiment, ring A is selected from the group consisting of:

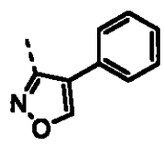
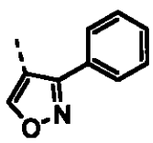
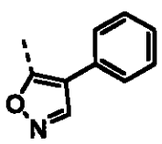
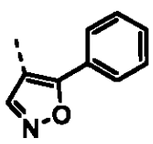


wherein R_8 is H, alkyl (for example methyl, ethyl or propyl) or acyl (for example acetyl). In a particular embodiment R_8 is H.

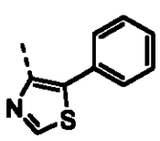
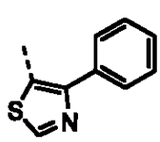
In another embodiment ring A is oxazole optionally substituted with alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, a heterocycle or a heterocycle-alkyl optionally substituted with halogen hydroxyl, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, aryl or heteroaryl. In an embodiment ring A is substituted with an aryl or heteroaryl group. In a particular embodiment, ring A is selected from the group consisting of:

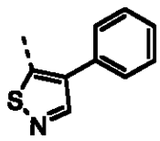
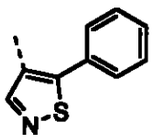
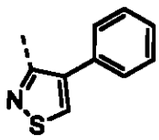
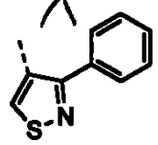
In another embodiment ring A is isoxazole optionally substituted with alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, a heterocycle or a heterocycle-alkyl optionally substituted with halogen hydroxyl, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, aryl or heteroaryl. In an embodiment ring A is substituted with an aryl or heteroaryl group. In a particular embodiment, ring A is selected from the group consisting of:

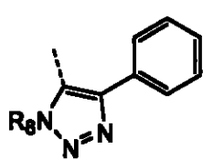
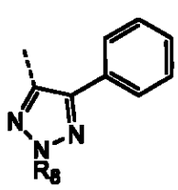
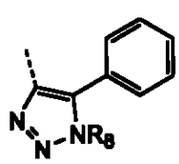
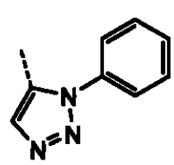
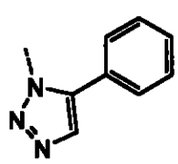
In another embodiment ring A is thiazole optionally substituted with alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, a heterocycle or a heterocycle-alkyl optionally substituted with halogen hydroxyl, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, aryl or heteroaryl. In an embodiment ring A is substituted with an aryl or heteroaryl group. In a particular embodiment, ring A is selected from the group consisting of:

In another embodiment ring A is isothiazole optionally substituted with alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, a heterocycle or a heterocycle-alkyl optionally substituted with halogen hydroxyl, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, aryl or heteroaryl. In an embodiment ring A is substituted with an aryl or heteroaryl group. In a particular embodiment, ring A is selected from the group consisting of:

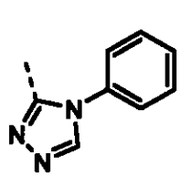
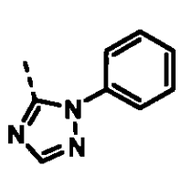
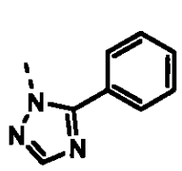
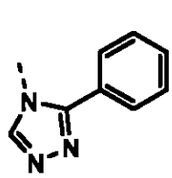





In another embodiment ring A is 1,2,3-triazole optionally substituted with alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, a heterocycle or a heterocycle-alkyl optionally substituted with halogen hydroxyl, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, aryl or heteroaryl. In an embodiment ring A is substituted with an aryl or heteroaryl group. In a particular embodiment, ring A is selected from the group consisting of:

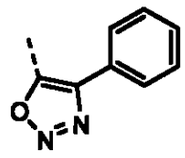
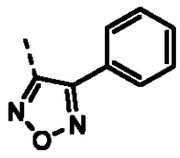
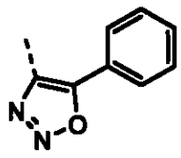






wherein R_8 is H, alkyl (for example methyl, ethyl or propyl) or acyl (for example acetyl). In a particular embodiment R_8 is H.

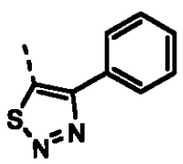
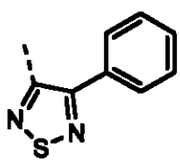
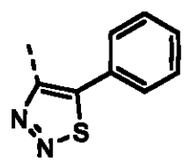
In another embodiment ring A is 1,2,4-triazole optionally substituted with alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, a heterocycle or a heterocycle-alkyl optionally substituted with halogen hydroxyl, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, aryl or heteroaryl. In an embodiment ring A is substituted with an aryl or heteroaryl group. In a particular embodiment, ring A is selected from the group consisting of:

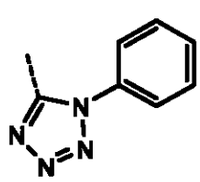
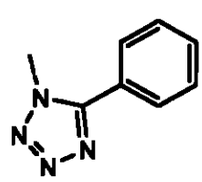
In another embodiment ring A is oxadiazole optionally substituted with alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, a heterocycle or a heterocycle-alkyl optionally substituted with halogen hydroxyl, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, aryl or heteroaryl. In an embodiment ring A is substituted with an aryl or heteroaryl group. In a particular embodiment, ring A is selected from the group consisting of:

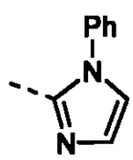
In another embodiment ring A is thiadiazole optionally substituted with alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, a heterocycle or a heterocycle-alkyl optionally substituted with halogen hydroxyl, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, aryl or heteroaryl. In an embodiment ring A is substituted with an aryl or heteroaryl group. In a particular embodiment, ring A is selected from the group consisting of:

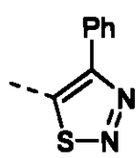
In another embodiment ring A is tetrazole optionally substituted with alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, a heterocycle or a heterocycle-alkyl optionally substituted with halogen hydroxyl, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, aryl or heteroaryl. In an embodiment ring A is substituted with an aryl or heteroaryl group. In a particular embodiment, ring A is selected from the group consisting of:

In a particular embodiment ring A is:



In a particular embodiment ring A is:

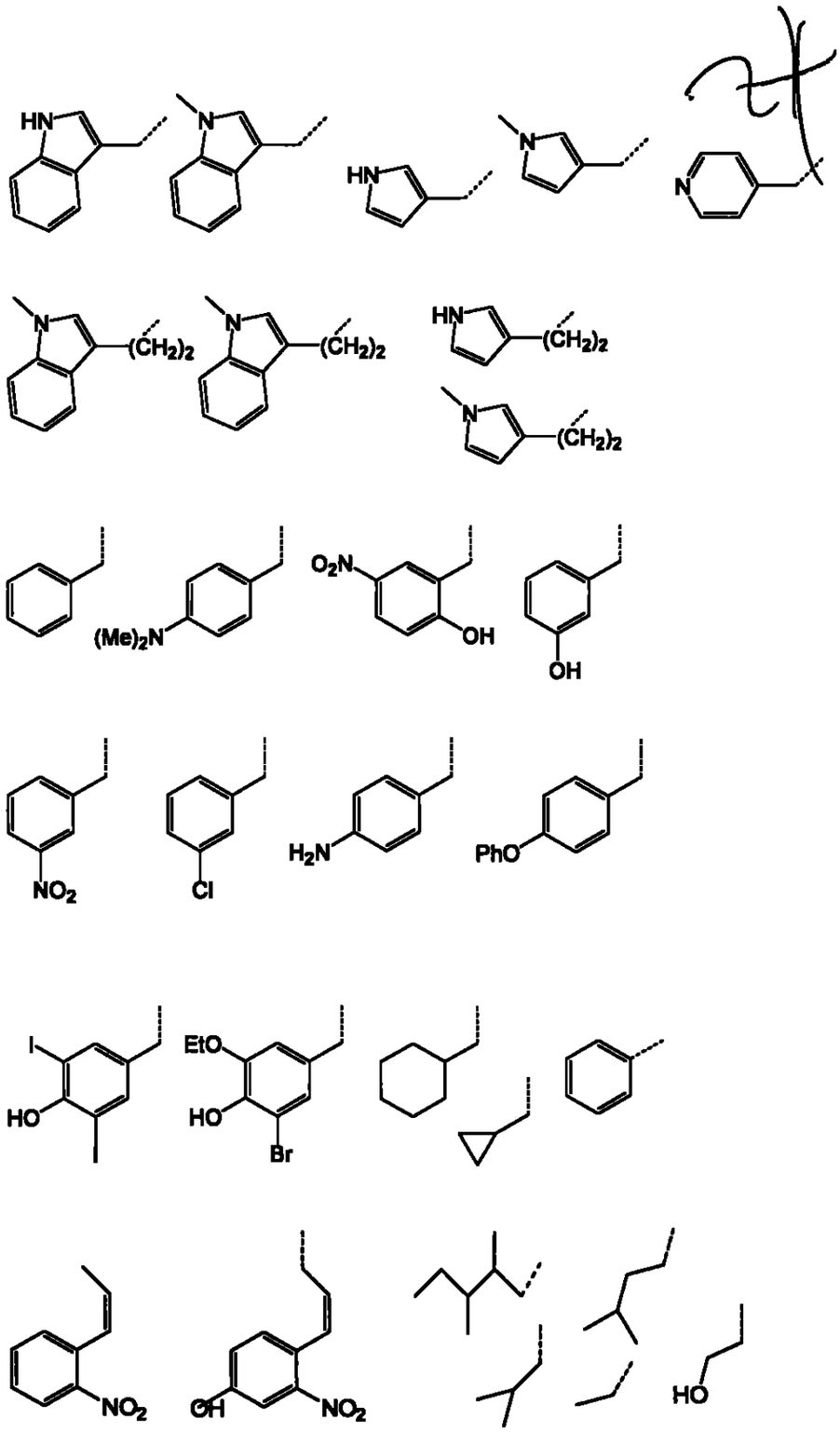


R_1 is H or R_1 and R_2 together form a 5-8 member ring. In a particular embodiment, R_1 is H. In a particular embodiment, R_1 and R_2 together form a 6-member ring. In a particular embodiment, R_1 and R_2 together form a 7-member ring. In another particular embodiment, R_1 and R_2 together form an 8-member ring. In another particular embodiment, R_1 and R_2 together form a 7-member ring while Y is S. In another particular embodiment, R_1 is H, while Y is CH_2. In another particular embodiment, R_1 is H, while Y is S. In another particular embodiment, R_1 is H, while Y is O.

R_2 is alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, a heterocycle or heterocyclylalkyl. In a preferred embodiment R_2 is alkyl or cycloalkyl. In an embodiment, each R_2 group is each optionally substituted with hydroxyl, mercapto, halogen, amino, carboxyl, alkyl, haloalkyl, alkoxy or alkylthio; In an embodiment of the invention R_2 is t-butyl, isopropyl, cyclohexyl, cyclopentyl or phenyl. In a particular embodiment, R_2 is cyclohexyl. In another embodiment R_2 is tetrahydropyran-4-yl. In another particular embodiment, R_2 is isopropyl (i.e. the valine amino acid side chain). In another particular embodiment, R_2 is t-butyl. In a particular embodiment R_2 is oriented such that the amino acid, or amino acid analogue, which it comprises is in the L-configuration.

R_3 is H or alkyl. In a preferred embodiment R_3 is H or methyl, ethyl, propyl or isopropyl. In a particularly preferred embodiment R_3 is H or methyl. In a most preferred embodiment R_3 is methyl. In another particular embodiment, R_3 is t-butyl. In a preferred embodiment R_3 is oriented such that the amino acid, or amino acid analogue, which it comprises is in the L-configuration.

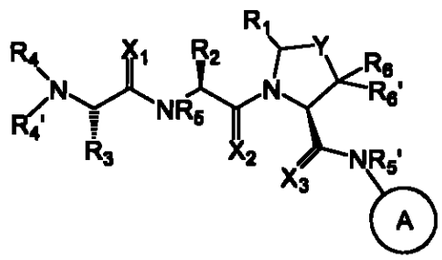
R_4 and R_4' are independently H, hydroxyl, amino, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, or heteroarylalkyl wherein each alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl and heteroarylalkyl is optionally substituted with halogen, hydroxyl, mercapto, carboxyl, alkyl, alkoxy, amino and nitro. In a particular embodiment R_4 and R_4' are both H. In another particular embodiment R_4 is methyl and R_4' is H. In a particular embodiment one of R_4 and R_4' is hydroxyl (OH) while the other is H. In another embodiment, one of R_4 and R_4' is amino, such as NH_2, NHMe and NHEt, while the other is H. In a particular embodiment, R_4' is H and R_4 is H, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl or heteroarylalkyl. In a particular embodiment R_4 is a group selected from the group consisting of:



R_5 and R_5' are each independently H or alkyl. In a preferred embodiment, R_5 and R_5' are H or methyl. In a particular embodiment, R_5 is H and R_5' is methyl. In another particular embodiment, R_5 is methyl and R_5' is H. In another particular embodiment R_5 and R_5' are both methyl. In another particular embodiment, R_5 and R_5' are both H.

R_6, and R_6' are each independently H, alkyl, aryl or aralkyl. In a particular embodiment, R_6 is alkyl, for example methyl . In another particular embodiment R_6 is aryl, for example phenyl. In another particular embodiment R_6 is aralkyl, for example benzyl. In a particular embodiment R_6 and R_6' are the same, for example both alkyl, e.g. both methyl. In another particular embodiment R_6 is methyl and R_6' is H.

Compounds of the invention contain one or more asymmetric carbon atoms. Accordingly, the compounds may exist as diastereomers, enantiomers or mixtures thereof. The syntheses of the compounds may employ racemates, diastereomers or enantiomers as starting materials or as intermediates. Diastereomeric compounds may be separated by chromatographic or crystallization methods. Similarly, enantiomeric mixtures may be separated using the same techniques or others known in the art. Each of the asymmetric carbon atoms may be in the R or S configuration and both of these configurations are within the scope of the invention. Preferably, compounds of the invention have the following stereochemical configuration of formula I'



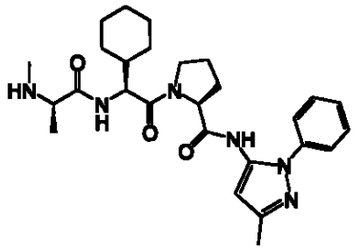
I'

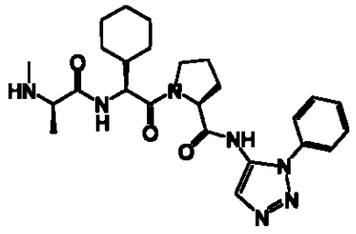
wherein X, Y, A, R_1, R_2, R_3, R_4, R_4', R_5, R_5', R_6 and R_6' are as described herein.

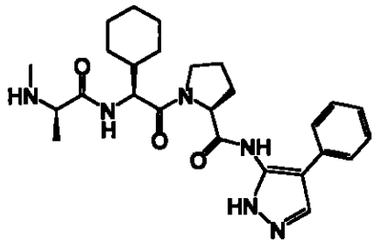
The invention also encompasses prodrugs of the compounds described above. Suitable prodrugs where applicable include known amino-protecting and carboxy-protecting groups which are released, for example hydrolyzed, to yield the parent compound under physiologic conditions. A preferred class of prodrugs are compounds in which a nitrogen atom in an amino, amidino, aminoalkyleneamino, iminoalkyleneamino or guanidino group is substituted with a hydroxy (OH) group, an alkylcarbonyl (-CO-R) group, an alkoxycarbonyl (-CO-OR), an acyloxyalkyl-alkoxycarbonyl (-CO-O-R-O-CO-R) group where R is a monovalent or divalent group and as defined above or a group having the formula -C(O)-O-CP1P2-haloalkyl, where P1 and P2 are the same or different and are H, lower alkyl, lower alkoxy, cyano, halo lower alkyl or aryl. Preferably the nitrogen atom is one of the nitrogen atoms of the amidino group of the compounds of the invention. These prodrug compounds are prepared reacting the compounds of the invention

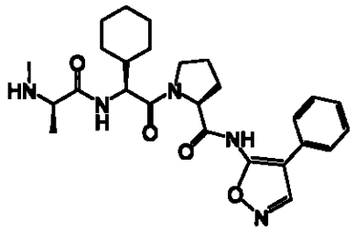
described above with an activated acyl compound to bond a nitrogen atom in the compound of the invention to the carbonyl of the activated acyl compound. Suitable activated carbonyl compounds contain a good leaving group bonded to the carbonyl carbon and include acyl halides, acyl amines, acyl pyridinium salts, acyl alkoxides, in particular acyl phenoxides such as p-nitrophenoxy acyl, dinitrophenoxy acyl, fluorophenoxy acyl, and difluorophenoxy acyl. The reactions are generally exothermic and are carried out in inert solvents at reduced temperatures such as –78 to about 50C. The reactions are usually also carried out in the presence of an inorganic base such as potassium carbonate or sodium bicarbonate, or an organic base such as an amine, including pyridine, triethylamine, etc. One manner of preparing prodrugs is described in USSN 08/843,369 filed April 15, 1997 (corresponding to PCT publication WO9846576) the contents of which are incorporated herein by reference in their entirety.

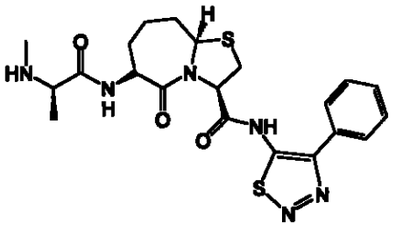
Particular compounds of formula I include the following:

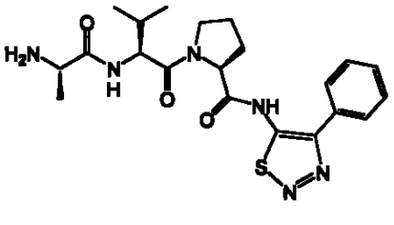
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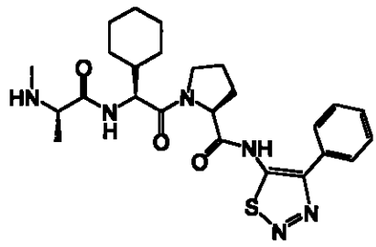
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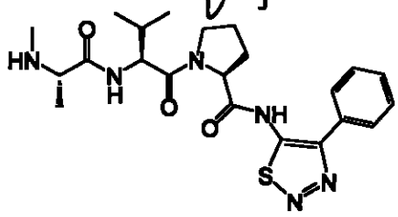
5 

6 

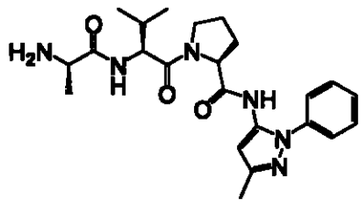
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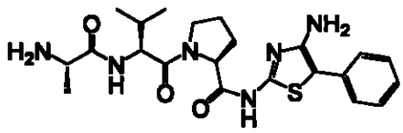
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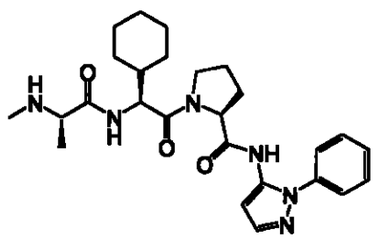
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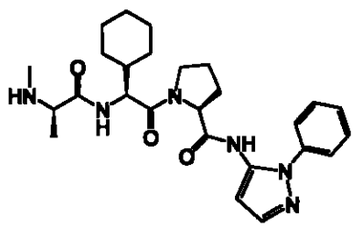
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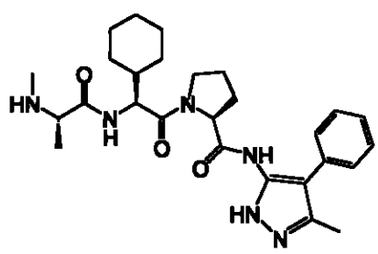
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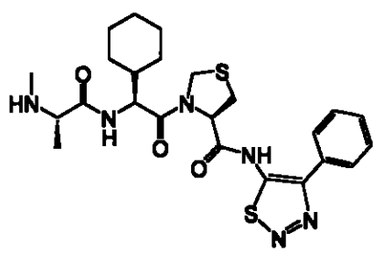
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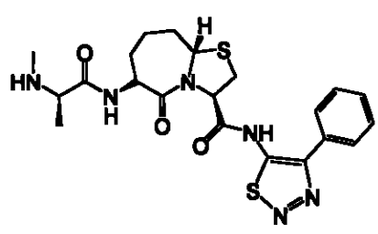
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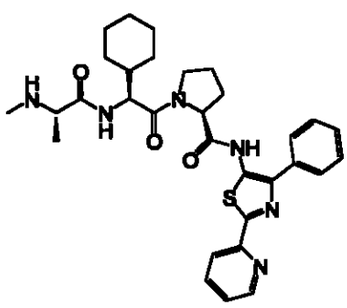
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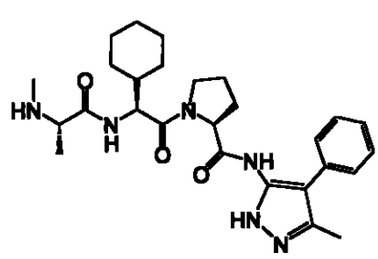
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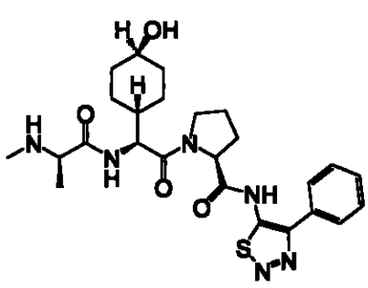
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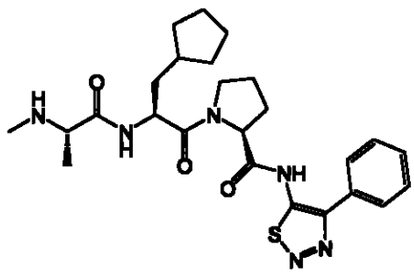
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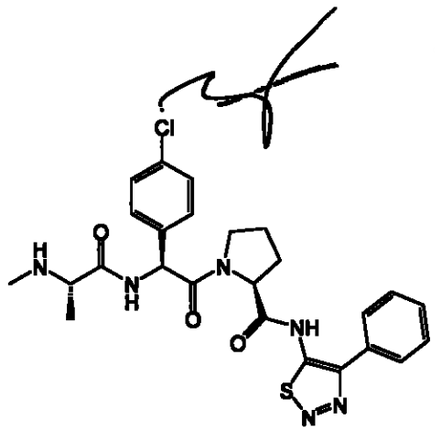
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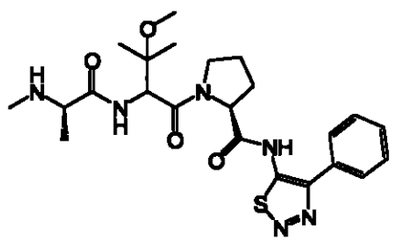
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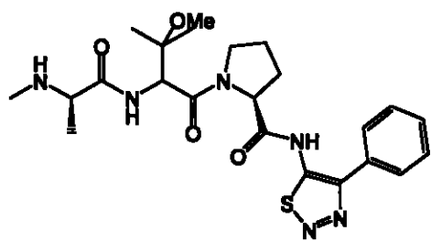
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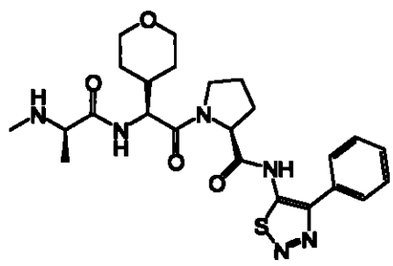
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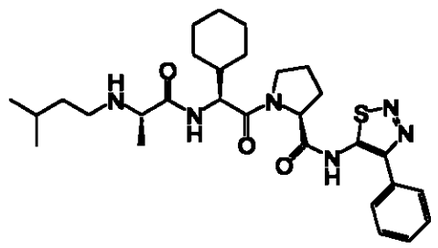
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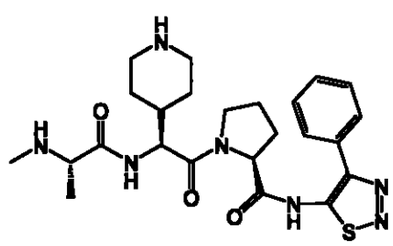
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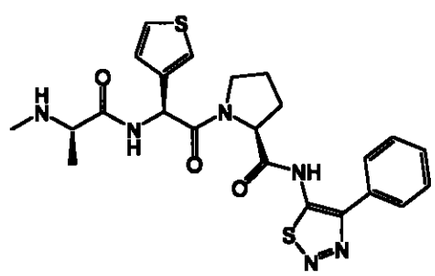
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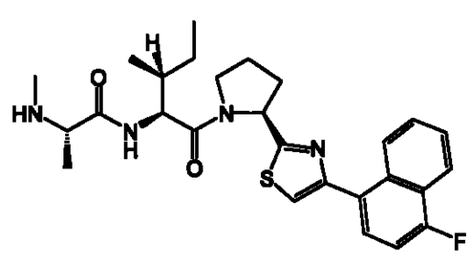
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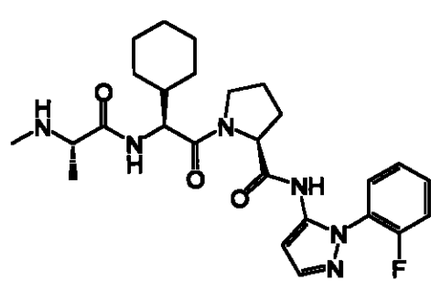
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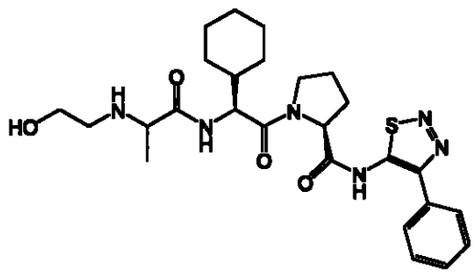


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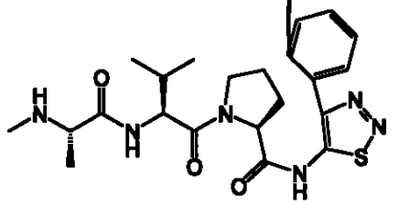


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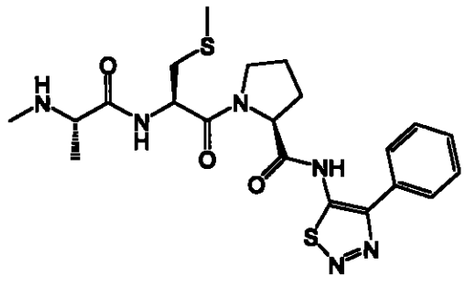
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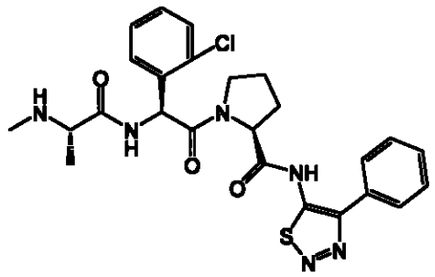
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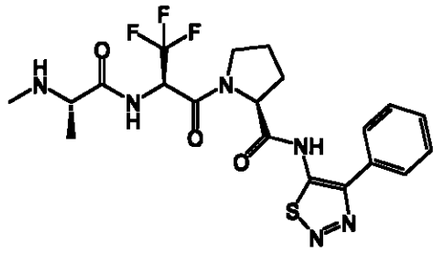
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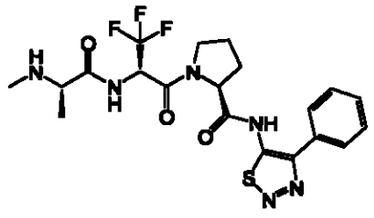
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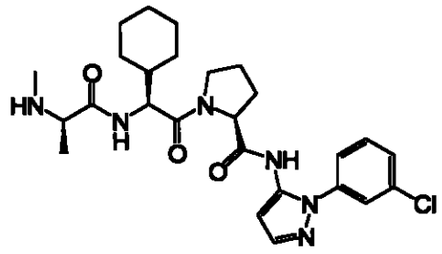
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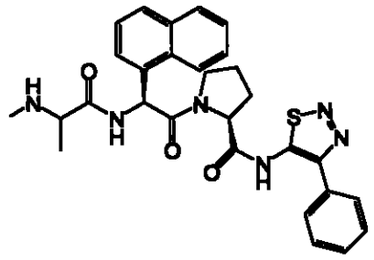
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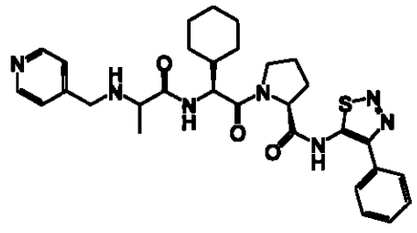
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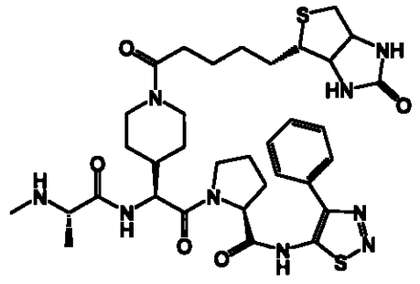
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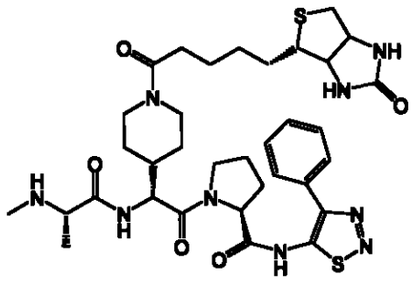
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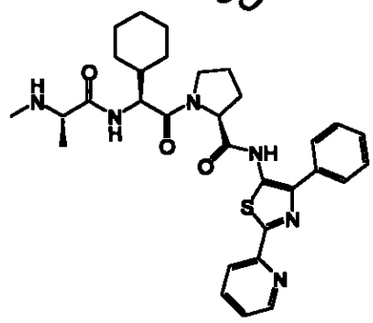
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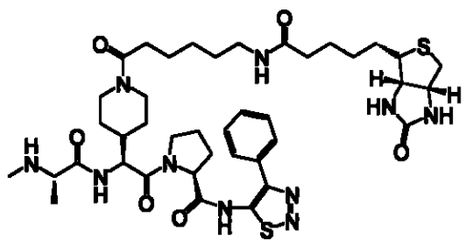
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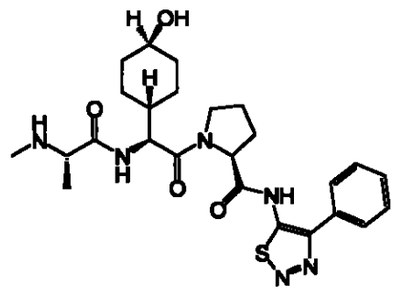
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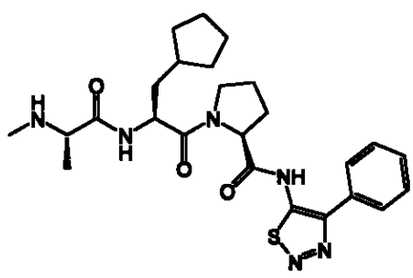
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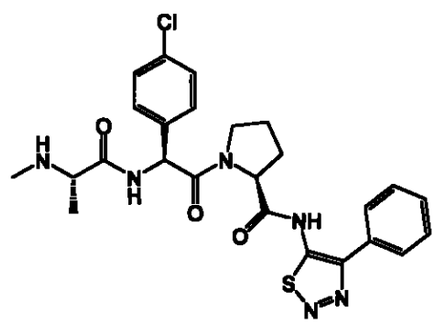
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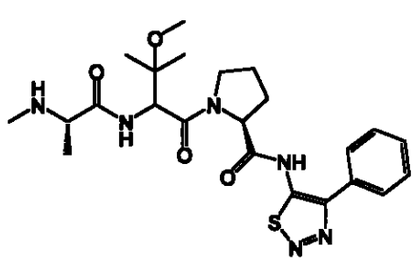
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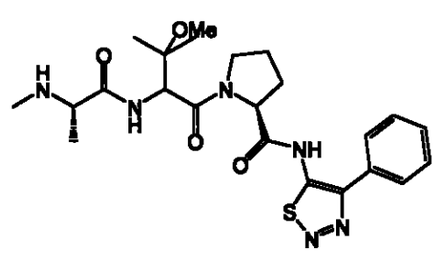
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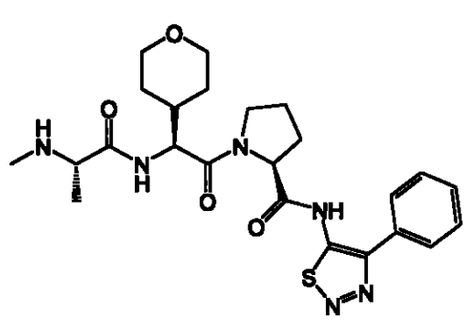
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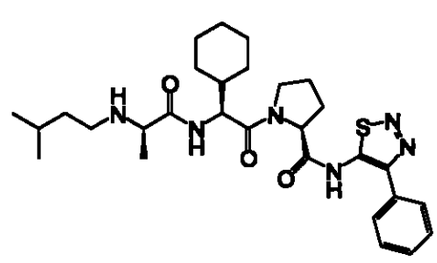
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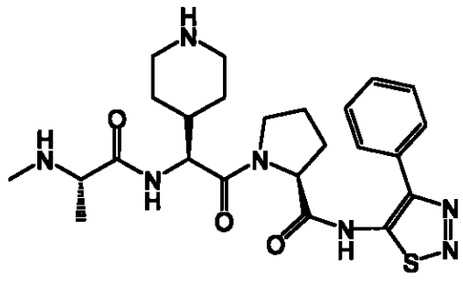
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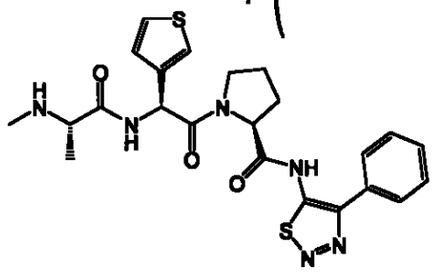
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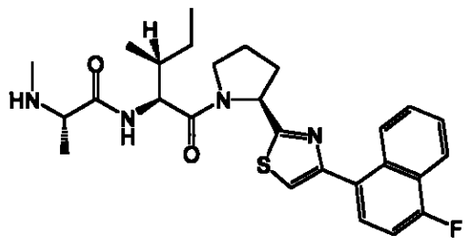
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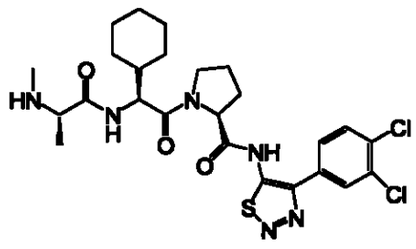
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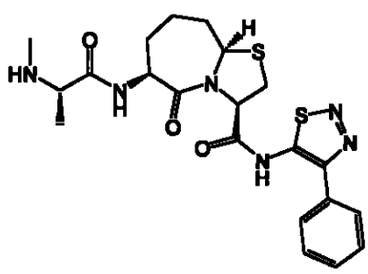
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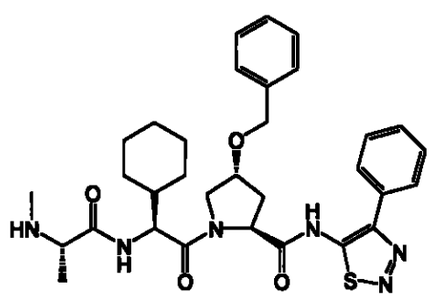
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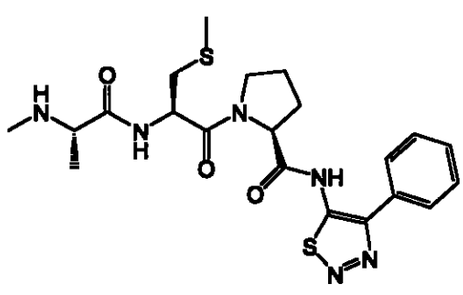
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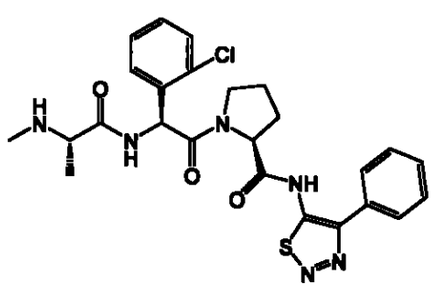
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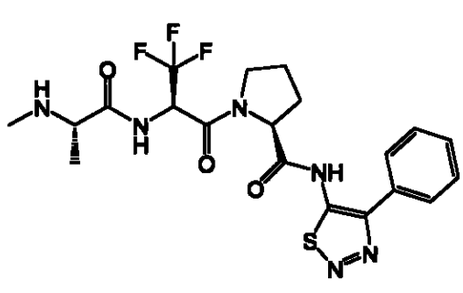
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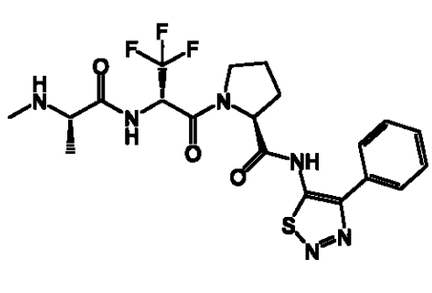
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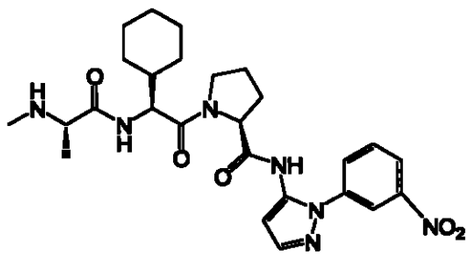
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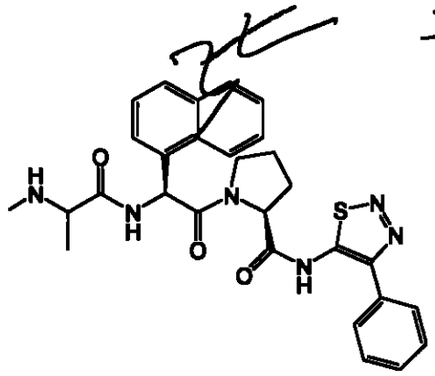
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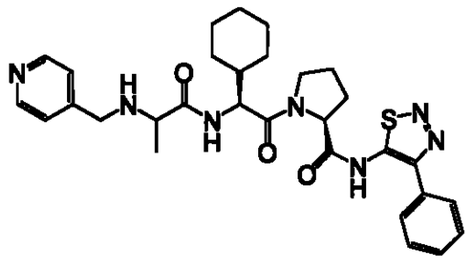
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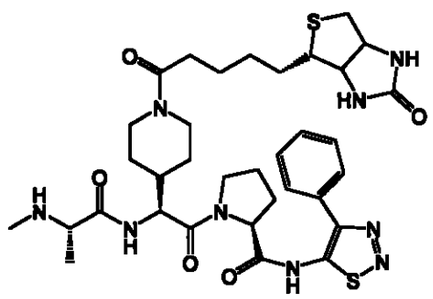
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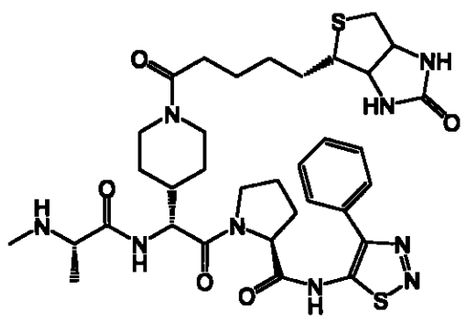
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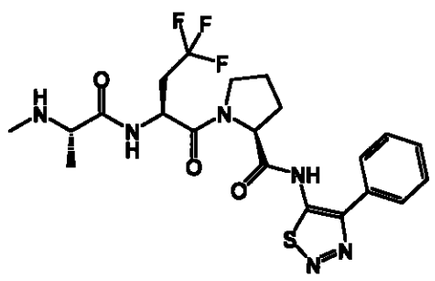
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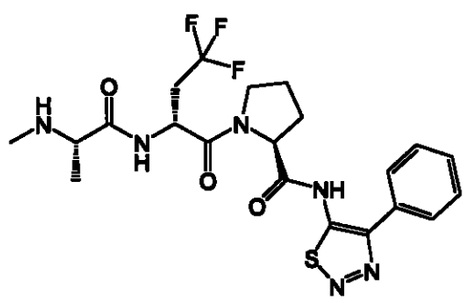
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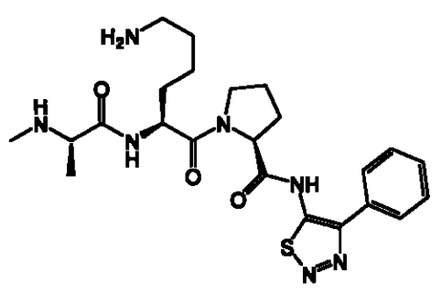
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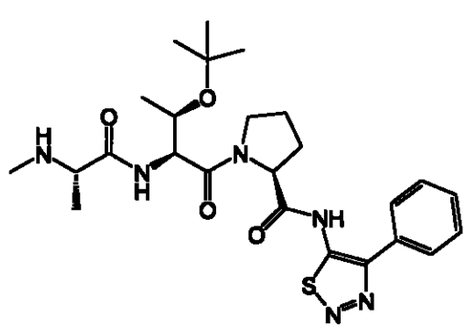
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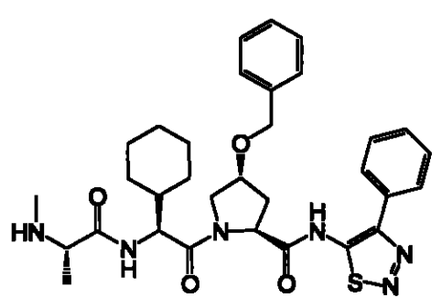
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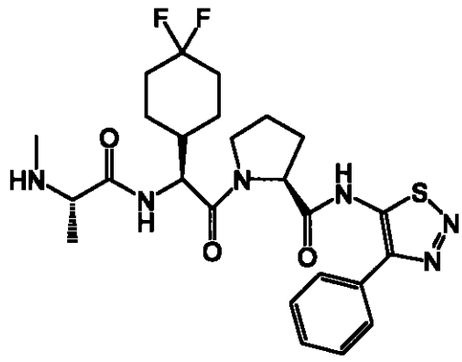
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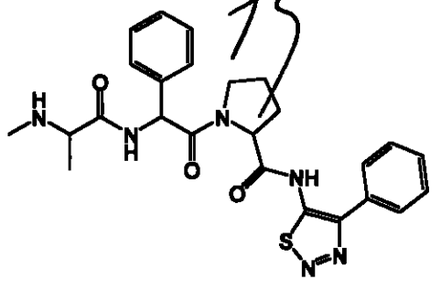
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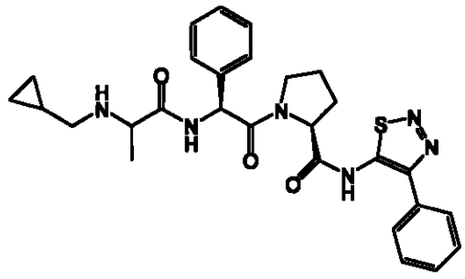
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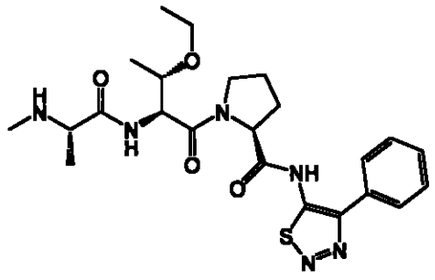
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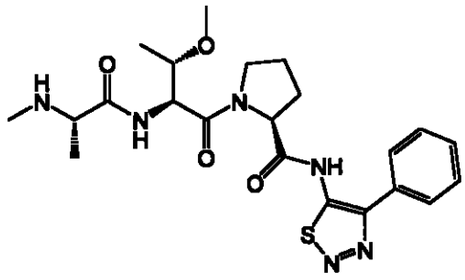
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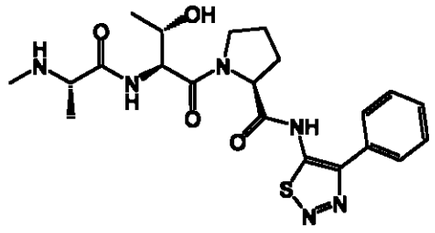
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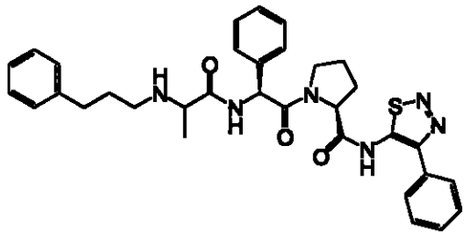
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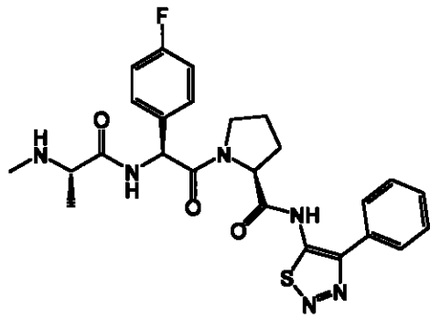
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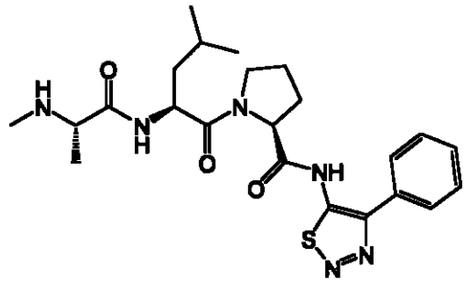
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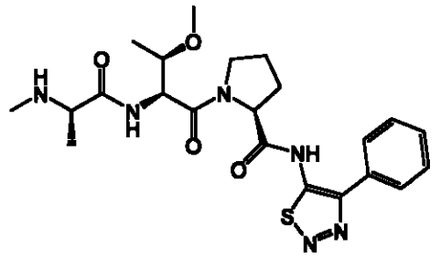
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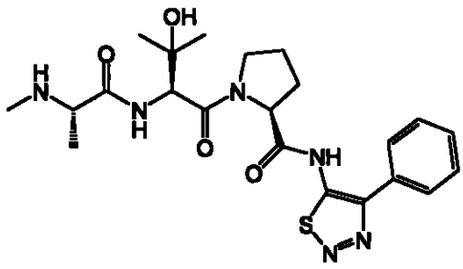


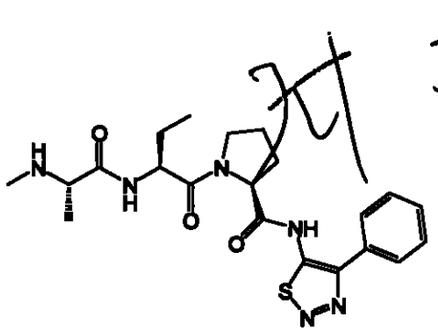
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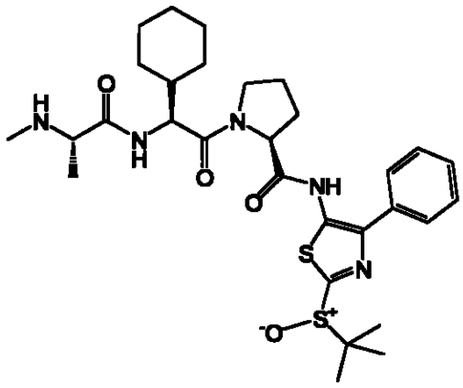


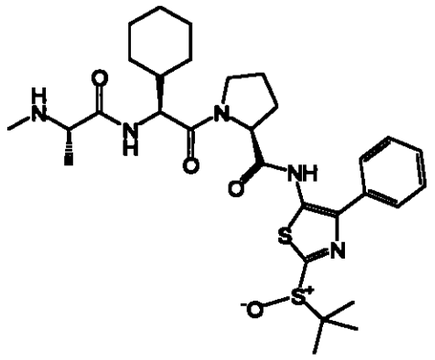
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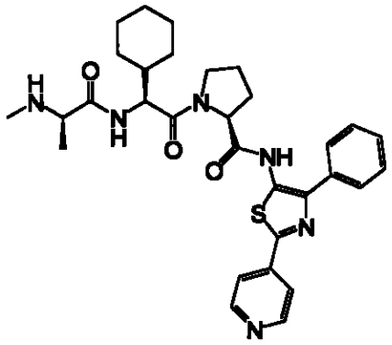


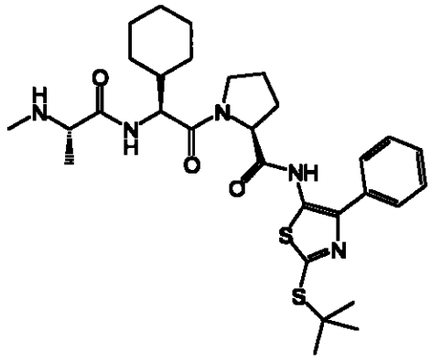
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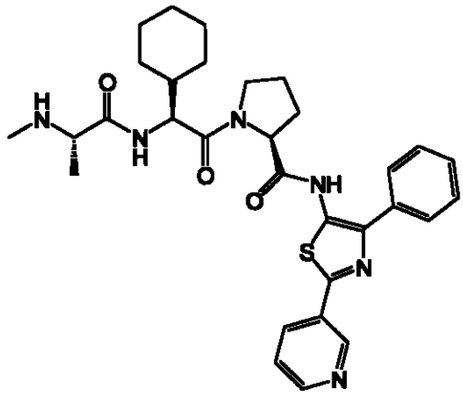
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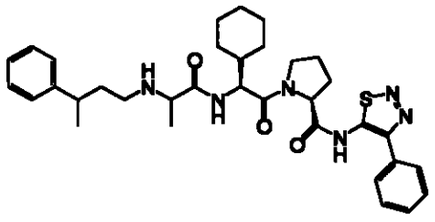
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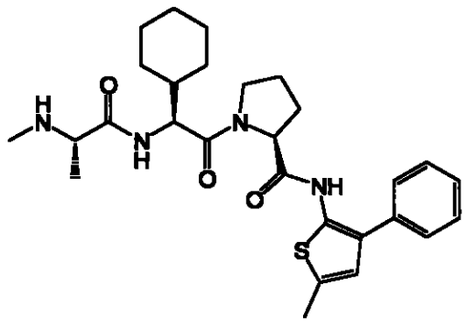
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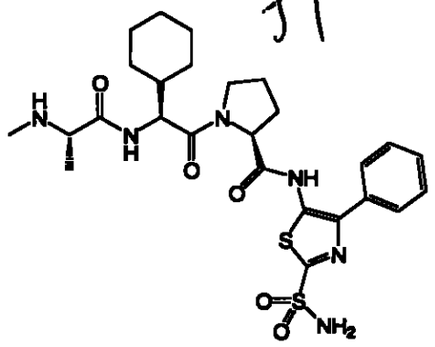
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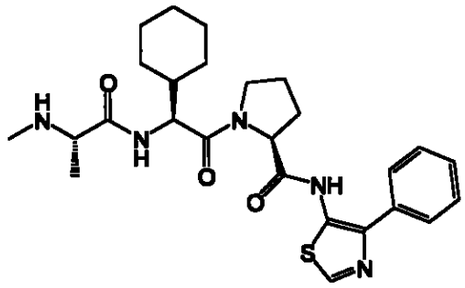
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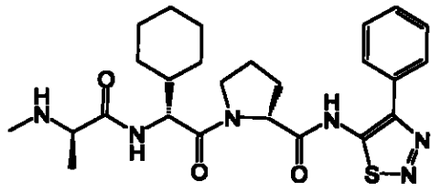
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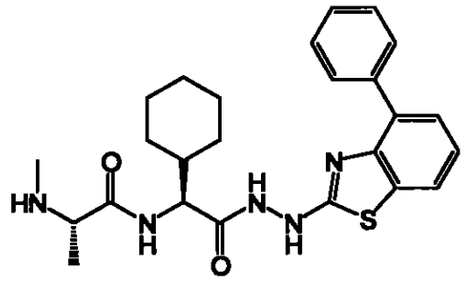
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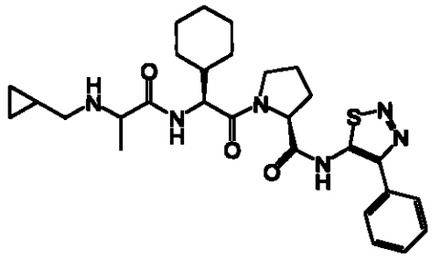
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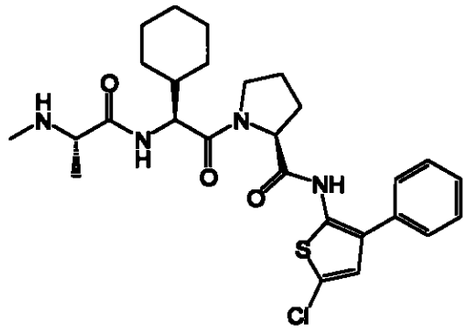
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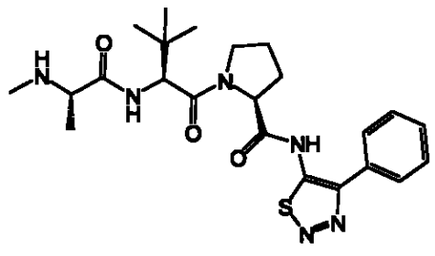
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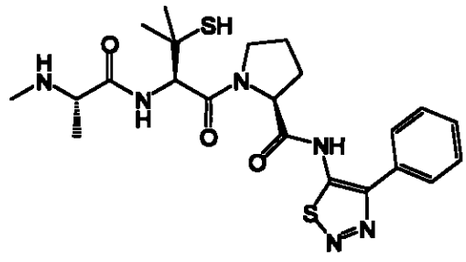
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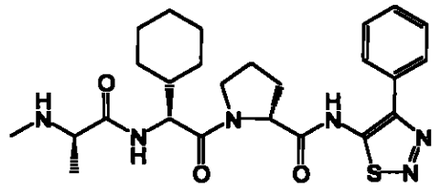
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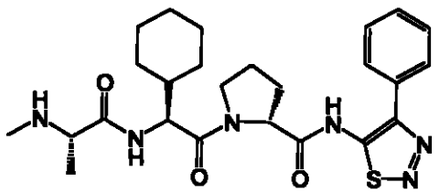


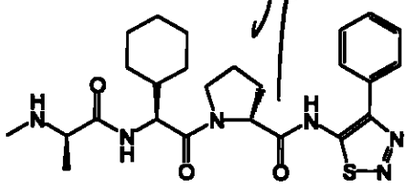
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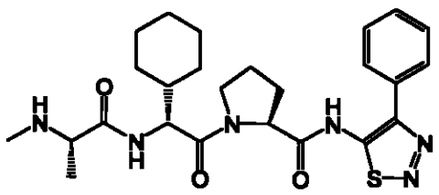


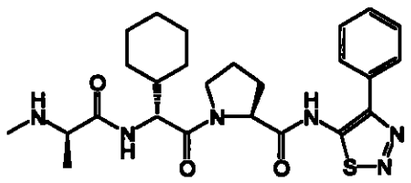
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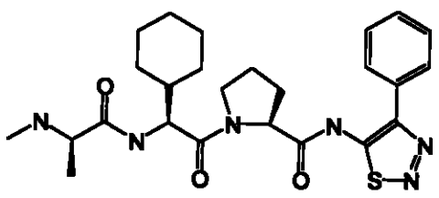


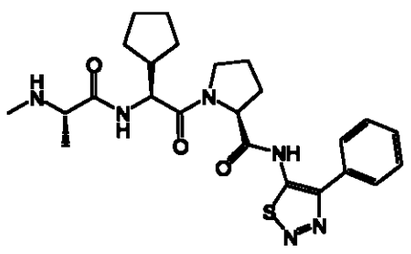
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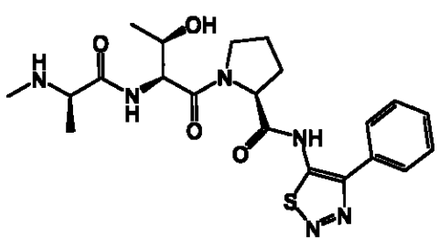
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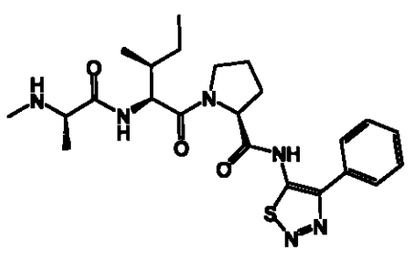
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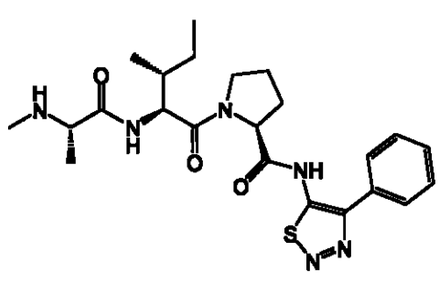
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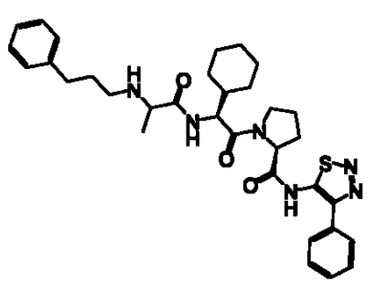
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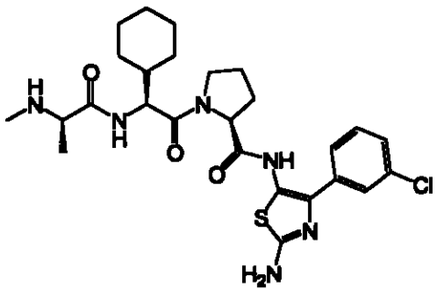
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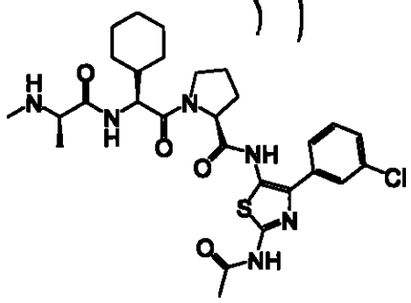
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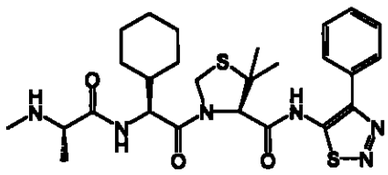
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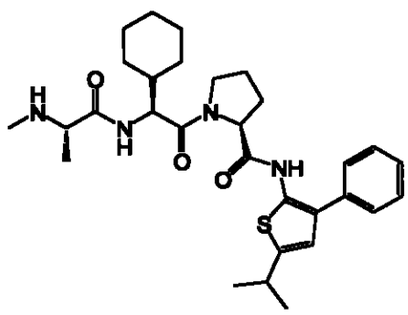
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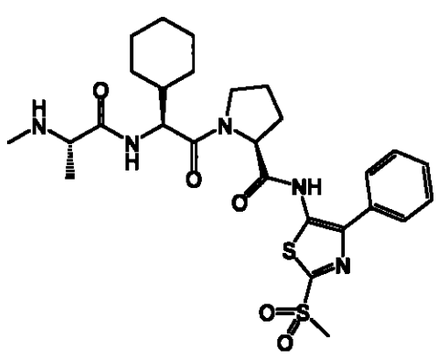
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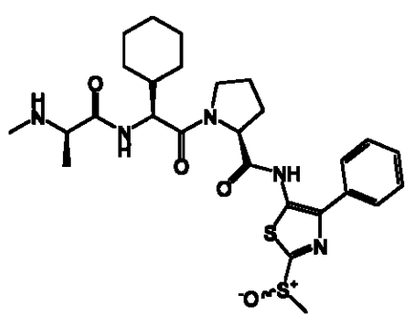
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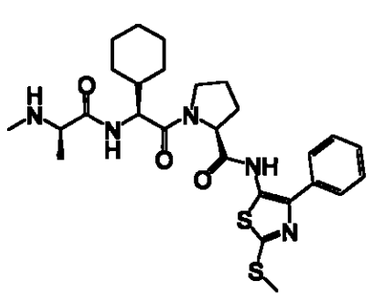
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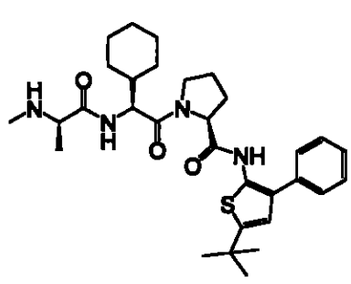
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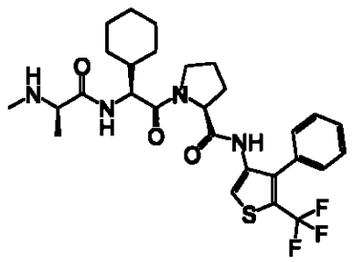
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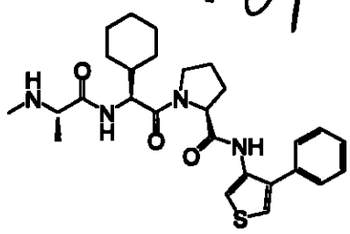


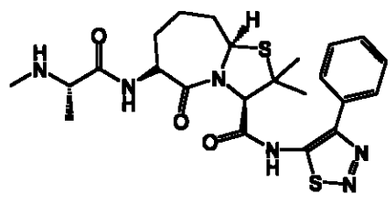
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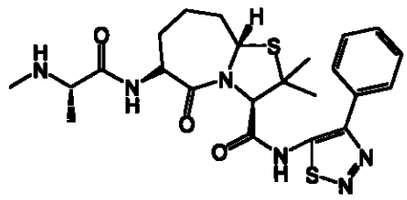


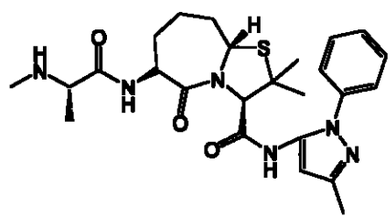
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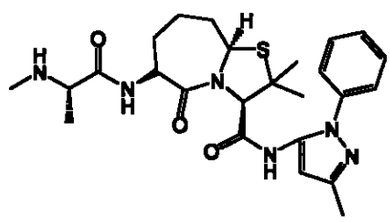
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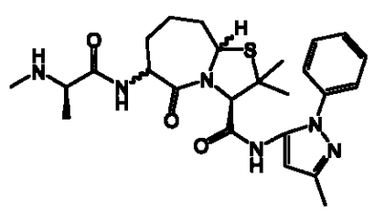
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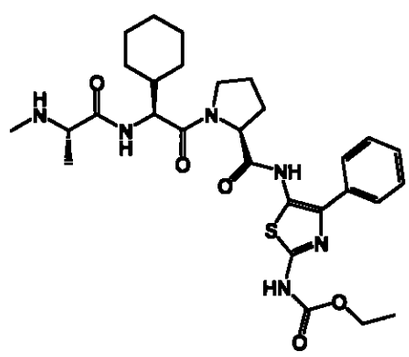
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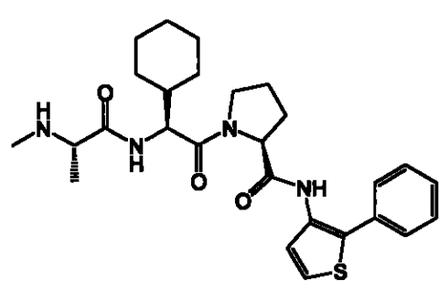
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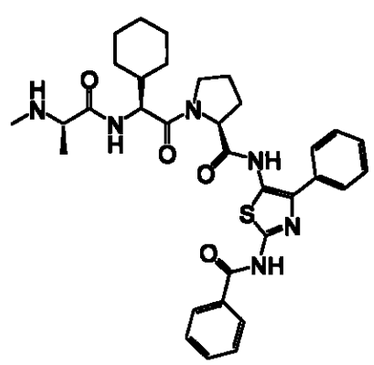
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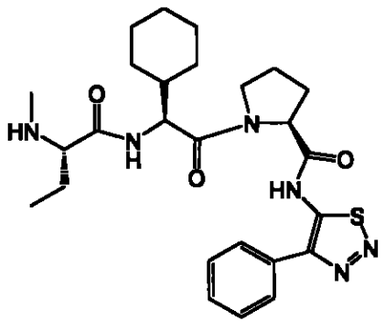
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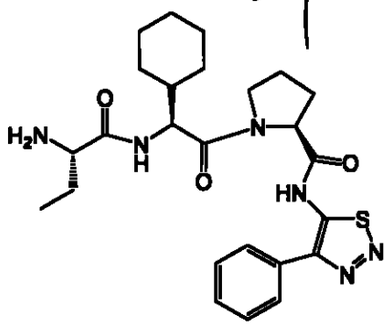
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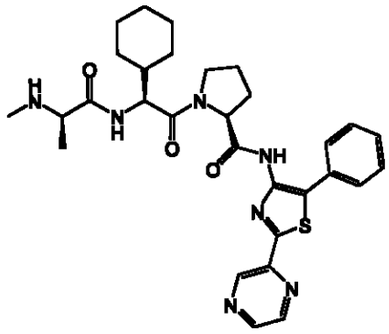
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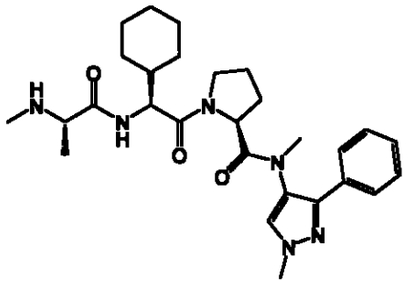
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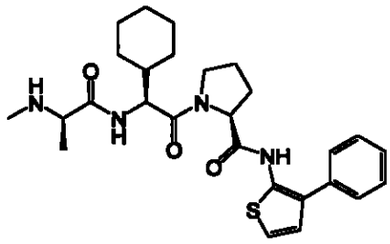
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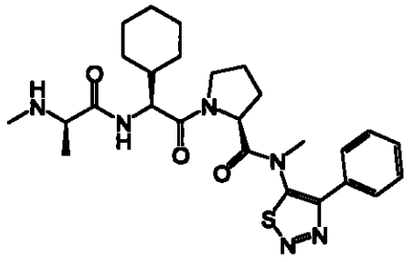
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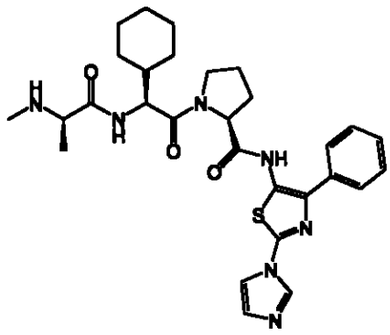
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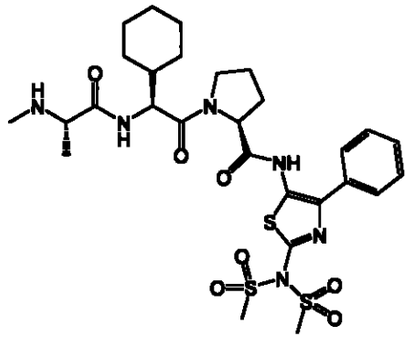
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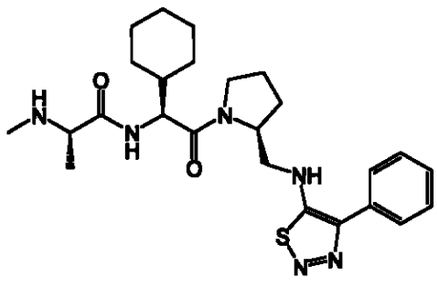


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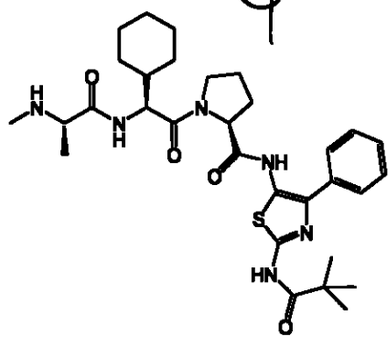


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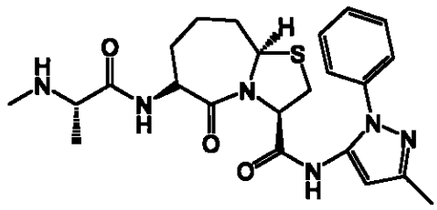
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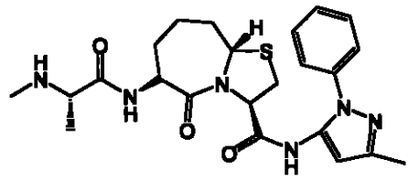
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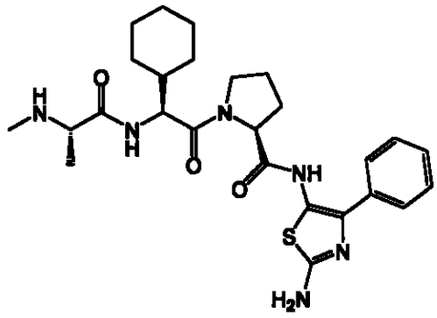
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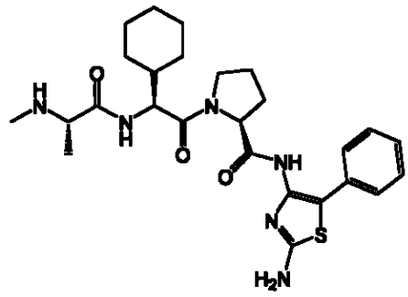
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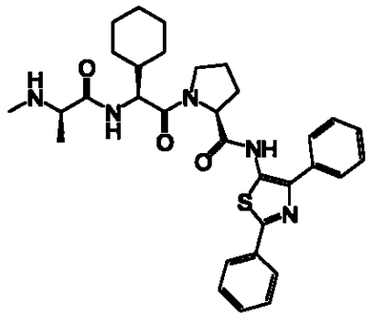
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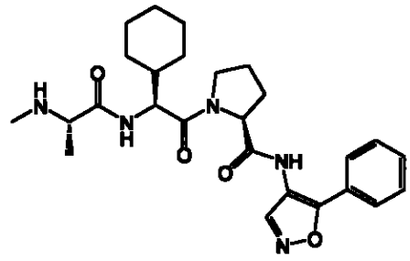
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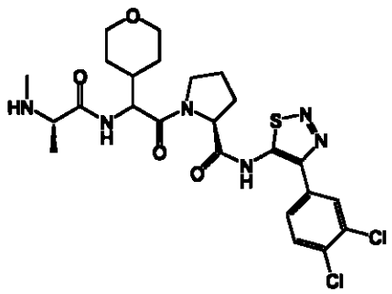


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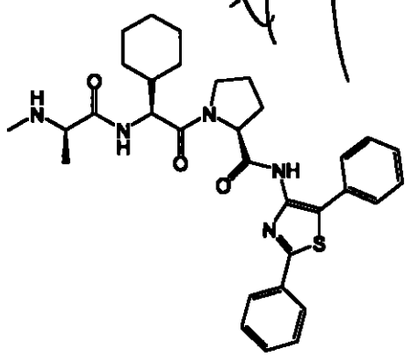


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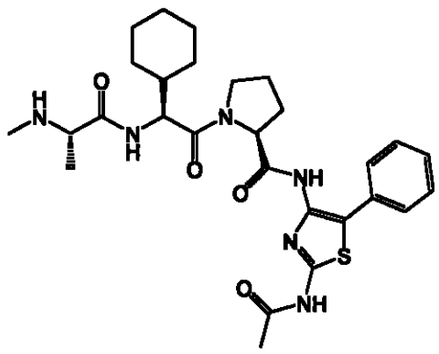
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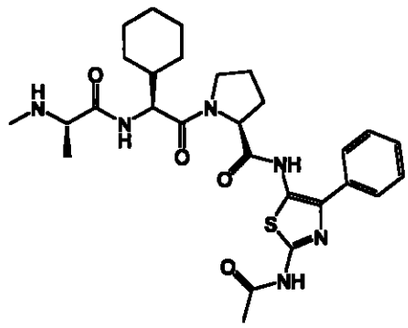
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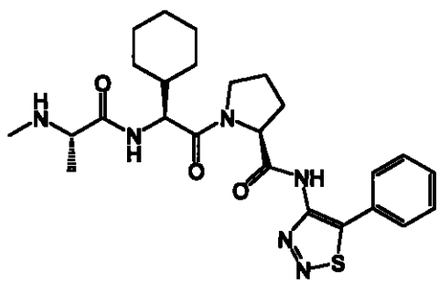
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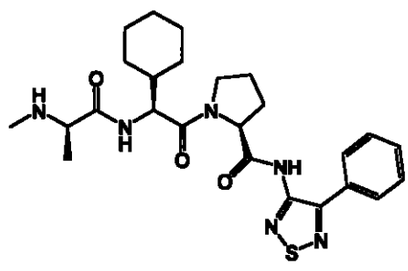
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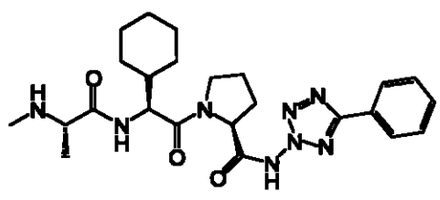
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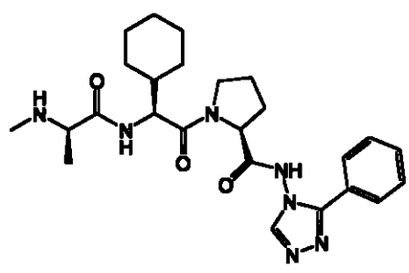
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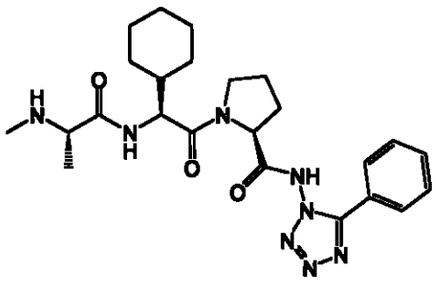
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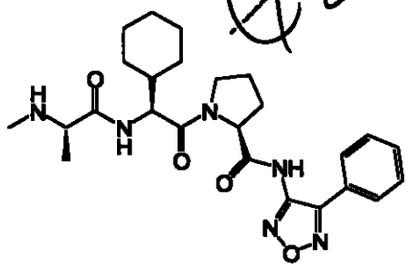
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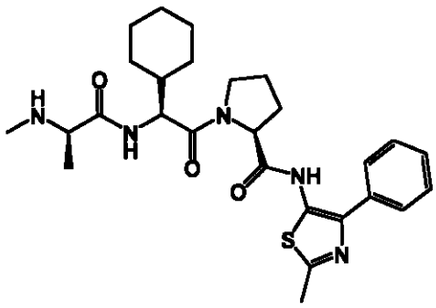
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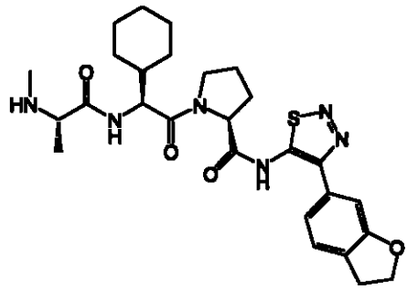
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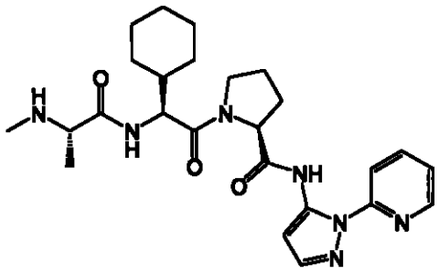
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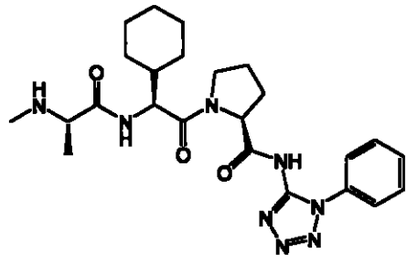
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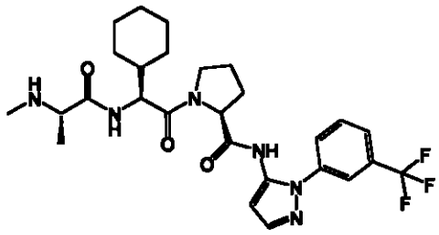
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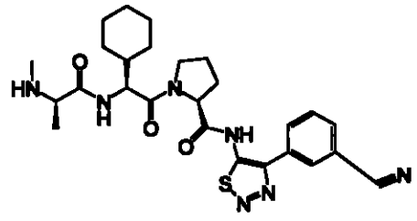
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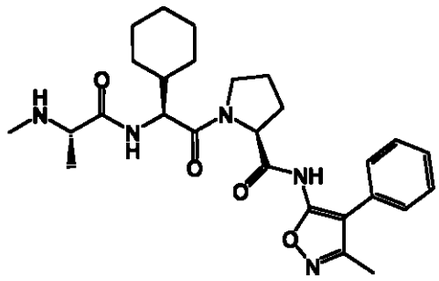
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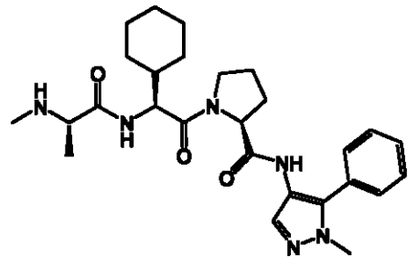
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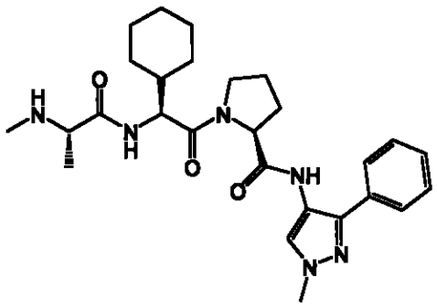


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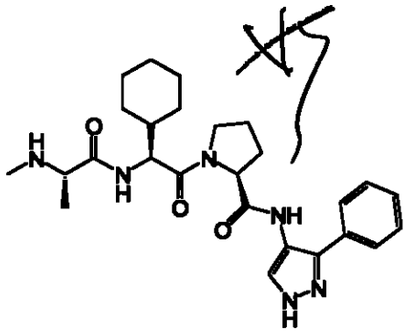


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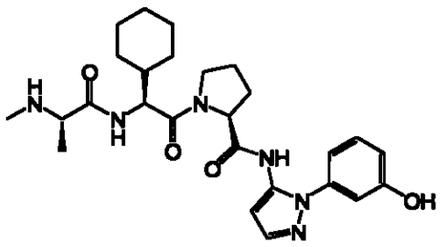
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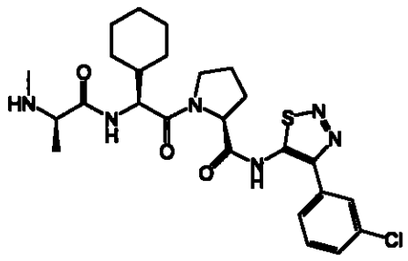
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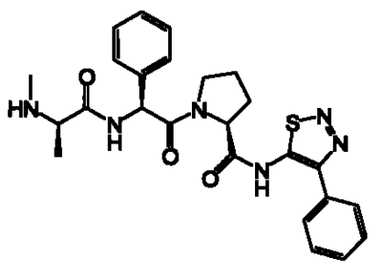
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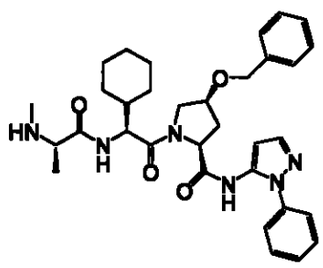
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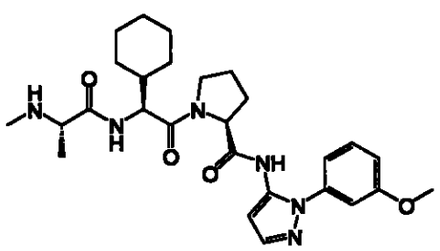
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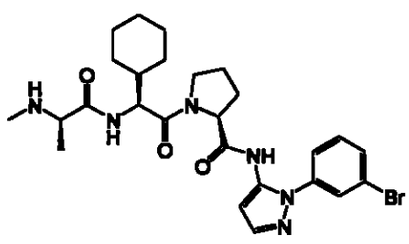
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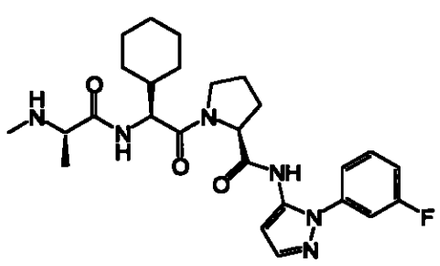
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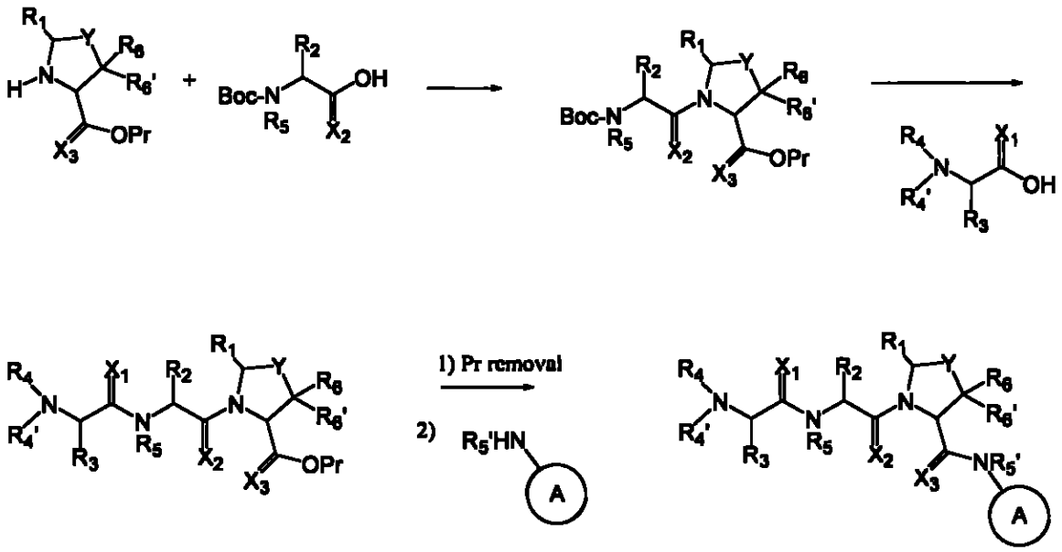
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SYNTHESIS

Compounds of the invention are prepared using standard organic synthetic techniques from commercially available starting materials and reagents. It will be appreciated that synthetic procedures employed in the preparation of compounds of the invention will depend on the particular substituents present in a compound and that various protection and deprotection may be required as is standard in organic synthesis. In a general synthetic scheme compounds of the invention may be prepared using typical peptide chemistry techniques by coupling the amino acid residue analogues with typical amide coupling procedures. In scheme 1, amine-protected amino acid residue analogues are coupled and deprotected sequentially to give the final compounds.

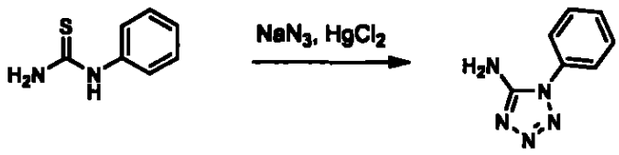
Scheme 1



It will be appreciated that the amino acid analogs may be coupled any order and may be prepared using solid phase support which is routine in the art.

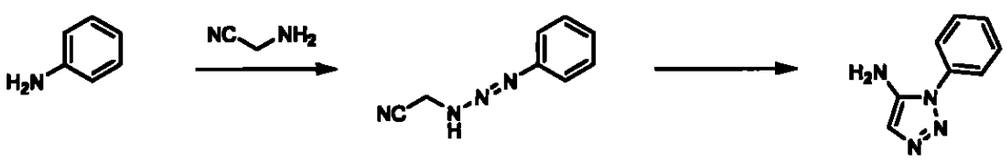
Amine substituted ring A which serves as an intermediate for preparing compounds of the invention are commercially available or else are prepared from commercially available reagents employing standard organic chemistry techniques. For example, 1-Aryl-5-aminotetrazoles, such as. phenyl-5-aminotetrazole, may be prepared according to scheme 2 from commercially available phenyl thiourea by reacting with sodium azide and mercuric chloride.

Scheme 2



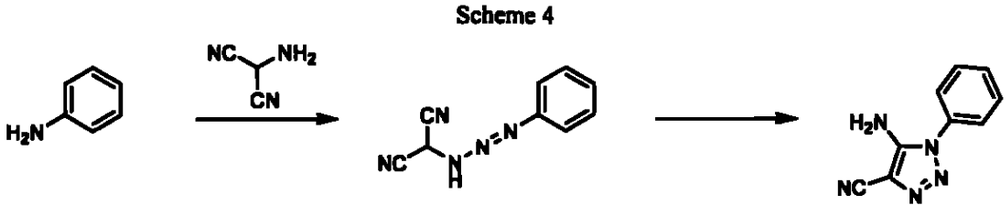
3-Aryl-5-amino-1,2,3-triazoles, such as 3-Phenyl-3H-[1,2,3]triazol-4-ylamine, may be prepared according to the procedures described in J. Org. Chem, 1981, 46:856-9 and illustrated in scheme 3 below by reacting phenylamine with aminoacetonitrile.

Scheme 3



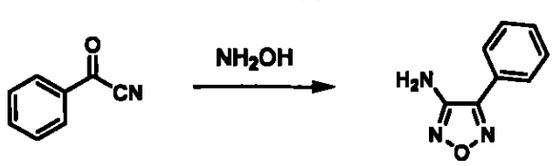
Similarly, 5-Amino-1-phenyl-1H-[1,2,3]triazole-4-carbonitrile may be prepared by reacting phenylamine with 2-amino-malononitrile as illustrated in scheme 4.

Scheme 4



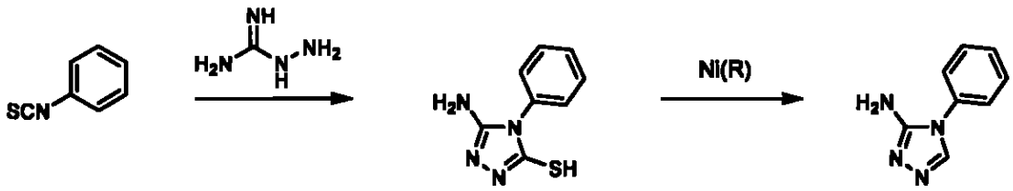
4-Aryl-5-amino-1,2,5-oxadiazoles, such as 4-phenyl-furazan-3-ylamine, may be prepared according to the procedures described in Lakhan et al, (Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal Chemistry (1987), 26B(7), 690-2) and illustrated in Scheme 5 by reacting benzoyl cyanide with hydroxylamine.

Scheme 5



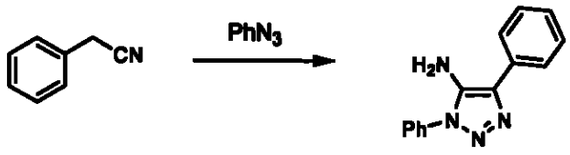
4-Aryl-3-amino-1,2,4-triazoles, such as 4-phenyl-4H-[1,2,4]triazol-3-ylamine, may be prepared by reacting phenylisothiocyanate with hydrazinecarboximidamide to give 5-amino-4-phenyl-4H-[1,2,4]triazole-3-thiol in which the thiol group may be removed with Raney nickel catalyst as illustrated in scheme 6.

Scheme 6



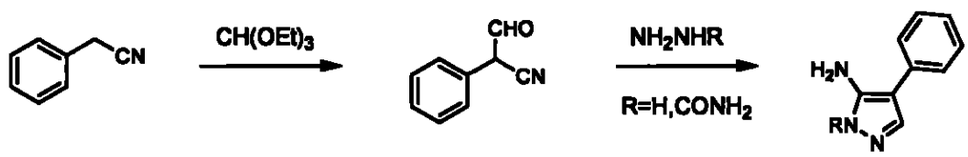
4-Aryl-5-amino-1,2,3-triazoles such as 3,5-diphenyl-3H-[1,2,3]triazol-4-ylamine according to the procedures described in J. Org. Chem., 1990, 55:3351-62 and illustrated in scheme 7, by reacting benzeneacetonitrile with azidobenzene (or alternatively trimethylsilylazide, TMS-N_3).

Scheme 7



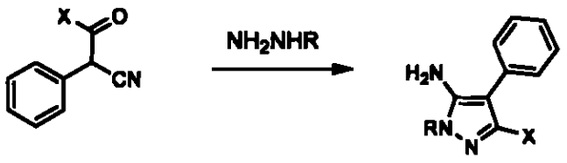
4-Aryl-3-aminopyrazoles such as 4-phenyl-2H-pyrazol-3-ylamine may be prepared according to the procedures described in patent EP269,859 and illustrated in scheme 8, by reacting benzeneacetonitrile with orthoformic acid triethyl ester to give 3-oxo-2-phenyl-propionitrile which is reacted with hydrazine.

Scheme 8



Various hydrazines and derivatives of benzeneacetonitrile can be used to prepare substituted-4-aryl-3-aminopyrazoles as illustrated in scheme 9.

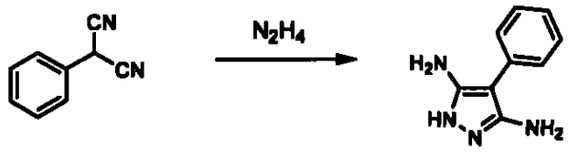
Scheme 9



X = H, Me, Et, CO_2Et, CF_3

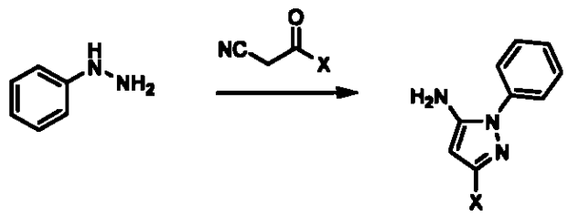
R = H, $CONH_2$





1-Aryl-5-aminopyrazoles such as 2-phenyl-2H-pyrazol-3-ylamine may be prepared by reacting phenylhydrazine with 3-oxo-propionitrile. Various nitriles can be used to introduce substitution at the 3-position of the pyrazole ring as illustrated in scheme 10.

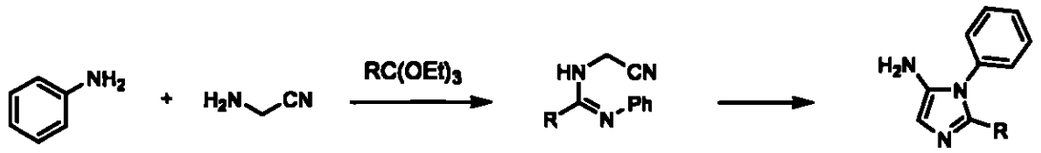
Scheme 10



X= H, Me, Et, CO_2Et, CF_3

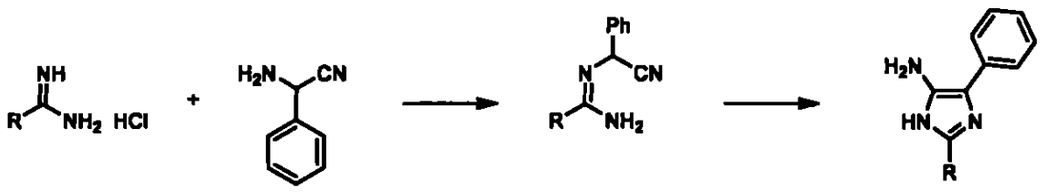
3-Aryl-4-aminoimidazoles such as 3-phenyl-3H-imidazol-4-ylamine may be prepared by reacting phenylamine with aminoacetonitrile and orthoformic acid triethyl ester as illustrated in scheme 11. Substitution at the 2-position of the imidazole can be introduced using analogs of the orthoformic acid triethylester as follows.

Scheme 11



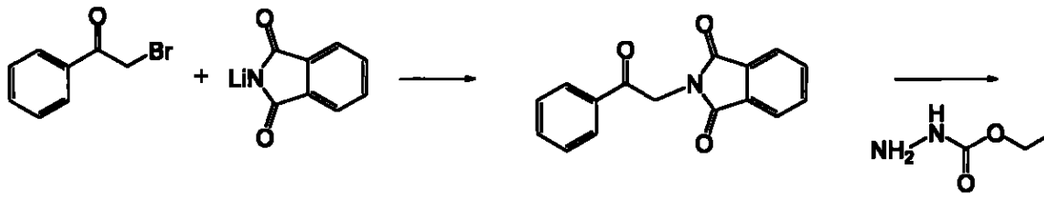
5-Aryl-4-aminoimidazoles such as 5-phenyl-3H-imidazol-4-ylamine may be prepared by reacting formamidine with aminophenylacetonitrile as illustrated in scheme 12. Substitution at the 2-position of the imidazole ring can be introduced using analogs of the formamidine.

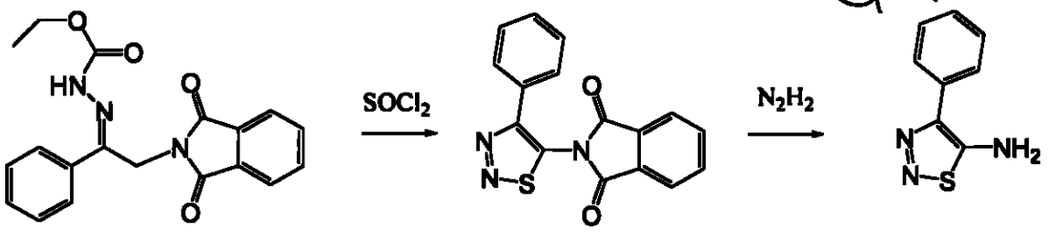
Scheme 12



4-Aryl-[1,2,3]thiadiazol-5-ylamines such as 4-phenyl-[1,2,3]thiadiazol-5-ylamine may be prepared by procedure illustrated in scheme 13. 2-bromo-1-phenyl-ethanone is reacted with lithium phthalimide and the substitution product is reacted with hydrazinecarboxylate ethyl ester. The resulting hydrazinecarboxylate ethyl ester is cyclized to form a thiadiazole by reacting with thionyl chloride followed by removal of the phthalimide group with hydrazine.

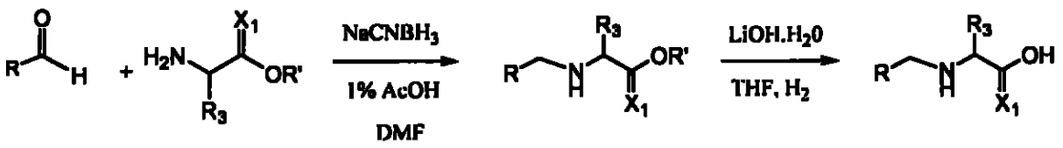
Scheme 13





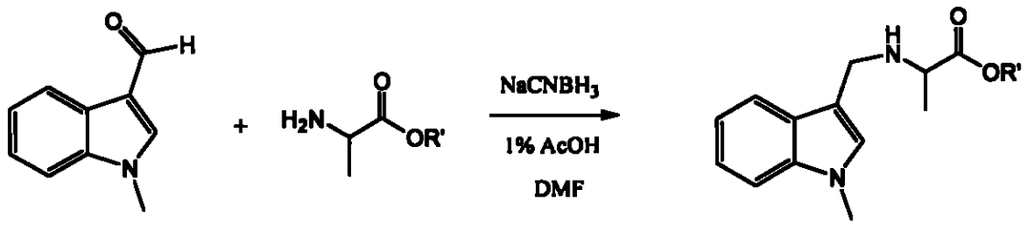
Compounds of the invention in which R_4 or R_4' are other than H may be prepared according to standard organic chemistry techniques, for example by reductive amination in which a starting amino acid residue analog e.g. NH_2-$CH(R_3)$-C(O)-OH is reacted with a suitable aldehyde or ketone to give the desired R_4 and R_4' substituents. See scheme 14. The resulting R_4/R_4' substituted amino acid intermediate can then be conjugated to the next amino acid intermediate or the remainder of the compound using standard peptide coupling procedures.

Scheme 14



In a particular embodiment, alanine is reacted with 1-methylindole-2-carboxaldehyde and reduced with sodium cyanoborohydride dissolved in 1% HOAc/DMF to give the N-substituted alanine residue which may be used in preparing compounds of the invention. See scheme 15.

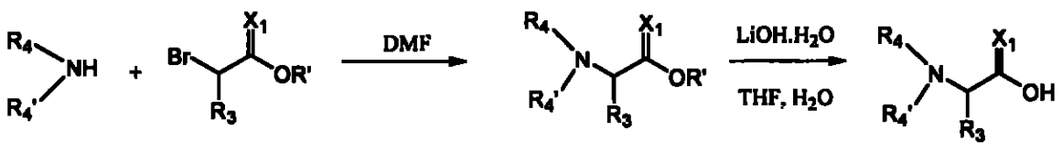
Scheme 15



Alternatively, the reductive amination procedure to introduce R_4/R_4' substituents is the final step in the preparation of the compound.

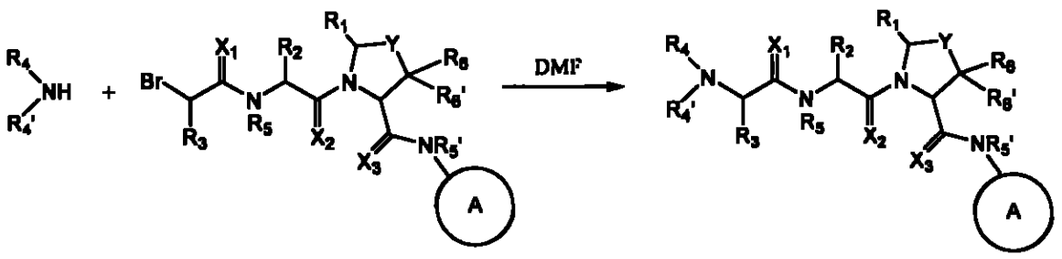
When compounds of the invention incorporate R_4 or R_4' substituents other than H, they may also be prepared by substitution of a suitable acid intermediate which incorporates a leaving group with a desired amine. For example Br-CH(R_3)-C(O)-OH is substituted with an amine R_4-NH_2 or R_4-NH-R_4' according to scheme 16.

Scheme 16

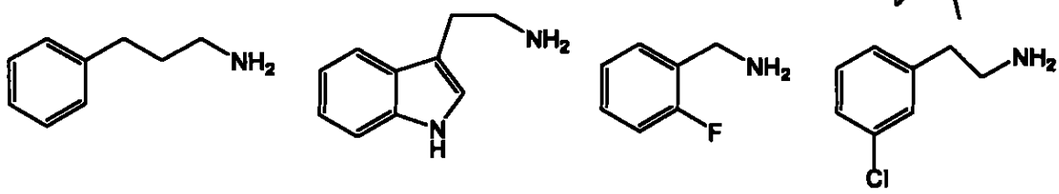
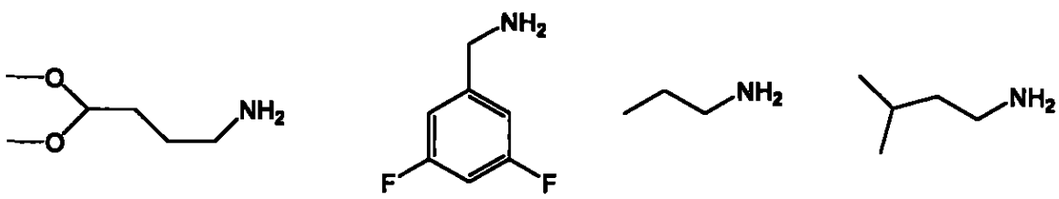
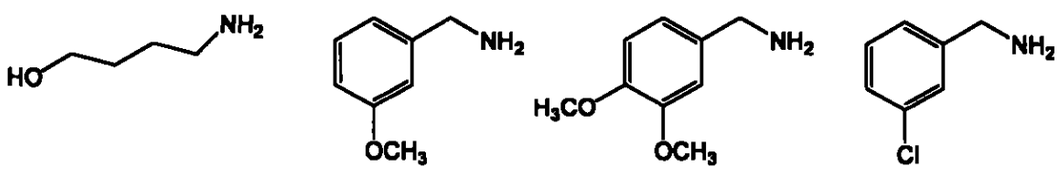


Alternatively, the substitution reaction introducing R_4 or R_4' substituents may be performed as a final step in the preparation of the compound as illustrated in scheme 17.

Scheme 17



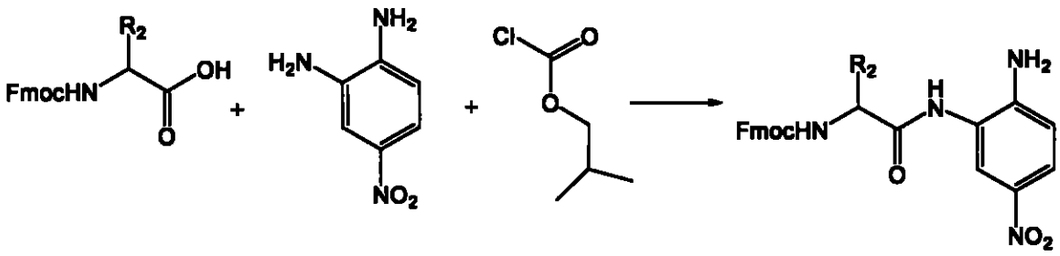
In a particular embodiment, 2-bromopropionic acid is reacted with the following amines dissolved in DMF and bubbled for until substitution is complete to form N-substituted alanine residues:

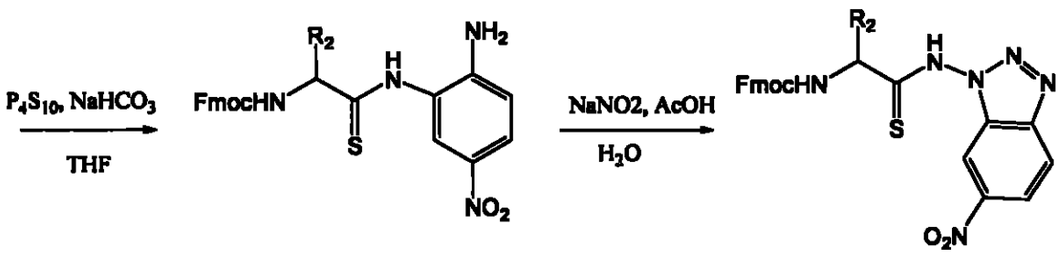




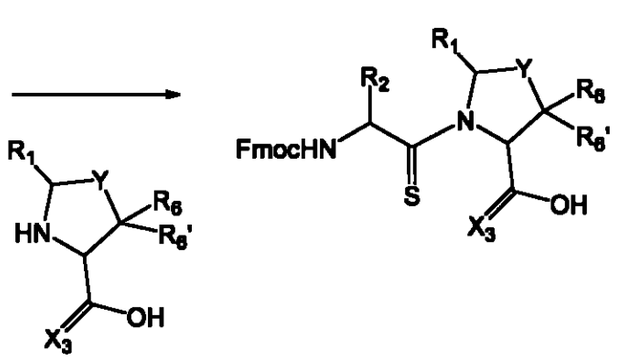

Compounds of the invention in which any one or more of X_1, X_2 and X_3 are sulfur, i.e. the compound incorporates a thioamide, may be prepared according to established organic chemistry techniques. For example, compounds in which X_2 is sulfur can be prepared according to scheme 18 starting from an Fmoc protected amino acid residue analog NH_2-CH(R_2)-COOH which is dissolved in THF and cooled to –25°C, with addition of DIPEA followed by addition of isobutylchloroformate. After 10 minutes, the diamine, 4-nitrobenzene-1,2-diamine, is added and the reaction mixture is continuously stirred at -25°C for 2 hours, then at room temperature overnight. THF is vacuumed off and the mixture is then subjected to flash chromatography using 50% EtOAc/Hexane to yield the product. The Fmoc-alanine derivative, phosphorus pentasulfide and sodium carbonate are mixed in THF and stirred overnight. The solution is concentrated and direct chromatography using 80% EtOAc/Hexane yields the activated thioalanine. The activated thioalanine and sodium nitrite are then mixed in acetic acid and diluted with H_2O. The resulting precipitant is filtered and dried to yield the product. The thioalanine is coupled to an OH-protected

proline amino acid residue analog by dissolving both in DMF. The thioamide product may then be deprotected with 20% PIP/DMA for 15 minutes and used to conjugate to the R_4/R_4'-N-CH(R_3)-COOH amino acid residue analog followed by OH-deprotection and coupling to an amino-substituted A ring intermediate. Alternatively the Fmoc-protected thioamide is first coupled to an amino substituted A ring intermediate followed by Fmoc deprotection and subsequent coupling to the R_4/R_4'-N-CH(R_3)-COOH amino acid residue analog.

Scheme 18







UTILITY

The compounds of the invention inhibit the binding of IAP proteins to caspases, in particular X-IAP binding interaction with caspases 3 and 7. The compounds also inhibit the binding of ML-IAP to Smac protein. Accordingly, the compounds of the invention are useful for inducing apoptosis in cells or sensitizing cells to apoptotic signals, in particular cancer cells. Compounds of the invention are useful for inducing apoptosis in cells that overexpress IAP proteins. Alternatively, compounds of the invention are useful for inducing apoptosis in cells in which the mitochondrial apoptotic pathway is disrupted such that release of Smac from ML-IAP proteins is inhibited, for example by up regulation of Bcl-2 or down regulation of Bax/Bak. More broadly, the compounds can be used for the treatment of all cancer types which fail to undergo apoptosis. Examples of such cancer types include neuroblastoma, intestine carcinoma such as rectum carcinoma, colon carcinoma, familiary adenomatous polyposis carcinoma and hereditary non-polyposis colorectal cancer, esophageal carcinoma, labial carcinoma, larynx carcinoma, hypopharynx carcinoma, tong carcinoma, salivary gland carcinoma, gastric carcinoma, adenocarcinoma, medullary thyroidea carcinoma, papillary thyroidea carcinoma, renal carcinoma, kidney parenchym carcinoma, ovarian carcinoma, cervix carcinoma, uterine corpus carcinoma, endometrium carcinoma, chorion carcinoma, pancreatic carcinoma, prostate carcinoma, testis carcinoma, breast carcinoma, urinary carcinoma, melanoma, brain tumors such as glioblastoma, astrocytoma, meningioma, medulloblastoma and peripheral neuroectodermal tumors, Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, acute lymphatic leukemia (ALL), chronic lymphatic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), adult T-cell leukemia lymphoma, hepatocellular carcinoma, gall bladder carcinoma, bronchial carcinoma, small cell lung carcinoma, non-small cell lung carcinoma, multiple myeloma, basalioma, teratoma, retinoblastoma, choroidea melanoma, seminoma, rhabdomyo sarcoma, craniopharyngeoma, osteosarcoma, chondrosarcoma, myosarcoma, liposarcoma, fibrosarcoma, Ewing sarcoma and plasmocytoma.

Compounds of the invention are useful for sensitizing cells to apoptotic signals. Accordingly, the compounds may be administered prior to, concomitantly with, or following administration of radiation therapy or cytostatic or antineoplastic chemotherapy. Suitable cytostatic chemotherapy compounds include, but are not limited to (i) antimetabolites, such as cytarabine, fludarabine, 5-fluoro-2'-deoxyuiridine, gemcitabine, hydroxyurea or methotrexate; (ii) DNA-fragmenting agents, such as bleomycin, (iii) DNA-crosslinking agents, such as chlorambucil, cisplatin,

cyclophosphamide or nitrogen mustard; (iv) intercalating agents such as adriamycin (doxorubicin) or mitoxantrone; (v) protein synthesis inhibitors, such as L-asparaginase, cycloheximide, puromycin or diphtheria toxin; (Vi) topoisomerase I poisons, such as camptothecin or topotecan; (vii) topoisomerase II poisons, such as etoposide (VP-16) or teniposide; (viii) microtubule-directed agents, such as colcemid, colchicine, paclitaxel, vinblastine or vincristine; (ix) kinase inhibitors such as flavopiridol, staurosporin, STI571 (CPG 57148B) or UCN-01 (7-hydroxystaurosporine); (x) miscellaneous investigational agents such as thioplatin, PS-341, phenylbutyrate, ET-18- OCH_3, or farnesyl transferase inhibitors (L-739749, L-744832); polyphenols such as quercetin, resveratrol, piceatannol, epigallocatechine gallate, theaflavins, flavanols, procyanidins, betulinic acid and derivatives thereof; (xi) hormones such as glucocorticoids or fenretinide; (xii) hormone antagonists, such as tamoxifen, finasteride or LHRH antagonists. In a preferred embodiment, compounds of the present invention are coadministered with a cytostatic compound selected from the group consisting of cisplatin, doxorubicin, taxol, taxotere and mitomycin C. Most preferred, the cytostatic compound is doxorubicin.

Another class of active compounds which can be used in the present invention are those which are able to sensitize for or induce apoptosis by binding to death receptors ("death receptor agonists"). Such agonists of death receptors include death receptor ligands such as tumor necrosis factor a (TNF-α), tumor necrosis factor ß (TNF-ß, lymphotoxin-α) , LT-ß (lymphotoxin-ß), TRAIL (Apo2L, DR4 ligand), CD95 (Fas, APO-1) ligand, TRAMP (DR3, Apo-3) ligand, DR6 ligand as well as fragments and derivatives of any of said ligands. Preferably, the death receptor ligand is TNF-α. More preferably the death receptor ligand is Apo2L/TRAIL. Furthermore, death receptors agonists comprise agonistic antibodies to death receptors such as anti-CD95 antibody, anti-TRAIL-R1 (DR4) antibody, anti-TRAIL-R2 (DR5) antibody, anti-TRAIL-R3 antibody, anti-TRAIL-R4 antibody, anti-DR6 antibody, anti-TNF-Rl antibody and anti-TRAMP (DR3) antibody as well as fragments and derivatives of any of said antibodies.

For the purpose of sensitizing cells for apoptosis, the compounds of the present invention can be also used in combination with radiation therapy. The phrase "radiation therapy" refers to the use of electromagnetic or particulate radiation in the treatment of neoplasia. Radiation therapy is based on the principle that high-dose radiation delivered to a target area will result in the death of reproducing cells in both tumor and normal tissues. The radiation dosage regimen is generally defined in terms of radiation absorbed dose (rad), time and fractionation, and must be carefully defined by the oncologist. The amount of radiation a patient receives will depend on various consideration but the two most important considerations are the location of the tumor in relation to

other critical structures or organs of the body, and the extent to which the tumor has spread. Examples of radiotherapeutic agents are provided in, but not limited to, radiation therapy and is known in the art (Hellman, Principles of Radiation Therapy, Cancer, in Principles I and Practice of Oncology, 24875 (Devita et al., 4th ed., vol 1, 1993). Recent advances in radiation therapy include three-dimensional conformal external beam radiation, intensity modulated radiation therapy (IMRT), stereotactic radiosurgery and brachytherapy (interstitial radiation therapy), the latter placing the source of radiation directly into the tumor as implanted "seeds". These newer treatment modalities deliver greater doses of radiation to the tumor, which accounts for their increased effectiveness when compared to standard external beam radiation therapy.

Ionizing radiation with beta-emitting radionuclides is considered the most useful for radiotherapeutic applications because of the moderate linear energy transfer (LET) of the ionizing particle (electron) and its intermediate range (typically several millimeters in tissue). Gamma rays deliver dosage at lower levels over much greater distances. Alpha particles represent the other extreme, they deliver very high LET dosage, but have an extremely limited range and must, therefore, be in intimate contact with the cells of the tissue to be treated. In addition, alpha emitters are generally heavy metals, which limits the possible chemistry and presents undue hazards from leakage of radionuclide from the area to be treated. Depending on the tumor to be treated all kinds of emitters are conceivable within the scope of the present invention.

Furthermore, the present invention encompasses types of non-ionizing radiation like e.g. ultraviolet (UV) radiation, high energy visible light, microwave radiation (hyperthermia therapy), infrared (IR) radiation and lasers. In a particular embodiment of the present invention UV radiation is applied.

The invention also includes pharmaceutical compositions or medicaments containing the compounds of the invention and a therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments. Typically, the compounds of formula I used in the methods of the invention are formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but preferably ranges anywhere from about 3 to about 8. Formulation in an acetate buffer at pH 5 is a suitable embodiment.

The inhibitory compound for use herein is preferably sterile. The compound ordinarily will be stored as a solid composition, although lyophilized formulations or aqueous solutions are acceptable.

The composition of the invention will be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The "effective amount" of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to inhibit IAP interaction with caspases, induce apoptosis or sensitize a malignant cell to an apoptotic signal. Such amount is preferably below the amount that is toxic to normal cells, or the mammal as a whole.

Generally, the initial pharmaceutically effective amount of the compound of the invention administered parenterally per dose will be in the range of about 0.01-100 mg/kg, preferably about 0.1 to 20 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day. Oral unit dosage forms, such as tablets and capsules, preferably contain from about 25 to about 1000 mg of the compound of the invention.

The compound of the invention may be administered by any suitable means, including oral, topical, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. An example of a suitable oral dosage form is a tablet containing about 25mg, 50mg, 100mg, 250mg, or 500mg of the compound of the invention compounded with about 90-30 mg anhydrous lactose, about 5-40 mg sodium croscarmellose, about 5-30mg polyvinylpyrrolidone (PVP) K30, and about 1-10 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An aerosol formulation can be prepared by dissolving the compound, for example 5-400 mg, of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g. a salt such sodium chloride, if desired. The solution is typically filtered, e.g. using a 0.2 micron filter, to remove impurities and contaminants.

EXAMPLES

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention. Abbreviations used herein are as follows:

ACN: acetonitrile;

Chg: cyclohexylglycine;

DCM: dichloromethane

DIPEA: diisopropylethylamine;

DMAP: 4- dimethylaminopyridine;

DME: 1,2-dimethoxyethane;

DMF: dimethylformamide;

DMSO: dimethylsulfoxide

EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide;

EEDQ: 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline

LCMS: liquid chromatography mass spectrometry;

HATU: O-(7-Azobenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate;

HOBt: N-Hydroxybenzotriazole

HBTU: 2-(1H-Benzotriazol-1-yl)-1,1,3,3-Tetramethyl-uronium Hexafluorophosphate

HPLC: high performance liquid chromatography;

NBS: N-bromosuccinamide;

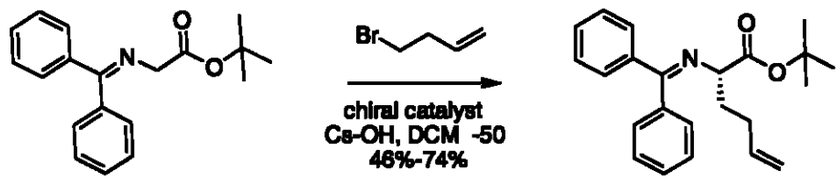
TASF: tris(dimethylamino)sulfonium difluorotrimethylsilicate;

TEA: triethylamine;

TFA: trifluoroacetate;

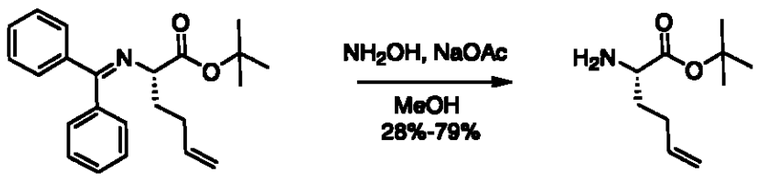
THF: tetrahydrofuran;

Example 1 6-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-5-oxo-octahydro-thiazolo[3,2-a]azepine-3-carboxylic acid ethyl ester



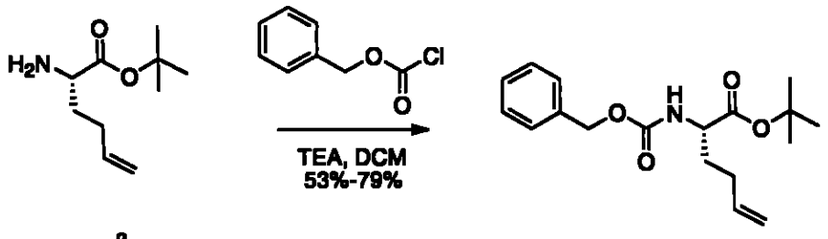
1 2

To a stirred solution of N-(Diphenylmethylene) glycine t-butyl ester 1 (3.0 g, 10.1 mmol) and chiral catalyst O-Allyl-N-(9-anthracenylmethyl)-cinchonidium bromide (613 mg, 1.0 mmol) in dry DCM (30 mL) was added cesium hydroxide (17 g, 101 mmol). The reaction was cooled to -78°C in a dry ice acetone bath and 4-bromo-1-butene was added dropwise. After addition the reaction was stirred vigorously under N_2 at -48°C for 48 hours. Ethyl ether was added followed by H_2O. The organic layer was seperated and washed 2x with H_2O, 1x brine, dried with $MgSO_4$ and concentrated. The product was purified by SiO_2 chromatography over a gradient of 0-10% EtOAc in Hexanes to give 2 in 65% yield.



2 3

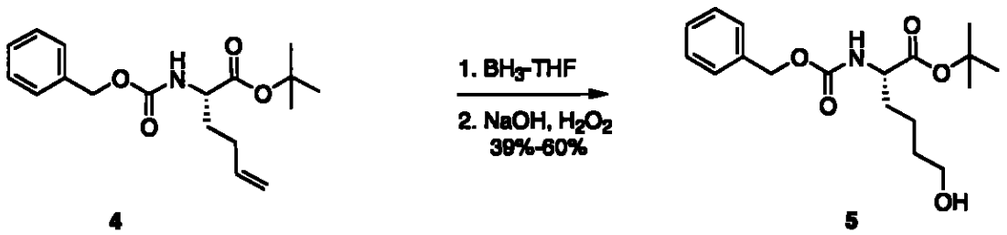
To a stirred solution of 2 (1.52 g, 4.3 mmol) in dry MeOH (50 mL) was added NaOAc (720 mg, 8.6 mmol) and NH_2OH·HCl (540 mg, 7.6 mmol). Stirred under N_2 at room temperature for 2 hours. DCM and 0.1 N NaOH were added. The aqueous layer was separated and extracted 3x with DCM, dried with Na_2SO_4 and the DCM fractions were combined and concentrated. The product was purified by SiO_2chromatography, 0-10% MeOH in DCM with 0.05% TEA to give 3 in 70% yield.



3 4

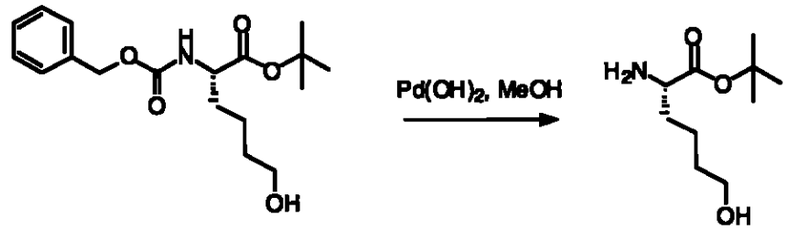
To a solution of 3 (610 mg, 3.3 mmol) in dry DCM (20 mL) was added triethylamine (550 µL, 3.9 mmol) and benzyl chloroformate (550 µL, 3.9 mmol). The reaction was stirred at room

temperature for 2 hours. The solution was concentrated and purified by SiO_2 chromatography over a gradient of 0-30% EtOAc in Hexanes to give 4 in 66% yield.



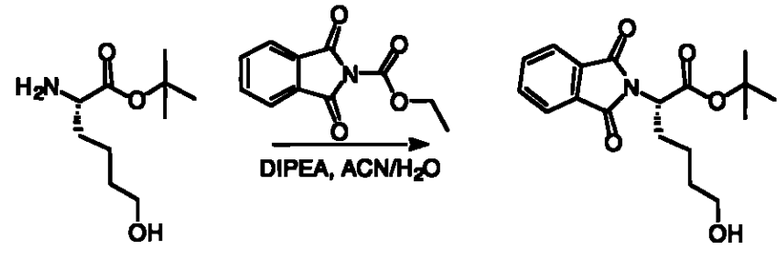
4 5

To a stirred solution of 4 (577 mg, 1.8 mmol) in THF (20 mL) under N_2 was added BH_3·THF. After 1 hour 3 N NaOH (300 µL, 0.9 mmol) and H_2O_2 (306 µL, 2.7 mmol) was added. The reaction was stirred overnight and subsequently diluted with H_2O, extracted 2x with ethyl ether, dried with $MgSO_4$ and concentrated. The product was purified by SiO_2 chromatography over a gradient of 10-45% EtOAc in Hexanes to give 5 in 50% yield.



5 6

To a stirred solution of 5 (71 mg, 0.21 mmol) in MeOH (2 mL) under 1 atm H_2 10% palladium hydroxide on carbon (30 mg) was added. The reaction was complete after 30 minutes. The reaction was filtered over Celite and concentrated to give 6 in quantitative yield.



6 7

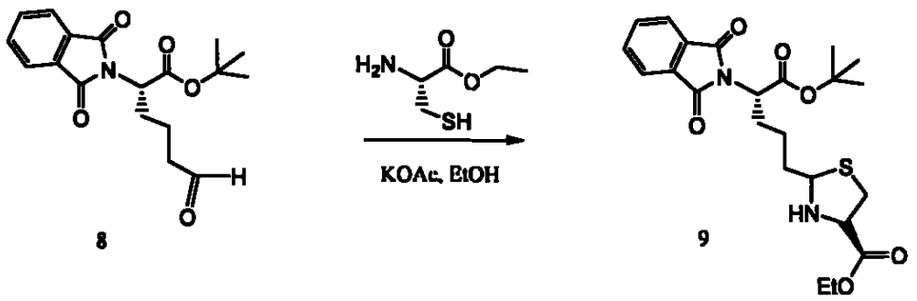
To 6 (42 mg, 0.21 mmol) in ACN (2 mL) carbethoxyphthalimide (50 mg, 0.23 mmol) was added with DIPEA (40 µL, 0.23 mmol) and stirred at room temperature for 2 hours. H_2O (1 mL) was added and stirred for an additional 10 minutes. The ACN was evaporated off and DCM and 10%

citric acid were added. The aqueous layer was seperated and extracted 3x with DCM, the DCM portions were combined, dried with Na_2SO_4, and concentrated to give 7 in 95% yield.



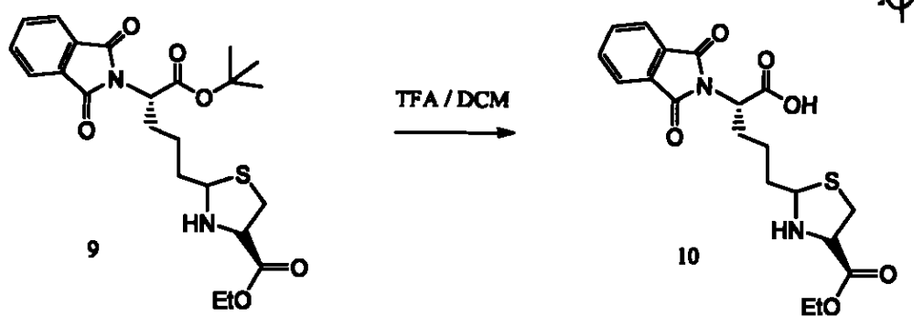
7 8

Oxalyl chloride (561 µL, 6.60 mmol) was dissolved in DCM (35 mL), cooled to -78°C, stirred for 5 minutes followed by addition of a solution of dimethylsulfoxide (870 µL, 12.3 mmol) in DCM (2.5 mL). After stirring for 5 minutes 7 (1.05 g, 3.15 mmol) in dichloromethane (20 mL) was added followed by triethylamine (2.37 mL, 17.0 mmol). The reaction was slowly warmed to room temperature. DCM and H_2O were added, the aqueous layer seperated and extracted 2x with DCM. The DCM portions were combined, filtered through Na_2SO_4, and concentrated to give 8 in 95% yield.

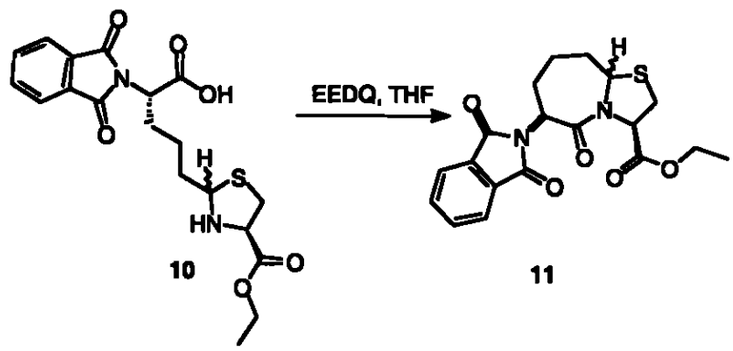


8 9

L-cysteine ethyl ester hydrochloride (643 mg, 3.5 mmol) and potassium acetate (343 mg, 3.5 mmol) were dissolved in stirring EtOH (13 mL), and cooled to 0°C in an ice water bath. Compound 8 was dissolved in EtOH (13 mL) and added. The reaction was stirred at 0°C for 4 hours, LCMS confirmed the conversion of 8 into two diastereomeric products. The reaction was filtered, EtOH evaporated, redissolved in DCM and washed with brine, dried with $MgSO_4$ and concentrated to give a 1:1 mixture of diastereomers 9 in quantitative yield.

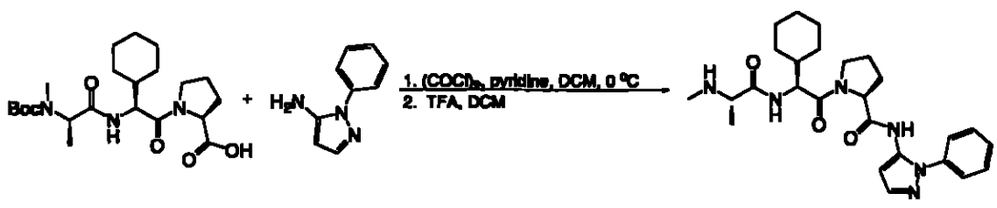


The diastereomers were redissolved in 1:1 TFA:DCM (10 mL) and stirred for 1 hour at room temperature. LCMS showed complete conversion to **10** . The reaction was concentrated to give **10** in 95% yield for the two diastereomers.



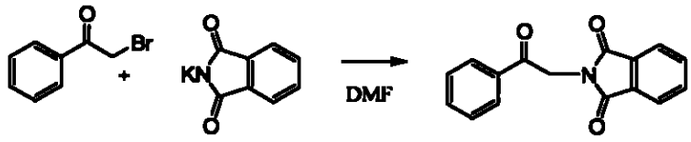
To a stirred solution of **10** (675 mg, 1.67 mmol) in THF (20 mL), EEDQ (619 mg, 2.50 mmol) was added. Stirred at room temperature for 2 days. The THF was removed under reduced pressure, the product redissoved in EtOAc. The organic layer was washed with 0.5 N HCl, 0.5% $NaHCO_3$, H_2O, brine. The EtOAc solution was dried with $MgSO_4$ and concentrated. The product was purified via reverse phase HPLC 10-70% ACN in H_2O to give two diastereomers *11*, 20% yield for diastereomer 1 and 18% yield for diastereomer 2.

Example 2 1-[2-Cyclohexyl-2-(2-methylamino-propionylamino)-acetyl]-pyrrolidine-2-carboxylic acid (2-phenyl-2H-pyrazol-3-yl)-amide



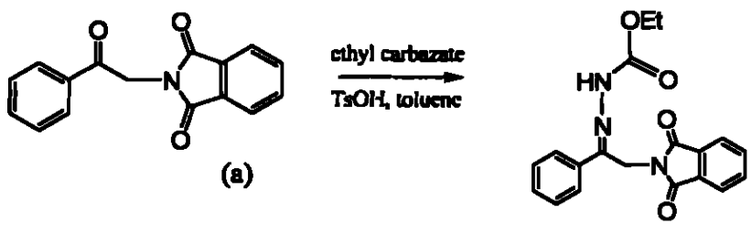
A solution of Boc-MeAla-Chg-Pro-OH (47.0 mg, 0.107 mmol) and pyridine (26 µl, 0.32 mmol) in anhydrous dichloromethane (300 µl) was cooled to 0°C and a solution of oxalyl chloride in dichloromethane (54 µl, 2.0 M, 0.11 mmol) was added dropwise over 10 minutes. The mixture was stirred at 0°C for 15 minutes, then at ambient temperature for 45 minutes, and a solution of 5-amino-1-phenylpyrazole (15.9 mg, 0.100 mmol; TCI America catalog # A0174) and pyridine (15.5 µl, 0.191 mmol) in dichloromethane (0.5 ml) was added. The resulting mixture was stirred at ambient temperature for 16 hours, diluted with dichloromethane to 20 ml, and washed with 0.2 N aqueous sodium hydroxide (20 ml). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 60% ethyl acetate in hexanes, then 100% ethyl acetate) to yield a yellow oil: *m/z* 581 ($M+H^+$). The oil was treated with 5% trifluoroacetic acid in dichloromethane (2 ml), and after 18 hours the solvent was removed *in vacuo*. The resulting oil (29.3 mg, 57% yield over 2 steps) was further purified by reversed-phase HPLC to yield the product (TFA salt, 9.6 mg, 15% yield): *m/z* 481 ($M+H^+$), 503 ($M+Na^+$).

Example 3 4-Phenyl-[1,2,3]thiadiazol-5-ylamine



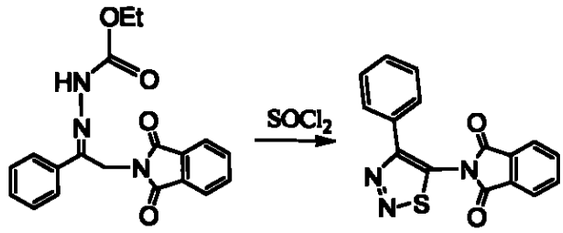
(a)

2-bromoacetophenone was dissolved in DMF (3 vol) and potassium phthalimide (1.leq.) was added. The reaction, initially mildly exothermic, was stirred overnight at room temperature. The DMF was removed in vacuo and the reaction was diluted with DCM (~3 vol) followed by 0.1N NaOH (~3 vol; 1:1 aq/org) and stirred vigorously then extracted. The organic layer, containing some solid material, was concentrated in vacuo and the resulting solid was slurried in diethyl ether and collected by suction filtration to give (a) as a white crystalline solid in ~95% yield.



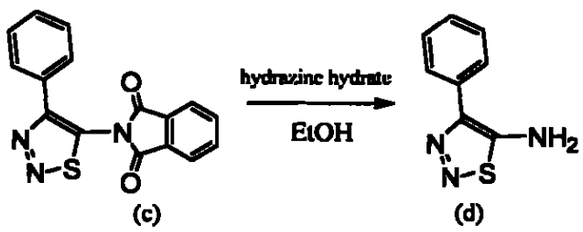
(a) (b)

Compound (a), ethyl carbazate (1.5eq) and TsOH-H,O (0,1eq) were combined in toluene (5 vol) and heated to reflux using a Dean-Stark trap to remove water. The solution turned a dark red color and was complete by TLC in ~2hrs. Approximately half of the toluene was removed by distillation, the solution was cooled to r.t. and concentrated in vacuo. The resulting solid was slurried in EtOH (the minimum volume necessary for stirring), heated to reflux for 30 min and then cooled on ice to facilitate precipitation of both isomers. The solid was collected by suction filtration, washed with cold EtOH and dried under vacuum to give both isomers of compound (b) as an off-white solid in ~90% yield.



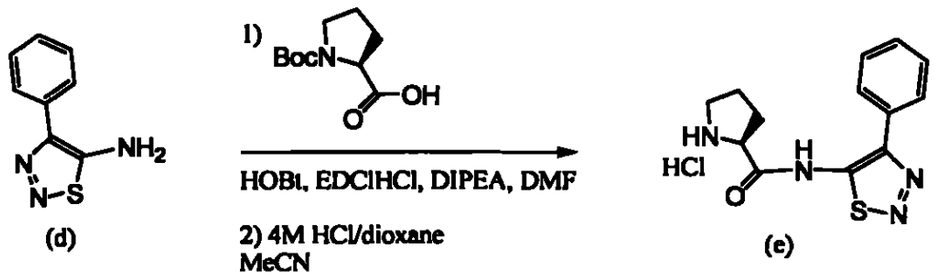
(b) (c)

To ice-cooled thionyl chloride (4eq, ~0.85 vol) was added, portion-wise (in order to control the exotherm), the isomer mixture of (b). The ice bath was removed and the reaction warmed to r.t and stirred overnight. Thionyl chloride was removed in vacuo, DCM (1 vol) was added and the reaction was stirred with 0.1M NaOH (1 vol; 1:1 aq/org). The suspension was extracted and the organics were concentrated in vacuo, slurried in refluxing EtOAc (the minimum volume necessary for easy stirring) for 30 min, cooled to r.t., collected by suction filtration and washed with a minimum of cold EtOAc to give (c) as an off-white crystalline solid in ~80% yield.



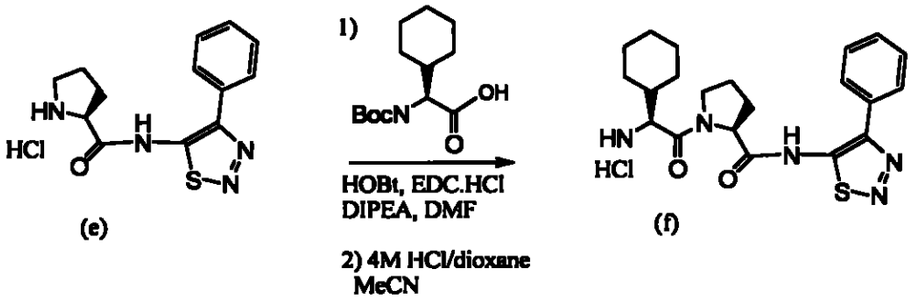
A solution of hydrazine hydrate (2.4eq) in EtOH (1 vol) was added dropwise to a refluxing solution of (c) in EtOH (8 vol). A precipitate formed almost immediately and the reaction was completed by TLC in ~3hrs. The solution was cooled to r.t. and the phthalimide cleavage by-product was filtered away and washed with DCM. The EtOH/DCM filtrate was concentrated in vacuo until crystal formation was observed. This suspension was stirred overnight and the crystalline/solid mixture was collected by suction filtration and washed with cold EtOH until colored impurities were removed, giving the thiadiazole amine (d) in ~75% yield as an off-white crystalline solid.

Example 4 1-[2-Cyclohexyl-2-(2-methylamino-propionylamino)-acetyl]-pyrrolidine-2-carboxylic acid (4-phenyl-[1,2,3]thiadiazol-5-yl)-amide

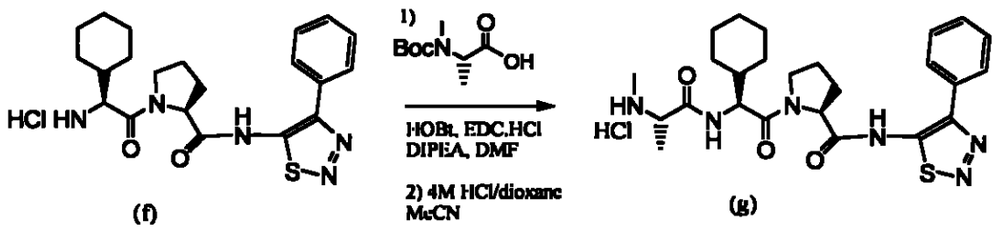


Boc-L-Pro (2eq), HOBt (1.9eq), EDC-HCl (1.9eq) and DIPEA (5eq) were dissolved in DMF (10-15 vol). To this was then added the thiadiazole amine (d). The reaction, initially mildy exothermic, was heated to 75°C and stirred overnight, cooled to room temperature and the DMF was partially removed in vacuo. Dilution with EtOAc (10-15 vol) was followed by washing with 1M HCl (2x), $NaHCO_3$ (1 x), and brine (1x) (1:1 aq/org). The organic layer was concentrated in vacuo and the resulting solid was slurried in refluxing MeCN (a minimum volume necessary for easy stirring) for 30min and then cooled to r.t. Suction filtration gave Boc-protected conjugation product as an off-white crystalline solid in ~77% yield. The Boc-protected product was suspended in a solution of 4M HCl/dioxane (4-5eq acid) and MeCN (1 vol eq to the dioxane solution) and stirred at r.t. until

LCMS indicated complete deprotection, ~1hr. The reaction mixture was concentrated in vacuo and the resulting solid was vigorously slurried in refluxing MeCN (a minimum volume necessary for easy stirring), cooled to r.t., and the solid collected by suction filtration and washed with cold MeCN until residual color was removed from the cake to yield the HCl salt (e) as an off-white solid in approximately quantitative yield.



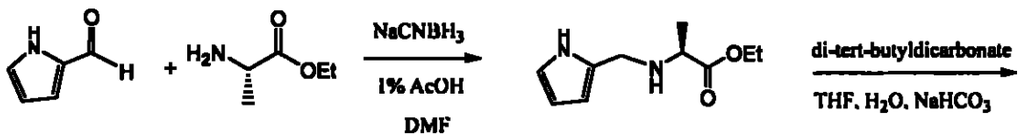
The HCl salt (e) was dissolved in DMF (10-15 vol) and DIPEA (5eq). To this was added the Boc-L-Chg (1.5eq), HOBt (1.4eq) and EDC-HCl (1.4eq). Coupling was complete after ~2hrs by LCMS. The reaction was diluted with EtOAc (15 vol) and washed with 1M HCl (2x), $NaHCO_3$ (1x), and brine (1x) (1:1 aq/org). The organic extract was dried over sodium sulfate and concentrated in vacuo. The resulting solid is slurried in EtOH/Hexane (20:80) (a minimum volume necessary for easy stirring) and filtered to give Boc-protected conjugate product as a fluffy white solid in ~80% yield. The Boc-protected was dissolved in a solution of 4M HCl/dioxane (4-5eq acid) and MeCN (0.25 volume eq to the dioxane solution) and stirred at r.t. until LCMS indicated complete deprotection, ~1 hr. The reaction was concentrated to dryness with toluene (2x) (the same volume as the deprotection solution) to yield the HCl salt (f) as a white crystalline solid in approximately quantitative yield.

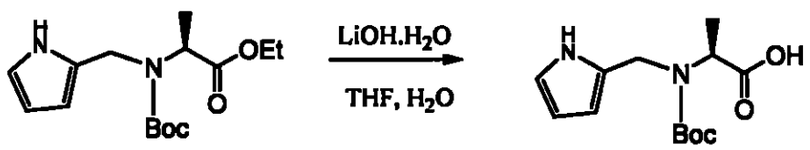


The HCl salt (f) was dissolved in DMF (10-15 vol) and DIPEA (5eq). To this was added the Boc-L-N-methyl Ala (1.5eq), HOBt (1.4eq), and EDC-HCl (1.4eq). Coupling was complete after ~1hr by LCMS. The reaction was diluted with EtOAc (15 vol) and washed with 1M HCl (2x), $NaHCO_3$ (1x), and brine (1x) (1:1 aq/org). The organic extract was dried over sodium sulfate and concentrated in vacuo to give the Boc-protected conjugate product as a beige, foamy solid in ~85% yield. The Boc-protected conjugate was dissolved in a solution of 4M HCl/dioxane (4-5eq acid) and MeCN (0.25 volume eq to the dioxane solution) and stirred at r.t. until LCMS indicated complete deprotection, ~1hr. The reaction was concentrated to dryness with toluene

(2x) (same volume as deprotection solution) and the resulting solid was slurried in a solution of MTBE/EtOAc (70:30) (minimal volume necessary for easy stirring), filtered and collected to yield crude (g) as an off-white free-flowing solid. The crude HCl salt (g) was suspended in MeOH (4 vol minimum) and dissolved with stirring at 65°C. Warm Isopropyl Acetate (6-8 vol) is added in two portions, keeping the temperature at approx. 60°C, and the solution was allowed to cool with stirring. Crystallization took place rapidly, the suspension was stirred at room temperature for several hours, then stirred at 0°C for an hour before the solid was collected by suction filtration, washed with MeOH/iPrOAc (1:4, 2 vol) and dried to yield final the product as a white/off-white crystalline solid in ~80% yield from (f).

Example 5 2-[tert-butoxycarbonyl-(1H-pyrrol-2-ylmethyl)-amino]-propionic acid





Alanine ethyl ester (5g, 32.5mmol), pyrrole-2-carboxaldehyde (3.1g, 32.5mmol), sodium cyanoborohydride (2.04g, 32.5mmol) and AcOH (1%) were mixed in DMF and stirred overnight. The reaction was quenched with H_2O, and DMF was evaporated. The mixture was diluted with EtOAc, washed by 0.1N NaOH, dried and concentrated to yield product 2.5g. The resulting ester (2.5g, 12.8mmol), di-tert-butyldicarbonate (3.06g, 14mmol) were mixed in THF, H_2O with $NaHCO_3$ and stirred overnight. THF was evaporated, and the mixture was diluted with EtOAc, washed by 1N NaOH, sat. NH_4Cl and brine. After dried, the mixture was concentrated to yield the Boc-protected ester 3.3g. The Boc-protected ester (1.67g, 5.6mol), lithium hydroxide mono hydrate (284mg, 6.77mmol) were mixed in THF and H_2O at 0°C. THF was vacuumed off, and the solution was acidified by dilute H_2SO_4, extracted by EtOAc twice. Organic layers were combined, dried and evaporated.

Example 6 tetrahydropyranylglycine

Tetrahydropyranylglycine was purchased from NovaBiochem, or synthezed according to the literature: Ghosh, A. K.; Thompson, W. J.; holloway, M. K.; McKee, S. P.; Duong, T. T.; Lee, H. Y.; Munson, P. M.; Smith, A. M.; Wai, J. M; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleife, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem*, 1993, *36*, 2300-2310.

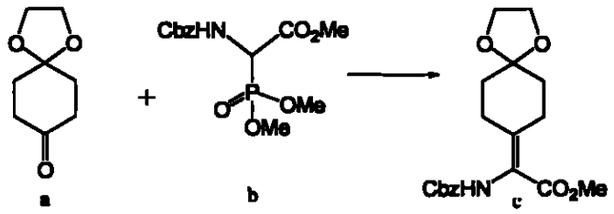
Example 7 piperidinylglycine

Piperidinylglycine was synthesized according to the literature: Shieh, W-C.; Xue, S.; Reel, N.; Wu. R.; Fitt, J.; Repic, O. *Tetrahedron: Asymmetry*, 2001, *12*, 2421-2425.

Example 8 4,4-difluorocyclohexylglycine

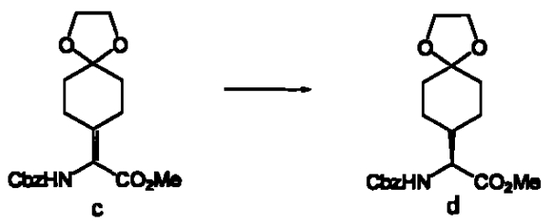
4,4-difluorocyclohexylglycine was made according to the procedures described in US 2003/0216325.

Example 9 Boc (S)-2-amino-2-(4-hydroxycyclohexyl)acetic acid



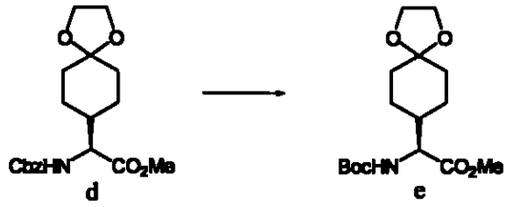
a b c

Following the procedure of Sheih, (*Tetrahedron: Asymmetry*, 2001, *12*, 2421-2425), a solution of ketone **a** (8.4 g) and EtOAc (30 mL) was added to a solution of *N*-Cbz-phosphonoglycine methyl ester **b**, TMG (4.5 mL) and EtOAc (30 mL). The solution was maintained at rt for 48h, then washed with 1N HCl (3x50 mL), brine (1x50 mL) dried (Na_2SO_4), filtered, and concentrated. The residue was adsorbed onto Celite, and purified by chromatography, then further purified by re-crystalization from EtOAc/hexanes to afford 5.2 g of product **c**.

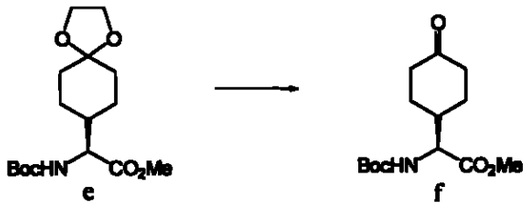


c d

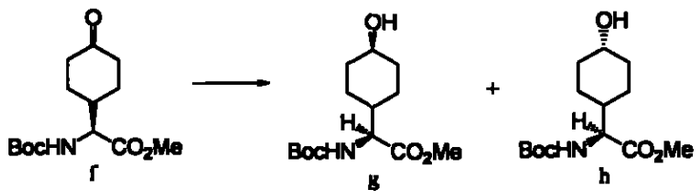
Following the procedure of Sheih, (*Tetrahedron: Asymmetry*, 2001, *12*, 2421-2425), a solution of enecamide c (5.0 g), (S,S)-Me-BPE-Rh(I) (1.5g, Strem Chemicals, Newburyport, MA), and MeOH (100 mL) was shaken virgorously under 70psi of H_2 for 48h. The solvent was removed under reduced pressure. The residue was taken up in EtOAc, and filtered through SiO_2 with more EtOAc. The solvent was removed under reduced pressure to afford 4.0g of product d as a colorless solid.



A mixture of Cbz-carbamate d, (4.0g) Boc_2O, (2.9g), 20% $Pd(OH)_2$•C (1.0g) and MeOH (30 mL) was maintained under an atmosphear of H_2 for 6h. The mixture was filtered through Celite with MeOH. The solvent was removed under reduced pressure to afford 4.5 g of residue e, which was taken on directly.

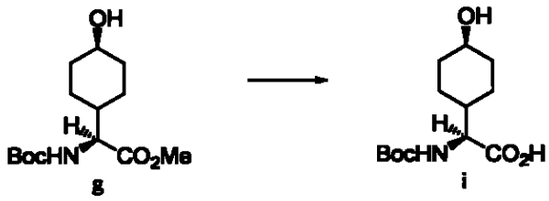


The residue e from above was dissolved in H_2O (10 mL), AcOH (30 mL), THF (5 mL), and dichloroacetic acid (3 mL) and maintained at rt overnight. Water (5 mL) was added and the solution and maintaned until hyrolysis was complete, as monitored by HPLC-MS. Solid Na_2CO_3 was added cautiously until gas evolution ceased, the mixture was diluted with aq $NaHCO_3$, and extracted with 10%EtOAc/DCM. The combined organic phases were washed once with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography to afford 2.9g of product f.



A mixture of ketone f (1.5g) MeOH (50 ml) was treated with NaBH4 (290 mg) at 0 °C for 20 min. The mixture was acidifed to ~pH1 with 10%aq citric acid and the MeOH was removed under reduced pressure. The residue was diluted with water and extraced with 20%EtOAc/DCM. The

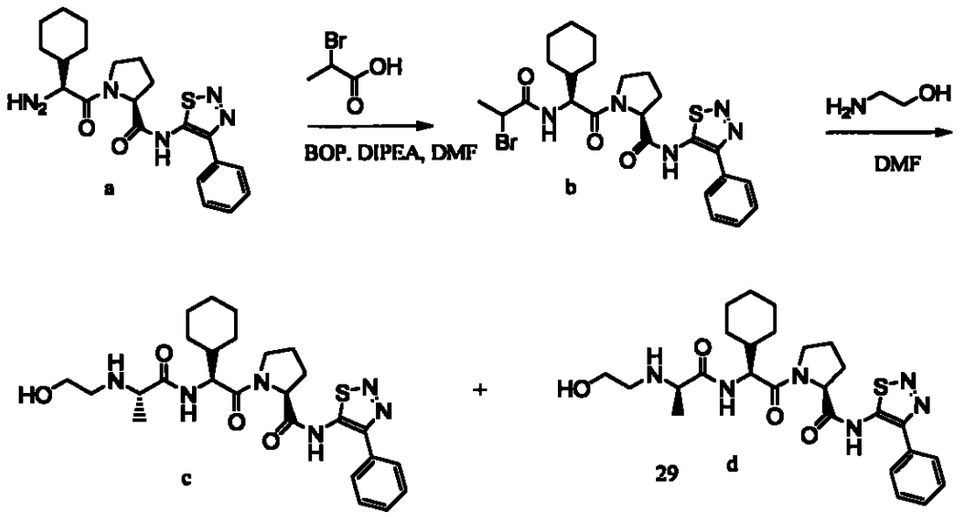
combined organic phases were washed once with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography to afford 1.17g of product g and 0.23g of product h.



g i

A mixture of ester g (1.17g) LiOH•H2O (160mg), THF (3 mL) and water (4.5 mL) was stirred vigorously at rt overnight. The mixture was diluted with brine and exaustivly extraced with EtOAc. The combined organic phases were washed once with brine, dried (Na_2SO_4), filtered, and concentrated to afford acid i (525mg).

Example 10 compound 29

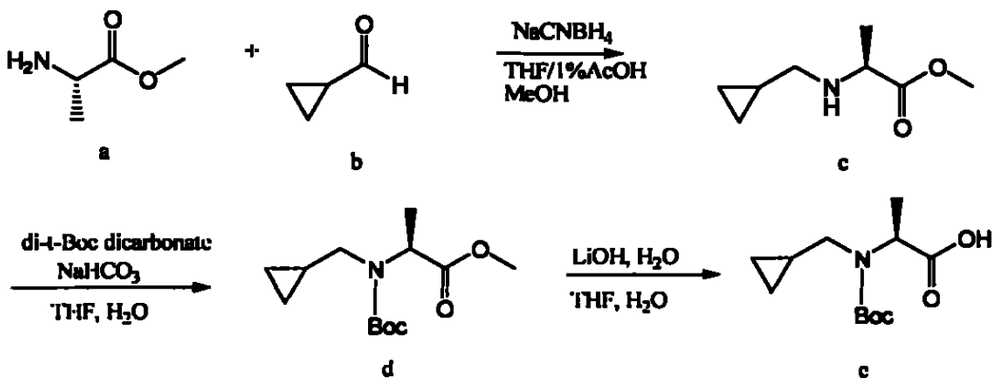


a b c 29 d

A mixture of amine a (1.56 mmol), 2-Bromopropionic acid (0.72g, 4.68mmol), BOP (2.1g, 4.68mmol) and DIPEA (1.6ml, 9.36mmol) in 10ml DMFwas stirred at room temperature for 2 hours. LCMS analysis indicated reaction completed. 100 ml EtOAc was added to the reaction and organic layer was washed with sat. $NaHCO_3$ followed by brine, dried over Na_2SO_4 and concentrated to dryness. The crude material was purified by chromatography using 50% EtOAc/hexane to obtain compound b.

The compound b (0.832g, 1.5mmol) was treated with ethanolamine (200ul, 2.73mmol) in 3 ml DMF and stirred overnight for completion. The reaction mixture was purified by reverse phase HPLC to obtain two diastereomers c (53mg) and d (compound 29) (150mg).

Example 11 N-Boc-N-cyclopropylmethyl-L-alanine

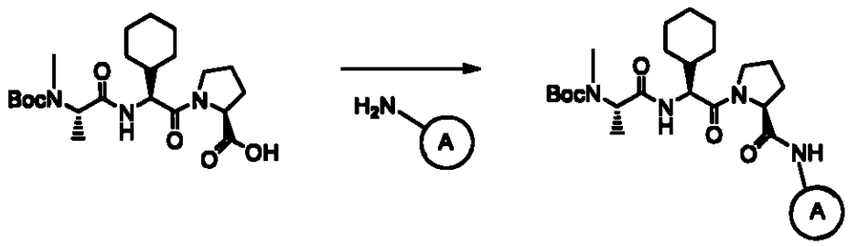


a b c d e

L-alanine methyl ester hydrochloride a (5g, 35.8mmol) and cyclopropanecarboxaldehyde b (2.67ml, 35.8mmol) were suspended in 50ml THF w/1% AcOH. Addition of 5ml of CH_3OH made the cloudy solution turned to clear. $NaCNBH_4$ (2.25g, 35.8mmol) was added and the reaction mixture stirred overnight. The reaction was quenched by addition of 1N aq. NaOH, extracted by EtOAc twice, organic layers were dried over Na_2SO_4 and concentrated to dryness. The crude material was purified by chromatography using 30% EtOAc/hexane (stained by ninhydrin) to obtain the compound c (1g, 18%).

The compound c (1g, 6.37mmol) and di-t-bocdicarbonate (2.1g, 9.55mmol) were diluted in THF (20ml) and H_2O (20ml), $NaHCO_3$ (1.3g, 15.9mmol) was added. The reaction mixture stirred overnight for completion. THF was removed under reduced pressure, and the aqueous layer was extracted by EtOAc 3 times. Combined organic layers were washed by 1N NaOH, sat, NH_4Cl followed by brine, the concentrated to dryness. The Boc-protected compound d (1.39g, 5.40mmol) was stirred with $LiOH.H_2O$ (1.14g, 27mmol) in THF (20ml) and H_2O (20ml) overnight at room temperature. THF was stripped off, and the aqueous layer was adjusted to pH=4 by adding 10% citric acid, then extracted by EtOAc 3 times. Combined organic layers were washed by brine and concentrated. The crude was purified by reverse phase C-18 column eluted by 0%-50% acetonitrile/H_2O to give pure compound e as a white solid (794mg).

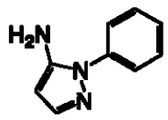
Example 12 acid fluoride coupling procedure



A solution of Boc-MeAla-Chg-Pro-OH (2.3 mmol) and pyridine (6.9 umol) in anhydrous dichloromethane (23 ml) was cooled to 0°C and cyanuric fluoride (2.3 mmol) added dropwise over 30 sec. The mixture was stirred at 0°C for 15 min, at ambient temperature for 5 hr, and then quenched with water. The mixture was extracted three times with dichloromethane (total 100 ml), and the combined organic phases washed with brine and dried over anhydrous sodium sulfate. Filtration and concentration *in vacuo* yielded the peptide acid fluoride as a clear, colorless oil used directly without further purification.

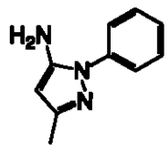
A solution of the crude acid fluoride (0.50 mmol) and pyridine (1.5 mmol) in dichloromethane (2.5 ml) was added to the solid amine (0.50 mmol), and the resulting mixture stirred either at ambient temperature or at 50°C (sealed vessel). The mixture was poured into aqueous sodium bicarbonate and the extracted three times with dichloromethane (total 100 ml). The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude peptide amide was used directly without further purification.

Example 13 1-phenyl-1H-pyrazol-5-amine



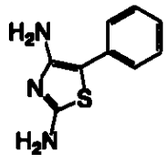
1-phenyl-1H-pyrazol-5-amine is commercially available from TCI America (catalog# A0174).

Example 14 3-methyl-1-phenyl-1H-pyrazol-5-amine



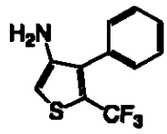
3-methyl-1-phenyl-1H-pyrazol-5-amine is commercially available from TCI America (catalog# A1311).

Example 15 5-phenylthiazole-2,4-diamine



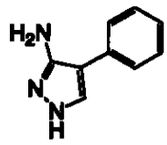
5-phenylthiazole-2,4-diamine is commercially available from Acros Organics (catalog# 11234-0010).

Example 16 5-(trifluoromethyl)-4-phenylthiophen-3-amine



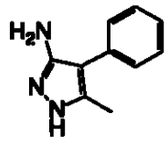
5-(trifluoromethyl)-4-phenylthiophen-3-amine is commercially available from Acros Organics (catalog# SEW03133DA).

Example 17 4-phenyl-1H-pyrazol-3-amine



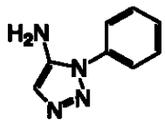
4-phenyl-1H-pyrazol-3-amine was prepared according to the procedures described in E. L. Anderson *et al.*; *J. Med. Chem.*, 1964, *7*, 259-268.

Example 18 5-methyl-4-phenyl-1H-pyrazol-3-amine



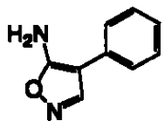
5-methyl-4-phenyl-1H-pyrazol-3-amine was prepared according to the procedures described in E. L. Anderson *et al.*; *J. Med. Chem.*, 1964, *7*, 259-268.

Example 19 3-phenyl-3H-1,2,3-triazol-4-amine

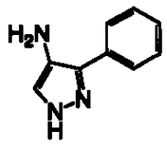


3-phenyl-3H-1,2,3-triazol-4-amine was prepared according to the procedures described in K. M. Baines, T. W. Rourke, K. Vaughan; *J. Org. Chem.*, 1981, *46*, 856-859.

Example 20 4-phenylisoxazol-5-amine



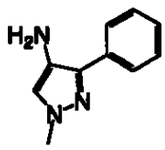
4-phenylisoxazol-5-amine was prepared according to the procedures described in H. Peeters, W. Vogt; EP 43024.



Example 21 3-phenyl-1H-pyrazol-4-amine

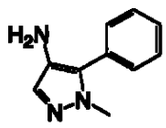
3-phenyl-1H-pyrazol-4-amine was prepared according to the procedures described in C. Chen, K. Wilcoxen, J. R. McCarthy; *Tetrahedron Lett.*, 1988, *39*, 8229-8232.

Example 22 1-methyl-3-phenyl-1H-pyrazol-4-amine



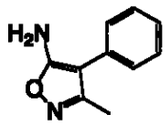
1-methyl-3-phenyl-1H-pyrazol-4-amine was prepared according to the procedures described in C. Chen, K. Wilcoxen, J. R. McCarthy; *Tetrahedron Lett.*, 1988, *39*, 8229-8232.

Example 23 1-methyl-5-phenyl-1H-pyrazol-4-amine



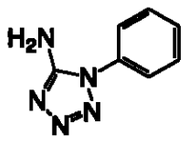
1-methyl-5-phenyl-1H-pyrazol-4-amine was prepared according to the procedures described in C. Chen, K. Wilcoxen, J. R. McCarthy; *Tetrahedron Lett.*, 1988, *39*, 8229-8232.

Example 24 3-methyl-4-phenylisoxazol-5-amine

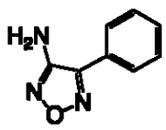


3-methyl-4-phenylisoxazol-5-amine was prepared according to the procedures described in H. Peeters, W. Vogt; EP 43024.

Example 25 1-phenyl-1H-tetrazol-5-amine

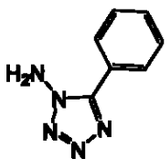


1-phenyl-1H-tetrazol-5-amine was prepared according to the procedures described in R. A. Batey, D. A. Powell; *Org. Lett.*, 2000, *2*, 3237-3240.

Example 26 4-phenyl-1,2,5-oxadiazol-3-amine 

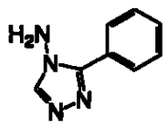
4-phenyl-1,2,5-oxadiazol-3-amine was prepared according to the procedures described in R. Lakhan, O. P. Singh; *Ind. J. Chem.*, 1987, *26B*, 690-692.

Example 27 1-amino-5-phenyl-1H-tetrazole



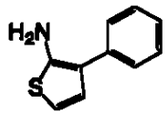
1-amino-5-phenyl-1H-tetrazole was prepared according to the procedures described in T. L. Gilchrist, G. E. Gymer, C. W. Rees; *J. Chem. Soc., Perkin Trans. 1*, 1975, 1747-1750.

Example 28 4-amino-3-phenyl-4H-1,2,4-triazole



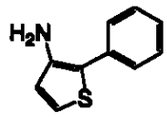
4-amino-3-phenyl-4H-1,2,4-triazole was prepared according to the procedures described in A. A. Ikizler, N. Yildirim; *J. Heterocyclic Chem.*, 1998, *35*, 377-380.

Example 29 3-phenylthiophen-2-amine



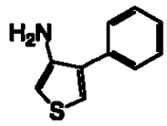
3-phenylthiophen-2-amine was prepared according to the procedures described in Y. Yoshikawa *et al.*; EP 737682 (US 5747518).

Example 30 2-phenylthiophen-3-amine



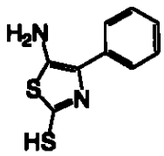
2-phenylthiophen-3-amine was prepared according to the procedures described in Y. Yoshikawa *et al.*; EP 737682 (US 5747518).

Example 31 4-phenylthiophen-3-amine



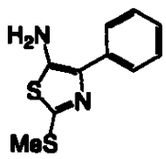
4-phenylthiophen-3-amine was prepared according to the procedures described in G. Kirsch, D. Cagniant, P. Cagniant; *J. Heterocyclic Chem.*, 1982, *19*, 443-445.

Example 32 5-amino-4-phenylthiazole-2-thiol



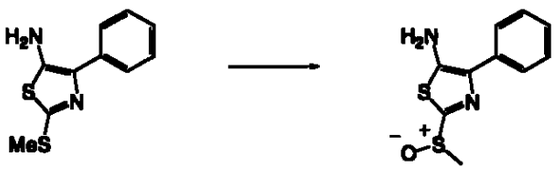
5-amino-4-phenylthiazole-2-thiol was prepared according to the procedures described in A. H. Cook, I. Heilbron, A. L. Levy; *J. Chem. Soc.*, 1947, 1598-1609.

Example 33 2-(methylthio)-4-phenylthiazol-5-amine



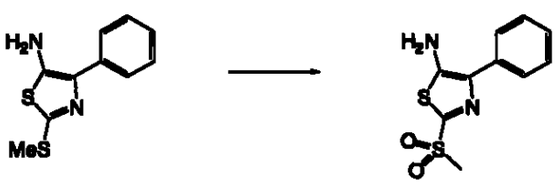
2-(methylthio)-4-phenylthiazol-5-amine was prepared according to the procedures described in A. H. Cook, I. Heilbron, A. L. Levy; *J. Chem. Soc.*, 1947, 1598-1609.

Example 34 5-amino-2-(methylsulfinyl)-4-phenylthiazole



To 5-amino-2-(methylsulfanyl)-4-phenylthiazole (305 mg, 1.37 mmol) in acetic acid (3.0 ml) was added aqueous hydrogen peroxide (660 µl, 30% wt, 6.9 mmol) dropwise at ambient temperature. After 4 hr the mixture was partitioned between dichloromethane (60 ml) and water (60 ml). The organic phase was separated, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography on silica gel (ethyl acetate/hexanes) yielded pure 5-amino-2-(methylsulfinyl)-4-phenylthiazole (285 mg, 87%).

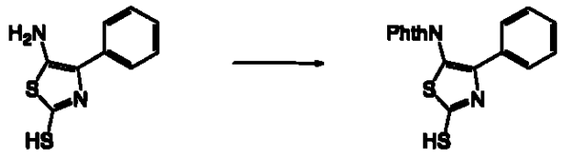
Example 35 5-amino-2-(methylsulfonyl)-4-phenylthiazole



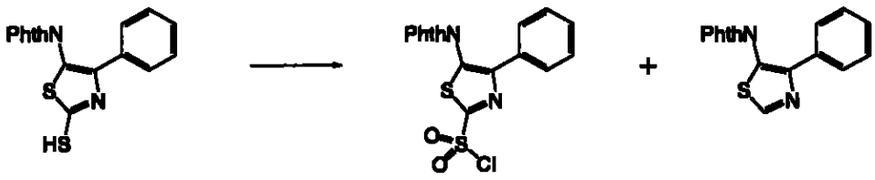
77

To 5-amino-2-(methylsulfanyl)-4-phenylthiazole (302 mg, 1.36 mmol) in dichloromethane (5.0 ml) was added portionwise 3-chloroperbenzoic acid (638 mg, 77% wt, 2.9 mmol) with cooling to 0°C. The mixture was diluted with dichloromethane (3.0 ml) and after 5 min allowed to warm to ambient temperature. After 3 hr a further quantity of 3-chloroperbenzoic acid (305 mg, 77% wt, 1.4 mmol) was added portionwise. After 20 hr the mixture was treated with sodium thiosulfate (2 ml, 1.0 M), poured into saturated aqueous sodium bicarbonate and extracted three times into dichloromethane (total 100 ml). The combined organic phases were washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate and concentrated *in vacuo* to give a dark brown foam. Flash chromatography on silica gel (ethyl acetate/hexanes) yielded pure 5-amino-2-(methylsulfonyl)-4-phenylthiazole (90 mg, 26%).

Example 36 *5-amino-2-(aminosulfonyl)-4-phenylthiazole and 5-amino-4-phenylthiazole*

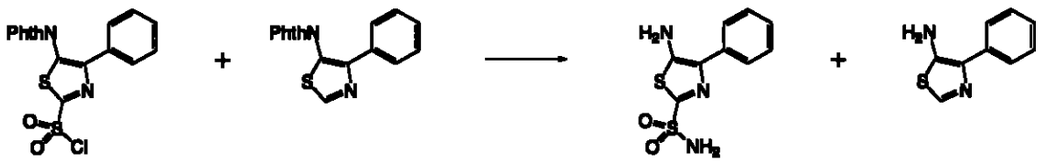


5-Amino-2-mercapto-4-phenylthiazole (1.01 g, 4.83 mmol) and phthalic anhydride (716 mg, 4.84 mmol) in acetic acid (20 ml) were heated at 100°C for 64 hr and allowed to cool. The mixture was diluted into cold water (150 ml) and the precipitate collected by filtration, washed with water (50 ml) and dried under high vacuum (1.46g, 90%). The phthalimide is contaminated with a minor quantity of disulfide but used without further purification.



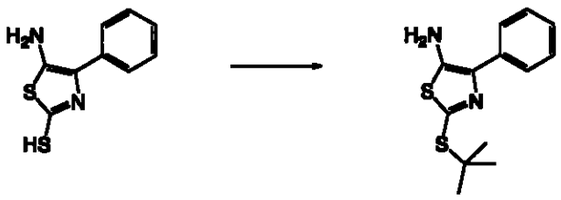
2-Mercapto-4-phenyl-5-phthalimido-thiazole (203 mg, 600 µmol) in acetic acid (4.5 ml) and water (0.5 ml) at 0°C was treated with N-chlorosuccinimide (243 mg, 1.82 mmol) in one portion. The mixture was stirred at 0°C for 10 min, allowed to warm to ambient temperature for 1 hr and then partitioned between dichloromethane (50 ml) and water (50 ml). The aqueous phase was extracted twice more with dichloromethane (2 × 25 ml), and the combined organic phases washed with brine

and dried over sodium sulfate. Filtration and concentration *in vacuo* yielded a mixture (231 mg) of 2-(chlorosulfonyl)-4-phenyl-5-phthalimido-thiazole (major component) with 4-phenyl-5-phthalimido-thiazole (ca. 2:1), used without purification.



The crude mixture of sulfonyl chloride with 4-phenyl-5-phthalimido-thiazole (231 mg) in dichloromethane (10 ml) was treated with ammonia in methanol (900 µl, 2.0 M) dropwise at ambient temperature. After 10 min the mixture was concentrated *in vacuo*. The residue was suspended in ethanol (10 ml), treated with ethanolic hydrazine (660 µl, 1.0 M, 660 µmol) and heated to reflux. After 1.5 hr a further portion of ethanolic hydrazine was added (660 µl, 1.0 M, 660 µmol) and reflux continued for 15 hr. The cooled mixture was filtered and concentrated *in vacuo*. Flash chromatography on silica gel (ethyl acetate/hexanes) yielded pure 5-amino-2-(aminosulfonyl)-4-phenylthiazole (56 mg, 36% for 3 steps) and 5-amino-4-phenylthiazole (17 mg, 16% for 3 steps).

Example 37 5-amino-2-(*tert*-butylsulfanyl)-4-phenylthiazole



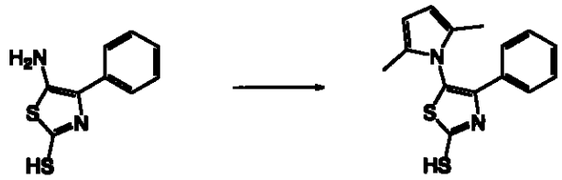
To a suspension of 5-amino-2-mercapto-4-phenylthiazole (210 mg, 1.01 mmol) in water (1.0 ml) and *tert*-butanol (82 mg, 1.1 mmol) was added concentrated sulfuric acid (3.0 ml) with cooling to ca. 20°C. After 1.5 hr at ambient temperature a further portion of *tert*-butanol in water (300 µl, 1.0 M, 300 µmol) was added. After 1.5 hr the mixture was poured into excess aqueous sodium bicarbonate and extracted three times into dichloromethane (total 120 ml). The combined organic phases were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography on silica gel (ethyl acetate/hexanes) yielded 5-amino-2-(*tert*-butylsulfanyl)-4-phenylthiazole (220 mg, 82%).

Example 38 5-amino-2-(*tert*-butylsulfinyl)-4-phenylthiazole

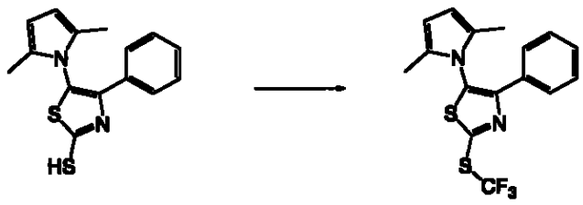


To 5-amino-2-(*tert*-butylsulfanyl)-4-phenylthiazole (102 mg, 385 μmol) in acetic acid (5.0 ml) was added aqueous hydrogen peroxide (218 μl, 30% wt, 1.9 mmol) dropwise at ambient temperature. After 5 hr the mixture was partitioned between dichloromethane (50 ml) and water (50 ml). The aqueous phase was separated and extracted with dichloromethane (20 ml). The combined organic phases were washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered and concentrated *in vacuo* to yield essentially pure 5-amino-2-(*tert*-butylsulfinyl)-4-phenylthiazole (110 mg, quant.).

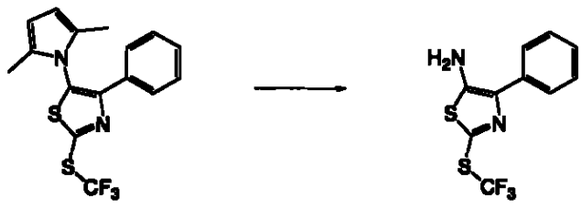
Example 39 5-amino-4-phenyl-2-(trifluoromethylsulfanyl)thiazole



A suspension of 5-amino-2-mercapto-4-phenylthiazole (503 mg, 2.41 mmol) in acetic acid (5.0 ml) was treated with hexane-2,5-dione (290 μl, 2.47 mmol) at ambient temperature for 14 hr and then heated to reflux for 3hr. The mixture became homogeneous at reflux and on cooling deposited a precipitate which was recovered by filtration, washed with acetic acid (3 × 1.0 ml) and dried *in vacuo* to yield the pure pyrrolidino-thiazole (624 mg, 90%) as a bright yellow microcrystalline solid.



A solution of the mercapto-thiazole (201 mg, 701 μmol) and potassium carbonate (291 mg, 2.11 mmol) in DMF (2.0 ml) was saturated with trifluoromethyl iodide by bubbling for 5 min, and the vessel sealed and heated at 50°C for 30 min. The cooled mixture was again saturated with trifluoromethyl iodide, and heated to 100°C for 1.5 hr. The mixture was once more saturated with trifluoromethyl iodide, returned to 100°C (total 24 hr) and allowed to cool. The mixture was poured into water and extracted three times into ethyl acetate (total 100 ml). The combined organic phases were washed with water and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash chromatography on silica gel (ethyl acetate/hexanes) yielded the pure (trifluoromethylsulfanyl)-thiazole (72 mg, 29%) as a colorless crystalline film.

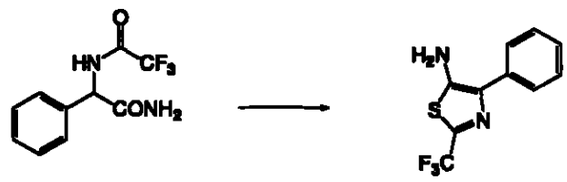


A suspension of the thiazole (72 mg) and hydroxylamine hydrochloride (71 mg, 1.0 mmol) in ethanol (5.0 ml) was heated to reflux for 17 hr, diluted with acetic acid (3 ml), refluxed for a further 2 hr, and concentrated to ca. 3 ml. The cooled mixture was treated with aqueous hydroxylamine (1.0 ml, 50% wt) and returned to reflux for 42 hr. The mixture was treated with water (50 ml) and saturated aqueous sodium bicarbonate (50 ml) and extracted three times into dichloromethane (total 100 ml). The combined organic phases were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography on silica gel (ethyl acetate/hexanes) yielded pure 5-amino-4-phenyl-2-(trifluoromethylsulfanyl)thiazole (12.5 mg, 22%).

Example 40 5-amino-4-phenyl-2-(trifluoromethyl)thiazole

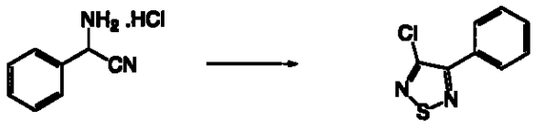


α-Aminophenylacetamide (2.00 g, 13.3 mmol) in methanol (50 ml) at 0°C was treated with ethyl trifluoroacetate (3.2 ml, 27 mmol) for 30 min and allowed to warm to ambient temperature for 18 hr. The mixture was concentrated *in vacuo*, made homogeneous with methanol and again concentrated top yield the pure trifluoroacetamide (3.27g, quant.).



The trifluoroacetamide (881 mg, 3.58 mmol) and Lawesson's reagent (1.45g, 3.59 mmol) were treated together with anhydrous pyridine (7.2 ml) and the mixture heated to 100°C for 20hr. The cooled mixture was poured into saturated aqueous sodium bicarbonate and extracted three times into chloroform (total 120 ml). The combined organic phases were washed with water containing one tenth volume saturated aqueous sodium bicarbonate, and brine, and dried over sodium sulfate. Filtration and concentration *in vacuo* yielded a red-brown oil (829 mg). The crude was treated with aqueous sodium hydroxide (25 ml, 1.0 N) for 15 min and extracted three times into dichloromethane (total 100 ml). The combined organic phases were washed with aqueous sodium hydroxide (25 ml, 1.0 N) and brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography on silica gel (ethyl acetate/hexanes) yielded pure 5-amino-4-phenyl-2-(trifluoromethyl)thiazole (65 mg, 7.5%).

Example 41 3-amino-4-phenyl-1,2,5-thiadiazole

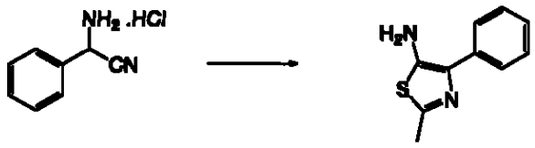


To a solution of sulfur monochloride (24.0 g, 178 mmol) in DMF (30 ml) at 0°C was added α-aminophenylacetonitrile hydrochloride (10.0 g, 59.3 mmol) portionwise over 20 min. After 40 min the mixture was allowed to warm to ambient temperature for 20 min, diluted with DMF (20 ml) and stirred for a further 20 hr before pouring into ice-water. The mixture was extracted with ether (200 ml), filtered, and the extracted twice more with ether (2 × 50 ml). The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to give 3-chloro-4-phenyl-1,2,5-thiadiazole as a mobile orange oil (10.1 g, 87%). Short-path distillation of this oil (9.35 g) at reduced pressure yielded a clear, colorless oil (7.75 g, 83%) which crystallized on standing.



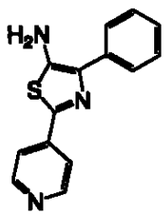
3-Chloro-4-phenyl-1,2,5-thiadiazole (3.19 g, 16.2 mmol) in THF (32 ml) at 0°C was treated dropwise with a solution of lithium bis(trimethylsilyl)amide in THF (17.0 ml, 1.0 M, 17.0 mmol). After 10 min the mixture allowed to warm to ambient temperature for 1.5 hr, treated with 1N hydrochloric acid, and extracted three times into ether (total 300 ml). The combined organic phases were washed with saturated aqueous sodium bicarbonate and brine, and dried over magnesium sulfate and concentrated *in vacuo*. The residue was dissolved in methanol (50 ml) and triethylamine (0.5 ml) was heated to reflux for 15 hr and again concentrated *in vacuo*. Flash chromatography on silica gel (ethyl acetate/hexanes) yielded 3-amino-4-phenyl-1,2,5-thiadiazole (1.96 g, 68%) as a colorless solid.

Example 42 5-amino-2-methyl-4-phenylthiazole



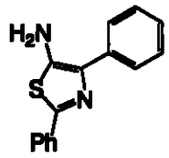
To a suspension of α-aminophenylacetonitrile hydrochloride (3.37 g, 20.0 mmol) and powdered sulfur (641 mg, 20.0 mmol) in ethanol (20 ml) at 0°C was added triethylamine (4.18 ml, 30.0 mmol) and then acetaldehyde (2.3 ml, 41 mmol). The vessel was sealed and heated to 60-70°C for 1 hr. The cooled mixture was filtered and concentrated in vacuo, and the residue treated with ethanol (20 ml) and hydrochloric acid (20 ml, 1N) for 15 hr. The mixture was treated with aqueous sodium carbonate and extracted three times into ethyl acetate (total 300 ml). The combined organic phases were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to give a dark brown oil. Flash chromatography on silica gel (ethyl acetate/hexanes) yielded 5-amino-2-methyl-4-phenylthiazole (1.31 g, 34%), which crystallized from toluene.

Example 43 5-amino-2-methyl-4-phenylthiazole



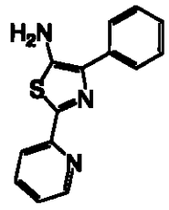
A suspension of α-aminophenylacetonitrile hydrochloride (1.69 g, 10.0 mmol), powdered sulfur (321 mg, 10.0 mmol) and 4-pyridinecarboxaldehyde (1.91 ml, 20.0 mmol) in ethanol (10 ml) was treated with triethylamine (2.09 ml, 15.0 mmol), and the mixture stirred at 50°C for 80 min. The cooled mixture was diluted with ethanol (5 ml) and treated with aqueous hydroxylamine (700 µl, 50% wt, 11 mmol) at ambient temperature for 15 hr, and diluted with dichloromethane (50 ml). Saturated aqueous sodium bicarbonate was added and the separated aqueous phase was extracted twice more with dichloromethane (total 100 ml). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo* to give a dark brown oily foam (3.23 g). Flash chromatography on silica gel (ethyl acetate/hexanes) yielded 5-amino-2-(4-pyridyl)-4-phenylthiazole (1.41 g, 56%).

Example 44 2,4-diphenylthiazol-5-amine



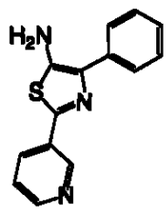
2,4-diphenylthiazol-5-amine was prepared according to the procedures described in K. Gewald, H. Schonfelder, U. Hain; *J. Prakt. Chem.*, 1974, *361*, 299-303.

Example 45 4-phenyl-2-(pyridin-2-yl)thiazol-5-amine



4-phenyl-2-(pyridin-2-yl)thiazol-5-amine was prepared according to the procedures described in K. Gewald, H. Schonfelder, U. Hain; *J. Prakt. Chem.*, 1974, *361*, 299-303

Example 46 4-phenyl-2-(pyridin-3-yl)thiazol-5-amine



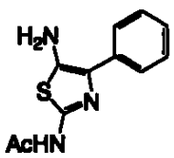
4-phenyl-2-(pyridin-3-yl)thiazol-5-amine was prepared according to the procedures described in K. Gewald, H. Schonfelder, U. Hain; *J. Prakt. Chem.*, 1974, *361*, 299-303

Example 47 5-amino-2-(Fmoc-amino)-4-phenylthiazole



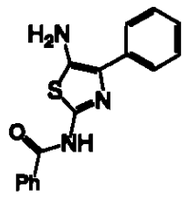
A suspension of α-aminophenylacetonitrile hydrochloride (3.19 g, 18.9 mmol) and Fmoc-isothiocyanate (5.31 g, 18.9 mmol) in DCM was treated with ethyldiisopropylamine (3.62 ml, 20.8 mmol) at 0°C for 1 hr and then at ambient temperature for 3 hr. The mixture was poured into saturated aqueous sodium bicarbonate and extracted three times into ethyl acetate. The combined organic phases were washed with water and brine, and dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography on silica gel (ethyl acetate/hexanes) yielded 5-amino-2-(Fmoc-amino)-4-phenylthiazole (3.75 g, 48%).

Example 48 N-(5-amino-4-phenylthiazol-2-yl)acetamide



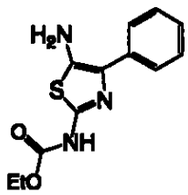
N-(5-amino-4-phenylthiazol-2-yl)acetamide was prepared according to procedures similar to those described in example 47.

Example 49 N-(5-amino-4-phenylthiazol-2-yl)benzamide



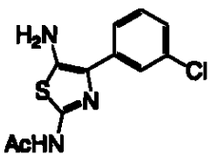
N-(5-amino-4-phenylthiazol-2-yl)benzamide was prepared according to procedures similar to those described in example 47.

Example 50 ethyl 5-amino-4-phenylthiazol-2-ylcarbamate



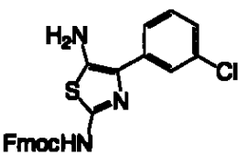
ethyl 5-amino-4-phenylthiazol-2-ylcarbamate was prepared according to procedures similar to those described in example 47.

Example 51 N-(5-amino-4-(2-chlorophenyl)thiazol-2-yl)acetamide



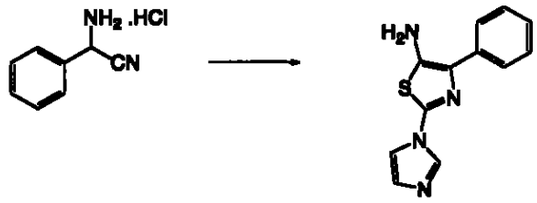
N-(5-amino-4-(2-chlorophenyl)thiazol-2-yl)acetamide was prepared according to procedures similar to those described in example 47.

Example 52 (9H-fluoren-9-yl)methyl 5-amino-4-(2-chlorophenyl)thiazol-2-ylcarbamate



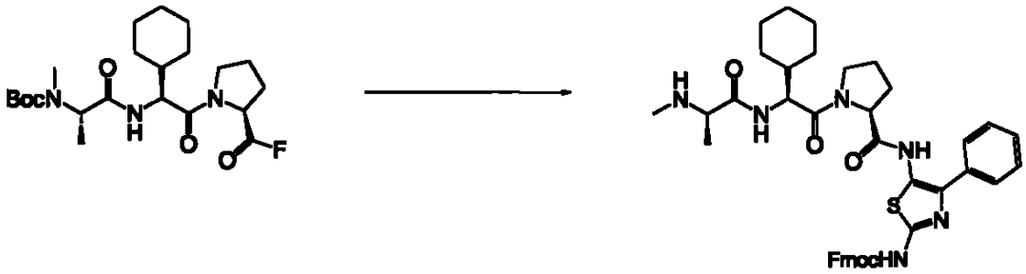
(9H-fluoren-9-yl)methyl 5-amino-4-(2-chlorophenyl)thiazol-2-ylcarbamate was prepared according to procedures similar to those described in example 47.

Example 53 5-amino-2-(1-imidazolyl)-4-phenylthiazole

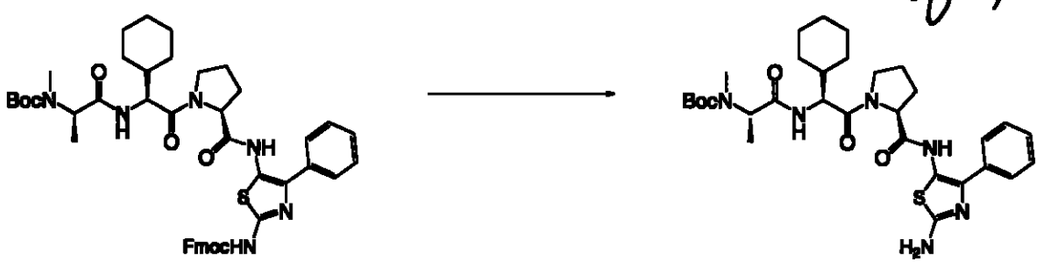


A suspension of α-aminophenylacetonitrile hydrochloride (5.01 g, 29.7 mmol) and thiocarbonyl diimidazole (5.30 g, 29.7 mmol) in DCM (100 ml) was treated with ethyldiisopropylamine (5.69 ml, 32.7 mmol) at 0°C for 15 min and then at ambient temperature for 3 hr. The mixture was poured into saturated aqueous sodium bicarbonate (50 ml) and water (150 ml), and extracted three times into dichloromethane (total 300 ml). The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to give a dark brown oil (8.18 g). Flash chromatography on silica gel (ethyl acetate/hexanes) yielded 5-amino-2-(1-imidazolyl)-4-phenylthiazole (2.47 g, 34%).

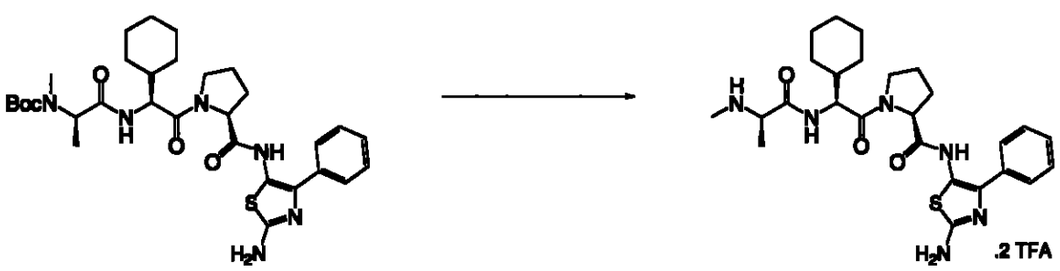
Example 54 MeAla-Chg-Pro peptide amide of 2,5-diamino-4-phenylthiazole



5-Amino-2-(Fmoc-amino)-4-phenylthiazole (250 mg, 605 μmol) was treated with the acid fluoride (730 μmol; derived form Boc-MeAla-Chg-Pro-OH as previously described) and pyridine (147 μl, 1.82 mmol) in dichloromethane (2.0 ml) at ambient temperature for 6 days. The mixture was poured into saturated aqueous sodium bicarbonate and extracted three times into dichloromethane (total 100 ml). The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to yield the crude peptide amide as a yellow oil (525 mg), used subsequently without purification.

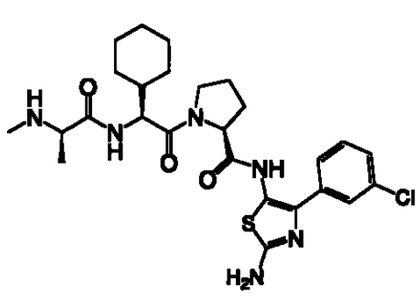


The crude peptide amide in DMF (9.0 ml) was treated with piperidine (1.0 ml) at ambient temperature for 20 min and then concentrated *in vacuo*. Flash chromatography on silica gel (ethyl acetate/hexanes) yielded the 2,5-diamino-4-phenylthiazole peptide amide (228 mg, 61% for 2 steps).



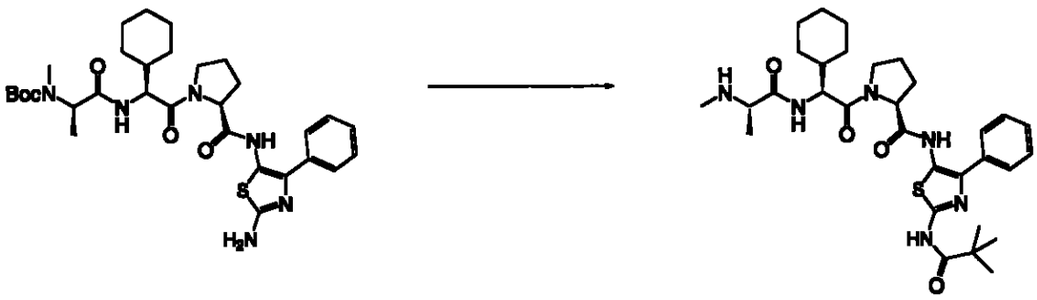
The crude peptide amide (48 mg, 78 μmol) in dichloromethane (2.0 ml) was treated with trifluoroacetic acid (2.0 ml) at ambient temperature for 30 min. The mixture was concentrated *in vacuo*, made homogeneous with dichloromethane and again concentrated. The residue was purified by preparative reverse phase HPLC (acetonitrile/water) to yield the fully deprotected peptide amide trifluoroacetic acid salt (42 mg, 73%) as a white amorphous solid.

Example 55 MeAla-Chg-Pro peptide amide of 2,5-diamino-4-(3-chlorophenyl)thiazole



MeAla-Chg-Pro peptide amide of 2,5-diamino-4-(3-chlorophenyl)thiazole was prepared using the same procedures described in example 55.

Example 56 MeAla-Chg-Pro amide of 5-amino-2-(pivaloylamino)-4-phenylthiazole



The Boc-peptide amino-thiazole (48 mg, 78 µmol) and ethyldiisopropylamine (140 µl, 0.80 mmol) in dichloromethane (2.0 ml) were treated with pivaloyl chloride (50 µl, 0.40 mmol) at ambient temperature for 3 hr, and then with saturated aqueous sodium bicarbonate and extracted three times into dichloromethane (total 60 ml). The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude oil was treated with trifluoroacetic acid (5.0 ml) in dichloromethane (5.0 ml) at ambient temperature for 20 min. The mixture was concentrated *in vacuo*, made homogeneous with dichloromethane and again concentrated. The residue was dissolved in aqueous acetic acid (50%) for purification by preparative reverse phase HPLC (acetonitrile/water) to yield the pure peptide amide trifluoroacetic acid salt (38 mg, 68% for 2 steps) as a white amorphous solid.

Example 57 MeAla-Chg-Pro amide of 5-amino-2-(pivaloylamino)-4-phenylthiazole



The Boc-peptide amino-thiazole (38 mg, 62 µmol) and ethyldiisopropylamine (107 µl, 0.61 mmol) in dichloromethane (2.0 ml) were treated with methanesulfonyl chloride (24 µl, 0.31 mmol) at ambient temperature for 20 min, and then with saturated aqueous sodium bicarbonate and extracted three times into dichloromethane. The combined organic phases were washed with brine, dried

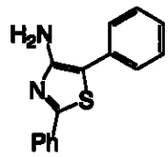
over magnesium sulfate and concentrated *in vacuo*. The crude oil was treated with trifluoroacetic acid (4 ml) in dichloromethane (4 ml) at ambient temperature for 20 min. The mixture was concentrated *in vacuo*, made homogeneous with dichloromethane and again concentrated. The residue was dissolved in aqueous acetic acid (50%) for purification by preparative reverse phase HPLC (acetonitrile/water) to yield the pure peptide amide trifluoroacetic acid salt (11 mg, 23% for 2 steps) as a white amorphous solid.

Example 57 2-(acetylamino)-4-amino-5-phenylthiazole



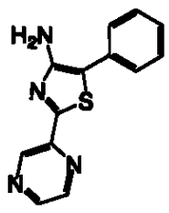
α-Bromophenylacetonitrile (1.08 g, 5.48 mmol) in ethanol (10 ml) was treated with N-acetylthiourea (649 mg, 5.49 mmol) at ambient temperature for 4 hr, and then heated to reflux for 3.5 hr. The cooled mixture was concentrated *in vacuo* and then partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography on silica gel (ethyl acetate/hexanes) yielded 2-(acetylamino)-4-amino-5-phenylthiazole (295 mg, 23%).

Example 58 2,5-diphenylthiazol-4-amine



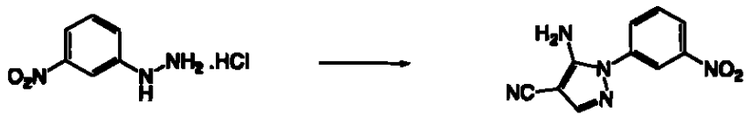
2,5-diphenylthiazol-4-amine was prepared using the same procedures described in example 57.

Example 59 5-phenyl-2-(pyrazin-2-yl)thiazol-4-amine

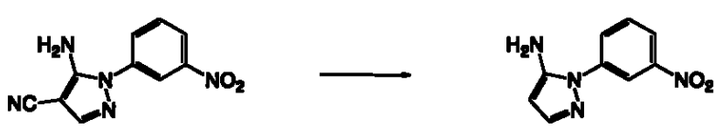


5-phenyl-2-(pyrazin-2-yl)thiazol-4-amine was prepared using the same procedures described in example 57.

Example 60 5-amino-1-(3'-nitrophenyl)pyrazole

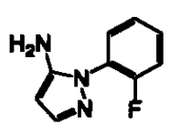


3-Nitrophenylhydrazine hydrochloride (7.03 g, 36.3 mmol), diisopropylethylamine (9.5 ml, 54.5 mmol), and ethanol (60 ml) were stirred under nitrogen at room temperature for 2 h. Ethoxymethylenemalononitrile (4.52 g, 36.3 mmol) was added, after which the reaction was refluxed for 1 h. Reaction was cooled to room temperature. Solvent was removed under reduced pressure until precipitate crashed out. The solid was filtered to yield 6.54 g of the cyclized product (78% yield).



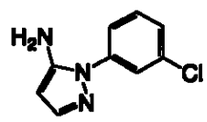
5-amino-1-(3'-nitrophenyl)-4-cyanopyrazole (559 mg, 2.44 mmol) and phosphoric acid (86%, 6 ml) were refluxed at 170°C for 15 h. The reaction was cooled to room temperature and neutralized with ammonium hydroxide. The organics were extracted three times with diethyl ether (total 40 ml), washed with brine, and dried over magnesium sulfate. Removal of solvent gave 5-amino-1-(3'-nitrophenyl)-pyrazole as a yellow powder (398 mg, 80% yield).

Example 61 1-(2-fluorophenyl)-1H-pyrazol-5-amine



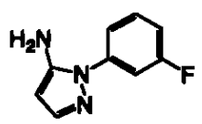
1-(2-fluorophenyl)-1H-pyrazol-5-amine was prepared using the same procedures described in example 60.

Example 62 1-(3-chlorophenyl)-1H-pyrazol-5-amine



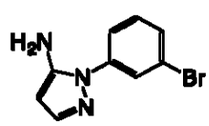
1-(3-chlorophenyl)-1H-pyrazol-5-amine was prepared using the same procedures described in example 60.

Example 63 1-(3-fluorophenyl)-1H-pyrazol-5-amine



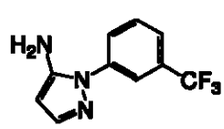
1-(3-fluorophenyl)-1H-pyrazol-5-amine was prepared using the same procedures described in example 60.

Example 64 1-(3-bromophenyl)-1H-pyrazol-5-amine



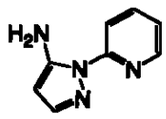
1-(3-bromophenyl)-1H-pyrazol-5-amine was prepared using the same procedures described in example 60.

Example 65 1-(3-trichloromethylphenyl)-1H-pyrazol-5-amine



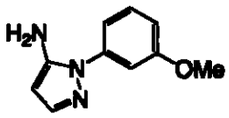
1-(3-trichloromethylphenyl)-1H-pyrazol-5-amine was prepared using the same procedures described in example 60.

Example 66 1-(pyridin-2-yl)-1H-pyrazol-5-amine



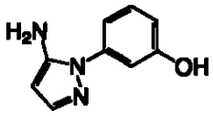
1-(pyridin-2-yl)-1H-pyrazol-5-amine was prepared using the same procedures described in example 60.

Example 67 1-(3-methoxyphenyl)-1H-pyrazol-5-amine



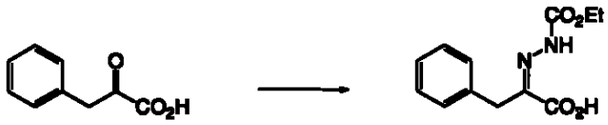
1-(3-methoxyphenyl)-1H-pyrazol-5-amine was isolated following decyanation of 5-amino-4-cyano-1-(3'-methoxyphenyl)pyrazole in example 60.

Example 67 1-(3-hydroxyphenyl)-1H-pyrazol-5-amine



1-(3-hydroxyphenyl)-1H-pyrazol-5-amine was prepared using the same procedures described in example 60.

Example 68 4-amino-5-phenyl-1,2,3-thiadiazole



Phenylpyruvic acid (25 g, 149 mmol) and ethyl carbazate (16 g, 149 mmol) were refluxed in benzene (225 ml) for 2 hr, and the mixture concentrated *in vacuo*. The crude was dissolved in minimum warm dichloromethane to yield the hydrazone as a yellow precipitate upon cooling to ambient temperature, isolated by filtration (30.4 g, 81%) and used without further purification.



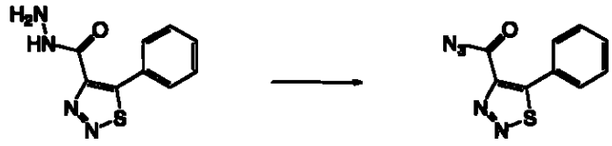
Diazomethane was generated by adding a solution of Diazald (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide; 18.6 g, 86.9 mmol) in diethyl ether (180 ml) to a solution of potassium hydroxide (18.2 g, 325 mmol) in water (37 ml) and 2-(2-ethoxyethoxy)-ethanol (37 ml) at 65°C, dropwise over 45 min. Distillation thus produced an ethereal solution of diazomethane which was added directly to a stirred solution of the hydrazone (10.9 g, 43.5 mmol) in methanol (150 ml) at 0°C. The system was rinsed with excess diethyl ether until distillate became clear, the mixture treated with acetic acid (1 ml), and concentrated *in vacuo*. The resulting oil was partitioned between ethyl acetate (200 ml) and sodium bicarbonate (200 ml), and the organic phase dried over sodium sulfate. Filtration and concentration *in vacuo* yielded the methyl ester as a yellow solid (10.2 g, 89%).



The hydrazone-methyl ester (10.2 g, 38.6 mmol) was treated with thionyl chloride (25 ml, 343 mmol) at ambient temperature for 24 hr, and the mixture concentrated *in vacuo*. Crystallization from hexanes yielded the thiadiazole-methyl ester (4.81 g, 56%).



The thiadiazole-methyl ester (2.79 g, 12.7 mmol) was treated with hydrazine hydrate (1.09 ml, 93.9 mmol) in methanol (50 ml) at ambient temperature for 24 hr, and the resulting white precipitate recovered by filtration. Recrystallization from isopropanol yielded the thiadiazole-hydrazide (3.99 g, 83%).



The thiadiazole-hydrazide (3.99 g, 18.1 mmol) in water (40 ml) and concentrated hydrochloric acid (1.8 ml, 21.9 mmol) was treated dropwise with a solution of sodium nitrite (1.52 g, 21.3 mmol) in water (15 ml) at 0°C for 2 hr. The resulting precipitate was recovered by filtration to yield the thiadiazole-acid azide as an off-white solid (3.95 g, 94%).



According to the procedures described in K. Masuda *et al.*; *Chem. Pharm. Bull.*, 1981, *29*, 1743-1747, the thiadiazole-acid azide (3.95 g, 17.1 mmol) was at reflux in ethanol (40 ml) for 45 min, and the mixture concentrated *in vacuo*. Crystallization from benzene yielded the ethyl carbamate (3.37 g, 74%).



The ethyl carbamate (399 mg, 1.60 mmol) and hydrogen bromide in acetic acid (3 ml, 30% wt) were heated in a sealed vessel at 80°C for 18 hr. The cooled mixture was partitioned between ethyl acetate (15 ml) and water (15 ml), and the organic phase concentrated *in vacuo*. Flash chromatography on silica gel (ethyl acetate/hexanes) yielded 4-amino-5-phenyl-1,2,3-thiadiazole (136 mg, 49%).

Example 69 4-amino-5-phenylisoxazole



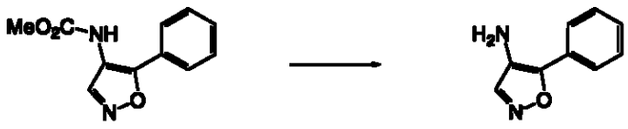
5-Phenyl-4-isoxazolecarboxylic acid (460 mg, 2.36 mmol) and thionyl chloride (1.71 ml, 23.6 mmol) were heated at reflux for 3 hr, and the mixture concentrated *in vacuo* to yield the acid chloride which was used without purification.



The crude acid chloride in acetone (7 ml) was treated with a solution of sodium azide (165 mg, 2.62 mmol) in water (2 ml) at 0°C for 1.5 hr, and allowed to warm to ambient temperature and concentrated *in vacuo*. The resulting white solid was washed with water and dried *in vacuo*, and used without purification.

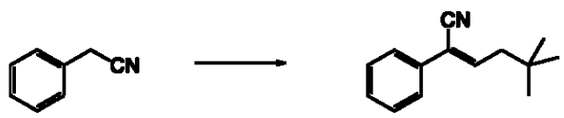


The acid azide (409 mg, 1.91 mmol) was heated at reflux in methanol for 6 hr, and the mixture concentrated *in vacuo* to yield the methyl carbamate as a white solid, used without purification.

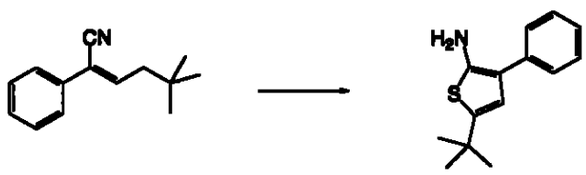


The methyl carbamate (378 mg, 1.73 mmol) was treated with hydrobromic acid (13 ml, 48% wt, 115 mmol), made homogeneous with acetic acid (2 ml), and heated at 65°C for 48 hr, and allowed to cool. The mixture was neutralized with aqueous sodium hydroxide and extracted with ethyl acetate (2 × 125 ml). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo* to yield 4-amino-5-phenylisoxazole as a white solid (193 mg, 70%).

Example 70 Synthesis of 5-alkyl-2-amino-3-phenylthiophenes



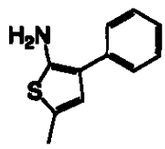
Benzyl cyanide (2.33 ml, 20 mmol) was treated with Verkade's base (2,8,9-trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane; 441 mg, 2.0 mmol) and 3,3-dimethylbutyraldehyde (2.64 ml, 200 mmol) in methanol (4 ml) and the mixture heated in a sealed vessel at 45°C for 16 hr. The cooled mixture was concentrated *in vacuo* to yield the unsaturated nitrile as a colorless oil, used without purification.



The nitrile (10.0 mmol), potassium carbonate (2.34 g, 23.4 mmol) and powdered sulfur (330 mg, 10.3 mmol) in ethanol (2 ml) were heated in a sealed vessel at 160°C for 24 hr. The cooled mixture was diluted with water, extracted twice into diethyl ether and the combined organics concentrated *in vacuo*. Flash chromatography on silica gel (ethyl acetate/hexanes) yielded 5-amino-2-*tert*-butyl-4-phenylthiazole (75%).

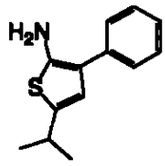
Example 71 5-methyl-3-phenylthiophen-2-amine

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5-methyl-3-phenylthiophen-2-amine was prepared using the same procedures described in example 70.

Example 72 5-isopropyl-3-phenylthiophen-2-amine

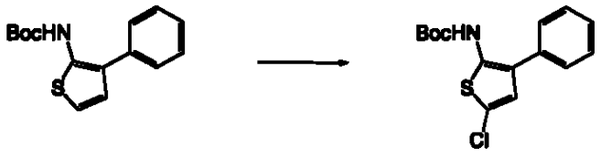


5-isopropyl-3-phenylthiophen-2-amine was prepared using the same procedures described in example 70.

Example 73 2-amino-5-chloro-3-phenylthiophene



2-Amino-3-phenyl-thiophene (12.0 mmol) in THF (7 ml) was treated with di-*tert*-butyl dicarbonate (2.97 g, 13.3 mmol) and diisopropylethylamine (3.15 ml, 18.1 mmol) at ambient temperature for 60 hr, and the mixture concentrated *in vacuo*. Flash chromatography on silica gel (ethyl acetate/hexanes) yielded 2-(*N*-Boc-amino)-3-phenyl-thiophene (1.98 g, 59%).



To 2-(*N*-Boc-amino)-3-phenyl-thiophene (89 mg, 0.32 mmol) in dichloromethane (4 ml) at 0°C was slowly added *N*-chlorosuccinimide (48 mg, 0.36 mmol), and the mixture allowed warm to ambient temperature for 16 hr. The mixture was diluted with dichloromethane, washed with water, and the organic phase concentrated *in vacuo*. Flash chromatography on silica gel (ethyl acetate/hexanes) yielded 2-(*N*-Boc-amino)-5-chloro-3-phenyl-thiophene (66 mg, 66%).

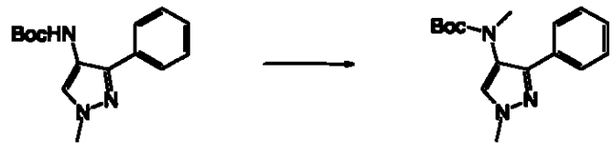


2-(*N*-Boc-amino)-5-chloro-3-phenyl-thiophene (66 mg, 0.21 mmol) was treated with trifluoroacetic acid (1 ml) in dichloromethane (3 ml) at ambient temperature for 1 hr. The mixture was diluted with DMF (1 ml) and the more volatile materials removed under reduced pressure. The resulting DMF solution of 2-amino-5-chloro-3-phenylthiophene was used in the subsequent coupling step without purification.

Example 74 1-Methyl-4-(methylamino)-3-phenylpyrazole



To 1-methyl-4-amino-3-phenylpyrazole (572 mg, 3.30 mmol) and di-*tert*-butyl dicarbonate (799 mg, 3.66 mmol) in THF (10 ml) and water (3 ml) was added dropwise saturated aqueous sodium bicarbonate (3 ml, 1.2 M, 3.6 mmol). The mixture was stirred at ambient temperature for 7 hr and then poured into aqueous citric acid (0.5 M) and extracted three times into ether (total 100 ml). The combined organic phases were washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated *in vacuo* to yield the crude carbamate as a brown oil (920 mg), used subsequently without purification.

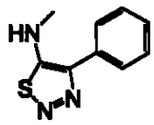


A suspension of sodium hydride in mineral oil (327 mg, 60% wt, 8.18 mmol) was washed with THF (2 × 5 ml) and suspended in THF (3.0 ml) at 0°C. To this was added dropwise the pyrazole (744 mg, 2.72mmol) in THF (5.0 ml), and after 15 min, methyl iodide (187 µl, 3.00 mmol). After a further 30 min at 0°C the mixture was allowed to warm to ambient temperature for 18 hr and then treated with saturated aqueous ammonium chloride and sufficient water to dissolve solids. The mixture was extracted three times into ether (total 120 ml), and the combined organic phases washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to yield the crude *N*-methyl carbamate as a amber oil (750 mg, 96%), used without purification.



The crude *N*-methyl carbamate in DCM (1.0 ml) was treated with trifluoroacetic acid (1.0 ml) at ambient temperature for 40 min. The mixture was concentrated *in vacuo*, made homogeneous with dichloromethane and again concentrated to yield essentially pure 1-methyl-4-(methylamino)-3-phenylpyrazole (150 mg, quant.) as a brown oil.

Example 75 N-methyl-4-phenyl-1,2,3-thiadiazol-5-amine

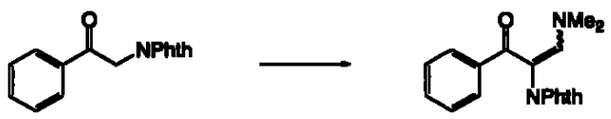


N-methyl-4-phenyl-1,2,3-thiadiazol-5-amine was prepared using the same procedures described in example 74.

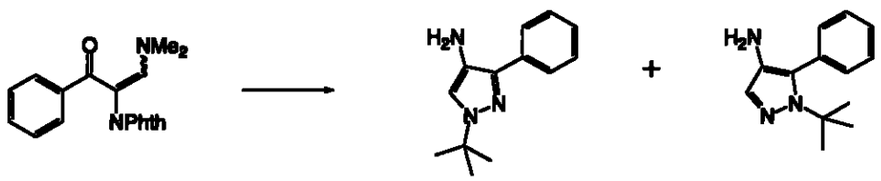
Example 76 1-*tert*-Butyl-4-amino-3-phenylpyrazole and 1-*tert*-butyl-4-amino-5-phenylpyrazole



A solution of 2-bromoacetophenone (30.0 g, 151 mmol) in DMF (120 ml) was treated with potassium phthalimide (30.8 g, 166 mmol) portionwise at ambient temperature, and then heated to 40°C for 3.5 hr. The cooled mixture was poured into water (600 ml) and extracted with chloroform (300 ml then 100 ml). The combined organic phases were washed with sodium hydroxide (200 ml, 0.2 N), water (2 × 100 ml) and brine (100 ml), dried over magnesium sulfate and concentrated *in vacuo*. The resulting cream solid was suspended in ether (100 ml), recovered by filtration, washed with ether (100 ml) and dried *in vacuo* to yield pure 2-phthalimido-acetophenone as a white solid (34.3 g, 86%).

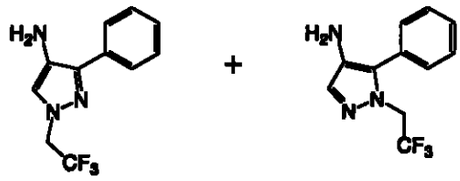


According to the procedures described in C. Chen, K. Wilcoxen, J. R. McCarthy; *Tetrahedron Lett.*, 1988, *39*, 8229-8232 a suspension of 2-phthalimidoacetophenone (13.3 g, 50.0 mmol) in dimethylformamide dimethyl acetal (26.7 ml, 200 mmol) was heated at reflux for 28 hr and concentrated *in vacuo*. The resulting amber oil was crystallized form isopropanol (100 ml) and washed with isopropanol (2 × 5 ml) to yield of 3-(dimethylamino)-1-phenyl-2-phthalimido-2-propen-1-one as yellow needles (13.7 g, 85%).



A mixture of 3-(dimethylamino)-1-phenyl-2-phthalimido-2-propen-1-one (3.00 g, 9.38 mmol) and *tert*-butyl hydrazine hydrochloride (1.29 g, 10.3 mmol) in ethanol (94 ml) and water (9.4 ml) was stirred at ambient temperature for 64 hr and then heated at reflux for 24 hr. The cooled mixture was treated with hydrazine (590 µl, 18.8 mmol) and returned to reflux for 75 min. On cooling and standing at ambient temperature a precipitate formed. The mixture was filtered, the solid washed with a mixture of ethanol (5 ml) and water (0.5 ml), and the filtrate concentrated *in vacuo*. The residue was partitioned between ether (250 ml) and saturated aqueous sodium bicarbonate (50 ml) diluted with water (100 ml), and the aqueous phase extracted twice more with ether (2 × 50 ml). The combined organic phases were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to give a pale solid (1.92 g). Flash chromatography on silica gel (ethyl acetate/hexanes) yielded 1-*tert*-butyl-4-amino-3-phenylpyrazole (1.52 g, 75% for 2 steps) and 1-*tert*-butyl-4-amino-5-phenylpyrazole (114 mg, 6% for 2 steps).

Example 77 1-(2,2,2-trifluoroethyl)-3-phenyl-1H-pyrazol-4-amine and 1-(2,2,2-trifluoroethyl)-5-phenyl-1H-pyrazol-4-amine



1-(2,2,2-trifluoroethyl)-3-phenyl-1H-pyrazol-4-amine and 1-(2,2,2-trifluoroethyl)-5-phenyl-1H-pyrazol-4-amine were prepared similarly from 2,2,2-trifluoroethylhydrazine according to the procedures described in example 76.

Example 78 IAP inhibition assays

In the following experiments was used a chimeric BIR domain referred to as MLXBIR3SG in which 11 of 110 residues correspond to those found in XIAP-BIR3, while the remainder correspond to ML-IAP-BIR. The chimeric protein MLXBIR3SG was shown to bind and inhibit

caspase-9 significantly better than either of the native BIR domains, but bound Smac-based peptides and mature Smac with affinities similar to those of native ML-IAP-BIR. The improved caspase-9 inhibition of the chimeric BIR domain MLXBIR3SG has been correlated with increased inhibition of doxorubicin-induced apoptosis when transfected into MCF7 cells.

MLXBIR3SG sequence:
MGSSHHHHHHSSGLVPRGSHMLETEEEEEEGAGATLSRGPAFPGMGSEELRLASFYDWP LTAEVPPELLAAAGFFHTGHQDKVRCFFCYGGLQSWKRGDDPWTEHAKWFPGCQFLLR SKGQEYINNIHLTHSL (SEQ ID NO.: 1)

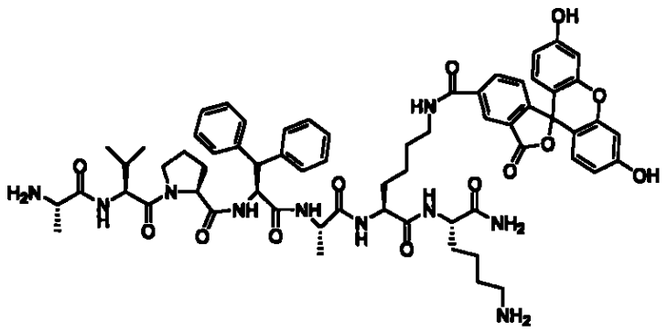
TR-FRET Peptide Binding Assay

Time-Resolved Fluorescence Resonance Energy Transfer competition experiments were performed on the Wallac Victor2 Multilabeled Counter Reader (Perkin Elmer Life and Analytical Sciences, Inc.) according to the procedures of Kolb et al (Journal of Biomolecular Screening, 1996, 1(4):203). A reagent cocktail containing 300 nM his-tagged MLXBIR3SG; 200 nM biotinylated SMAC peptide (AVPI); 5 μg/mL anti-his allophycocyanin (XL665) (CISBio International); and 200 ng/mL streptavidin-europium (Perkin Elmer) was prepared in reagent buffer (50 mM Tris [pH 7.2], 120 mM NaCl, 0.1% bovine globulins, 5mM DTT and 0.05% octylglucoside). (Alternatively, this cocktail can be made using europium-labeled anti-His (Perkin Elmer) and streptavidin-allophycocyanin (Perkin Elmer) at concentrations of 6.5 nM and 25nM, respectively). The reagent cocktail was incubated at room temperature for 30 minutes. After incubation, the cocktail was added to 1:3 serial dilutions of an antagonist compound (starting concentration of 50 μM) in 384-well black FIA plates (Greiner Bio-One, Inc.). After a 90 minute incubation at room temperature, the fluorescence was read with filters for the excitation of europium (340 nm) and for the emission wavelengths of europium (615 nm) and a allophycocyanin (665 nm). Antagonist data were calculated as a ratio of the emission signal of allophycocyanin at 665 nm to that of the emission of europium at 615 nm (these ratios were multiplied by a factor of 10,000 for ease of data manipulation). The resulting values were plotted as a function of antagonist concentration and fit to a 4-parameter equation using Kaleidograph software (Synergy Software, Reading, PA). Indications of antagonist potency were determined from the IC50 values. Compounds of the invention where found to have IAP inhibitory activity which was demonstrated in this assay.

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Fluorescence Polarization Peptide Binding Assay

Polarization experiments were performed on an Analyst HT 96-384 (Molecular Devices Corp.) according to the procedure of Keating, S.M., Marsters, J, Beresini, M., Ladner, C., Zioncheck, K., Clark, K., Arellano, F., and Bodary., S.(2000) in *Proceedings of SPIE : In Vitro Diagnostic Instrumentation* (Cohn, G.E., Ed.) pp 128-137, Bellingham, WA. Samples for fluorescence polarization affinity measurements were prepared by addition of 1:2 serial dilutions starting at a final concentration of 5μM of MLXBIR3SG in polarization buffer (50 mM Tris [pH 7.2], 120 mM NaCl, 1% bovine globulins 5mM DTT and 0.05% octylglucoside) to 5-carboxyflourescein-conjugated AVPdi-Phe-NH_2 (AVP-diPhe-FAM) at 5 nM final concentration.



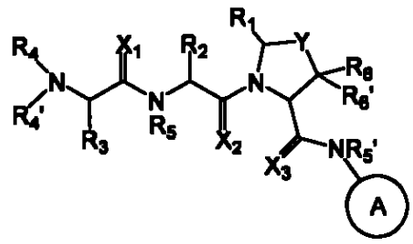
AVP-diPhe-FAM probe

The reactions were read after an incubation time of 10 minutes at room temperature with standard cut-off filters for the fluorescein fluorophore (λ_{ex} = 485 nm; λ_{em} = 530 nm) in 96-well black HE96 plates (Molecular Devices Corp.). Fluorescence values were plotted as a function of the protein concentration, and the IC50s were obtained by fitting the data to a 4-parameter equation using Kaleidograph software (Synergy software, Reading, PA). Competition experiments were performed by addition of the MLXBIR3SG at 30 nM to wells containing 5 nM of the AVP-diPhe-FAM probe as well as 1:3 serial dilutions of antagonist compounds starting at a concentration of 300 μM in the polarization buffer. Samples were read after a 10-minute incubation. Fluorescence polarization values were plotted as a function of the antagonist concentration, and the IC_{50} values were obtained by fitting the data to a 4-parameter equation using Kaleidograph software (Synergy software, Reading, PA). Inhibition constants (K_i) for the antagonists were determined from the IC_{50} values. Compounds of the invention where found to have IAP inhibitory activity which was demonstrated in this assay.

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WE CLAIM:

1. A compound of formula I:



I

wherein

X_1, X_2 and X_3 are independently O or S;

Y is $(CHR_7)_n$ O or S; wherein n is 1 or 2 and R_7 is H, halogen, alkyl, aryl, aralkyl, amino, arylamino, alkylamino, aralkylamino, alkoxy, aryloxy or aralkyloxy;

A is a 5-member heterocycle comprising 1 to 4 heteroatoms optionally substituted with amino, hydroxyl, mercapto, halogen, carboxyl, amidino, guanidino, alkyl, alkoxy, aryl, aryloxy, acyl, acyloxy, acylamino, alkoxycarbonylamino, cycloalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonylamino or a heterocycle; wherein each alkyl, alkoxy, aryl, aryloxy, acyl, acyloxy, acylamino, cycloalkyl and heterocycle substitution is optionally substituted with hydroxyl, halogen, mercapto, carboxyl, alkyl, alkoxy, haloalkyl, amino, nitro, cyano, cycloalkyl, aryl or a heterocycle;

R_1 is H or R_1 and R_2 together form a 5-8 member ring;

R_2 is alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, a heterocycle or heterocyclylalkyl; each optionally substituted with hydroxyl, mercapto, halogen, amino, carboxyl, alkyl, haloalkyl, alkoxy or alkylthio;

R_3 is H or alkyl;

R_4 and R_4' are independently H, hydroxyl, amino, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, or heteroarylalkyl wherein each alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl and heteroarylalkyl is optionally substituted with halogen, hydroxyl, mercapto, carboxyl, alkyl, alkoxy, amino and nitro;

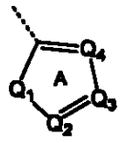
R_5, and R_5' are each independently H or alkyl;

R_6, and R_6' are each independently H, alkyl, aryl or aralkyl;

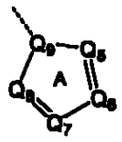
and salts and solvates thereof.

2. The compound of claim 1, wherein ring A has the formula IIa or IIb:

3.



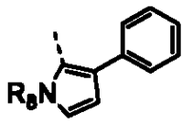
IIa

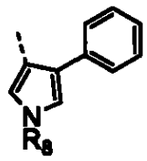


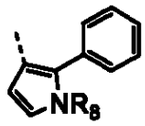
IIb

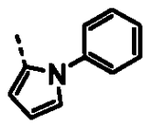
wherein Q_1 is NR_8, O or S; Q_2, Q_3, Q_4, Q_5, Q_6, Q_7, and Q_8, are independently CR_9 or N; wherein R_9 is H, amino, hydroxyl, mercapto, halogen, carboxyl, amidino, guanidino, alkyl, alkoxy, aryl, aryloxy, acyl, acyloxy, acylamino, cycloalkyl or a heterocycle; wherein each alkyl, alkoxy, aryl, aryloxy, acyl, acyloxy, acylamino, cycloalkyl and heterocycle substitution is optionally substituted with hydroxyl, halogen, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, cycloalkyl, aryl or a heterocycle; R_8 is H, alkyl, acyl, aryl, cycloalkyl or a heterocycle; wherein each alkyl, aryl, cycloalkyl and heterocycle is optionally substituted with hydroxyl, halogen, mercapto, carboxyl, alkyl, haloalkyl, amino, nitro, cycloalkyl, aryl or a heterocycle; and Q_9 is CH or N..

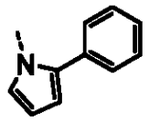
3. The compound of claim 1, wherein ring A is selected from the group consisting of:

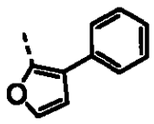


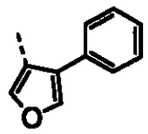


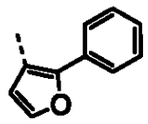


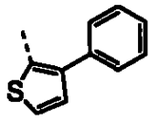


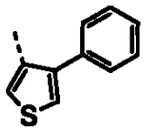


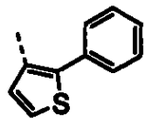


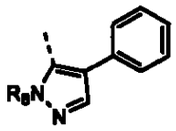


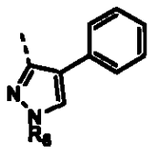


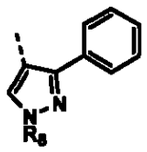


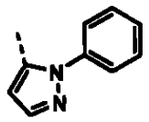


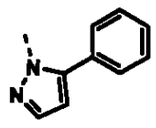






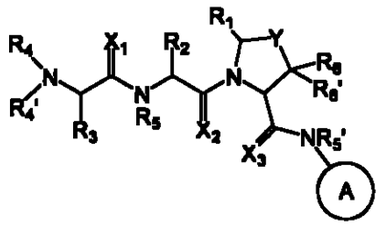






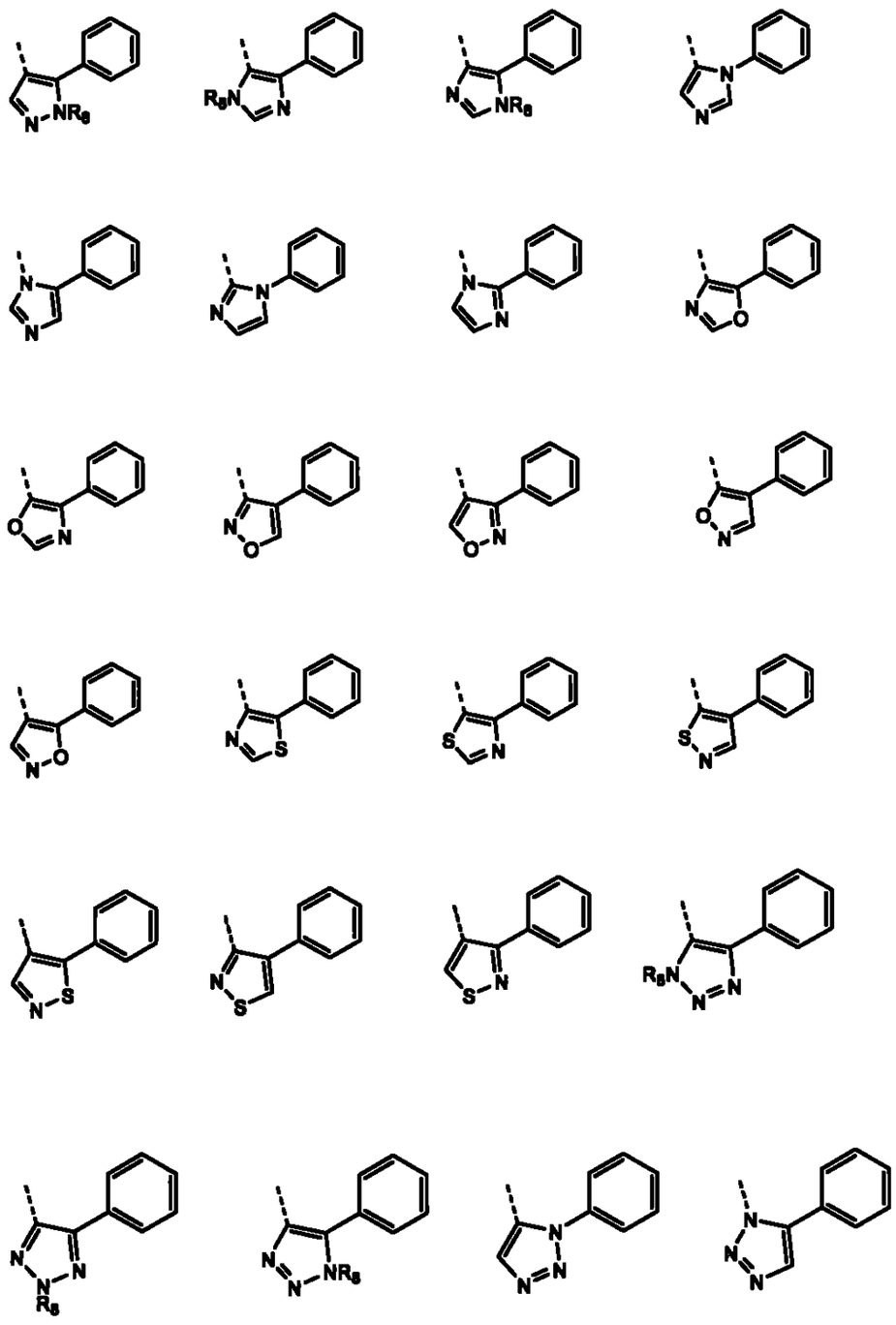
ABSTRACT

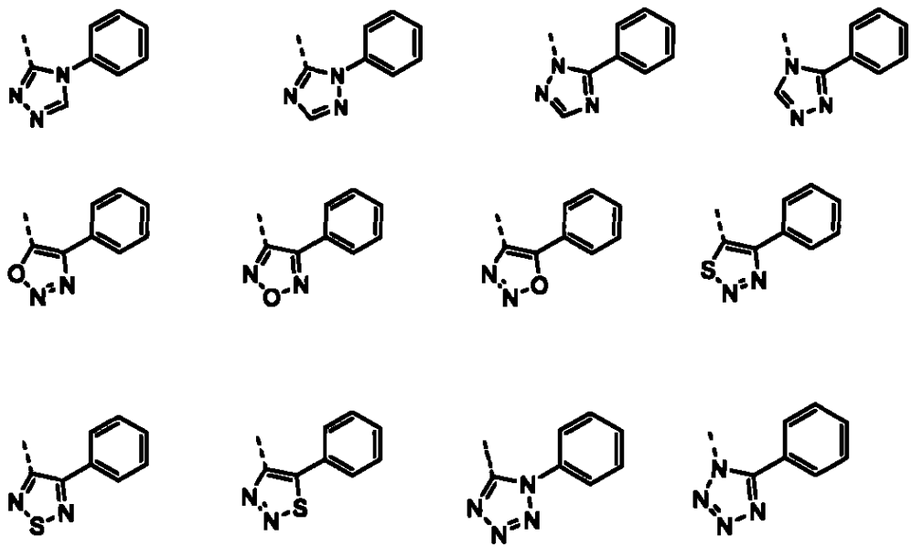
The invention provides novel inhibitors of IAP that are useful as therapeutic agents for treating malignancies where the compounds have the general formula I:



I

wherein X, Y, A, R_1, R_2, R_3, R_4, R_4', R_5, R_5', R_6 and R_6' are as described herein.





wherein R_8 is H, alkyl or acyl.

4. The compound of claim 3, wherein R_8 is H.

5. The compound of claim 1, wherein R_1 and R_2 together form a 5-8 member ring.

6. The compound of claim 1, wherein R_1 is H.

7. The compound of claim 1, wherein R_2 is alkyl or cycloalkyl.

8. The compound of claim 1, wherein R_2 is isopropyl, t-butyl, or cyclohexyl.

9. The compound of claim 1, wherein R_3 is methyl.

10. The compound of claim 1, wherein R_4 is H or methyl, and R_4' is H.

11. The compound of claim 1, wherein R_5 and R_5' are independently H or methyl.

12. The compound of claim 1, wherein R_6 and R_6' are independently H or methyl.

13. The compound of claim 1, wherein each of X_1, X_2 and X_3 are O.

14. The compound of claim 2, wherein R_1 is H; R_2 is isopropyl, t-butyl, or cyclohexyl; R_3 is methyl; R_4 is H or methyl, and R_4' is H, R_5 and R_5' are H or methyl; X_1, X_2 and X_3 are O.

15. A method of inducing apoptosis in a cell comprising introducing into said cell a compound of claim 1.

16. A method of sensitizing a cell to an apoptotic signal comprising introducing into said cell a compound of claim 1.

17. The method of claim 16, wherein said apoptotic signal is induced by contacting said cell with a compound selected from the group consisting of cytarabine, fludarabine, 5-fluoro-2'-deoxyuiridine, gemcitabine, methotrexate, bleomycin, cisplatin, cyclophosphamide, adriamycin (doxorubicin), mitoxantrone, camptothecin, topotecan, colcemid, colchicine, paclitaxel, vinblastine, vincristine, tamoxifen, finasteride, taxotere and mitomycin C.

18. The method of claim 16, wherein said apoptotic signal is induced by contacting said cell with Apo2L/TRAIL.

19. A method for inhibiting the binding of an IAP protein to a caspase protein comprising contacting said IAP protein with a compound of claim 1.

20. A method for treating a disease or condition associated with the overexpression of an IAP in a mammal, comprising administering to said mammal an effective amount of a compound of claim 1.

21. A method for treating cancer, comprising administering to said mammal an effective amount of a compound of claim 1.

Sequence Listing

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<130> P2154R1

<140> US 11/174,784
<141> 2005-07-05

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             65                  70                  75

His Thr Gly His Gln Asp Lys Val Arg Cys Phe Phe Cys Tyr Gly
             80                  85                  90

Gly Leu Gln Ser Trp Lys Arg Gly Asp Asp Pro Trp Thr Glu His
             95                 100                 105

Ala Lys Trp Phe Pro Gly Cys Gln Phe Leu Leu Arg Ser Lys Gly
            110                 115                 120

Gln Glu Tyr Ile Asn Asn Ile His Leu Thr His Ser Leu
            125                 130
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(81) Estados Designados ***(a menos que se indique otra cosa para cada clase de protección nacional disponible)***: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

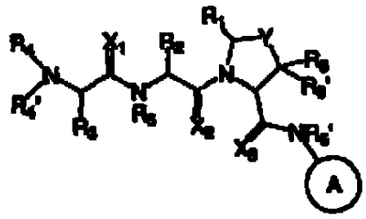
(84) Estados Designados ***(a menos que se indique otra cosa para cada clase de protección nacional disponible)***: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Eurasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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(54) Título: INHIBIDORES DE IAP



(I)

(57) RESUMEN: La invención suministra inhibidores novedosos de IAP que son útiles como agentes terapéuticos para el tratamiento de malignidades en donde los compuestos tienen la fórmula general I: en donde X, Y, A, R_1, R_2, R_3, R_4, R_4', R_5, R_5', R_6 Y R_6' son como se describe aquí

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INHIBIDORES DE IAP

CAMPO DE LA INVENCIÓN

La presente invención se relaciona con compuestos orgánicos útiles para la terapia y/o profilaxis en un mamífero, y en particular con inhibidores de proteínas IAP útiles para tratar canceres.

ANTECEDENTES DE LA INVENCIÓN

La apoptosis o muere celular programada es un mecanismo genética y bioquímicamente regulado que juega un papel importante en el desarrollo de la homeostasis en invertebrados así como también vertebrados. Las aberrancias en apoptosis que conducen a la muerte celular prematura ya está obligada a una variedad de desordenes de desarrollo. Las deficiencias en la apoptosis que resultan de la falta de muerte celular han estado ligadas a cánceres y a infecciones virales crónicas (Thompson et al., (1995) Science 267, 1456-1462).

Una de las moléculas efectuadoras clave en la apoptosis son las caspasas (proteasas especificas de aspartato que contiene cisteína). Las caspasas son proteasas fuertes, que clivan después de los residuos de ácido aspártico y una vez activadas, digieren las proteínas celulares vitales desde dentro de la célula. Desde que en razón a que las caspasas son proteasas fuertes, el estricto control de esta familia de proteínas es necesario para evitar la muerte celular prematura. En general, las caspasas son

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sintetizadas como zimógenos grandemente inactivos que requieren procesamiento proteolítico por el fin de ser activos. Este procesamiento proteolítico es solamente una de las maneras en las cuales las caspasas son reguladas. El segundo mecanismo es a través de una familia de proteínas que se une e inhibe las caspasas.

Una familia de moléculas que inhibe las caspasas son las Inhibitorias de Apoptosis (IAP)(Deveraux et al., J Clin Immunol (1999), 19:388-398). Las IAP fueron originalmente descubiertas en baculovirus por su capacidad funcional para sustituir la proteína P35, y el gen anti-apoptósico (Crook et al., (1993) J Virogoy 67, 2168-2174). Las IAP se han descrito en organismos que varían desde *Drosofila* a humanos. Sin importar su origen, estructuralmente, las IAP comprenden uno a tres dominios de repeticiones IAP de Baculovirus (BIR), y la mayoría de ellas también poseen un motivo de dedo RING carboxiterminal. El dominio BIR en si mismo es un dominio que se une a zinc y aproximadamente 70 residuos que comprenden 4 hélices alfa y tres hebras beta, con residuos de cisteína e histidina que coordinan el ion zinc (Hinds et, al (1999) Nat. Struct. Biol. 6, 648-651). Este es el dominio BIR que se cree que origina el efecto antiapoptósico al inhibir las caspasas y así inhibir la apoptosis. Como un ejemplo, el cromosoma X humano ligado a IAP (XIAP) inhibe la casposa 3, casposa 7 y la activación mediada por C del citrocromo Apaf-1 de la caspasa 9 (Deveraux et al., (1998) EMBO J. 17, 2215-2223). Las caspasas 3 y 7 son inhibidas por el dominio BIR2 del XIAP, mientras que el dominio BIR3 del XIAP es responsable por la inhibición de la actividad de la caspasa 9. El XIAP se expresa

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ubicuamente en la mayoría de los adultos en tejidos fetales (Liston et al, Nature, 1996, 379(6563):349), y se sobre expresa en un número de líneas celulares de tumor del panel de la línea celular NCI 60 (Fong et al, Genomics, 2000, 70:113; Tamm et al, Clin. Cáncer Res. 2000, 6(5):1796). La sobre expresión del XIAP en células de tumor ha demostrado que confiere protección contra una variedad de estímulos proapoptósicos y promueve resistencia a quimioterapia (LaCasse et al, Oncogene, 1998, 17(25):3247). Consistente con esto, una fuerte correlación entre los niveles de proteína XIAP y la supervivencia se ha demostrado para pacientes con leucemia mielogena aguda (Tamm et al, supra). La infraregulación de la expresión XIAP mediante oligonucleótidos contra sentido se ha mostrado que sensibiliza las células tumorales a la muerte inducida mediante un amplio rango de agentes proapoptósicos, tanto *in vitro* como *in vivo* (Sasaki et al, Cáncer Res., 2000, 60(20):5659; Lin et al, Biochem J., 2001, 353;299; Hu et al, Clin. Cancer Res., 2003, 9(7):2826). Los péptidos derivados de Smac/DIABLO se han demostrado que sensibilizan un número de diferentes líneas celulares tumulares a la apoptosis inducida mediante una variedad de drogas proapoptósicas (Arnt et al, J. Biol. Chem., 2002, 277(46):44236; Fulda et al, Nature Med., 2002, 8(8):808; Guo et al, Blood, 2002, 99(9):3419; Vucic et al, J. Biol. Chem., 2002, 277(14):12275; Yang et al, Cancer Res., 2003, 63(4):831).

El melanoma IAP (ML-IAP) es un IAP no detectable en la mayoría de los tejidos de adulto normales pero es fuertemente sobrerregulado el melanoma (Vucic et al., (2000) Current Bio 10:1359-1366). La determinación de la estructura de proteína demostró homologia

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significativa de los dominios de dedo ML-IAP BIR y RING a los correspondientes dominios presentes en el XIAP, C-IAP1 y C-IAP2 humano. El dominio BIR del ML-IAP las mayores similitudes con el BIR2 y el BIR3 del XIAP, C-IAP1 y C-IAP2, y parece ser responsable de la inhibición de apoptosis, determinado mediante análisis de supresión. Adicionalmente, Vucic et al., demostró que ML-IAP podía inhibir el agente quimioterapéutico inducido por apoptosis. Los agentes tales como la adriamicina y el butilfenol 4-terciario (4-TBP) se desarrollaron en un sistema de cultivo celular de melanomas que sobreexpresan ML-IAP y de agentes quimioterapéuticos fueron significativamente menos efectivos para matar las células cuando se compararon con un control de melanocito normal. El mecanismo mediante el cual el ML-IAP produce una actividad antiapoptósica está en parte a través de la inhibición de la caspasa 3 y 9. El ML-IAP no inhibe efectivamente las caspasas 1, 2, 6 u 8.

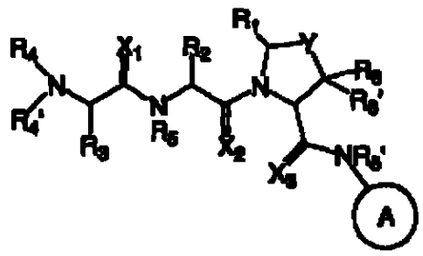
En razón a que la apoptosis es una senda estrictamente controlada con múltiples factores interactuantes, el descubriendo de que los IAP mismos son regulados no fue usual. En la mosca de fruta Drosofila, el Reaper (rpr), el Defecto de involución de Cabeza (hid) y las proteínas GRIM físicamente interactúan e inhiben la actividad antiapoptósica de la familia Drosofila de los IAP. En el mamífero, las proteínas SMAC/DIABLO actúan para bloquear los IAP y permiten la apoptosis que procede a la apoptosis. Se mostró que durante la apotosis normal, el SMAC es procesado en una forma activa y es liberado de las mitocondrias en el citoplasma donde éste se une al IAP y evita que el IAP se una a la caspasa. La inhibición de los IAP le permite a la caspasa permanecer activa y

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así proceder con la apoptosis. De manera interesante, la homología de secuencia entre los inhibidores IAP muestra que existe un motivo de cuatro aminoácidos en el N-terminal de las proteínas procesadas, activas. Este tetrapéptido parece unirse en un bolsillo hidrófobo en el dominio BIR e irrumpe el dominio BIR que se une a las caspasas (Chai et al., (2000) Nature 406:855-862, Liu et al., (2000) Nature 408: 1004-1008, Wu et al., (2000) Nature 408 1008-1012).

RESUMEN DE LA INVENCIÓN

En un aspecto de la presente invención se suministra inhibidores novedosos de proteínas IAP que tienen la fórmula general (I)



I

en donde

X_1, X_2 y X_3 son independientemente O o S.

Y es $(CHR_7)_n$, O o S; en donde n es 1 o 2 y R_7 es H, halógeno, alquilo, arilo, aralquilo, amino, arilamino, alquilamino, aralquilamino, alcoxi, ariloxio o aralquiloxi;

A es un heterociclo de 5 miembros que comprende 1 a 4 heteroátomos opcionalmente sustituidos con amino, hidroxilo, mercapto, halógeno, carboxilo, amidino, guanidino, alquilo,

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alcoxi, arilo, ariloxi, acilo, aciloxi, acilamino, alcoxicarbonilo, cicloalquilo, alquiltio, alquilsulfinilo, alquilsulfonilo, aminosulfonilo, alquilaminosulfonilo, alquilsulfonilamino, o un heterociclo; en donde cada sustitución de alquilo, alcoxi, arilo, ariloxi, acilo, aciloxi, acilamino, cicloalquilo y heterociclo es opcionalmente sustituido con hidroxilo, halógeno, mercapto, carboxilo, alquilo, alcoxi, haloalquilo, amino, nitro, ciano, cicloalquilo, arilo o un heterociclo;

R_1 es H o R_1 y R_2 juntos forman un anillo de 5-8 miembros;

R_2 es alquilo, cicloalquilo, cicloalquilalquilo, arilo, aralquilo, un heterociclo o heterocicloalquilo; uno opcionalmente sustituido con hidroxilo, mercapto, halógeno, amino, carboxilo, alquilo, haloalquilo, alcoxi o alquiltio;

R_3 es H o alquilo;

R_4 y R_4' son independientemente H, hidroxilo, amino, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo, o heteroarilalquilo en donde cada alquilo, arilo, aralquilo, cicloalquilalquilo, heteroarilo y heteroarilalquilo es opcionalmente sustituido con halógeno, hidroxilo, mercapto, carboxilo, alquilo, alcoxi, amino y nitro.

R_5, y R_5' son cada uno independientemente H o alquilo;

R_6, y R_6' son cada uno independientemente H, alquilo, arilo o aralquilo;

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Y sales y solvatos de estos.

En otro aspecto de la invención, se suministran composiciones que comprenden los compuestos de la fórmula I y un vehiculo, diluyente o excipiente.

En otro aspecto de la invención, se suministra un método para inducir la apoptosis en una célula que comprende introducir en dicha célula un compuesto de fórmula I.

En otro aspecto de la invención, se suministra un método para sensibilizar una célula o una señal apoptótica que comprende introducir dicha célula a un compuesto de fórmula I.

En otro aspecto de la invención, se suministra un método para inhibir la unión de una proteína IAP a una proteína caspasa que comprende poner en contacto dicha proteína IAP con un compuesto de fórmula I.

En otro aspecto de la invención, se suministra un método para tratar una enfermedad o condición asociada con la sobre expresión de una proteína IAP en un mamífero, que comprende administrar a dicho mamífero una cantidad efectiva de un compuesto de fórmula I.

DESCRIPCIÓN DETALLADA DE LAS MODALIDADES PREFERIDAS

"Alquilo" significa un grupo hidrocarburo alifático ramificado o no ramificado, saturado o insaturado (es decir, alquenilo,

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alquinilo), que tiene hasta 12 átomos de carbono a menos que se especifique otra cosa. Cuando se utiliza como parte de otro termino, por ejemplo "alquilamino", en la porción alquilo es preferiblemente una cadena de hidrocarburo saturado, sin embargo también incluye cadenas de carbono de hidrocarburo insaturadas tales como "alquenilamino" y "alquinilamino". Ejemplos de grupos alquilo preferidos incluyen metilo, etilo, n-propilo, isopropilo, n-butilo, iso-butil, sec-butilo, terc-butilo, n-pentilo, 2-metilbutilo, 2,2-dimetilpropilo, n-hexilo, 2-metilpentilo, 2,2-dimetilbutilo, n-heptilo, 2-metilhexilo, y similares. Los términos "alquilo inferior" "alquilo C_1-C_4" y "alquilo de 1 a 4 átomos de carbono" son sinónimos y se utilizan intercambiablemente para significar metilo, etilo, 1-propilo, isopropilo, ciclopropilo, 1-butilo, sec-butilo o t-butilo. A menos que se especifique, los grupos alquilo sustituidos pueden contener 1 (preferiblemente), dos, tres o cuatro sustituyentes que pueden ser iguales o diferentes. Ejemplos de los grupos alquilo anteriores sustituidos incluyen, pero no están limitados a; cianometilo, nitrometilo, hidroximetilo, tritiloximetilo, propioniloximetilo, aminometilo, carboximetilo, carboxietilo, carboxipropilo, alquiloxicarbonilmetilo, aliloxicarbonilaminometilo, varbamoiloximetilo, metoximetilo, etoximetilo, t-butoximetilo, acetoximetilo, clorometilo, bromometilo, yodometilo, trifluorometilo, 6-hidroxihexilo, 2,4-dicloro(n-butilo), 2-amino(iso-propilo), 2-carbamoiloxietilo y similares. El grupo alquilo también puede ser sustituido por un grupo carbociclo. Ejemplos incluyen ciclopropilmetilo, ciclobutilmetilo, ciclopentilmetilo, y grupos ciclohexilmetilo, así como también los correspondientes grupos -etilo, -propilo, -

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butilo, -pentilo, -hexilo, etc. Los alquilos sustituidos preferidos son metilos sustituidos por ejemplo grupo metilo sustituido por los mismos sustituyentes que el grupo "alquilo C_n-C_m sustituido". Ejemplos de grupo metilo sustituido incluyen grupos tales como hidroximetilo protegido (por ejemplo tetrahidropiraniloximetilo), acetiloximetilo, carbamoiloximetilo, trifluorometilo, clorometilo, carboximetilo, bromometilo y yodometilo.

"Amidina" denota un grupo -C(NH)-NHR en donde R es H o alquilo o aralquilo. Una amidina preferida es el grupo $-NH-C(NH)-NH_2$.

"Amino" denota aminas primarias (es decir $-NH_2$), secundarias (es decir -NRH) y terciarias (es decir -NRR). Las aminas secundarias y terceras preferidas son alquilamina, dialquilamina, arilaminia, diarilamina, aralquilamina, y diaralquilamina. Las aminas secundarias y terciarias preferidas particulares son metilamina, etilamina, propilamina, isopropilamina, fenilamina, bencilamina, dimetilamina, dietilamina, diopropilamina y dispopropilamina.

"Grupo protector amino" como se utiliza aquí se refiere a un derivado de los grupos comúnmente empleados para bloquear o proteger un grupo amino mientras que las reacciones son llevadas a cabo sobre otros grupos funcionales sobre el compuesto. Ejemplos de tales grupos protectores incluyen grupos carbamatos, amidas, alquilo y arilo, iminas, así como también muchos derivados de N-heteroátomos los cuales se pueden remover para generar el grupo amida deseado. Los grupos protectores amino preferidos son Boc, Fmoc y Cbz. Ejemplos adicionales de estos

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grupos se encuentran en T. W. Greene y P.G. M. Wuts "Protective Groups in Organic Synthesis", 2nd ed., John Wiley & Sons, Inc., New York, NY, 1991, chapter 7; E. Haslam, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, y T.W. Greene "Protective Groups in Organic Synthesis", John Wiley Sons, New York, NY, 1981. El termino "amino protegido" se refiere a un grupo amino sustituido con uno de los grupos protectores amino anteriores.

"Arilo" cuando se utiliza solo o como parte de otro termino significa un grupo aromático carbocíclico sea o no fusionado que tiene el número de átomos de carbono designado o sin ningún número es designado, hasta 14 átomos de carbono. Los grupos arilo preferidos incluyen fenilo, naftilo, bifenilo, fenantrenilo, naftacenilo, y similares (see e.g. *Lang's Handbook of Chemistry* (Dean, J. A., ed) 13th ed. Table 7-2 [1985]) y más preferido fenilo. El fenilo sustituido o el arilo sustituido denota al grupo fenilo o un grupo arilo sustituido con uno, dos, tres, cuatro o cinco, preferiblemente 1-2, 1-3 o 1-4 sustituyentes escogidos, al menos que se especifique otra cosa, de halógeno (F, Cl, Br, I), hidroxi, hidroxi protegido, ciano, nitro, alquilo (preferiblemente alquilo C_1-C_6), alcoxi (preferiblemente alcoxi C_1-C_6), benciloxi, carboxi, carboxi protegido, carboximetilo, carboxi metilo protegido, hidroximetilo, hidroximetilo protegido, aminometilo, aminometilo protegido, trifluorometilo, alquilsulfonilamino, arilosulfonilamino, heterociclilsulfonilamino, heterociclilo, arilo, o otros grupos especificados. Uno o más grupos metilo (CH) y/o metileno (CH_2) en estos sustituyentes pueden a sus vea ser sustituidos con un grupo

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similar a aquellos denotados anteriormente. Ejemplos de termino "fenilo sustituido" incluyen pero no están limitados a un grupo mono- o di(halo)fenilo tal como 2-clorofenilo, 2-bromofenilo, 4-clorofenilo, 2,6-diclorofenilo, 2,5-diclorofenilo, 3,4-diclorofenilo, 3-clorofenilo, 3-bromofenilo, 4-bromofenilo, 3,4-dibromofenilo, 3-cloro-4-fluorofenilo, 2-fluorofenilo y similares; un grupo mono- o di(hidroxi)fenilo tal como 4-hidroxifenilo, 3-hidroxifenilo, 2,4-dihidroxifenilo, los derivados hidroxi protegidos de estos y similares; el grupo nitrofenilo tal como 3- o 4-nitrofenilo; un grupo cianofenilo, por ejemplo, 4-cianofenilo; un grupo mono- o di(alquilo inferior)fenilo tal como 4-metilfenilo, 2,4-dimetilfenilo, 2-metilfenilo, 4-(iso-propil)fenilo, 4-etilfenilo, 3-(n-propil)fenilo y similares; un grupo mono o di(alcóxi)fenilo, por ejemplo, 3,4-dimetoxifenilo, 3-metoxi-4-benciloxifenilo, 3-metoxi-4-(1-clorometil)benciloxi-fenilo, 3-etoxifenilo, 4-(isopropoxi)fenilo, 4-(t-butoxi)fenilo, 3-etoxi-4-metoxifenilo y similares; 3- o 4- trifluorometilfenilo; un grupo mono- o dicarboxifenilo o (carboxi protegido)fenilo tal como 4-carboxifenilo, ; un mono- o di(hidroximetil)fenilo o (hidroximetil protegido)fenilo tal como 3-(hidroximetil protegido)fenilo o 3,4-di(hidroximetil)fenilo; un mono- o di(aminometil)fenilo o (aminometil protegido)fenilo tal como 2-(aminometil)fenilo o 2,4- (aminometil protegido)fenilo; o un mono- o di(N-(metilsulfonilamino))fenilo tal como 3-(N-metilsulfonilamino))fenilo. También, el termino "fenilo sustituido" representa grupos fenilos en y sustituidos donde los sustituyentes son diferentes, por ejemplo, 3-metil-4-hidroxifenilo, 3-cloro-4-hidroxifenilo, 2-metoxi-4-bromofenilo,

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4-etil-2-hidroxifenilo, 3-hidroxi-4-nitrofenilo, 2-hidroxi-4-clorofenilo, y similares, así como también grupos fenilo trisustituidos donde los sustituyentes son diferentes, por ejemplo 3-metoxi-4-benciloxi-6-metil sulfonilamino, 3-metoxi-4-benciloxi-6-fenil sulfonilamino, y grupos fenilos tetrasustituidos donde los sustituyentes son diferentes tal como 3-metoxi-4-benciloxi-5-metil-6-fenilo sulfonilamino. Los grupos fenilo sustituidos preferidos incluyen los grupos 2-clorofenilo, 2-aminofenilo, 2-bromofenilo, 3-metoxifenilo, 3-etoxi-fenilo, 4-benciloxifenilo, 4-metoxifenilo, 3-etoxi-4-benciloxifenilo, 3,4-dietoxifenilo, 3-metoxi-4-benciloxifenilo, 3-metoxi-4-(1-clorometil)benciloxi-fenilo, 3-metoxi-4-(1-clorometil)benciloxi - 6- metilo sulfonilo aminofenilo. Los anillos de arilo fusionados también se pueden sustituir con cualquiera, preferiblemente 1, 2 o 3, de los sustituyentes especificados aquí de la misma manera que los grupos alquilo sustituidos.

"Carbociclilo", "carbociclilico", "carbociclo" y "carbociclo" solos o cuando se utilizan como una porción en un grupo complejo tal como un grupo un grupo carbocicloalquilo, se refieren a unos anillos mono-, bi-, o triciclico alifático que tiene 3 a 14 átomos de carbono y preferiblemente 3 a 7 átomos de carbono que pueden ser saturados e insaturados, aromáticos o no aromáticos. Los grupos carboxílicos saturados preferidos incluyen ciclopropilo, ciclobutilo, ciclopentilo y grupo ciclohexilo y más preferido son ciclopropilo y ciclohexilo y más preferido es ciclohexilo. Los cabociclo insaturados preferidos son aromáticos por ejemplo grupos arilo como se definió previamente, los más preferidos siendo fenilo. Los términos "carbociclilo sustituido",

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"carbociclo" y "carbociclo" significan estos grupos sustituidos por los mismos sustituyentes que el grupo "alquilo sustituido".

"Grupo protector carboxi" como se utiliza aquí se refiere a uno de los derivados de éster de grupo de ácido carboxílico comúnmente empleado para bloquear o proteger el grupo de ácido carboxílico mientras que loas reacciones son llevadas a cabo sobre otros grupos funcionales sobre el compuesto. Ejemplos de tales grupos protectores de ácido carboxílico incluyen 4-nitrobencilo, 4-metoxibencilo, 3,4-dimetoxibencilo, 2,4-dimetoxibencilo, 2,4,6-trimetoxibencilo, 2,4,6-trimetilbencilo, pentametilbencilo, 3,4-metilenedioxibencilo, bencidrilo, 4,4'-dimetoxibecidrilo, 2,2' ,4,4'-tetrametoxibencidrilo, alquilo tal como t-butilo o t-amilo, tritolo, 4-metoxitritilo, 4,4'-dimetoxitritilo, 4,4',4''trimetoxitritilo, 2-feniloprop-2-ilo, trimetilsililo, t-butildimetilsililo, fenacilo, 2,2,2-tricloroetilo, beta-(trimetilsilil)etilo, beta-(di(n-butil)metilsilil)etilo, p-toluenesulfoniloetilo, 4-nitrobencilsulfoniloetilo, alilo, cinamolo, 1-(trimetilsililmetil)prop-1-en-3-ilo, y porciones similares. Las especies de los grupos protectores carboxi empleadas no son críticas en tanto que el ácido carboxílico derivado sea estable a la condición del o las reacciones subsecuentes sobre otras posiciones de la molécula y se puedan remover en el punto apropiado sin afectar el resto de la molécula. En particular, es importante no someter la molécula de carboxi protegida a bases nucleofílicas fuertes, tales como hidróxido de litio o NaOH, o condiciones reductoras que empleen hidruros de metal altamente activados tales como $LiAlH_4$. (Tales condiciones de remoción

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rigurosas se evitan también cuando se remueven los grupos amino protegidos y los grupos hidroxi protegidos, discutidos adelante). Los grupos protectores de ácido carboxílico preferidos son el alquilo (por ejemplo metilo, etilo, t-butilo), alilo, bencilo y p-nitrobencilo. Los grupos carboxi protectores similares utilizados en la técnica de cefalosporina, penicilina y péptidos también se puede utilizar para proteger sustituyentes del grupo carboxi. Ejemplos adicionales de estos grupos se encuentran en T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley & Sons, Inc., New York, N. Y., 1991, chapter 5; E. Haslam, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, N. Y., 1973, Chapter 5, and T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1981, Chapter 5. El término "carboxi protegido" se refiere a un grupo carboxi sustituido con uno de los grupos protectores carboxi anteriores.

"Guanidina" denota el grupo -NH-C(NH)-NHR donde R es H o alquilo o aralquilo. La guanidina preferida es el grupo $-NH-C(NH)-NH_2$.

"El grupo protector Hidroxi" como se utiliza aquí se refiere a un derivado del grupo hidroxi comúnmente empleado para bloquear o proteger el grupo hidroxi mientras que las reacciones son llevadas a cabo sobre otros grupos funcionales sobre el compuesto. Ejemplos de tales grupos protectores incluyen los grupos tetrahidropiraniloxi, benzoilo, acetoxi, carbamoiloxo, bencilo, y sililéteres (por ejemplo TBS, TBDPS). Ejemplos adicionales de estos grupos se encuentran en T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed.,

John Wiley & Sons, Inc., New York, NY, 1991, chapters 2-3; E. Haslam, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, and T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1981. El término "hidroxi protegido" se refiere a un grupo hidroxi sustituido con uno de los grupos protectores hidroxi anteriores.

"Grupo heterocíclico", "heterocíclico", "heterociclo", "heterociclilo", o "heterociclo" solo o cuando se utiliza como una porción en un grupo complejo tal como el grupo de heterocicloalquilo, se utiliza intercambiablemente y se refiere a cualquier anillo aromático (heteroarilo) o no aromático mono-, bi-, o tricíclico, saturado o insaturado que tiene el número de átomos designado, generalmente de 5 a aproximadamente 14 átomos por anillo, en donde los átomos por anillos son carbón y al menos un heteroátomo (nitrógeno, sulfuro o oxígeno) y preferiblemente 1 a 4 heteroátomos. Típicamente, un anillo de 5 miembros 0 a 2 dobles enlaces y un anillo de 6 o 7 tiene 0 a 3 dobles enlaces y los heteroátomos de nitrógeno o azufre pueden opcionalmente oxidados (por ejemplo SO, SO_2), y cualquier heteroátomo de nitrógeno puede opcionalmente ser cuarternarizado. Los heterociclos no aromáticos preferidos no incluyen morfolinilo (morfolino), pirrolidinilo, oxiranilo, oxetanilo, tetrahidrofuranilo, 2,3-dihidrofuranilo, 2H-piranilo, tetrahidropiranilo, tiiranilo, tietanilo, tetrahidrotietanilo, aziridinilo, azetidinilo, 1-metil-2-pirrolilo, piperazinilo y piperidinilo. Un grupo "heterocicloalquilo" es un grupo heterociclo como se definió anteriormente covalentemente unido a

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un grupo alquilo como se definió anteriormente. Los heterociclos de 5 miembros preferidos que contienen una toma de azufre de oxígeno y uno a treinta átomos de nitrógeno incluyen tiazolilo, en particular tiazol-2-ilo y tiazol-2-ilo N-óxido, tiadiazolilo, en particular 1,3,4-tiadiazol-5-ilo y 1,2,4-tiadiazol-5-ilo, oxazolilo, preferiblemente oxazol-2-ilo, y oxadiazolilo, tal como 1,3,4-oxadiazol-5-ilo, y 1,2,4-oxadiazol-5-ilo. Los heterociclos para anillo de 5 miembros preferidos contienen 2 a 4 átomos de nitrógeno que incluyen imidazolilo, preferiblemente imidazol-2-ilo; triazolilo, preferiblemente 1,3,4-triazol-5-ilo; 1,2,3-triazol-5-ilo, 1,2,4-triazol-5-ilo, y tetrazolilo, preferiblemente 1H-tetrazol-5-ilo. Los heterociclos de 5 miembros benzofucionados preferidos son, benzoxazol-2-ilo, benzotiazol-2-ilo y benzimidazol-2-ilo. Los heterociclos de 6 miembros que contiene uno a tres átomos de nitrógeno y opcionalmente un átomo de azufre u oxígeno, por ejemplo piridilo, tal como pirid-2-ilo, pirid-3-ilo, y pirid-4-ilo; pirimidilo, preferiblemente pirimid-2-ilo y pirimid-4-ilo; triazinilo, preferiblemente 1,3,4-triazin-2-ilo y 1,3,5-triazin-4-ilo; piridazinilo, en particular piridazin-3-ilo, y pirazinilo. Los N-óxidos de piridina y los N-óxidos piridazina y el piridilo, pirimid-2-ilo, pirimid-4-ilo, piridazinilo y los grupos 1,3,4-triazin-2-ilo, son los grupos preferidos. Los sustituyentes para los heterociclos sustituidos opcionales, y los ejemplos adicionales de un sistema de anillo 5- y 6-miembros discutidos anteriormente se pueden encontrar en W. Druckheimer et al, U.S. Patent No. 4,278,793.

"Heteroarilo" solo o cuando se utiliza como una porción en un grupo complejo tal como un grupo heteroaralquilo, se refiere aun

sistema de anillo aromático mono-, bi-, o tricíclico que tiene el número de átomos designado de al menos un anillo de 5-, 6- o 7 miembros que contiene de uno a cuatro heteroátomos seleccionados del grupo nitrógeno, oxígeno, y azufre, y preferiblemente al menos un heteroátomo que es nitrógeno (*Lang's Handbook of Chemistry, supra*). Incluido en la definición están los grupos bicíclicos donde cualquiera de los anillos heteroarilo anteriores están fusionados a un anillo de benceno. Los heteroarilos en los cuales el nitrógeno o oxígeno es el heteroátomo son los preferidos. Los siguientes sistemas de anillos son ejemplos del heteroarilo (sean grupos sustituidos o no sustituidos) de notados por el término "heteroarilo": tienilo, furilo, imidazolilo, pirazolilo, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, triazolilo, tiadiazolilo, oxadiazolilo, tetrazolilo, tiatriazolilo, oxatriazolilo, piridilo, pirimidilo, pirazinilo, piridazinilo, tiazinilo, oxazinilo, triazinilo, tiadiazinilo, oxadiazinilo, ditiazinilo, dioxazinilo, oxatiazinilo, tetrazinilo, tiatriazinilo, oxatriazinilo, ditiadiazinilo, imidazolinilo, dihidropirimidilo, tetrahidropirimidilo, tetrazolo[1,5-b]piridazinilo y purinilo, así como también derivados benzofucionados, por ejemplo benzoxazolilo, benzofurilo, benzotiazolilo, benzotiadiazolilo, benzotriazolilo, benzoimidazolilo y indolilo. Un grupo particularmente preferido de "heteroarilo" incluye; 1,3-tiazol-2-ilo, sal de 4-(carboximetil)-5-metil-1,3-tiazol-2-ilo, 4-(carboximetil)-5-metil-1,3-tiazol-2-ilo de sodio, 1,2,4-tiadiazol-5-ilo, 3-metil-1,2,4-tiadiazol-5-ilo, 1,3,4-triazol-5-ilo, 2-metil-1,3,4-triazol-5-ilo, 2-hidroxi-1,3,4-triazol-5-ilo, sal de 2-carboxi-4-metil-1,3,4-triazol-5-ilo de sodio, 2-carboxi-4-metil-1,3,4-

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triazol-5-ilo, 1,3-oxazol-2-ilo, 1,3,4-oxadiazol-5-ilo, 2-metil-1,3,4-oxadiazol-5-ilo, 2-(hidroximetil)-1,3,4-oxadiazol-5-ilo, 1,2,4-oxadiazol-5-ilo, 1,3,4-tiadiazol-5-ilo, 2-tiol-1,3,4-tiadiazol-5-ilo, 2-(metiltio)-1,3,4-tiadiazol-5-ilo, 2-amino-1,3,4-tiadiazol-5-ilo, 1H-tetrazol-5-ilo, 1-metil-1H-tetrazol-5-ilo, 1-(1-(dimetilamino)eth-2-ilo)-1H-tetrazol-5-ilo, 1-(carboximetil)-1H-tetrazol-5-ilo, sal de 1-(carboximetil)-1H-tetrazol-5-ilo de sodio, 1-(ácido metilsulfónico)-1H-tetrazol-5-ilo, sal de 1-(ácido metilsulfónic)-1H-tetrazol-5-ilo de sodio, 2-metil-1H-tetrazol-5-ilo, 1,2,3-triazol-5-ilo, 1-metil-1,2,3-triazol-5-ilo, 2-metil-1,2,3-triazol-5-ilo, 4-metil-1,2,3-triazol-5-ilo, pirid-2-ilo N-óxido, 6-metoxi-2-(n-óxido)-piridaz-3-ilo, 6-hidroxipiridaz-3-ilo, 1-metilpirid-2-ilo, 1-metilpirid-4-ilo, 2-hidroxipirimid-4-ilo, 1,4,5,6-tetrahidro-5,6-dioxo-4-metil-as-triazin-3-ilo, 1,4,5,6-tetrahidro-4-(formilmetil)-5,6-dioxo-as-triazin-3-ilo, 2,5-dihidro-5-oxo-6-hidroxi-astriazin-3-ilo, sal de 2,5-dihidro-5-oxo-6-hidroxi-as-triazin-3-ilo de sodio, sal de 2,5-dihidro-5-oxo-6-hidroxi-2-metil-astriazin-3-ilo de sodio, 2,5-dihidro-5-oxo-6-hidroxi-2-metil-as-triazin-3-ilo, 2,5-dihidro-5-oxo-6-metoxi-2-metil-as-triazin-3-ilo, 2,5-dihidro-5-oxo-as-triazin-3-ilo, 2,5-dihidro-5-oxo-2-metil-as-triazin-3-ilo, 2,5-dihidro-5-oxo- 2,6-dimetil-as-triazin-3-ilo, tetrazolo [1,5-b]piridazin-6-ilo y 8-aminotetrazolo[1,5-b]-piridazin-6-ilo. Un grupo alternativo de "heteroarilo" incluye; 4-(carboximetil)-5-metil-1,3-thiazol-2-ilo, sal de 4-(carboximetil)-5-metil-1,3-tiazol-2-ilo de sodio, 1,3,4-triazol-5-ilo, 2-metil-1,3,4-triazol-5-ilo, 1H-tetrazol-5-ilo, 1-metil-1H-tetrazol-5-ilo, 1-(1-(dimetilamino)eth-2-ilo)-1H-tetrazol-5-ilo, 1-(carboximetil)-1H-tetrazol-5-ilo, sal de 1-(carboximetil)-1H-tetrazol-5-ilo de

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sodio, 1-(ácido metilsulfónico)-1H-tetrazol-5-ilo, sal de 1-(ácido metilsulfónico)-1H-tetrazol-5-ilo de sodio, 1,2,3-triazol-5-ilo, 1,4,5,6-tetrahidro-5,6-dioxo-4-metil-as-triazin-3-ilo, 1,4,5,6-tetrahidro-4-(2-formilmetil)-5,6-dioxo-as-triazin-3-ilo, sal de 2,5-dihidro-5-oxo-6-hidroxi-2-metil-as-triazin-3-ilo de sodio, 2,5-dihidro-5-oxo-6-hidroxi-2-metil-as-triazin-3-ilo, tetrazolo[1,5-b]piridazin-6-ilo, y 8-aminotetrazolo[1,5-b]piridazin-6-ilo.

"Inhibidor" significa un compuesto que reduce o previene la unión de las proteínas IAP a las proteínas caspasa o que reduce o previene la inhibición de apoptosis ante una proteína IAP. Alternativamente "inhibidor" significa un compuesto que evita la interacción de unión del X-IAP con las capazas o la interacción de unión de ML-IAP con SMAC.

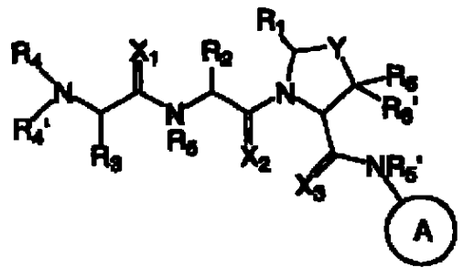
"Sales farmacéuticamente aceptables" incluyen tanto sales de adición ácida como básica. "Sal de adición ácida farmacéuticamente aceptable" se refiere a aquellas sales que retienen la efectividad biológica y las propiedades de las bases libres en las cuales no son biológicamente o de otra manera indeseables, formados con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido carbónico, ácido fosforito y similares, y los ácidos orgánicos se pueden seleccionar de ácidos alifático, cicloalifático, aromático, aralifático, heterocíclico, carboxílico, y las clases sulfonicas de ácidos orgánicos tales como ácido fórmico, ácido acético, ácido propiónico, ácido glicólico, ácido glucónico, ácido láctico, ácido pirúvico, ácido

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oxálico, ácido málico, ácido maléico, ácido maloneico, ácido succínico, ácido fumárico, ácido tartárico, ácido cítrico, ácido aspártico, ácido ascórbico, ácido glutámico, ácido antranílico, ácido benzoico, ácido cinámico, ácido mandélico, ácido embónico, ácido fenilacético, ácido metanosulfónico, ácido etanosulfónico, ácido p-toluenosulfónico, ácido salicílico y similares.

"Sales de adición de base farmacéuticamente aceptables" incluyen aquellas derivadas de bases inorgánicas tales como sales de sodio, potasio, litio, amonio, calcio, magnesio, hierro, zinc, cobre, manganeso, aluminio y similares. Las sales particularmente preferidas son las de amonio, potasio, sodio, calcio y magnesio. Las sales derivadas de bases no tóxicas orgánicas farmacéuticamente aceptables incluyen sales de aminas primarias, secundarias, y terciarias, aminas sustituidas que incluyen aminas sustituidas de ocurrencia natural, aminas cíclicas y resinas de intercambio de ion básicas, tales como isopropilamina, trimetilamina, dietilamina, trietilamina, tripropilaminea, etanolamina, 2-dietilaminoetanol, trimetamina, diclohexilamina, lisina, arginina, histidina, cafeína, procaína, hidrabamina, colina, betaina, etilenodiamina, glucosamina, metilglucamina, teobromina, purinas, piperazina, piperidina, N-etilpiperidina, resinas de poliamina y similares. Las bases no tóxicas orgánicas particularmente preferidas son isopropilamina, dietilamina, etanolamina, trimetilamina, diciclohexilamina, colina, y cafeína. La presente invención suministra compuestos novedosos que tienen la fórmula general I:

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I

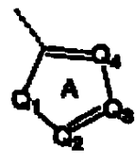
En donde X, Y, A, R_1, R_2, R_3, R_4, R_4', R_5, R_5', R_6 y R_6' se describen aquí.

X_1 y X_2 son cada uno independientemente O o S. En una modalidad preferida, X_1 y X_2 son ambas O. En otra modalidad preferida X_1 y X_2 son ambas S. En otra modalidad preferida, X_1 es S mientras que X_2 es O. En otra modalidad preferida, X_1 es O mientras que X_2 es S.

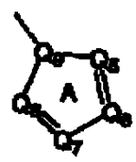
Y es $(CHR_7)_n$, O o S; en donde n es 1 o 2 y R_7 es H, halógeno, alquilo, arilo, aralquilo, amino, arilaminp, alquilamino, aralquilamino, alcoxi, ariloxi o aralquiloxi. En una modalidad particular, Y es CH_2. En una modalidad particular n es 1. En una modalidad particular n es 1 y Y es CHR_7 en donde R_7 es aralquiloxi por ejemplo benziloxi. En una modalidad particular n es 1 y Y es CHR_7 en donde R_7 es F. En una modalidad particular n es 1 y Y es CHR_7 en donde R_7 es aralquilamino, por ejemplo benzilamino. En otra modalidad particular Y es O. En otra modalidad particular Y es S.

El anillo "A" es un heterociclo de 5 miembros que comprenden 1 a 4 heteroátomos opcionalmente sustituidos con amino, hidroxilo, mercapto, halógeno, carboxilo, amidino, guanidino, alquilo, alcoxi, arilo, ariloxi acilo, aciloxi, acilamino,

alcoxicarbonilamino, cicloalquilo, alquiltio, alquilsulfinilo, alquilsulfonilo, aminosulfonilo, alquilaminosulfonilo, alquilsulfonilamino o un heterociclo; en donde cada sustitución de alquilo, alcoxi, arilo, ariloxi, acilo, aciloxi, acilamino, cicloalquilo y heterociclo es opcionalmente sustituido con hidroxilo, halógeno, mercapto, carboxilo, alquilo, alcoxi, haloalquilo, amino, nitro, ciano, cicloalquilo, arilo o un heterociclo. En una modalidad, los grupos A del anillo heterociclo de 5 miembros son opcionalmente sustituidos con amino, hidroxilo, mercapto, halógeno, carboxilo, amidino, guanidino, alquilo, alcoxi, arilo, ariloxi, acilo, aciloxi, acilamino, cicloalquilo o un heterociclo; en donde cada sustitución de alquilo, alcoxi, arilo, ariloxi, acilo, aciloxi, acilamino, cicloalquilo y heterociclo es opcionalmente sustituido con hidroxilo, halógeno, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, cicloalquilo, arilo o un heterociclo. En una modalidad particular el anillo A es aromático. En una modalidad particular el anillo A tiene la fórmula IIa o IIb:



IIa

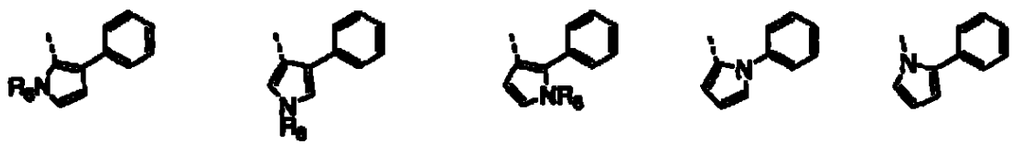


IIb

En donde Q_1 es NR_8, O o S; Q_2, Q_3, Q_4, Q_5, Q_6, Q_7, y Q_8, son independientemente CR_9 o N; en donde R_9 es H, amino, hidroxilo, mercapto, halógeno, carboxilo, amidino, guanidino, alquilo, alcoxi, arilo, ariloxi, acilo, aciloxi, acilamino, cicloalquilo o un heterociclo; en donde cada sustitución alquilo, alcoxi, arilo, ariloxi, acilo, aciloxi, aciloamino, cicloalquilo y heterociclo

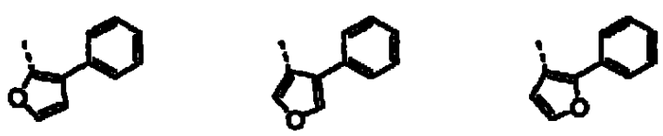
es opcionalmente sustituida con hidroxilo, halógeno, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, cicloalquilo, arilo o un heterociclo; R_8 es H, alquilo, acilo, arilo, cicloalquilo o un heterociclo; en donde cada alquilo, arilo, cicloalquilo y heterociclo es opcionalmente sustituido con hidroxilo, halógeno, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, cicloalquilo, arilo o un heterociclo; y Q_9 es CH o N. En una modalidad particular, el anillo A es un grupo de fórmula II. En una modalidad particular el anillo A es un grupo de fórmula II en donde Q_4 es CR_9 en donde R_9 es arilo o heteroarilo opcionalmente sustituido como se describió anteriormente. En una modalidad particular el anillo A es un grupo de fórmula II en donde Q_4 es CR_9 y R_9 es fenilo. En una modalidad particular, el anillo A es un grupo de fórmula II en donde Q_4 es CR_9 y R_9 es fenilo y Q_3 es CH o CF. En otra modalidad, el anillo A es un grupo de fórmula II en donde Q_4 es CR_9 y R_9 es piridin-2-ilo. En otra modalidad, el anillo A es un grupo de fórmula II en donde Q_4 es CR_9, R_9 es piridin-2-ilo y Q_3 es C-Me.

En otra modalidad, el anillo A de acuerdo con IIa o IIb es un anillo de pirrol opcionalmente sustituido con alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, un heterociclo o un heterociclo-alquilo opcionalmente sustituido con halógeno hidroxilo, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, arilo o heteroarilo. En una modalidad el anillo A está sustituido con un grupo arilo o heteroarilo. En una modalidad particular, el anillo A se selecciona del grupo que consiste de:

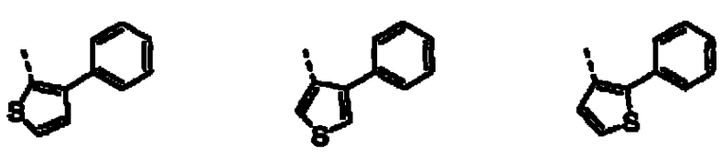


En donde R_8 es H, alquilo (por ejemplo metilo, etilo o propilo) o acilo (por ejemplo acetilo). En una modalidad particular R_8 es H.

En otra modalidad el anillo A es furano opcionalmente sustituido con alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, un heterociclo o un heterociclo-alquilo opcionalmente sustituido con hidroxil halógeno, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, arilo o heteroarilo. En una modalidad el anillo A está sustituido con grupo arilo o heteroarilo. En una modalidad particular, el anillo A se selecciona del grupo que consiste de:

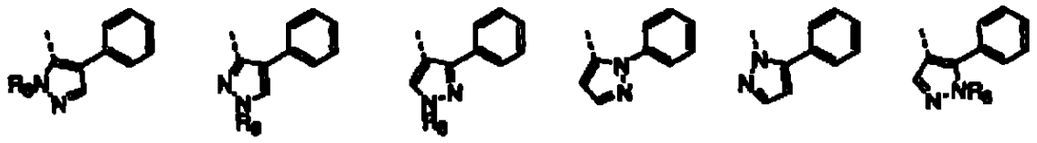


En otra modalidad el anillo A es tiofeno opcionalmente sustituido con alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, un heterociclo o un heterociclo-alquilo opcionalmente sustituido con hidroxil halógeno, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, arilo o heteroarilo. En una modalidad el anillo A está sustituido con un grupo arilo o heteroarilo. En una modalidad particular, el anillo A se selecciona del grupo que consiste de:

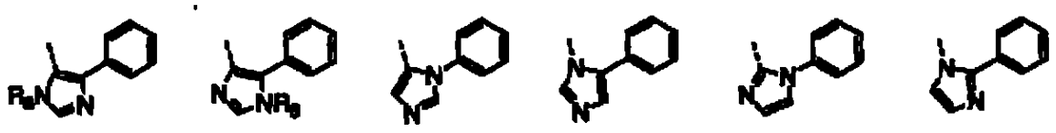


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En una modalidad el anillo A es pirazol opcionalmente sustituido con alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, un heterociclo o un heterociclo-alquilo opcionalmente sustituido con hidroxil halógeno, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, arilo o heteroarilo. En una modalidad el anillo A está sustituido con un grupo arilo o heteroarilo. En una modalidad particular, el anillo A se selecciona del grupo que consiste de:



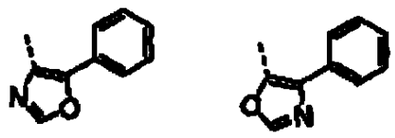
En donde R_8 es H, alquilo (por ejemplo metilo, etilo o propilo) o acilo (por ejemplo acetilo). En una modalidad particular R_8 es H. En otra modalidad el anillo A es imidazol opcionalmente sustituido con alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, un heterociclo o un heterociclo-alquilo opcionalmente sustituido con hidroxil halógeno, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, arilo o heteroarilo. En una modalidad el anillo A está sustituido con un grupo arilo o heteroarilo. En una modalidad particular, el anillo A se selecciona del grupo que consiste de:



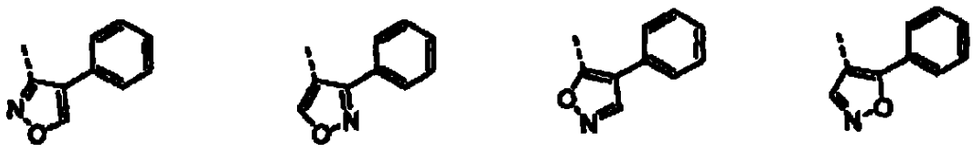
En donde R_8 es H, alquilo (por ejemplo metilo, etilo o propilo) o acilo (por ejemplo acetilo). En una modalidad particular R_8 es H.

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En otra modalidad el anillo A es oxazol opcionalmente sustituido con alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, un heterociclo o un heterociclo-alquilo opcionalmente sustituido con hidroxil halógeno, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, arilo o heteroarilo. En una modalidad el anillo A está sustituido con un grupo arilo o heteroarilo. En una modalidad particular, el anillo A se selecciona del grupo que consiste de:



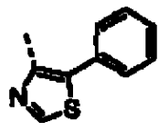
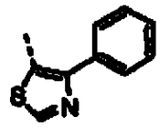
En otra modalidad el anillo A es isoxazol opcionalmente sustituido con alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, un heterociclo o un heterociclo-alquilo opcionalmente sustituido con hidroxil halógeno, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, arilo o heteroarilo. En una modalidad el anillo A está sustituido con un grupo arilo o heteroarilo. En una modalidad particular, el anillo A se selecciona del grupo que consiste de:



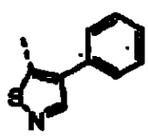
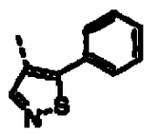
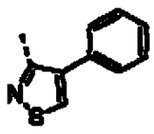
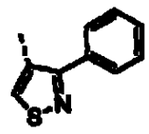
En otra modalidad el anillo A es tiazol opcionalmente sustituido con alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, un heterociclo o un heterociclo-alquilo opcionalmente sustituido con hidroxil halógeno, mercapto, carboxilo, alquilo, haloalquilo,

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amino, nitro, arilo o heteroarilo. En una modalidad el anillo A está sustituido con un grupo arilo o heteroarilo. En una modalidad particular, el anillo A se selecciona del grupo que consiste de:

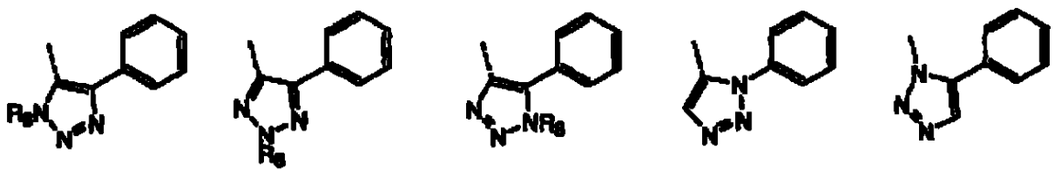



En otra modalidad el anillo A es isotiazol opcionalmente sustituido con alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, un heterociclo o un heterociclo-alquilo opcionalmente sustituido con hidroxil halógeno, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, arilo o heteroarilo. En una modalidad el anillo A está sustituido con un grupo arilo o heteroarilo. En una modalidad particular, el anillo A se selecciona del grupo que consiste de:

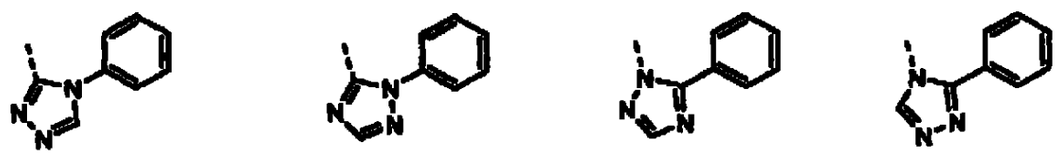





En otra modalidad el anillo A es 1,2,3-triazol opcionalmente sustituido con alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, un heterociclo o un heterociclo-alquilo opcionalmente sustituido con hidroxil halógeno, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, arilo o heteroarilo. En una modalidad el anillo A está sustituido con un grupo arilo o heteroarilo. En una modalidad particular, el anillo A se selecciona del grupo que consiste de:

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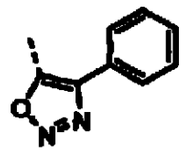
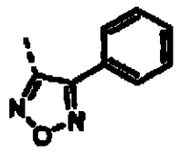
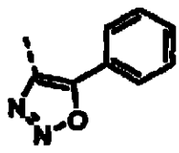


En donde R_8 es H, alquilo (por ejemplo metilo, etilo o propilo) o acilo (por ejemplo acetilo). En una modalidad particular R_8 es H. En otra modalidad el anillo A es 1,2,4-triazol opcionalmente sustituido con alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, un heterociclo o un heterociclo-alquilo opcionalmente sustituido con hidroxil halógeno, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, arilo o heteroarilo. En una modalidad el anillo A está sustituido con un arilo o heteroarilo. En una modalidad particular, el anillo A se selecciona del grupo que consiste de:

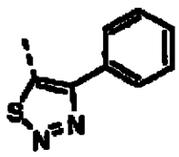
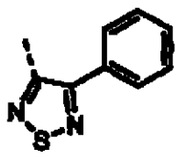
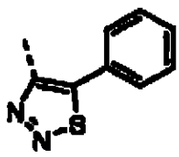


En otra modalidad el anillo A es oxadiazol opcionalmente sustituido con alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, un heterociclo o un heterociclo-alquilo opcionalmente sustituido con hidroxil halógeno, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, arilo o heteroarilo. En una modalidad el anillo A está sustituido con un grupo arilo o heteroarilo. En una modalidad particular, el anillo A se selecciona del grupo que consiste de:

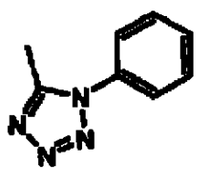
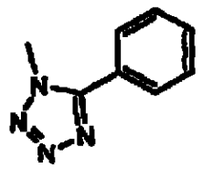
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En otra modalidad el anillo A es tiadiazol opcionalmente sustituido con alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, un heterociclo o un heterociclo-alquilo opcionalmente sustituido con hidroxil halógeno, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, arilo o heteroarilo. En una modalidad el anillo A está sustituido con un grupo arilo o heteroarilo. En una modalidad particular, el anillo A se selecciona del grupo que consiste de:

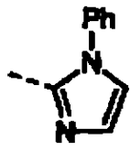




En otra modalidad el anillo A es tetrazol opcionalmente sustituido con alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, un heterociclo o un heterociclo-alquilo opcionalmente sustituido con hidroxil halógeno, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, arilo o heteroarilo. En una modalidad el anillo A está sustituido con un grupo arilo o heteroarilo. En una modalidad particular, el anillo A se selecciona del grupo que consiste de:

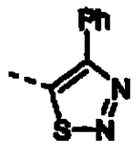



Ent 141

En una modalidad particular el anillo A es:



En una modalidad particular el anillo A es:



R_1 es H o R_1 y R_2 juntos forman un anillo de 5 a 8 miembros. En una modalidad particular, R_1 es H. En una modalidad particular, R_1 y R_2 juntos forman un anillo de 6 miembros. En una modalidad particular, R_1 y R_2 forman juntos un anillo de 7 miembros. En otra modalidad particular, R_1 y R_2 juntos forman un anillo de 8 miembros. En otra modalidad particular, R_1 y R_2 juntos forman un anillo de 7 miembros mientras que Y es S. En otra modalidad particular, R_1 es H, mientras que Y es CH_2. En otra modalidad particular, R_1 es H, mientras que Y es S. En otra modalidad particular, R_1 es H, mientras que Y es O.

R_2 es alquilo, cicloalquilo, cicloalquilalquilo, arilo, aralquilo, un heterociclo o heterociclilalquilo. En una modalidad preferida R_2 es alquilo o cicloalquilo. En una modalidad, cada grupo R_2 es cada uno opcionalmente sustituido con hidroxilo, mercapto, halógeno, amino, carboxilo, alquilo, haloalquilo, alcoxi o alquiltio; En una modalidad de la invención R_2 es t-butilo, isopropilo, ciclohexilo, ciclopentilo o fenilo. En una modalidad particular, R_2 es ciclohexilo. En otra modalidad R_2 es

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tetrahidropiran-4-ilo. En otra modalidad particular, R_2 es isopropilo (es decir la cadena lateral del aminoácido valina). En otra modalidad particular, R_2 es t-butilo. En una modalidad particular R_2 está orientado de tal forma que el aminoácido, o el análogo de aminoácido, que este comprende está en la configuración L. R_3 es H o alquilo. En una modalidad preferida R_3 es H o metilo, etilo, propilo o isopropilo. En una modalidad particularmente preferida R_3 es H o metilo. En una modalidad más preferida R_3 es metilo. En otra modalidad particular, R_3 es t-butilo. En una modalidad preferida R_3 está orientada de tal forma que el aminoácido, o el análogo de aminoácido, que este comprende está en la configuración L.

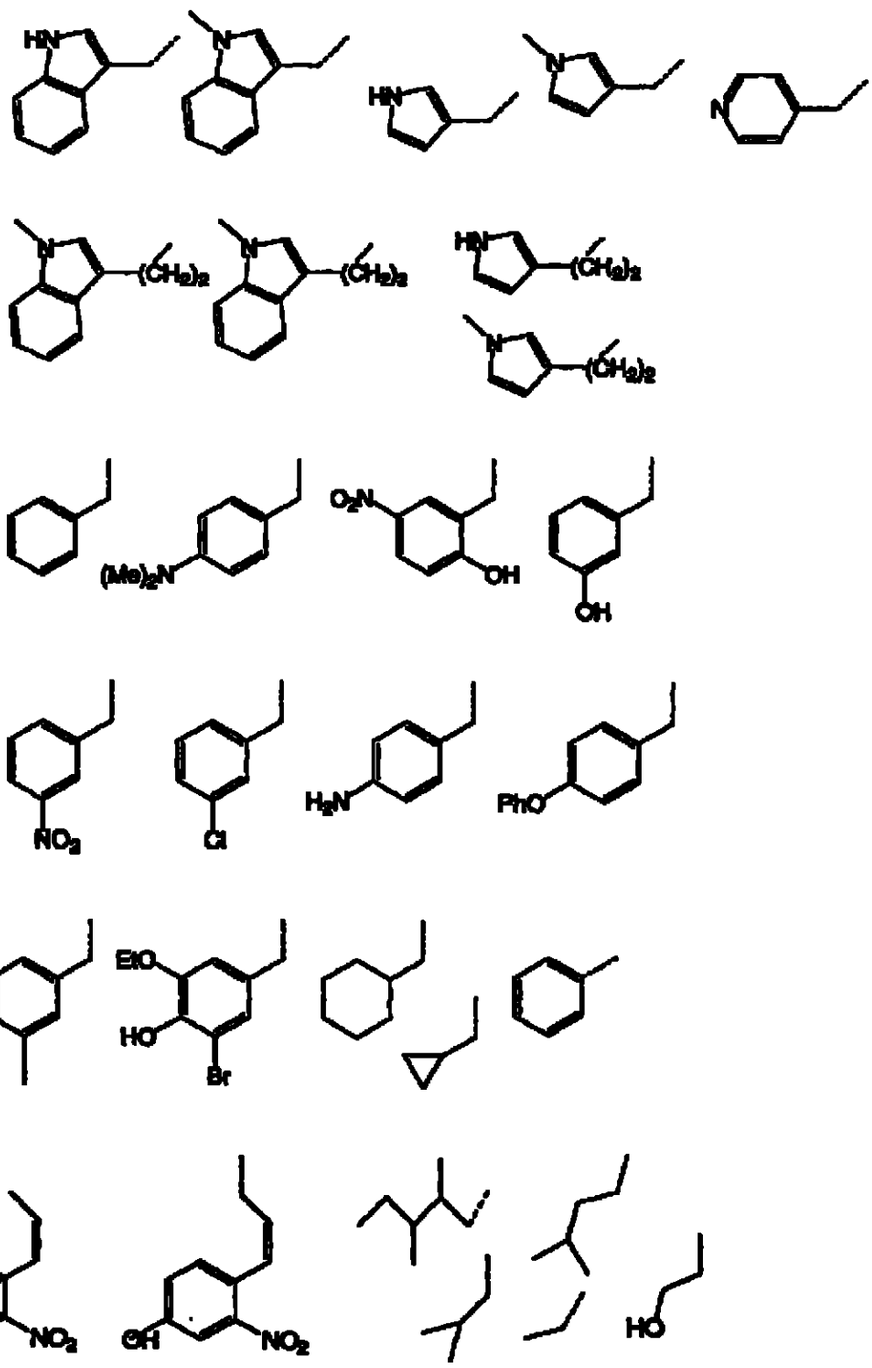
R_4 y R_4' son independientemente H, hidroxilo, amino, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo, o heteroarilalquilo en donde cada alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo y heteroarilalquilo está opcionalmente sustituido con halógeno, hidroxilo, mercapto, carboxilo, alquilo, alcoxi, amino y nitro. En una modalidad particular R_4 y R_4' son ambos H. En otra modalidad particular R_4 es metilo y R_4' es H. En una modalidad particular uno de R_4 y R_4' es hidroxilo (OH) mientras que el otro es H. En otra modalidad, uno de R_4 y R_4' es amino, tal como NH_2, NHMe y NHEt, mientras que el otro es H. En una modalidad particular, R_4' es H y R_4 es H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo o heteroarilalquilo. En una modalidad particular R_4 es un grupo seleccionado del grupo que consiste de:

R_3 es H o alquilo. En una modalidad preferida R_3 es H o metilo, etilo, propilo o isopropilo. En una modalidad particularmente

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preferida R_3 es H o metilo. En una modalidad más preferida R_3 es metilo. En otra modalidad particular, R_3 es t-butilo. En una modalidad preferida R_3 se orienta de tal forma que el aminoácido, o análogo de aminoácido, que este comprende está en la configuración L.

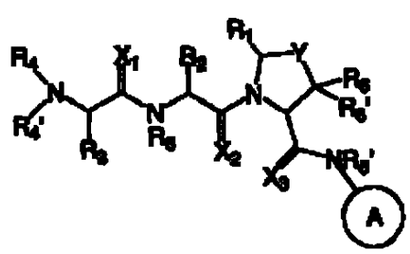
R^4 y $R^{4'}$ son independientemente H, hidroxilo, amino, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo, o heteroarilalquilo en donde cada alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo y heteroarilalquilo se sustituye opcionalmente con halógeno, hidroxilo, mercapto, carboxilo, alquilo, alcoxi, amino y nitro. En una modalidad particular R_4 y R_4' ambos son H. En otra modalidad particular R_4 es metilo y R_4' es H. En una modalidad particular uno de R_4 y R_4' es hidroxilo (OH) mientras que el otro es H. En otra modalidad, un uno de R_4 y R_4' es amino, tal como NH^2, NHMe y NHEt, mientras que el otro es H. En una modalidad particular, R_4' es H y R_4 es H, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo o heteroarilalquilo. En una modalidad particular R_4 es un grupo seleccionado de un grupo que consiste de:



R_5 y R_5' cada uno son independientemente H o alquilo. En una modalidad preferida, R_5 y R_5' son H o metilo. En una modalidad particular, R_5 es H y R_5' es metilo. En otra modalidad particular, R_5 es metilo y R_5' es H. En otra modalidad particular R_5 y R_5' ambos son metilo. En otra modalidad particular, R_5 y R_5' ambos son H.

R_6, y R_6' son cada uno independientemente H, alquilo, arilo o aralquilo. En una modalidad particular, R_6 es alquilo, por ejemplo metilo. En otra modalidad particular R_6 es arilo, por ejemplo fenilo. En otra modalidad particular R_6 es aralquilo, por ejemplo bencilo. En una modalidad particular R_6 y R_6' son los mismos, por ejemplo alquilo, por ejemplo metilo. En otra modalidad particular R_6 es metilo y R_6' es H.

Compuestos de la invención contienen uno o más átomos de carbono asimétricos. De acuerdo con esto, los compuestos pueden existir como diastereómeros, enantiómeros o mezclas de estos. La síntesis de los compuestos puede emplear racematos, diastereómeros o enantiómeros como materiales de partida o como intermediarios. Compuestos diastereoméricos se pueden separar por métodos de cristalización o cromatográficos. De forma similar, las mezclas enantioméricas se pueden separar utilizando las mismas técnicas u otras conocidas en el arte. Cada uno de los átomos de carbono asimétricos puede estar en la configuración R o S y ambas de estas configuraciones están dentro del alcance de la invención. Preferiblemente, los compuestos de la invención tienen la siguiente configuración estereoquímica de fórmula I'.



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en donde X, Y, A, R_1, R_2, R_3, R_4, R_4', R_5, R_5', R_6 Y R_6' son como se describe aquí.

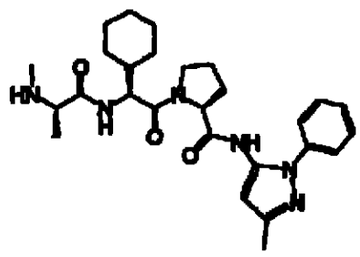
La invención también abarca prodrogas de los compuestos descritos aquí. Prodrogas adecuadas en donde los grupos incluyen grupos amino-protectores y carboxi-protectores los cuales son liberados, por ejemplo hidrolizados, para producir el compuesto pariente bajo condiciones fisiológicas. Una clase preferida de prodrogas son compuestos en los cuales un átomo de nitrógeno en un grupo amino, amidino, aminoalquilenoamino, iminoalquilenoamino o guanidino que se sustituye con un grupo hidroxi (OH), un grupo alquilcarbonilo (-CO-R), un grupo alcoxicarbonilo (-CO-OR), un grupo aciloxialquil- alcoxicarbonilo (-CO-O-R-O-CO-R) en donde R es un grupo monovalente o divalente y se define como la anterior o un grupo que tiene la fórmula -C(O)-O-CP 1P2-haloalquilo, en donde P1 y P2 son los mismos o diferentes y son H, alquilo inferior, alcoxi inferior, ciano, halo alquilo o halo arilo inferior. Preferiblemente el átomo de nitrógeno es uno de los átomos de nitrógeno del grupo amidino de los compuestos de la invención. Estos compuestos de prodroga se preparan al hacer reaccionar los compuestos de la invención descritos anteriormente con un compuesto acilo activo para unión de un átomo de nitrógeno en el compuesto de la invención al carbonilo del compuesto acilo activo. Compuesto carbonilos activos adecuados contienen un buen grupo de salida unido a el carbón carbonilo y que incluye haluros acilo, aminas acilo, sales de piridinio acilo, alcóxidos acilo, en particular fenóxidos acilo tal como p-nitrofenoxi acilo, dinitrofenoxi acilo, fluorofenoxi acilo, y difluorofenoxi acilo. Las reacciones son generalmente exotérmicas y se llevan a cabo en

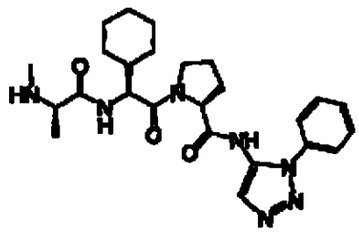
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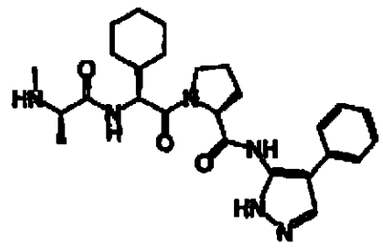
solventes inertes a temperaturas reducidas tal como -78 a aproximadamente 50C. Las reacciones son usualmente llevadas a acabo en la presencia de una base inorgánica tal como carbonato de potasio, bicarbonato de sodio o una base orgánica tal como una amina, que incluye piridina, trietilamina, etc. Una manera de preparar prodrogas se describe en USSN 08/843,369 presentada en Abril 15, 1997 (correspondiente a la publicación PCT WO9846576) los contenidos de los cuales son incorporados aquí como referencia en su totalidad

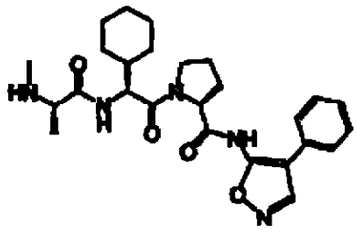
Compuestos particulares de fórmula I incluye los siguientes:

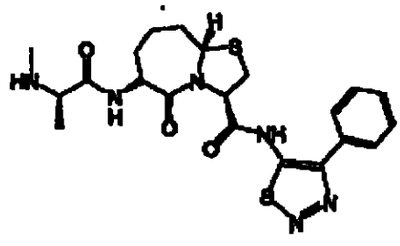
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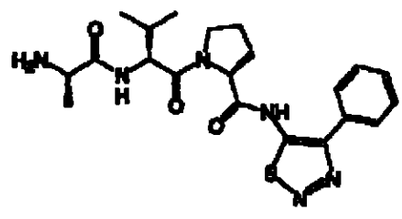
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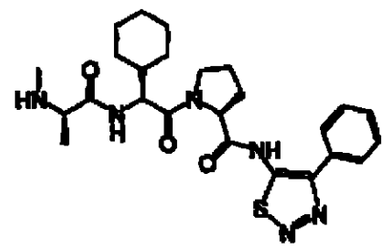
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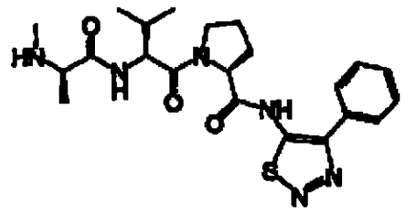
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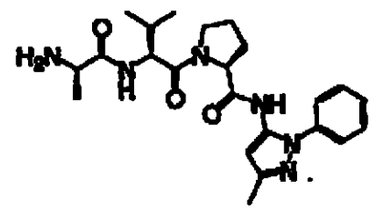
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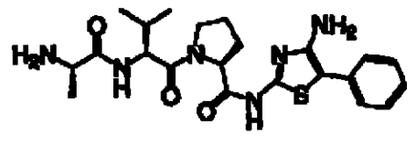
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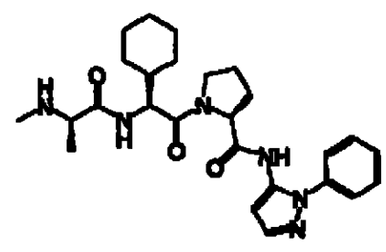
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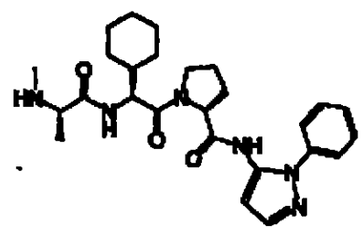
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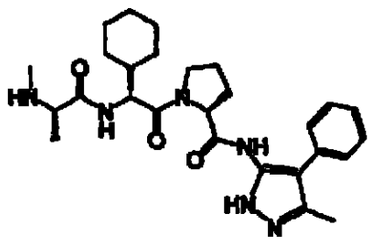
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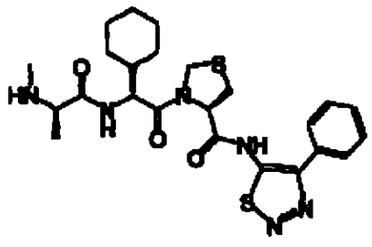
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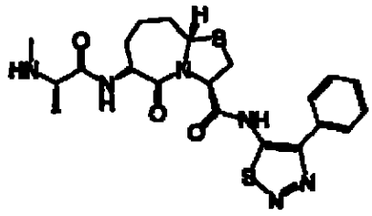
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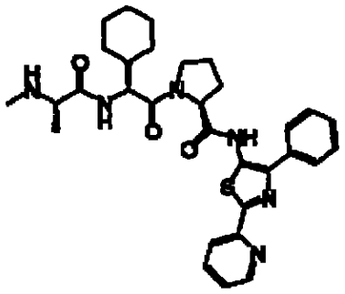
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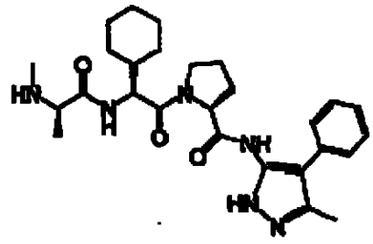
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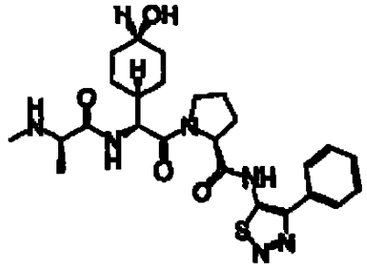
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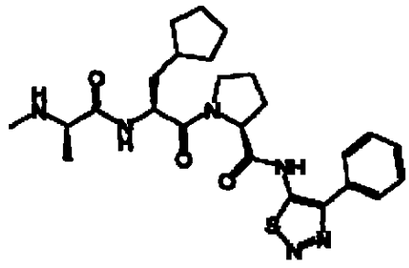
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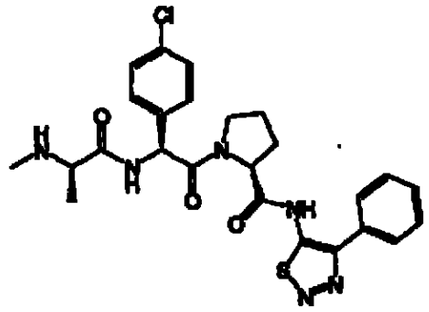
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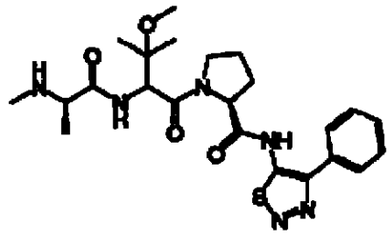
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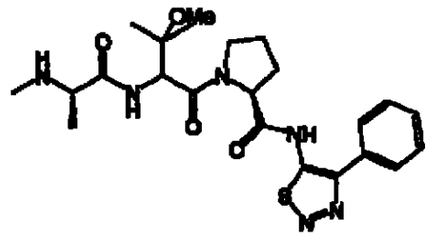
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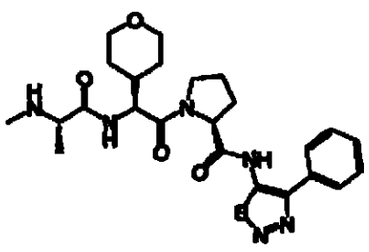
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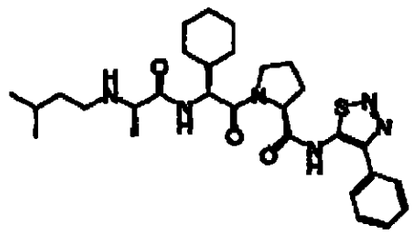
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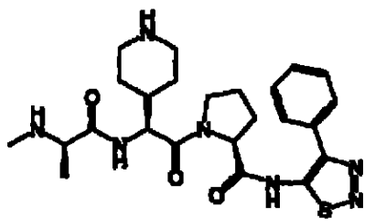
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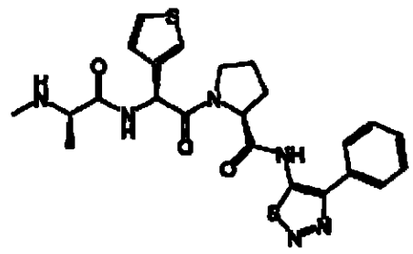
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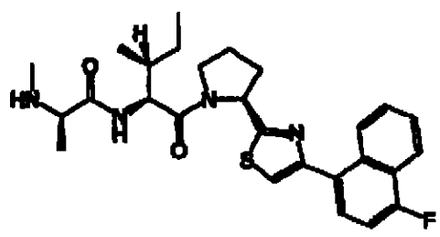
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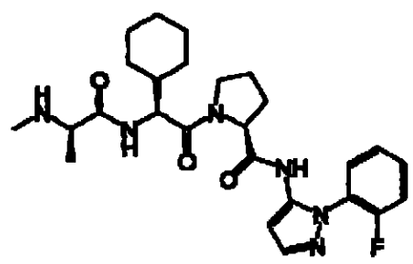
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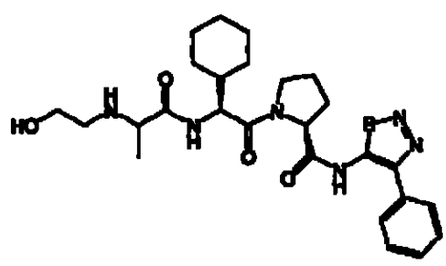
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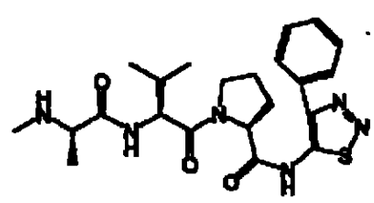
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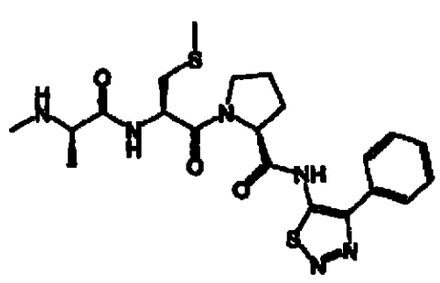
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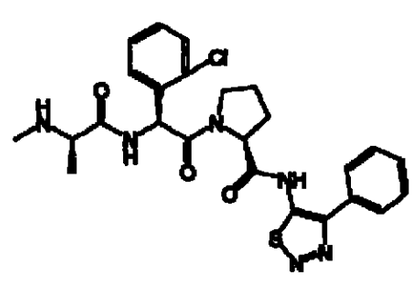
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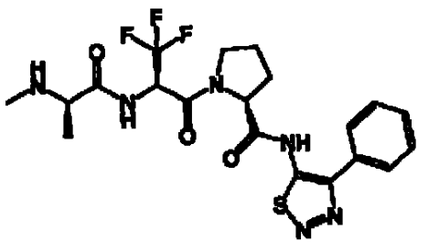


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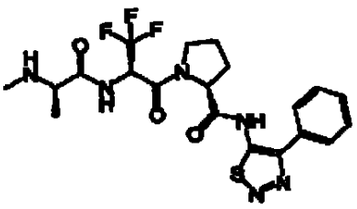


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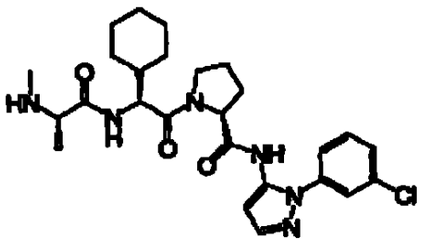
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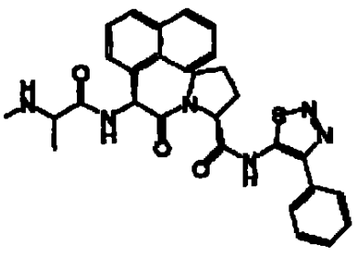
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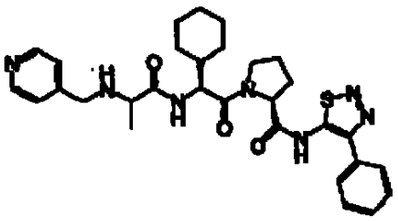
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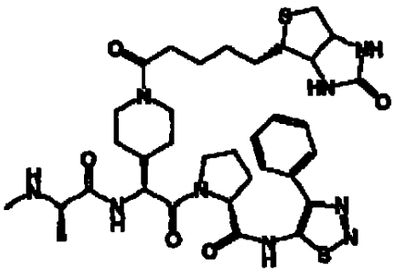
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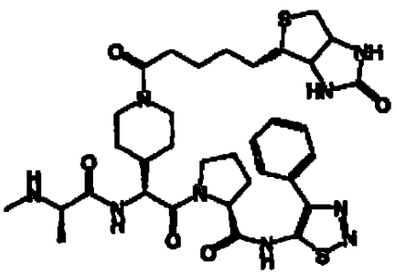
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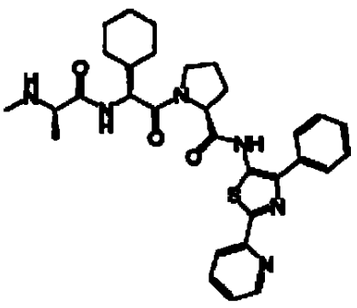
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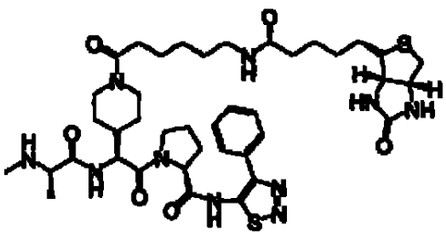
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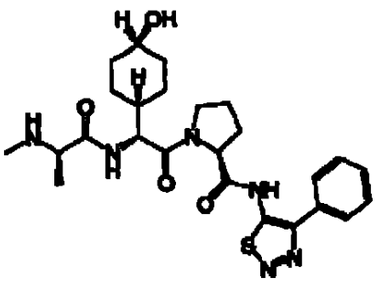
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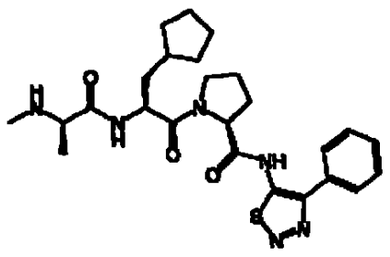


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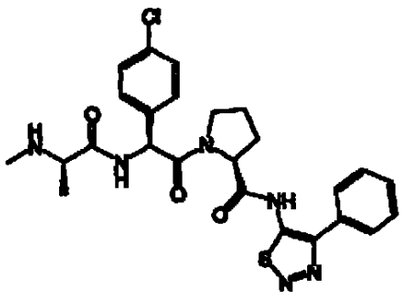


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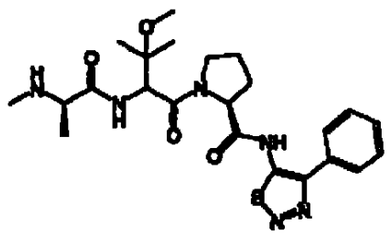
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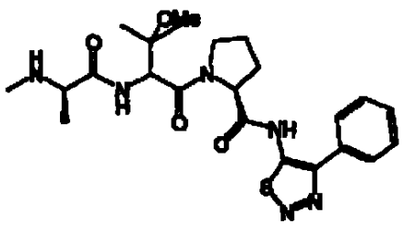
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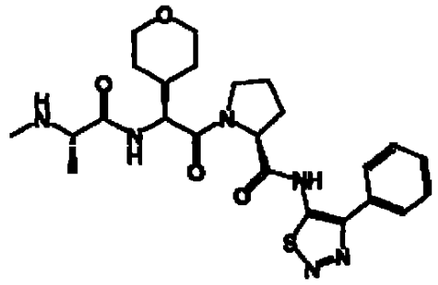
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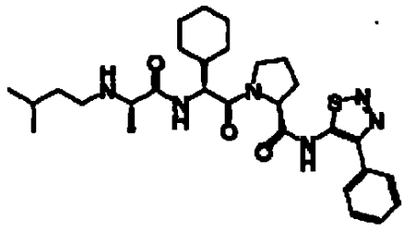
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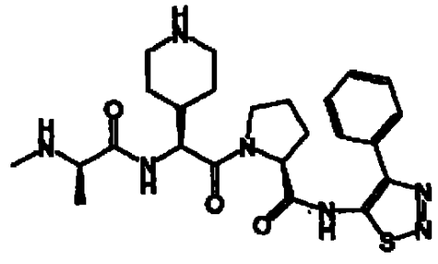
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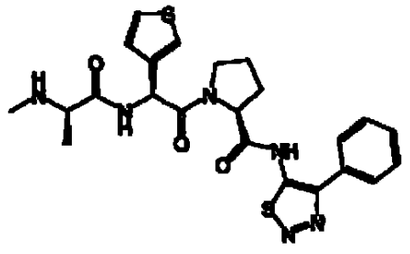
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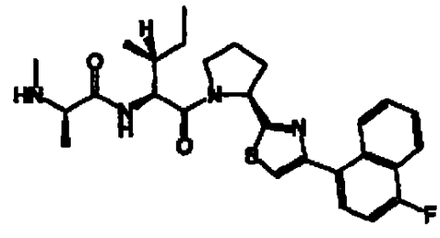
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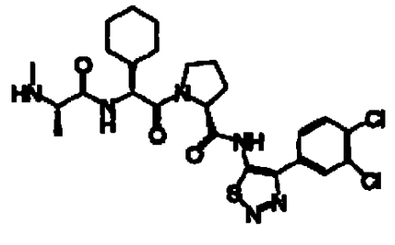
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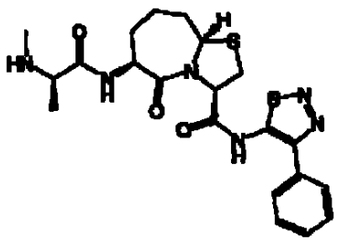
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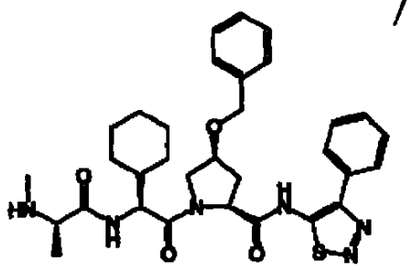


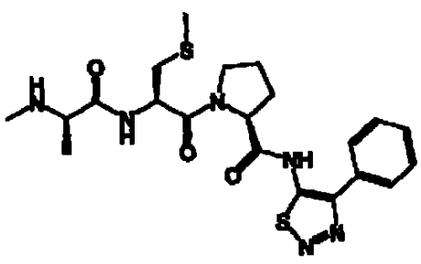
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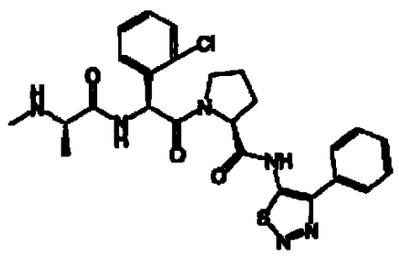


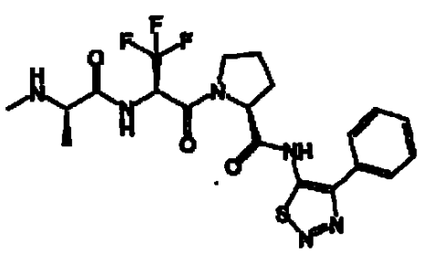
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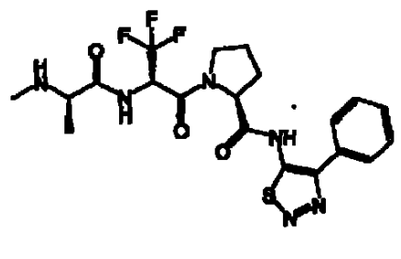
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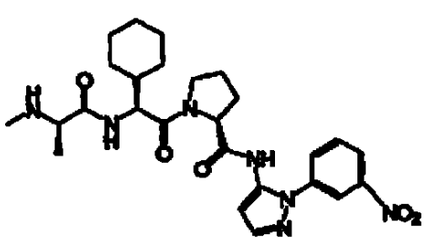
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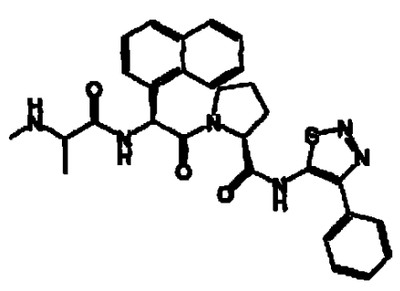
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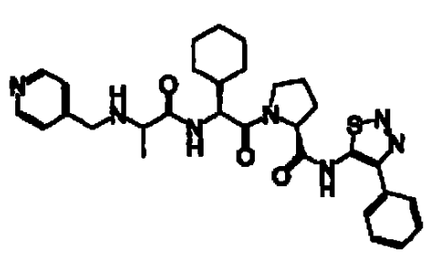
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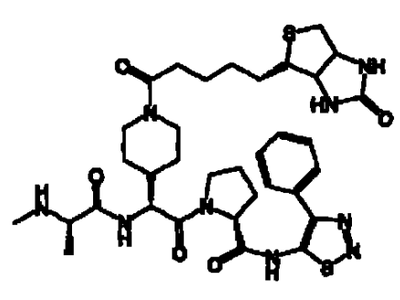
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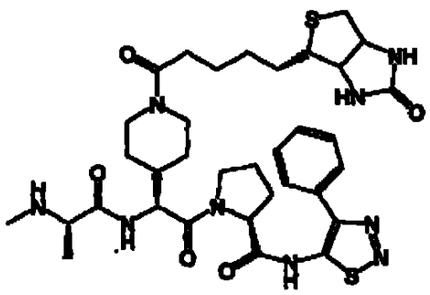
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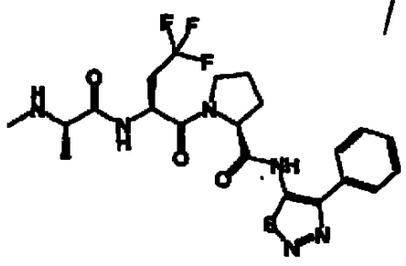
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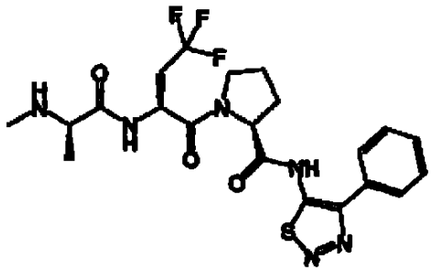
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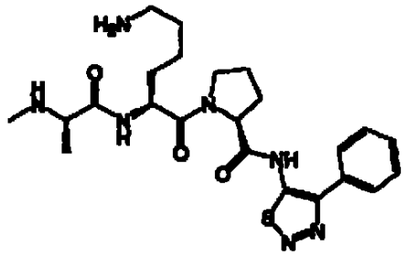
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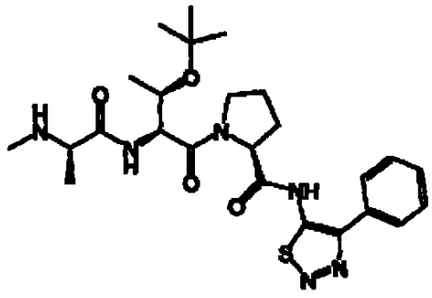
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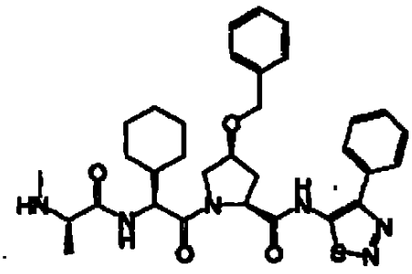
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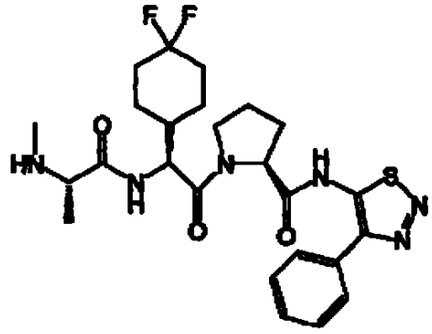
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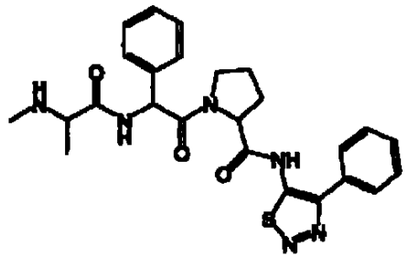
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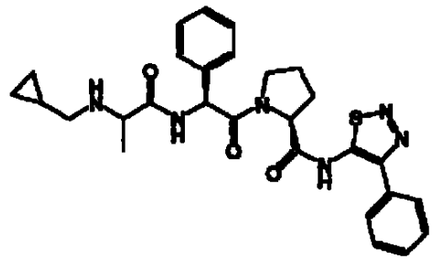
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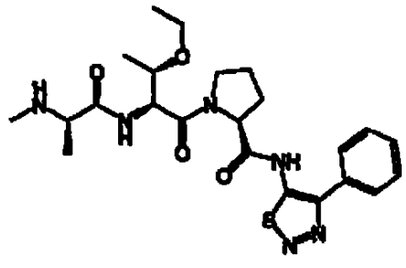
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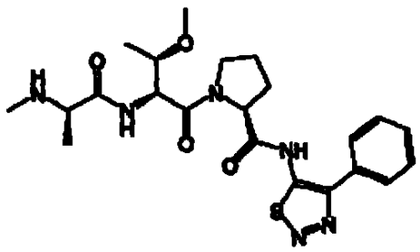


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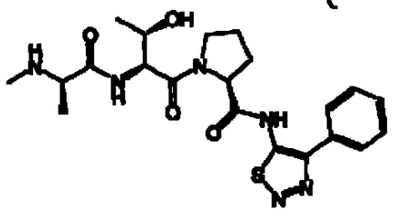


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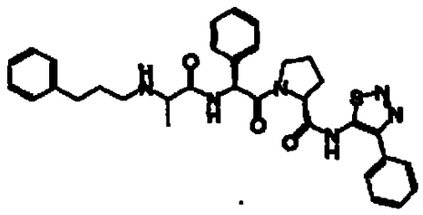
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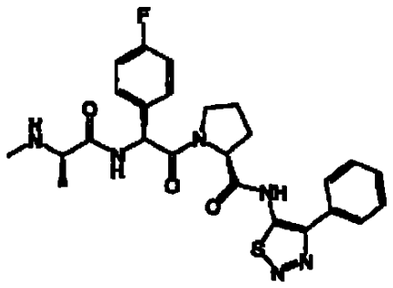
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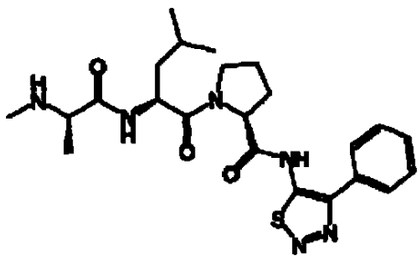
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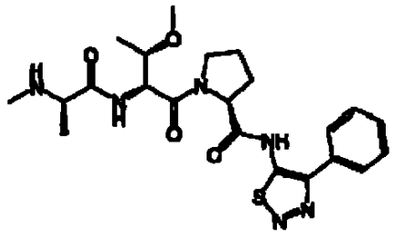
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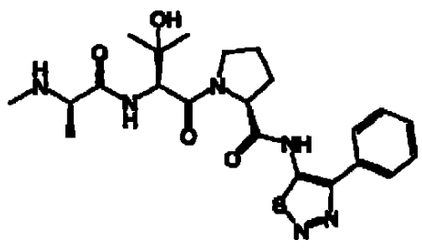
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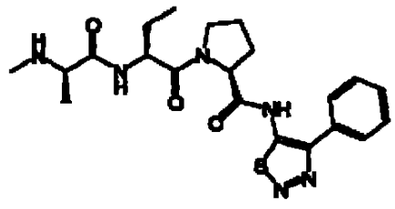
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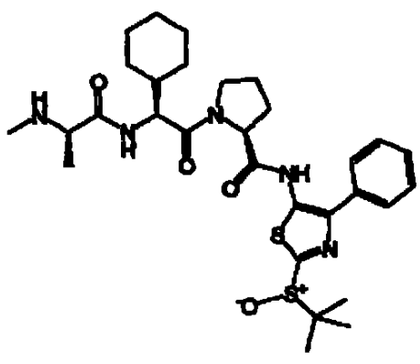
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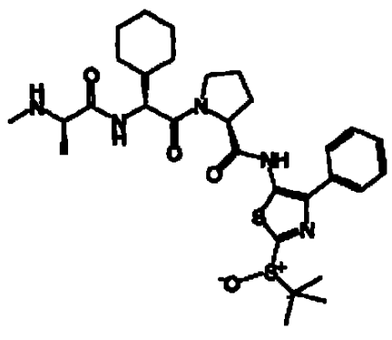
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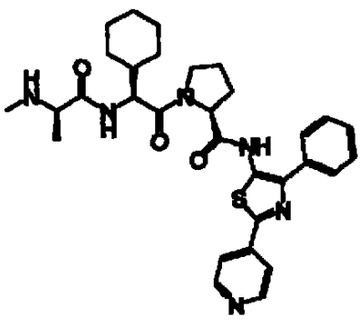


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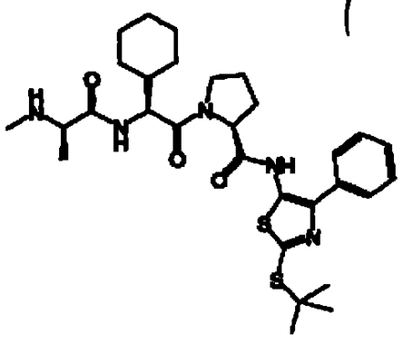


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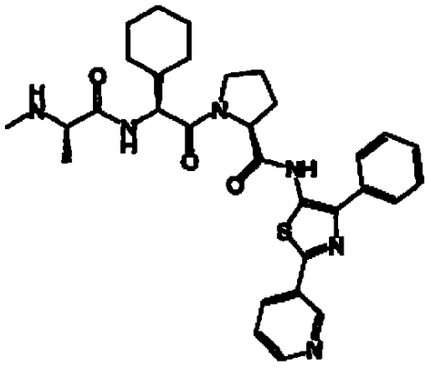
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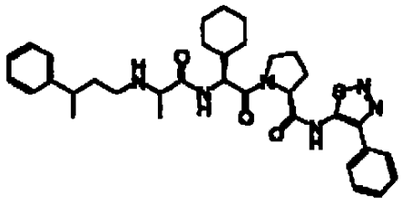
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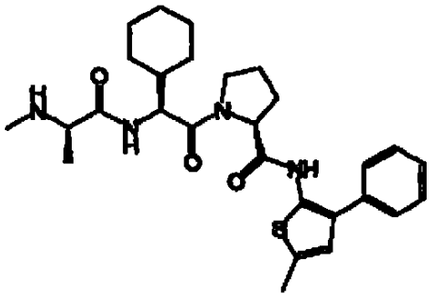
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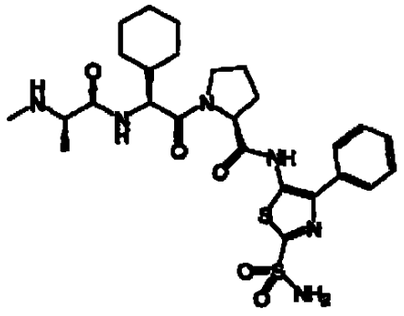
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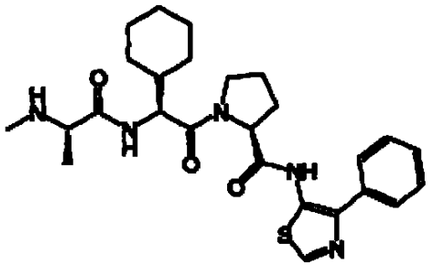
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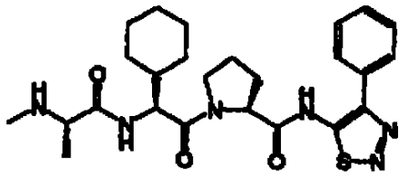
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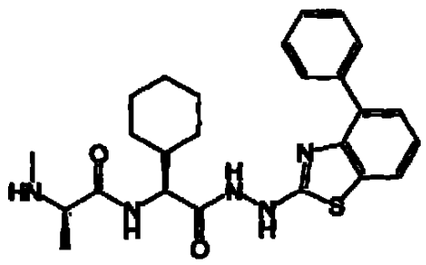


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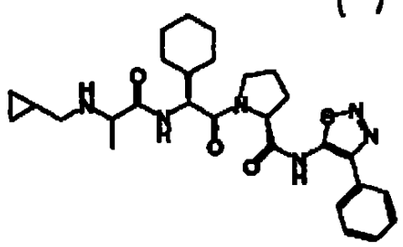


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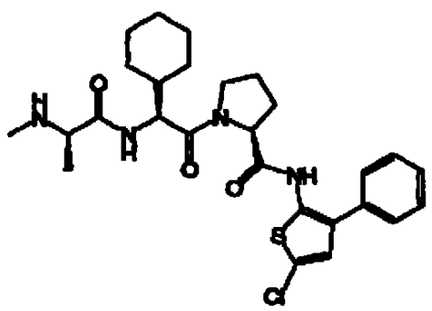
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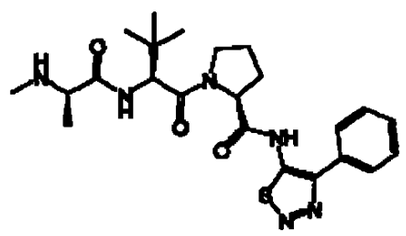
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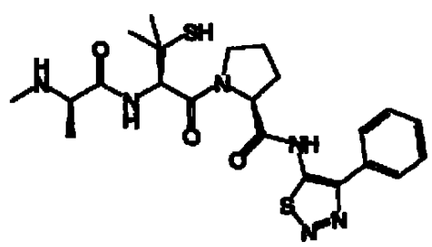
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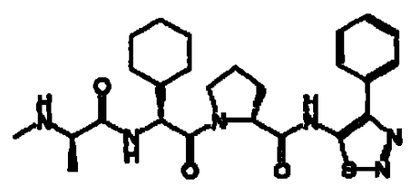
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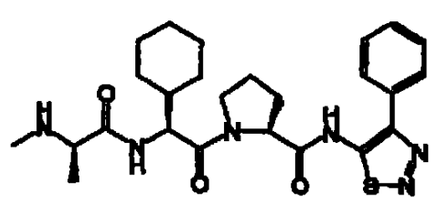
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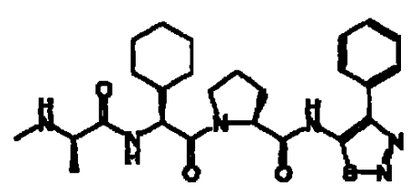
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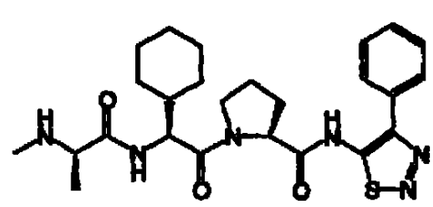
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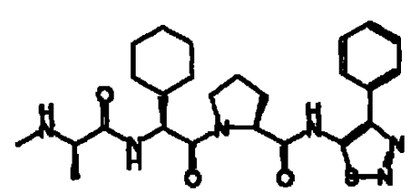
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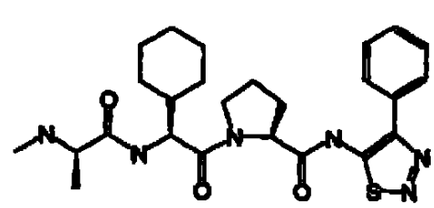
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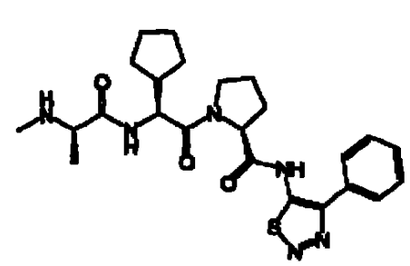
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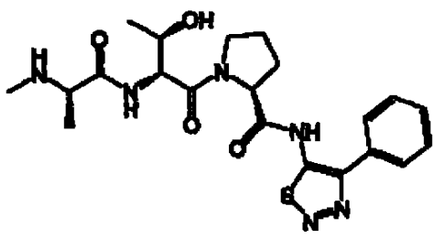


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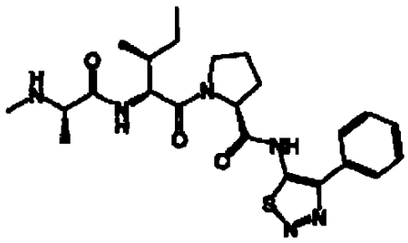


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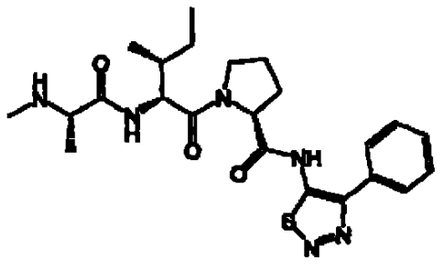
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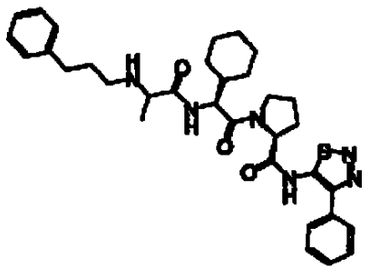
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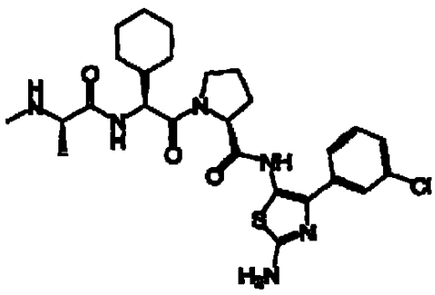
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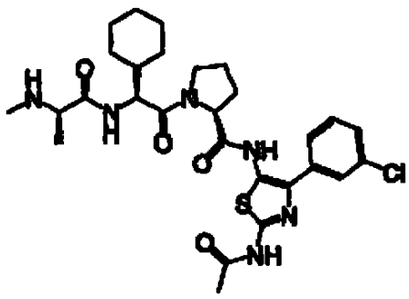
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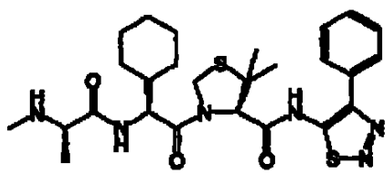
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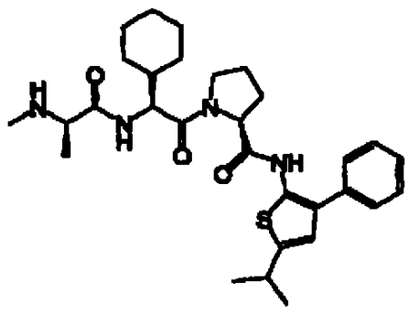
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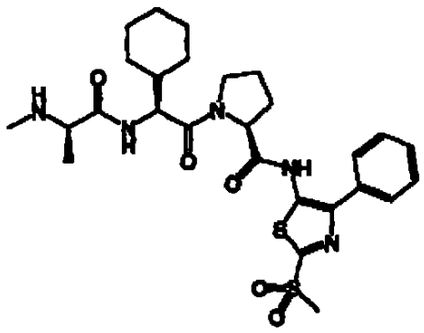
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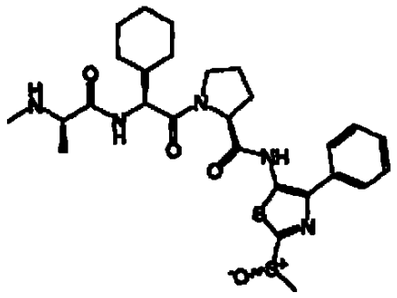


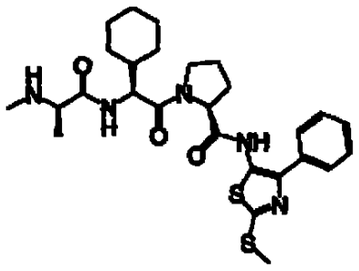
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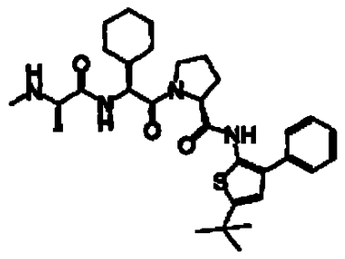


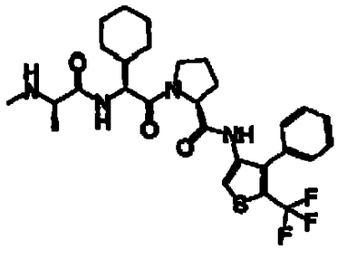
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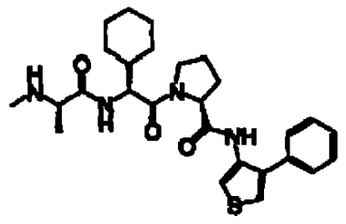
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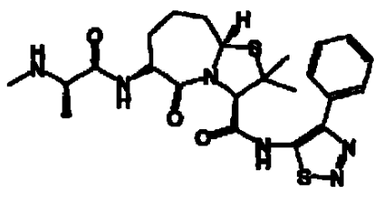
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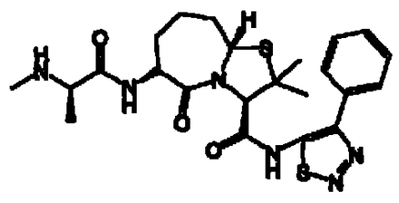
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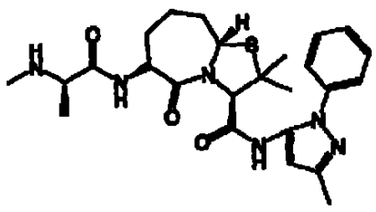
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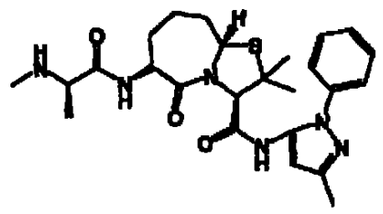
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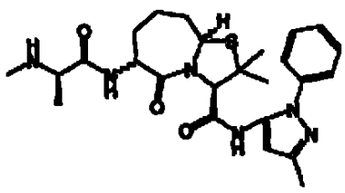
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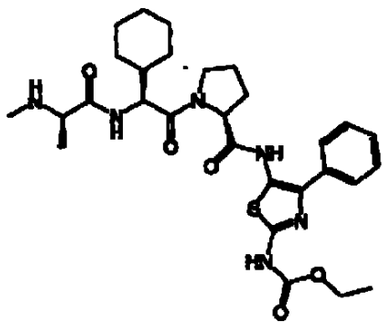
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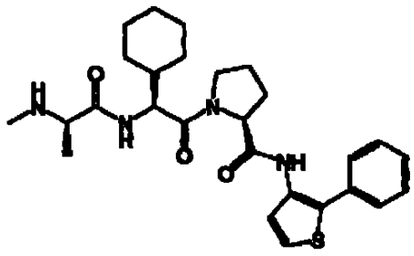
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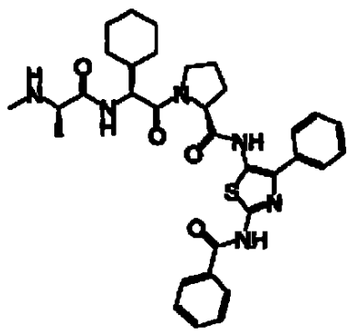
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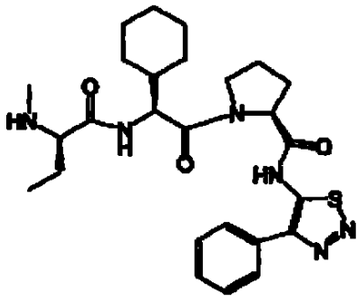
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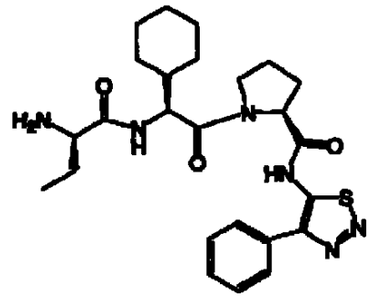
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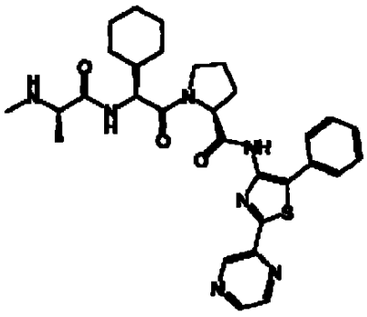
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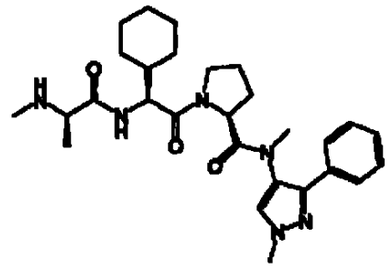
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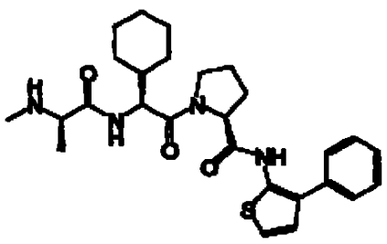


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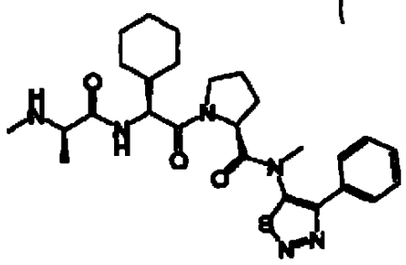


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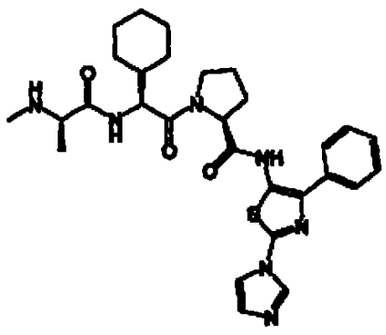
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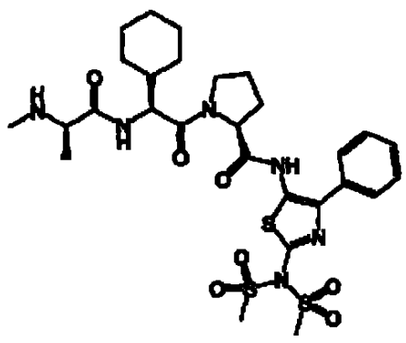
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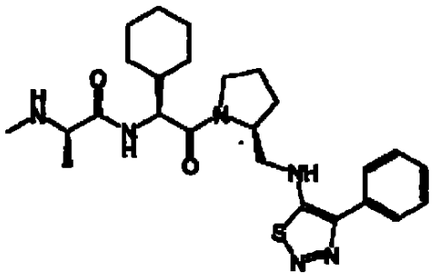
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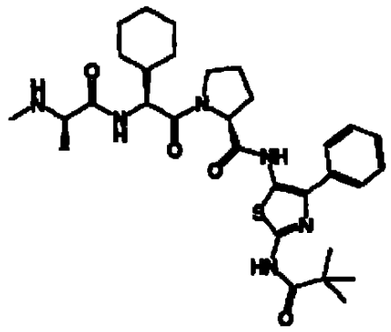
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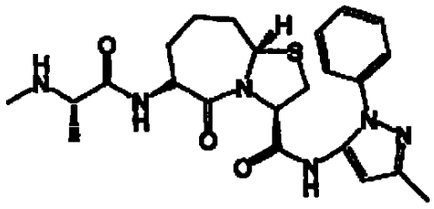
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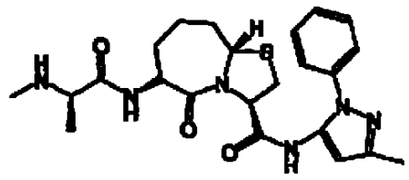
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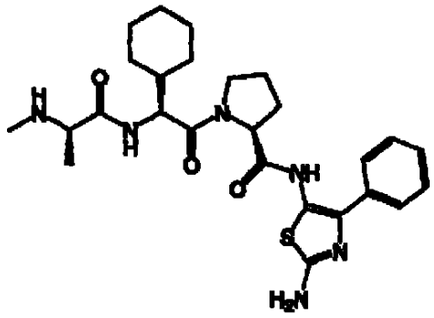
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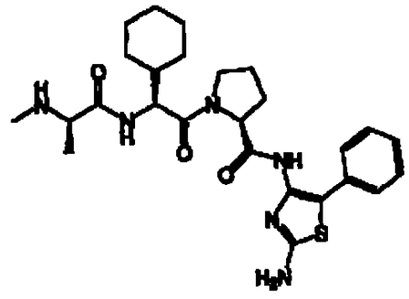
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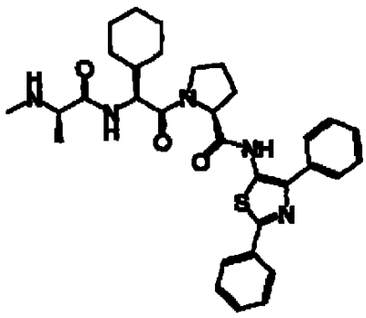


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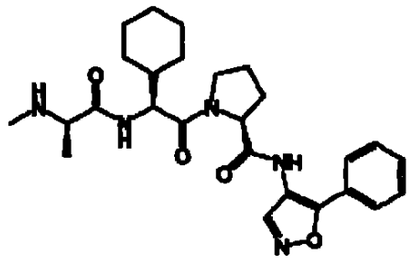


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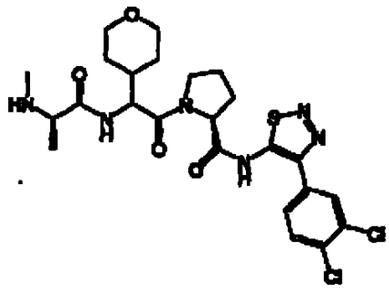
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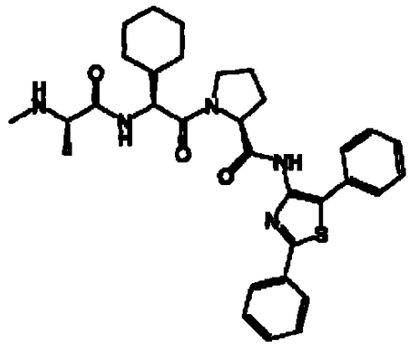
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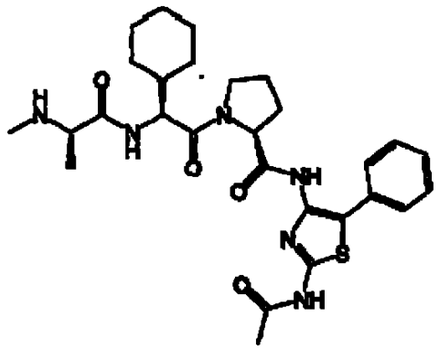
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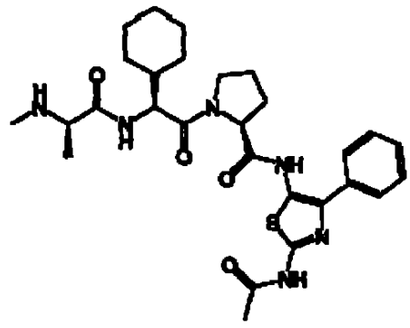
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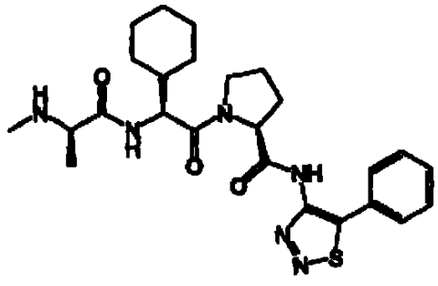
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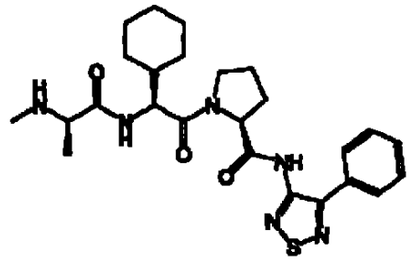
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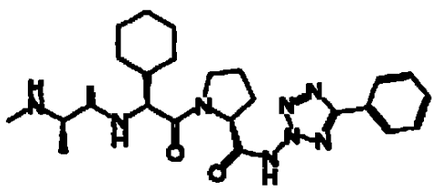


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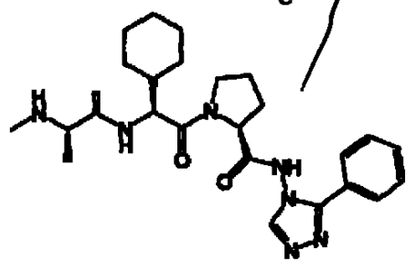


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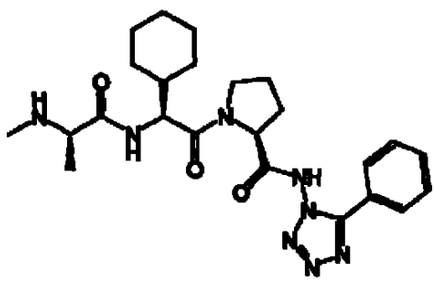
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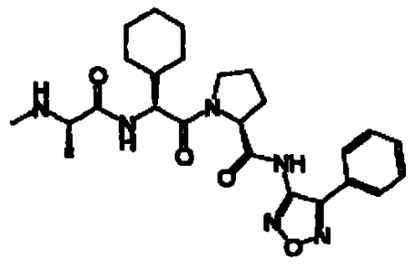
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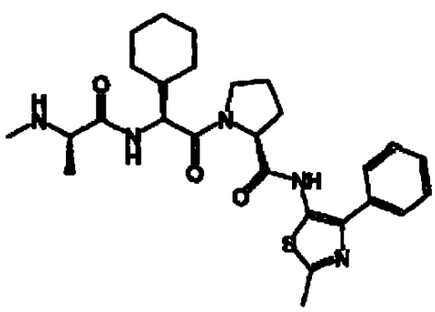
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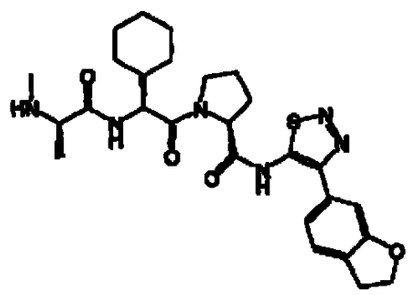
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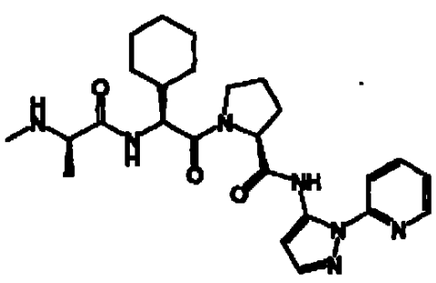
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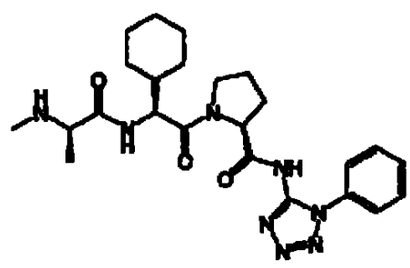
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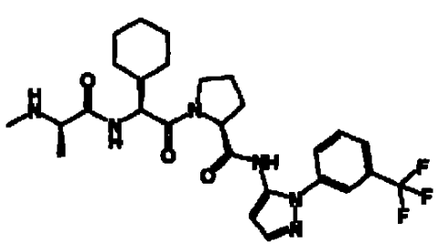
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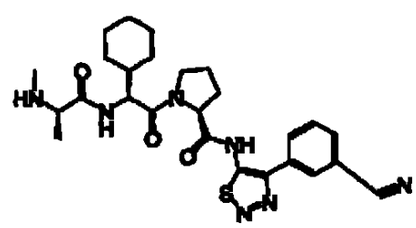
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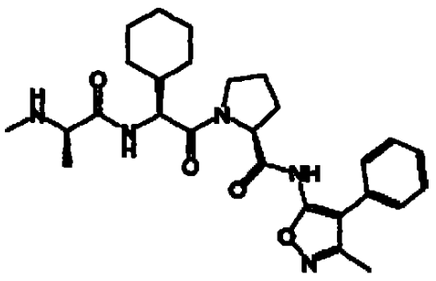


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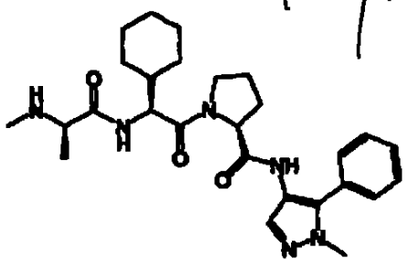


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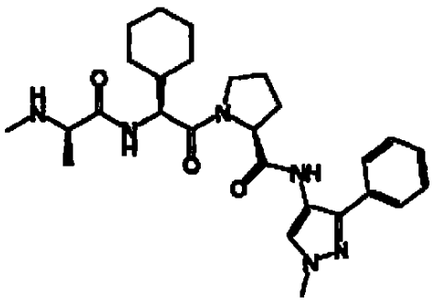
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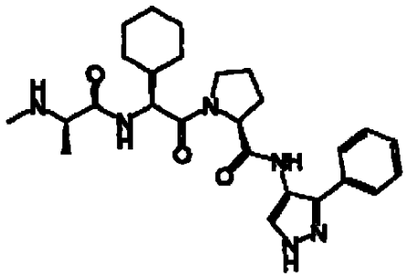
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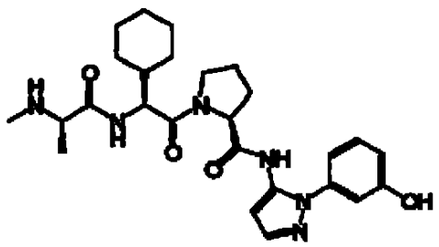
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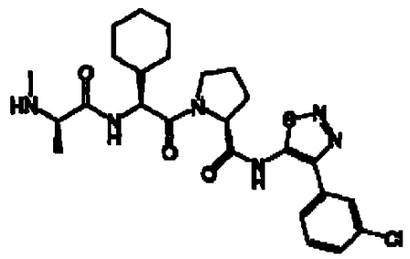
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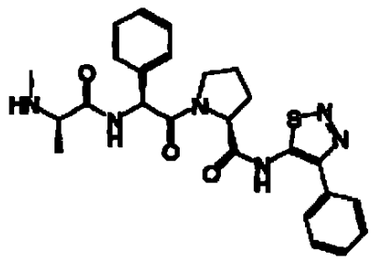
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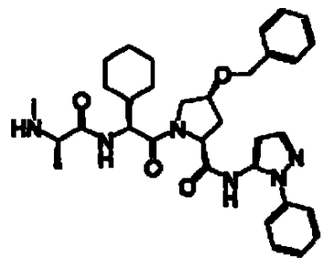
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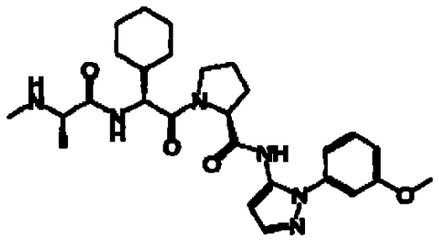
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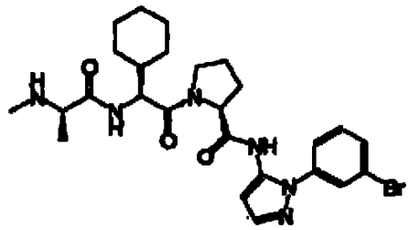
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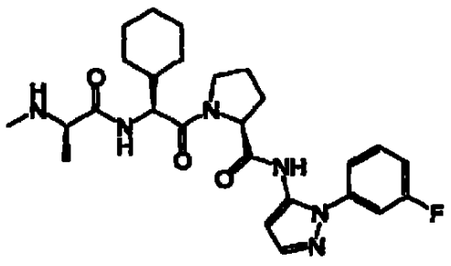
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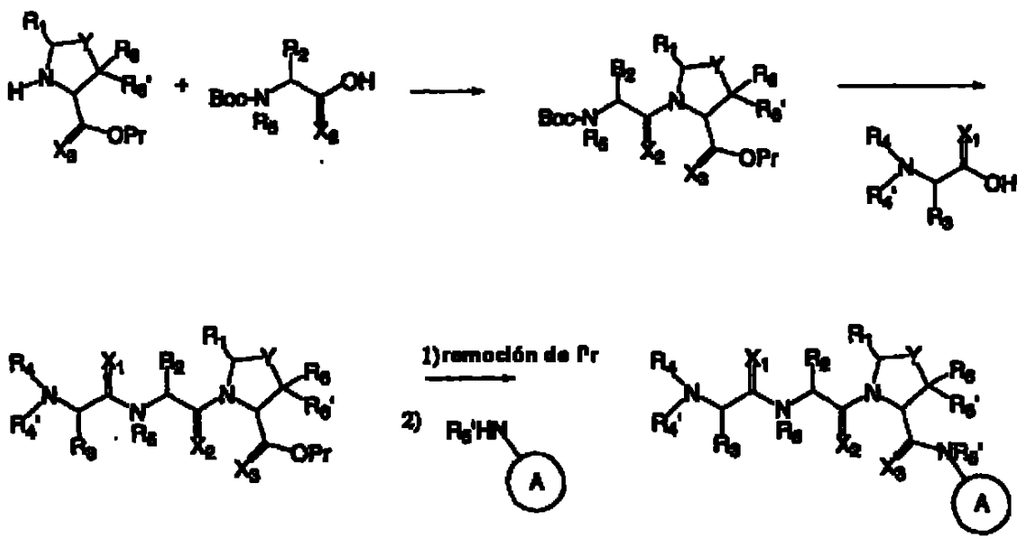
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SÍNTESIS

Los compuesto de la invención se prepara utilizando técnicas sintéticas orgánicas estándar de materiales de partida y reactivos disponibles comercialmente. Se apreciará que los procedimientos sintéticos empleados en la preparación de los compuestos de la invención dependerán de los sustituyentes particulares presentes en un compuesto y que se puede requerir varia protección y desprotección como es estándar en la síntesis orgánica. En un esquema sintético inicial los compuestos de la invención se pueden preparar utilizando técnicas químicas de péptido típicas al acoplar los análogos de residuos de aminoácidos con procedimientos de acoplamiento de amida típicos. En el esquema 1, un análogo de residuo aminoácido de amino-protegida se acopla y se desprotege secuencialmente para dar los compuestos finales.

Esquema 1

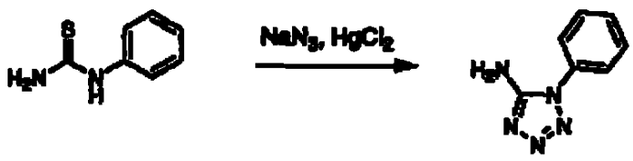


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Se apreciará que los análogos de aminoácido se pueden acoplar en cualquier orden y se pueden preparar utilizando soporte de fase sólida el cual es rutinario en la técnica.

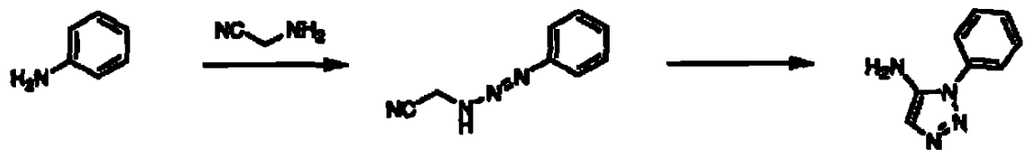
El anillo sustituido de amina A el cual sirve como un intermediario para prepara compuestos de la invención están comercialmente disponibles o también se preparan de reactivos disponibles comercialmente empleando técnicas de química orgánica estándar. Por ejemplo, 1-Aril-5-aminotetrazoles, tales como fenil-5-aminotetrazol, se pueden preparar de acuerdo al esquema 2 de tiourea fenilo comercialmente disponible al hacer reaccionar con azida de sodio y cloruro de mercurio.

Esquema 2



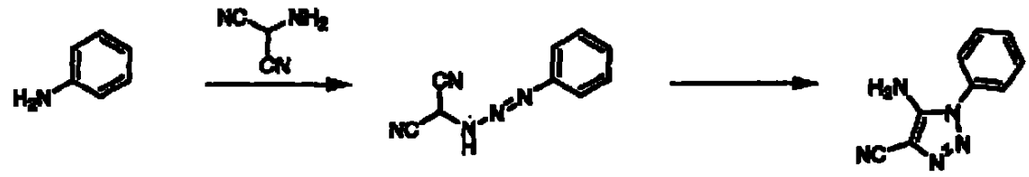
3-Aril-5-amino-1,2-,3-triazoles, tales como 3-Fenil-3H-[1,2,3]triazol-4-ilamina, se pueden preparar de acuerdo a los procedimientos descritos en J. Org. Chem, 1981, 46:856-9 y se ilustran en el esquema 3 adelante al hacer reaccionar fenilamina con aminoacetonitrilo.

Esquema 3



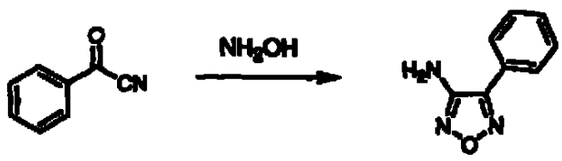
Similarmente, 5-Amino-1-fenil-1H-[1,2,3]triazol-4-carbonitrilo se pueden preparar al hacer reaccionar fenilamina con 2-amino-malononitrilo como se ilustra en el esquema 4.

Esquema 4



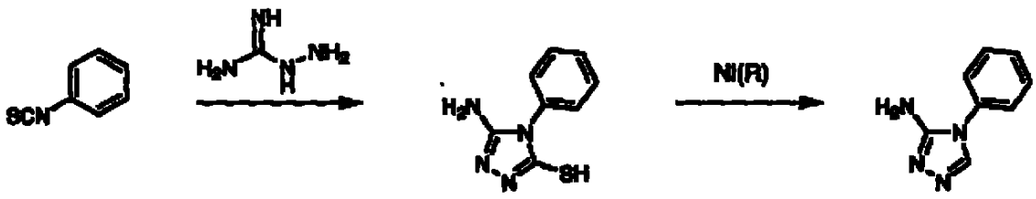
4-Aril-5-amino-1,2-,5-oxadiazoles, tales como 4-fenil-furazan-3-ilamina, se pueden preparar de acuerdo a los procedimientos descritos en Lakhan et al, (Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal Chemistry (1987), 26B(7), 690-2) y se ilustran en el esquema 5 al hacer reaccionar cianuro de benzoilo con hidroxilamina.

Esquema 5



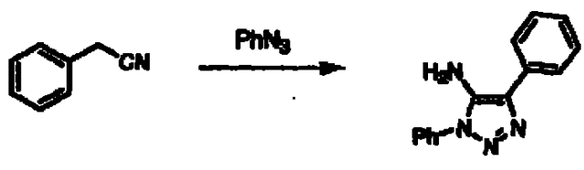
4-Aril-3-amino-1,2-,4-triazoles, tales como 4-fenil-4H-[1,2,4]triazol-3-ilamina, se pueden preparar al hacer reaccionar fenilisotiocianato con hidrazinacarboximidamida para dar 5-amino-4-fenil-4H-[1,2,4]triazol-3-tiol en el que el grupo tiol puede ser removido con Catalizador de níquel Raney como se ilustra en el esquema 6.

Esquema 6



4-Aril-5-amino-1,2-,3-triazoles tales como 3,5-difenil-3H-[1,2,3]triazol-4-ilamina de acuerdo al procedimiento descrito en J. Org. Chem., 1990, 55:3351-62 y se ilustran en el esquema 7, al hacer reaccionar bencenoacetonitrilo con azidobenceno (o alternativamente trimetilsililazida, TMS-N3).

Esquema 7

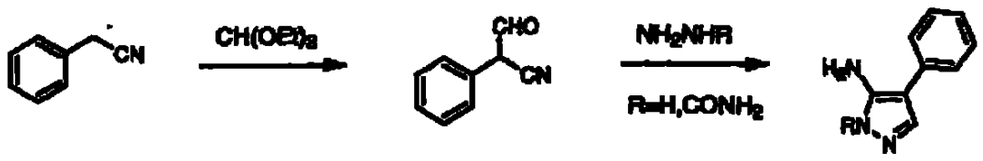


4-Aril-3-aminopirazoles tales como 4-fenil-2H-pirazol-3-ilamina se pueden preparar de acuerdo a los procedimientos descritos en la patente EP269,859 y se ilustran en el esquema 8, al hacer

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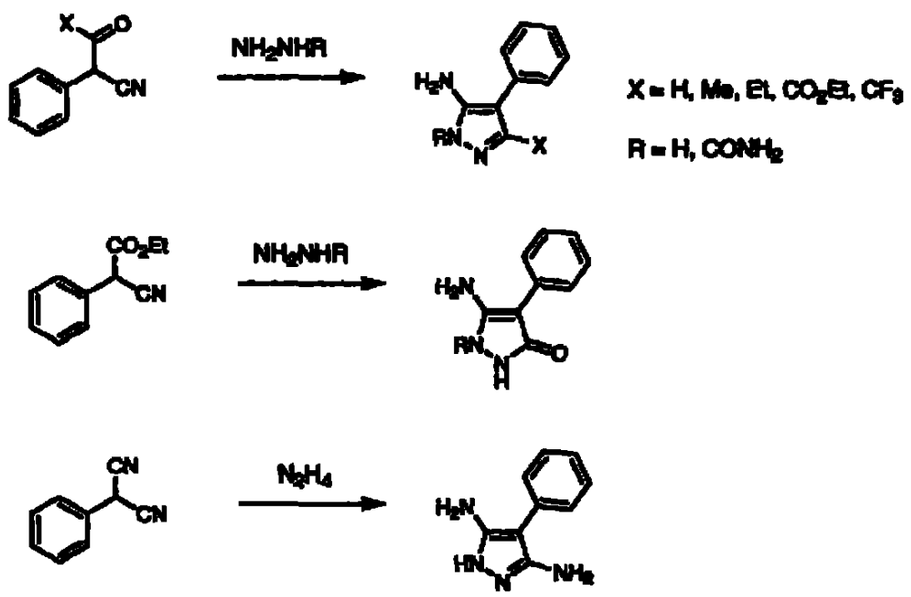
reaccionar bencenoacetonitrilo con éster de etilo de ácido ortofórmico para dar 3-oxo-2-fenil-propionitrilo el cual se hace reaccionar con hidrazina.

Esquema 8



Varias hidrazinas y derivados de bencenoacetonitrilo se pueden usar para preparar 4-aril-3-aminopirazoles sustituidos como se ilustra en el esquema 9.

Esquema 9

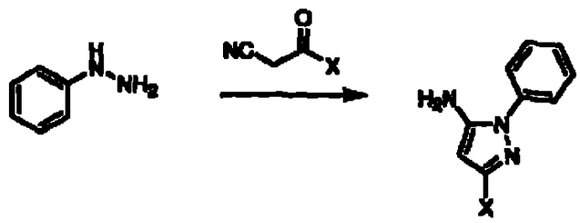


1-Aril-5-aminopirazoles tales como 2-fenil-2H-pirazol-3-ilamina se pueden preparar al hacer reaccionar fenilhidrazina con 3-oxo-

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propionitrilo. Varios nitrilos se pueden utilizar para introducir una sustitución a la posición 3 del anillo de pirazol como se ilustra en el esquema 10.

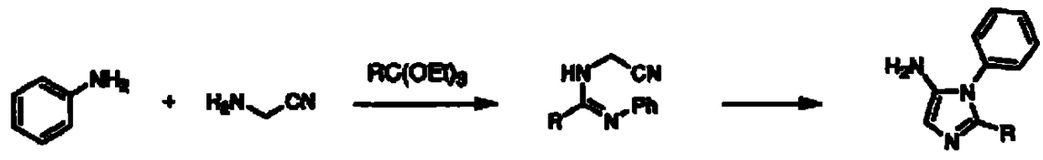
Esquema 10



X= H, Me, Et, CO_2Et, CF_3

3-Aril-4-aminoimidazoles tales como 3-fenil-3H-imidazol-4-ilamina se pueden preparar al hacer reaccionar fenilamina con aminoacetonitrilo y éster de trietilo de ácido ortofórmico como se ilustra en el esquema 11. La sustitución en la posición 2 del imidazol se puede introducir utilizando análogos del trietiléster de ácido ortofórmico como sigue.

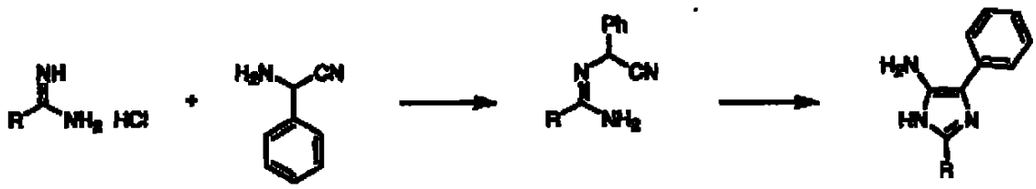
Esquema 11



5-Aril-4-aminoimidazoles tales como 5-fenil-3H-imidazol-4-ilamina se pueden preparar al hacer reaccionar formamidina con aminofenilacetonitrilo como se ilustra en el esquema 12. La

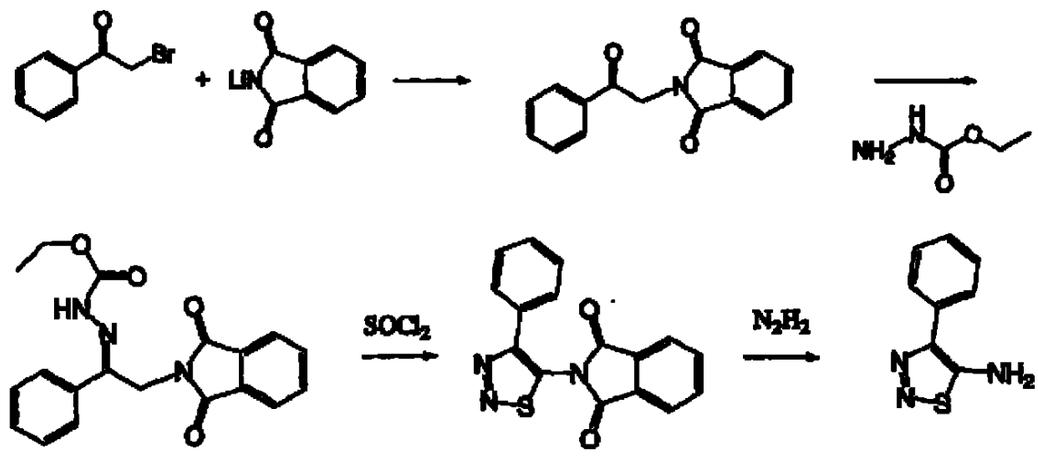
sustitución en la posición 2 del anillo de imidazol se puede introducir utilizando análogos de la formamidina.

Esquema 12



4-Aril-[1,2,3]tiadiazol-5-ilaminas tales como 4-fenil-[1,2,3]tiadiazol-5-ilamina se puede preparar mediante el procedimiento que se ilustra en el esquema 13. Se hace reaccionar 2-bromo-1-fenil-etanona con ftalamida de litio y el producto de sustitución se hace reaccionar con hidrazinacarboxilato de éster de etilo. El hidrazinacarboxilato de éster de etilo resultante se ciclan para formar un tiadiazol al hacerlo reaccionar con cloruro de tionilo seguido por remoción del grupo ftalimida con hidrazina.

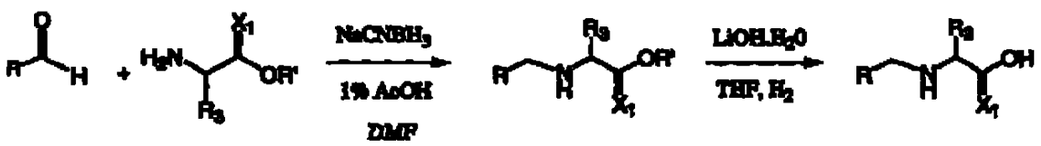
Esquema 13



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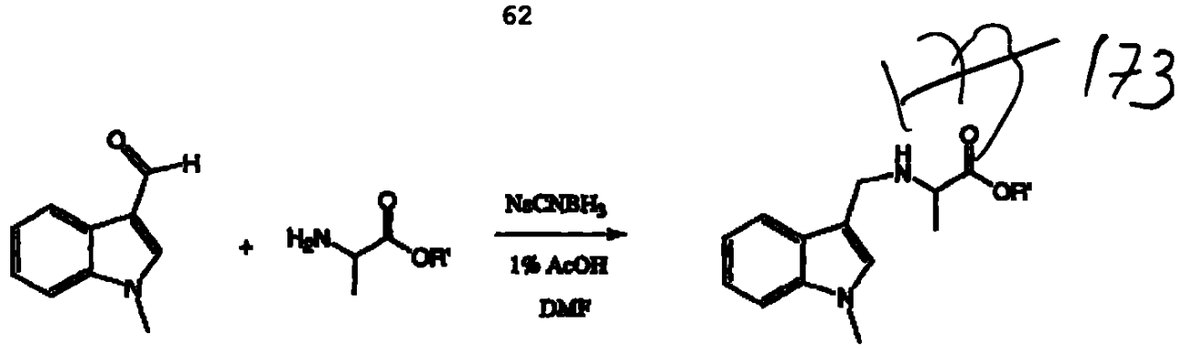
Los compuestos de la invención en los que R_4 o R_4' son diferentes de H se pueden preparar de acuerdo a técnicas de química orgánica estándar, por ejemplo mediante aminación reductora en la cual un análogo de residuo de aminoácido de partida por ejemplo NH_2-$CH(R_3)$-C(O)-OH se hace reaccionar con un aldehído o cetona adecuado para dar los sustituyente R_4 y R_4' deseados. Ver esquema 14. El intermedio de aminoácido sustituido R_4/R_4'resultante entonces se puede conjugar al próximo intermedio de aminoácido o el restante del compuesto utilizando procedimientos de acoplamiento de péptido estándar:

Esquema 14



En una modalidad particular, la alanina se hace reaccionar con 1-metilindol-2-carboxaldehído y se reduce con cianoborohidruro de sodio disuelto en 1% de HOAc/DMF para el residuo de alanina N sustituida el cual puede ser utilizada en la preparación de los compuestos de la invención. Ver esquema 15.

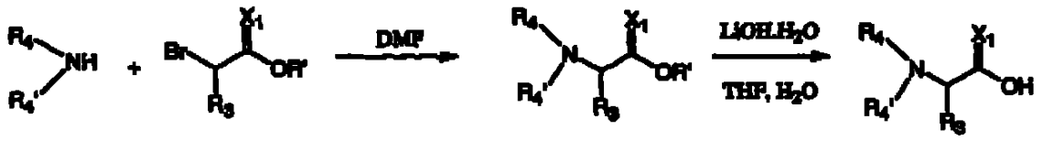
Esquema 15



Alternativamente, el procedimiento de afinación reductora para introducir sustituyentes R_4/R_4' es la etapa final en la preparación del compuesto.

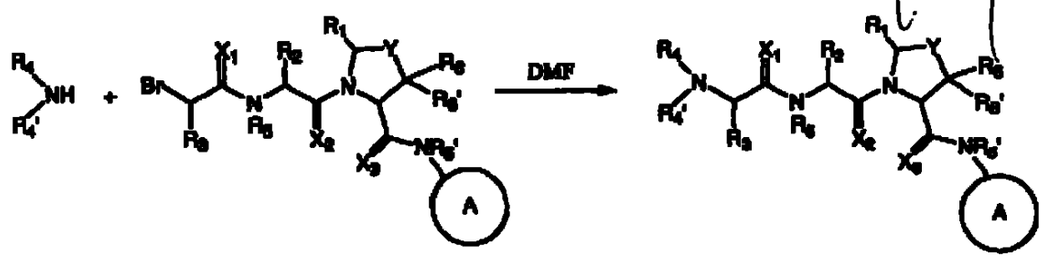
Cuando los compuestos de la invención incorporan sustituyentes R_4 o R_4' diferentes de H, ellos también pueden ser preparados mediante sustitución de intermedios de ácido adecuados los cuales incorporan un grupo saliente con una amina deseada. Por ejemplo $Br-CH(R_3)-C(O)-OH$ se sustituye con una amina R_4-NH_2 o R_4-NH-R_4' de acuerdo al esquema 16.

Esquema 16

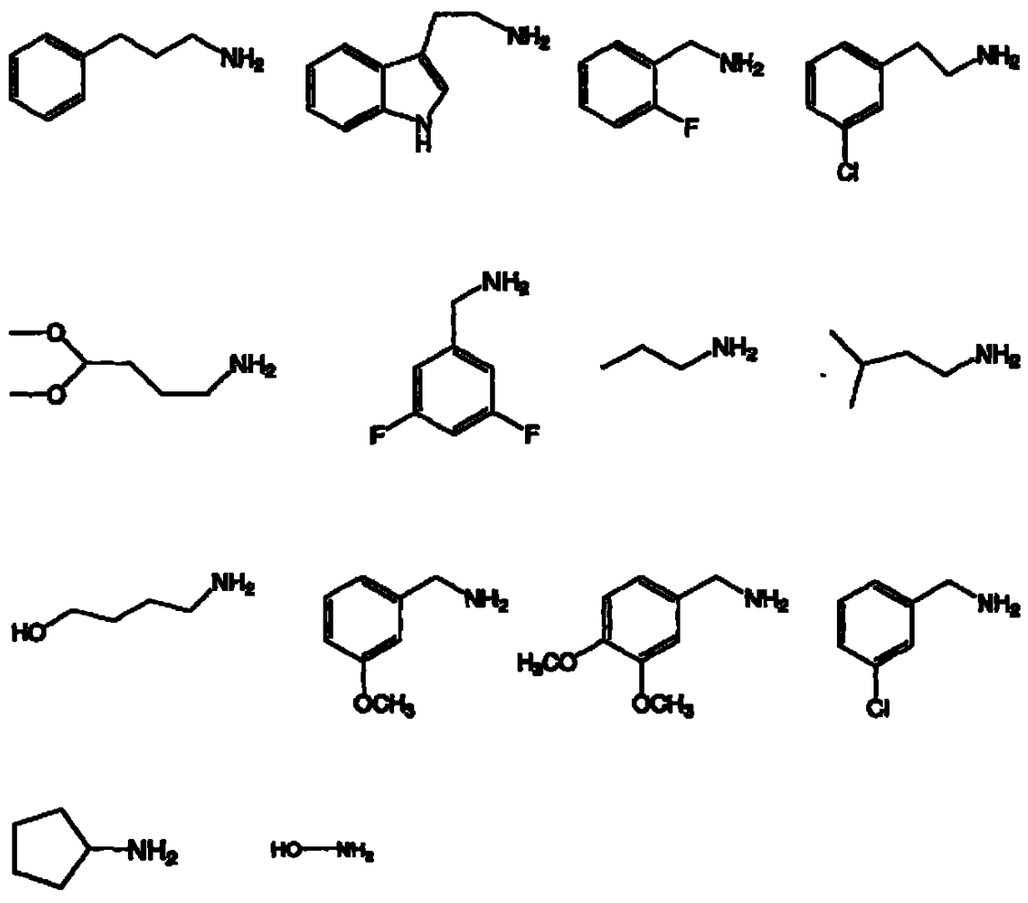


Alternativamente, la reacción de sustitución que introduce sustituyentes R_4 o R_4' se puede desarrollar como una etapa final en la preparación del compuesto como se ilustra en el esquema 17.

Esquema 17



En una modalidad particular, se hace reaccionar ácido 2-bromopropiónico con las siguientes aminas disueltas en DMF y se burbujea hasta que se completa la sustitución para formar residuos alanita N-sustituidos:

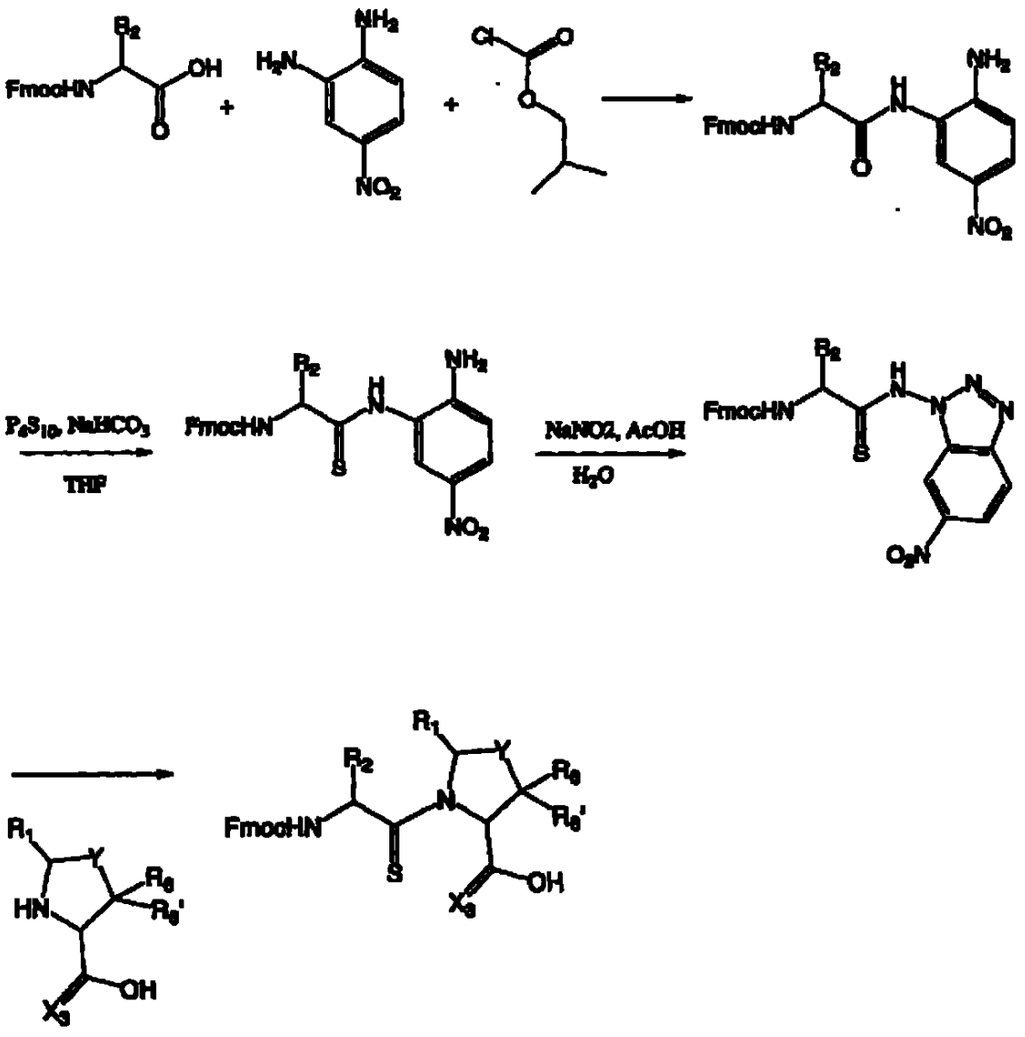


Los compuestos de la invención en el que uno cualquiera o más de X_1, X_2 y X_3 son azufre, es decir el compuesto incorpora una

tioamida, se puede preparar de acuerdo con técnicas de química orgánica establecidas. Por ejemplo, compuestos en los que X_2 es azufre se pueden preparar de acuerdo con el esquema 18 partiendo de un análogo de residuo de aminoácido protegido Fmoc NH_2-CH(R_2)-COOH que se disuelve en THF y se enfría a -25° C, con adición de DIPEA seguido por adición de isobutilcloroformato. Después de 10 minutos, la diamina, 4-nitrobenceno-1,2-diamina, se agrega y la mezcla de reacción se agita continuamente a -25° C durante 2 horas, luego a temperatura ambiente durante la noche. El THF se vacía y la mezcla se somete luego a cromatografía flash utilizando 50% de EtOAc/Hexano para dar el producto. El derivado Fmoc-alanina, bicarbonato de sodio y pentasulfuro de fósforo se mezclan en THF y se agitan durante la noche. La solución se concentra y la cromatografía directa utilizando 80% de EtOAc/Hexano da la tioalanina activada. La tioalanina y el nitrato de sodio activos se mezclan luego en ácido acético y se diluyen con H_2O. El precipitado resultante se filtra y se seca para dar el producto. La tioalanina se acopla a un análogo de residuo de aminoácido prolina OH protegido al disolver los en DMF. El producto de tioamida puede ser Lugo desprotegido con 20% de PIP/DMA durante 15 minutos y utilizado para conjugar el análogo de residuo de aminoácido R_4/R_4'-N-CH(R_3)-COOH seguido por desprotección OH y acoplamiento a un intermedio de anillo A amino-sustituido. Alternativamente la tioamida Fmoc protegida se acopla primero a un intermedio de anillo A amino sustituido seguido por desprotección Fmoc y posterior acoplamiento al análogo de residuo de aminoácido R_4/R_4'-N-CH(R_3)-COOH.

Esquema 18

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UTILIDAD

Los compuestos de la invención inhiben la unión de las proteínas IAP a caspasas, en particular la interacción de la unión X-IAP con caspasas 3 y 7. Los compuestos también inhiben la unión del ML-IAP a proteína Smac. De acuerdo con esto, los compuestos de la invención son útiles para inducir la apoptosis en células o sensibilizar células para señales apoptóticas, en particular células cancerígenas. Los compuestos de la invención son útiles para inducir apoptosis en células que sobreexpresan las proteínas

IAP. Alternativamente, los compuestos de la invención son útiles para inducir la apoptosis en células en las que la trayectoria apoptótica mitocondrial se interrumpe de tal forma que liberación del Smac de las proteínas ML-IAP se inhibe, por ejemplo mediante la regulación del Bcl-2 o subregulación del Bax/Bak. Más ampliamente, los compuestos se pueden utilizar para el tratamiento de todos los tipos de cáncer que experimentan apoptosis. Ejemplos de tales tipos de cáncer incluyen neuroblastoma, carcinoma de intestino tal como carcinoma de recto, carcinoma de colón, carcinoma de polipoisis adenomatoso familiar y cáncer colorectal no poliposis hereditario, carcinoma esofágico, carcinoma labial, carcinoma de laringe, carcinoma de hipofaringe, carcinoma de lengua, carcinoma de glándula salival, carcinoma gástrico adenocarcinoma, carcinoma de tiroide medular, carcinoma de tiroide papilar, carcinoma renal, carcinoma de parénquima de riñón, carcinoma de ovario, carcinoma de cerviz, carcinoma de cuerpo uterino, carcinoma de endometrio, carcinoma de corión, carcinoma de pancreático, carcinoma de próstata, carcinoma de testículo, carcinoma de seno, carcinoma de urinario, melanoma, tumores de cerebro tal como glioblastoma, astrocitoma, meningioma, meduloblastoma y tumor neuroectodérmico periférico, linfoma de Hodgkin, linfoma de no Hodgkin, linfoma de Burkitt, leucemia linfática aguda (ALL), leucemia linfática crónica (CLL), leucemia mieloide aguda (AML), leucemia mieloide crónica (CML), linfoma de leucemia de célula T, carcinoma hepatocelular, carcinoma de vesícula biliar, carcinoma bronquial, carcinoma de célula pequeña de pulmón, carcinoma de célula no pequeña de pulmón, mieloma múltiple, basalioma, teratoma, retinoblastoma, melanoma coroidea, seminoma, rabdomiosarcoma, craniofaringeoma,

osteosarcoma, condrosarcoma, miosarcoma, liposarcoma, fibrosarcoma, sarcoma de Swing y plasmocitoma.

Compuestos de la invención son útiles para sensibilizar células para señales apoptóticas. De acuerdo con esto, los compuestos se pueden administra antes de, concomitantemente con, o siguiendo la administración de terapia de radiación o quimioterapia citostática o anti neoplásica. Compuestos de quimioterapia cistostáticos adecuados incluyen, pero no están limitados a (i) metabolitos, tales como antimetabolitos, tal como citarabina, fludarabina, 5-fluoro-2'-desoxiuridina, gemcitabina, hidroxiurea o metotrexato; (ii) agentes de fragmentación de ADN, tal como bleomicina, (iii) agentes de reticulación de ADN, tal como clorambucil, cisplatina, ciclofosfamida o mostaza nitrógeno; (iv) agentes de intercalación tales como adriamicina (doxorubicina) o mitoxantrona; (v) inhibidores de síntesis de proteína, tal como L-asparaginasa, cicloheximida, puromicina o toxina difteria; (Vi) venenos I topoisomerasa, tal como camptotecina o topotecan; (vii) venenos topoisomerasa II , tal como etoposida (VP-16) o teniposida; (viii) agentes de microtúbulos dirigidos, tal como colcemid, colchicina, paclitaxel, vinblastina o vincristina; (ix) inhibidores de quinasa tales como flavopiridol, estaurosporin, STI571 (CPG 57148B) o UCN-01 (7-hidroxistaurosporina); (x) agentes de investigación miscelánea tales como tioplatin, PS-341, fenilbutirato, ET-18-OCH_3, o inhibidores de transferasa farnesil (L-739749, L-744832); polifenoles tal como quercetin, resveratrol, piceatanol, epigalocatechina gallato, teaflavinas, flavanoles, procianidinas, ácido botulínico y derivados de estos; (xi) hormonas tales como glucocorticoides o fenretinida; (xii)

antagonistas de hormona, tales como tamoxifen, finasterida o antagonistas LHRH. En una modalidad preferida, los compuestos de la presente invención se coadministran con un compuesto citostático seleccionado del grupo que consiste de cisplatina, doxorubicina, taxol, taxotere y mitomicina C. El compuesto citostático más preferido es doxorubicina.

Otra clase de compuestos activos que se puede utilizar en la presente invención son aquellos que son capaces de sintetizar o inducir apoptosis al unir a los receptores muertos ("antagonistas de receptor muerto"). Tales antagonistas de receptores muertos incluyen ligandos de receptor muerto tal como un factor de necrosis de tumor (TNF-(X), factor de necrosis de tumor β (TNF-β, linfotoxina-α), LT-β (linfotoxina-β), TRAIL (Apo2L, ligando DR4), ligando CD95 (Fas, APO-I), ligando TRAMP (DR3, Apo-3), ligando DR6 así como también fragmentos y derivados de cualquiera de dichos ligandos. Preferiblemente., el ligando de receptor muerto es TNF-α. Más preferiblemente el ligando de receptor muerto es Apo2L/TRAIL. Adicionalmente, los antagonistas de receptor muerto comprenden anticuerpos agonísticos para receptores muertos tales como anticuerpo anti-CD95 antibodi, anticuerpo anti-TRAIL-R1 (DR4), anticuerpo anti-TRAIL-R2 (DR5), anticuerpo anti-TRAIL-R3, anticuerpo anti-TRAIL-R4, anticuerpo anti-DR6, anticuerpo anti-TNF-R1 y anticuerpo anti-TRAMP (DR3) así como también fragmentos y derivados de cualquiera de dichos anticuerpos.

Para el propósito de sensibilizar células para apoptosis, los compuestos de la presente invención se pueden también utilizar en combinación con terapia de radiación, la frase terapia de

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radiación" se refiere al uso de radiación electromagnética o de partículas en el tratamiento de neoplasia. La terapia de radiación se basa en el principio de que la radiación de alta dosis suministrado a un área objetivo resultará en la muerte de las células que se reproducen en los tejidos normales y de tumor. El régimen de dosis de radiación se define generalmente en términos de dosis de radiación absorbida (rad), tiempo y fracción, y debe ser cuidadosamente definido por el oncólogo. La cantidad de radiación que un paciente recibe dependerá de varias consideraciones pero las dos consideraciones más importantes son la ubicación del tumor en relación con otras estructuras críticas u órganos del cuerpo, y el alcance al que se ha esparcido el tumor. Ejemplos de agentes radioterapéuticos se suministran en, pero no se limitan a, terapia de radiación y se conoce en la técnica (Hellman, Principles of Radiation Therapy, Cancer, in Principles I and Practice of Oncology, 24875 (Devita et al., 4th ed., vol 1, 1993). Avances resientes en terapia de radiación incluyen radiación de rayos externos con forma tridimensional, terapia de radiación de intensidad modulada (IMRT), radiocirugía esterotáctica y braquiterapia (terapia de radiación intersticial), la última coloca la fuente de radiación directamente en el tumor como "semillas" implantadas. Estas modalidades nuevas de tratamiento suministran grandes dosis de radiación al tumor, que cuenta por su actividad incrementada cuando se compara con terapia de radiación por rayo externo estándar.

La radiación de ionización con radionúclidos que emisores beta se considera los más útiles para aplicaciones radioterapéuticas

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debido a la transferencia de energía lineal moderada (LET) de la partícula de ionización (electrón) y su rango intermedio (típicamente varios milímetros de tejido). Los rayos gamma suministran dosis en bajos niveles sobre distancias mayores. Las partículas alfa representan el otro extremo, ellas suministran muy altas dosis LET, pero tienen un rango extremadamente limitado y deben, por lo tanto, estar en contacto íntimo con las células del tejido ha ser tratado. Adicionalmente, los emisores alfa son metales generalmente pesados, que limitan la química posible y presentan peligro de chorreadura de radionucleótido del área ha ser tratada. Dependiendo del tumor ha ser tratado todas las clases de emisores son concebibles dentro del alcance de la presente invención.

Adicionalmente, la presente invención abarca tipos de radiación no ionizante como por ejemplo radiación ultravioleta (UV), luz visible de alta energía, radiación de microondas (terapia de hipertermia), radiación infrarroja (IR) y láser. En una modalidad particular de la presente invención se aplica radicación UV.

La invención también incluye composiciones farmacéuticas o medicamentos que contienen los compuestos de la invención y un portador terapéuticamente inerte, diluyente o excipiente, así como también métodos para utilizar los compuestos de la invención para preparar tales composiciones y medicamentos. Típicamente, los compuestos de la fórmula I utilizados en los métodos de la invención se formulan al mezclar a temperatura ambiente en el pH apropiado, y en el grado deseado de pureza, con portadores fisiológicamente aceptables, es decir, portadores que no son

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tóxicos a los receptores en estas dosis y concentraciones empleadas en una forma de administración galénica. El pH de la formulación depende principalmente del uso particular y la concentración del compuesto, pero los rangos preferiblemente varían de aproximadamente 3 a aproximadamente 8. La formulación en un amortiguador de acetato en pH 5 es una modalidad adecuada.

El compuesto inhibidor para uso aquí es preferiblemente estéril. El compuesto ordinariamente se almacenará como una composición sólida aunque formulaciones liofilizadas o soluciones acuosas son aceptables.

La composición de la invención se formulará, dosificará y administrará en una forma consistente con la buena práctica médica. Factores para consideración en este contexto incluyen el trastorno particular a ser tratado, el mamífero particular a ser tratado, la condición clínica del paciente, la causa del trastorno, el sitio de suministro del agente, el método de administración, el programa de administración, y otros factores conocidos por los practicantes médicos. La "cantidad efectiva" del compuesto a ser administrado se regirá por tales consideraciones, y es la cantidad mínima necesaria para inhibir la interacción IAP con caspasas, inducir apoptosis o sensibilidad a una célula maligna para una señal apoptótica. Tal cantidad está preferiblemente por debajo de la cantidad que es tóxica a células normales o al mamífero como un todo.

De forma general, la cantidad farmacéuticamente efectiva inicial del compuesto de la invención administrada parenteralmente por dosis estará en el rango de aproximadamente 0.01-100 mg/kg,

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preferiblemente cerca de 0.1 a 20 mg/kg de peso corporal del paciente por día, con el rango inicial típico del compuesto utilizado que es de 0.3 a 15 mg/kg/día. Las formas de dosis unitaria oral, tales como tabletas y cápsulas, preferiblemente contienen de aproximadamente 25 a aproximadamente 1000 mg del compuesto de la invención.

El compuesto de la invención se puede administrar mediante cualquier medio adecuado, que incluye oral, tópico transdérmico, parenteral, subcutáneo, intraperitonial, intrapulmonar, e intranasal, y, si se desea para tratamiento local, administración intralesional. Infusiones parenterales incluyen intramuscular, intravenosa, intraarterial, intraperitonial, o administración subcutánea. Un ejemplo de una forma de dosis oral adecuada es un tableta que contiene aproximadamente 25 mg, 50 mg, 100 mg, 250 mg, o 500 mg del compuesto de la invención compuesto con aproximadamente 90-30 mg de lactosa anhidra, aproximadamente 5-30 mg de croscarmelosa de sodio, aproximadamente 5-30 mg de polivinilpirrolidina (PVP) K30, y aproximadamente 1-10 mg de estearato de magnesio. Los ingredientes en polvo se mezclan primero juntos y luego se mezclan con una solución del PVP. La composición resultante se puede secar, granular, mezclar con el estearato de magnesio y comprimir a forma de tabletas utilizando el equipo convencional. Se puede preparar una formulación en aerosol al disolver el compuesto, por ejemplo 5-400 mg, de la invención en una solución de amortiguación adecuada, por ejemplo, un amortiguador de fosfato, agregando un tonificador, por ejemplo una sal, tal como cloruro de sodio, si se desea. La solución se

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filtra típicamente, por ejemplo utilizando un filtro de 0.2 micrones, para remover impurezas y contaminantes.

EJEMPLOS

La invención se entenderá más completamente con referencia a los siguientes ejemplos. Ellos no deberían, sin embargo ser constituidos como limitante del alcance de la invención. Las abreviaturas utilizadas aquí son como sigue:

ACN: acetonitrilo;

Chg: ciclohexilglicina;

DCM: diclorometano

DIPEA: diisopropiletilamina;

DMAP: 4- dimetilaminopiridina;

DME: 1,2-dimetoxietano;

DMF: dimetilformamida;

DMSO: dimetilsulfóxido

EDC: 1-etil-3-(3-dimetilaminopropil)carbodiimida;

EEDQ: 2-etoxi-1-etoxicarbonil-1,2-dihidroquinolina

LCMS: espectrometría de masa de cromatografía líquida;

HATU: hexafluorofosfato de O-(7-Azobenzotriazol-1-il)-1,1,3,3-tetrametiluronio;

HOBt: N-Hidroxibenzotriazol

HBTU: Hexafluorofosfato de 2-(1H-Benzotriazol-1-il)-1,1,3,3-Tetrametil-uronio

HPLC: cromatografía líquida de alto desempeño;

NBS: N-bromosuccinamida;

TASF: difluorotrimetilsilicato tris(dimetilamino)sulfonio;

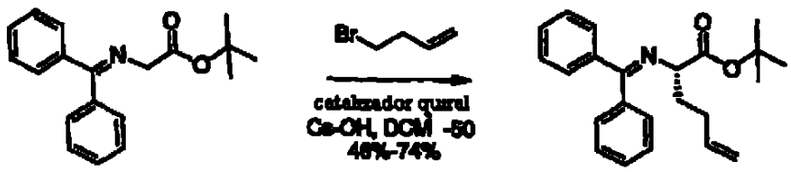
LHF 185

TEA: trietilamina;

TFA: trifluoroacetato;

THF: tetrahidrofurano;

Ejemplo 1 éster de etilo de ácido 6-(1,3-Dioxo-1,3-dihidro-isoindol-2-il)-5-oxo-octahidro-tiazolo[3,2-a]azepina-3-carboxílico



1 2

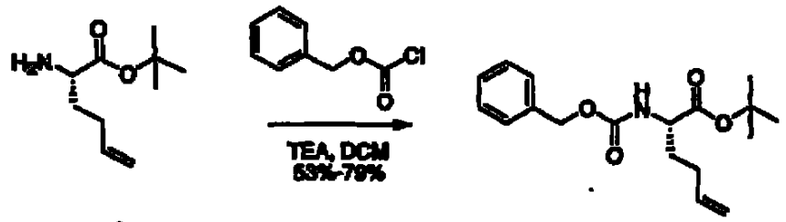
A una solución de N-(Difenilmetileno) éster de t-butilo glicina **1** (3.0 g, 10.1 mmol) y catalizador quiral de bromuro de O-Alil-N-(9-antracenilmetil)-cinconidio (613 mg, 1.0 mmol) en DCM seco (30 mL) se agrega hidróxido de cesio (17 g, 101 mmol). La reacción se enfría a -78° C en un baño de acetona en hielo seco y se agrega gota a gota 4-bromo-1-buteno. Después de adición la reacción se agita vigorosamente bajo N_2 a -48° C durante 48 horas. Se agrega éter de etilo seguido por H_2O. Se separa la capa orgánica y se lava 2x con H_2O, 1x solución salina, se seca con $MgSO_4$ y se concentra. El producto se purifica por cromatografía SiO_2 sobre un gradiente de 0-10% de EtOAc in Hexanos para dar **2** en 65% de rendimiento.

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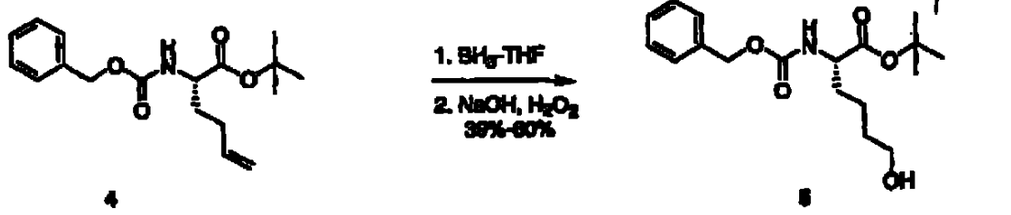
2 3

A una solución de **2** (1.52 g, 4.3 mmol) en MeOH seco (50 mL) se agrega NaOAc (720 mg, 8.6 mmol) y $NH_2OH \cdot HCl$ (540 mg, 7.6 mmol). Se agita bajo N_2 a temperatura ambiente durante 2 horas. Se agregan DCM y NaOH 0.1 N. La capa acuosa se separa y se extrae 3x con DCM, se seca con Na_2SO_4 y las fracciones DCM se combinan y se concentran. El producto se purifica por Cromatografía SiO_2, 0-10% de MeOH en DCM con 0.05% de TEA para dar **3** en 70% de rendimiento.



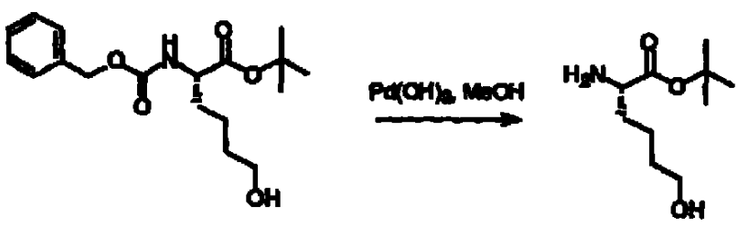
3 4

A una solución de **3** (610 mg, 3.3 mmol) en DCM seco (20 mL) se agrega trietilamina (550 µL, 3.9 mmol) y cloroformato de bencilo (550 µL, 3.9 mmol). La reacción se agita a temperatura ambiente durante 2 horas. La solución se concentra y se purifica por cromatografía SiO_2 sobre un gradiente de 0-30% de EtOAc en Hexanos para dar **4** en 66% de rendimiento.



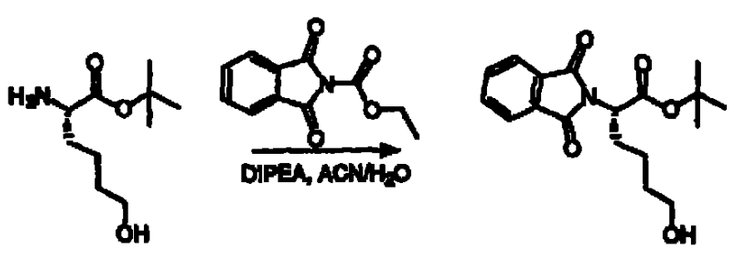
4 5

A una solución de **4** (577 mg, 1.8 mmol) en THF (20 mL) bajo N_2 se agrega BH3-THF. Después de 1 hora se agrega NaOH 3 N (300 µL, 0.9 mmol) y H_2O_2 (306 µL, 2.7 mmol). La reacción se agita durante la noche y posteriormente se diluye con H_2O, se extrae 2x con éter de etilo, se seca con $MgSO_4$ y se concentra. El producto se purifica por cromatografía SiO_2 sobre un gradiente de 10-45% de EtOAc en Hexanos para dar **5** en 50% de rendimiento.



5 6

A una solución de **5** (71 mg, 0.21 mmol) en MeOH (2 mL) bajo 1 atmósfera de H_2 se agrega 10% de hidróxido de paladio sobre carbono (30 mg). La reacción se completa después de 30 minutos. La reacción se filtra sobre Celita y se concentra para dar **6** en rendimiento cuantitativo.



6 7

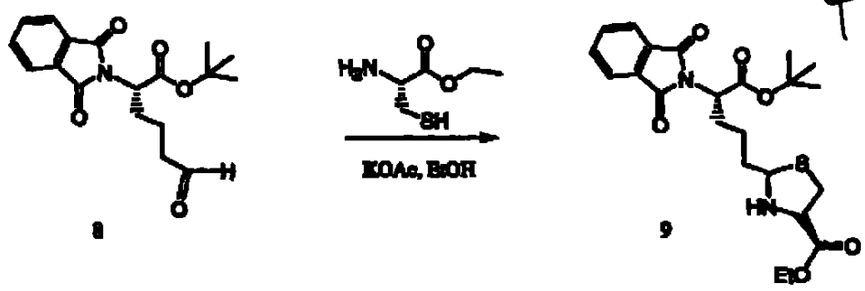
HTV 188

A **6** (42 mg, 0.21 mmol) en ACN (2 mL) se agrega carbetoxiftalimida (50 mg, 0.23 mmol) con DIPEA (40 µL, 0.23 mmol) y se agita a temperatura ambiente durante 2 horas. Se agrega H_2O (1 mL) y se agita adicionalmente durante 10 minutos. El ACN se evapora y se agregan DCM y 10% de ácido cítrico. La capa acuosa se separa y se extrae 3x con DCM, se combinan las porciones DCM, se secan con Na_2SO_4, y se concentran para dar **7** en 95% de rendimiento.



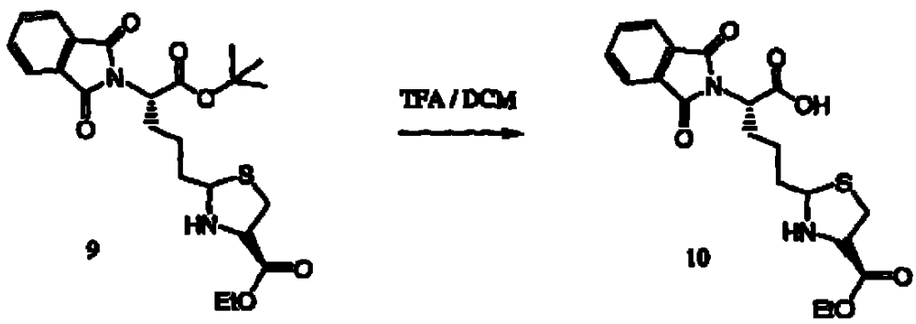
7 **8**

Se disuelve cloruro de oxalilo (561 µL, 6.60 mmol) en DCM (35 mL), se enfría a -78° C, se agita durante 5 minutos seguido por adición de una solución de dimetilsulfóxido (870 µL, 12.3 mmol) en DCM (2.5 mL). Después de agitar durante 5 minutos **7** (1.05 g, 3.15 mmol) en diclorometano (20 mL) se agrega seguido por trietilamina (2.37 mL, 17.0 mmol). La reacción se calienta lentamente a temperatura ambiente. Se agregan DCM y H_2O, la capa acuosa se separa y se extrae 2x con DCM. Las porciones DCM se combinan, se filtran a través de Na_2SO_4, y se concentran para dar **8** en 95% de rendimiento.



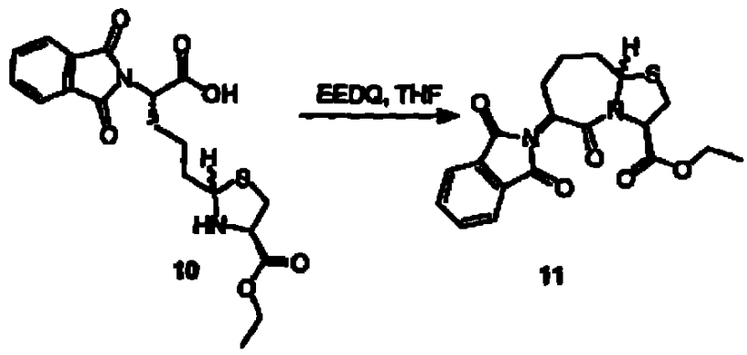
8 9

Se disuelven éster de etilo de L-cisteína (643 mg, 3.5 mmol) y acetato de potasio (343 mg, 3.5 mmol) en EtOH agitado (13 mL), y se enfría a 0° C en un baño de agua helada. Se disuelve el compuesto **8** en EtOH (13 mL) y se agrega. La reacción se agita a 0° C durante 4 horas, LCMS confirma la conversión de 8 en dos productos diastereoméricos. Se filtra la reacción, se evapora el EtOH, se redisuelve en DCM y se lava con solución salina, se seca con $MgSO_4$ y se concentra para dar una mezcla 1:1 de diastereómeros **9** en rendimiento cuantitativo.



9 10

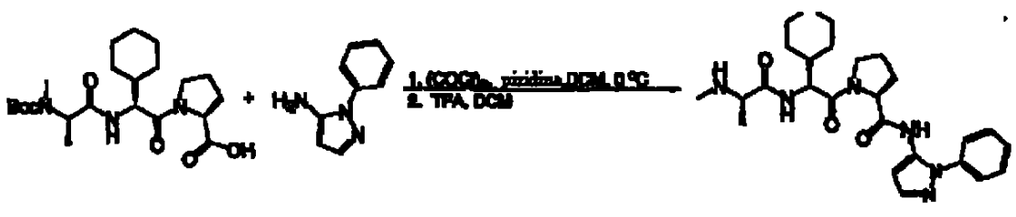
Los diastereómeros se redisuelven en 1:1 TFA:DCM (10 mL) y se agita durante 1 hora a temperatura ambiente. LCMS muestra la conversión completa a **10**. La reacción se concentra para dar **10** en 95% de rendimiento para los dos diastereómeros.



10 11

A una solución de 10 (675 mg, 1.67 mmol) en THF (20 mL), se agrega EEDQ (619 mg, 2.50 mmol). Se agita a temperatura ambiente durante 2 días. Se remueve el THF bajo presión reducida, el producto se redisuelve en EtOAc. Se lava la capa orgánica con HCl 0.5 N, 0.5% $NaHCO_3$, H_2O, solución salina. La solución de EtOAc se seca con $MgSO_4$ y se concentra. El producto se purifica por vía de HPLC de fase reversa 10-70% de AcN en H_2O para dar dos diastereómeros 11, 20% de rendimiento para diastereómero 1 y 18% de rendimiento para diastereómero 2.

Ejemplo 2 (2-fenil-2H-pirazol-3-il)-amida de ácido 1-[2-Ciclohexil-2-(2-metilamino-propionilamino)-acetil]-pirrolidina-2-carboxílico

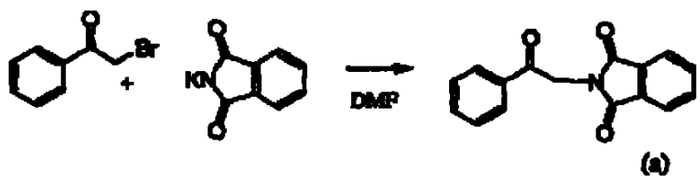


Una solución de Boc-MeAla-Chg-Pro-OH (47.0 mg, 0.107 mmol) y piridina (26 µl, 0.32 mmol) en diclorometano anhidro (300 µl) se enfría a 0° C y una solución de cloruro de oxalilo en

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diclorometano (54 µl, 2.0 M, 0.11 mmol) se agrega gota a gota durante 10 minutos. La mezcla se agita a 0° C durante 15 minutos, luego a temperatura ambiente durante 45 minutos, y se agrega una solución de 5-amino-1-fenilpirazol (15.9 mg, 0.100 mmol; TCI America catalog # A0174) y piridina (15.5 µl, 0.191 mmol) en diclorometano (0.5 ml). La mezcla resultante se agita a temperatura ambiente durante 16 horas, se diluye con diclorometano en 20 ml, y se lava con hidróxido de sodio acuoso 0.2 N (20 ml). La fase orgánica se seca ($MgSO_4$) y se concentra bajo presión reducida. El producto crudo se purifica por cromatografía de columna (gel de sílice, 60% de acetato de etilo en Hexanos, entonces 100% de acetato de etilo) para producir un aceite amarillo: *m/z* 581 ($M+H^+$). Se trata el aceite con 5% de ácido trifluoroacético en diclorometano (2 ml), y después de 18 horas se remueve el solvente *in vacuo*. El aceite resultante (29.3 mg, 57% de rendimiento durante 2 etapas) se purifica adicionalmente por HPLC de fase reversa para producir el producto (sal de TFA, 9.6 mg, 15% de rendimiento): *m/z* 481 ($M+H^+$), 503 ($M+Na^+$).

Ejemplo 3 4-Fenil-[1,2,3]tiadiazol-5-ilamina

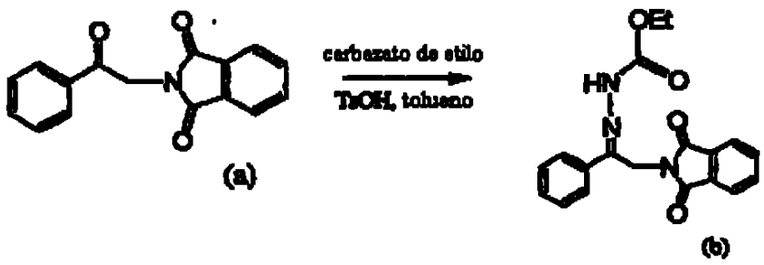


(a)

Se disuelve 2-bromoacetofenona en DMF (3 vol) y se agrega ftalamida de potasio (1.leq.). La reacción, inicialmente ligeramente exotérmica, se agita durante la noche a temperatura

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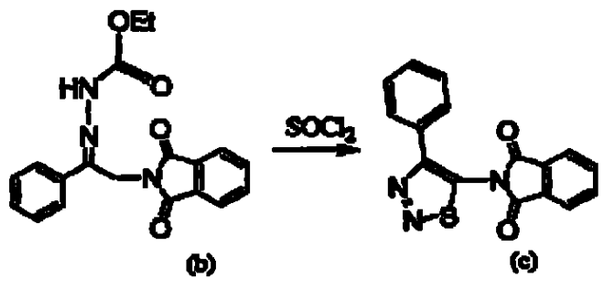
ambiente. El DMF se remueve *in vacuo* y la reacción se diluye con DCM (~3 vol) seguido por NaOH 0.1N (~3 vol; 1:1 ac/org) y se agita vigorosamente entonces se extrae. La capa orgánica, que contiene algún material sólido, se concentra in vacuo y el sólido resultante se suspende en dietil éter y se recolecta mediante filtración de succión para dar (a) como un sólido cristalino blanco en -95% de rendimiento.



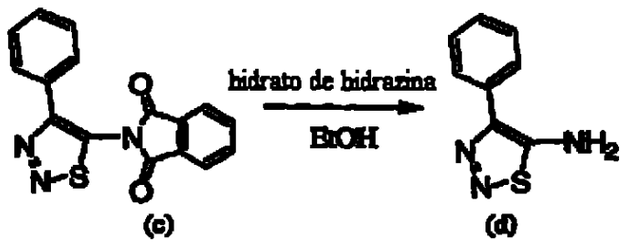
(a) (b)

El compuesto (a), carbazato de etilo (1.5 eq) y 'TsOH-H,O (0,1 eq) se combinan en tolueno (5 vol) y se calientan a reflujo utilizando un separador Dean-Stark para remover agua. La solución se torna a un color rojo oscuro y se completa mediante TLC en -2 hrs. Aproximadamente la mitad del tolueno se remueve mediante destilación, la solución se enfría a t.a. y se concentra in vacuo. El sólido resultante se suspende en EtOH (el volumen mínimo necesario para agitación), se calienta a reflujo durante 30 min y entonces se enfría en hielo para facilitar la precipitación de ambos isómeros. El sólido se recolecta mediante filtración de succión, se lava con EtOH frío y se seca bajo vacío para dar ambos isómeros del compuesto (b) como un sólido blancuzco en ~90% de rendimiento.

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Se agrega a cloruro de tionilo enfriado con hielo (4 eq, ~0.85 vol), en forma de porciones (en orden para control la exoterma), la mezcla de isómero de (b). El baño de hielo se remueve y la reacción se calienta a t.a. y se agita durante la noche. Se remueve cloruro de tionilo in vacuo, se agrega DCM (1 vol) y la reacción se agita con NaOH 0.1M (1 vol; 1:1 ac/org). Se extrae la suspensión y los orgánicos se concentran in vacuo, se suspenden en EtOAc de reflujo (el volumen mínimo necesario para fácil agitación) durante 30 min, se enfría a t.a., se recolecta mediante filtración de succión y se lava con un mínimo de EtOAc frío para dar (c) como un sólido cristalino blancuzco en ~80% de rendimiento.

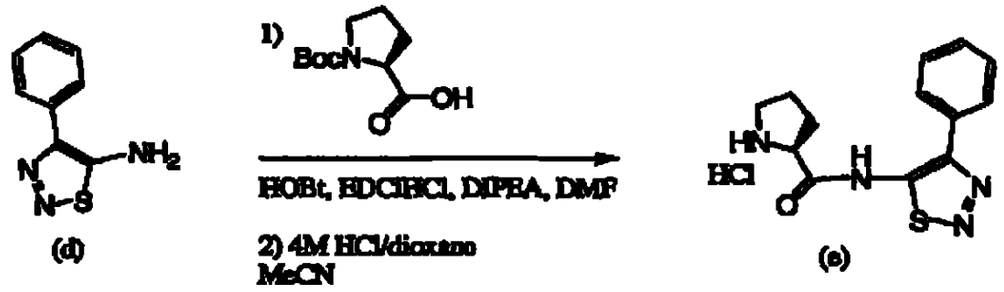


Una solución de hidrato de hidrazina (2.4 eq) en EtOH (1 vol) se agrega gota a gota a una solución de reflujo de (c) en EtOH (8 vol). Un precipitado se forma casi inmediatamente y la reacción se completa mediante TLC en ~3 hrs. La solución se enfría a t.a. y la ftalimida clivada por el producto se filtra lejos y se lava

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con DCM. El filtrado EtOH/DCM se concentra in vacuo hasta que se observa formación de cristal. Esta suspensión se agita durante la noche y la mezcla cristalino/sólida se recolecta mediante filtración de succión y se lava con EtOH frío hasta que se coloreen las impurezas las cuales se remueven, dando el tiadiazol amina (d) en ~75% de rendimiento como un sólido cristalino blancuzco.

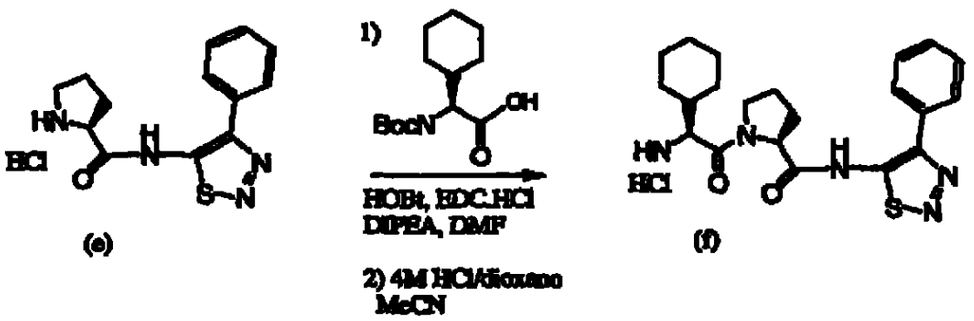
Ejemplo 4 (4-fenil-[1,2,3]tiadiazol-5-il)-amida de ácido 1-[2-Ciclohexil-2-(2-metilamino-propionilamino)-acetil]-pirrolidina-2- carboxílico



Se disuelven Boc-L-Pro (2 eq), HOBt (1.9 eq), EDC-HCl (1.9 eq) y DIPEA (5 eq) en DMF (10-15 vol). A estos entonces se agrega el tiadiazol amina (d). La reacción, inicialmente ligeramente exotérmica, se calienta a 75° C y se agita durante la noche, se enfría a temperatura ambiente y se remueve parcialmente el DMF in vacuo. La dilución con EtOAc (10-15 vol) se sigue mediante lavado con HCl 1M (2x), $NaHCO_3$ (1 x), y solución salina (1x) (1:1 ac/org). La capa orgánica se concentra in vacuo y el sólido resultante se suspende en MeCN de reflujo (un volumen mínimo necesario para fácil agitación) durante 30 min y entonces se enfría a t.a. La filtración por succión da producto de

[HF] 195

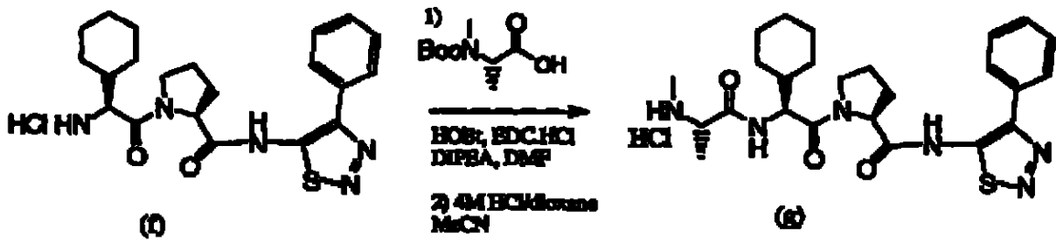
conjugación Boc-protegido como un sólido cristalino blancuzco en ~77% de rendimiento. El producto Boc-protegido se suspende en una solución de HCl 4M/dioxano (ácido 4-5 eq) y MeCN (1 vol eq a la solución de dioxano) y se agita a t.a. hasta que el LCMS indica desprotección completa, ~1 hr. La mezcla de reacción se concentra in vacuo y el sólido resultante se agita vigorosamente, se suspenden en reflujo MeCN (un volumen mínimo necesario para fácil agitación), se enfría a t.a., y el sólido se recolecta mediante filtración de succión y se lava con MeCN frío hasta que se remueve el color residual de la torta para producir la sal de HCl (e) como un sólido blancuzco en aproximadamente rendimiento cuantitativo.



La sal de HCl (e) se disuelve en DMF (10-15 vol) y DIPEA (5 eq). A esta se agrega el Boc-L-Chg (1.5 eq), HOBt (1.4 eq) y EDC-HCl (1.4 eq). Se completa el acoplamientos después de ~2 hrs mediante LCMS. La reacción se diluye con EtOAc (15 vol) y se lava con HCl 1M (2x), $NaHCO_3$ (1x), y solución salina (1x) (1:1 ac/org). El extracto orgánico se seca sobre sulfato de sodio y se concentra in vacuo. El sólido resultante se suspende en EtOH/Hexano (20:80) (un volumen mínimo necesario para fácil agitación) y se filtra para dar el producto conjugado Boc-protegido como un sólido

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blanco lanoso en ~80% de rendimiento. El Boc-protegido se disuelve en una solución de HCl 4M/dioxano (4-5 eq ácido) y MeCN (0.25 volumen eq a la solución de dioxano) y se agita a t.a. hasta que el LCMS indica la desprotección completa, ~1 hr. La reacción se concentra hasta secado con tolueno (2x) (el mismo volumen como la solución de desproteción) para producir la sal de HCl (f) como un sólido cristalino blanco en aproximadamente rendimiento cuantitativo.

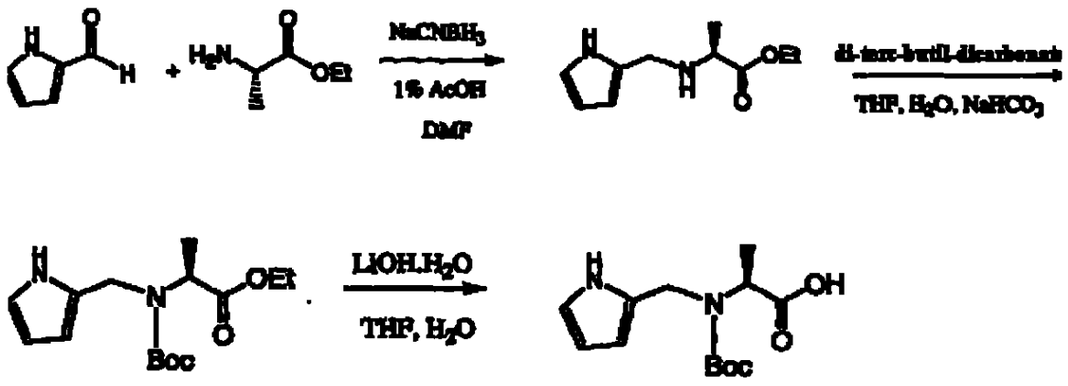


(f) (g)

La sal de HCl (f) se disuelve en DMF (10-15 vol) y DIPEA (5eq). A esta se agrega el Boc-L-N-metil Ala (1.5 eq), HOBt (1.4 eq), y EDC-HCl (1.4 eq). Se completa el acoplamiento después de ~1 hr. mediante LCMS. La reacción se diluye con EtOAc (15 vol) y se lava con HCl 1M (2x), $NaHCO_3$ (1x), y solución salina (1x) (1:1 ac/org). El extracto orgánico se seca sobre sulfato de sodio y se concentra in vacuo para dar el producto conjugado Boc-protegido como un sólido espumoso, beige en ~85% de rendimiento. El conjugado Boc-protegido se disuelve en una solución de HCl 4M/dioxano (4-5 eq ácido) y MeCN (0.25 volumen eq a la solución de dioxano) y se agita a t.a. hasta que el LCMS indica la desprotección completa, ~1 hr. La reacción se concentra hasta secado con tolueno (2x) (el mismo volumen como en la solución de desprotección) y el sólido resultante se suspende en una solución de MTBE/EtOAc (70:30) (volumen mínimo necesario para fácil

agitación), se filtra y se recolecta para producir (g) como un sólido libre de flujo blancuzco crudo. La sal de HCl cruda (g) se suspende en MeOH (4 vol mínimo) y se disuelve con agitación a 65° C. Se agrega Acetato de Isopropilo Caliente (6-8 vol) en dos porciones, se mantiene la temperatura a aproximadamente 60° C, y la solución se le permite enfriar con agitación. La cristalización sucede rápidamente, la suspensión se agita a temperatura ambiente durante varias horas, entonces se agita a 0° C durante una hora antes el sólido se recolecta mediante filtración de succión, se lava con MeOH/iPrOAc (1:4, 2 vol) y se seca para producir el producto final como un sólido cristalino blanco/blancuzco en ~80% de rendimiento de (f).

Ejemplo 5 ácido 2-[terc-butoxicarbonil-(1H-pirrol-2-ilmetil)-amino]-propiónico



Éster de etilo alanina (5 g, 32.5 mmol), pirrol-2-carboxaldehído (3.1 g, 32.5 mmol), cianoborohidruro de sodio (2.04 g, 32.5 mmol) y AcOH (1%) se mezclan en DMF y se agitan durante la noche. La reacción se apaga con H_2O, y DMF se evapora. La mezcla se diluye con EtOAc, se lava con NaOH0.1N, se seca y se concentra para

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producir 2.5 g del producto. El éster resultante (2.5 g, 12.8 mmol), di-terc-butildicarbonato (3.06 g, 14 mmol) se mezclan en THF, H_2O con $NaHCO_3$ y se agitan durante la noche. Se evapora THF, y la mezcla se diluye con EtOAc, se lava con NaOH 1N, NH_4Cl saturado y solución salina. Después de secado, la mezcla se concentra para producir el éster de Boc-protegido 3.3 g. El éster de Boc-protegido (1.67 g, 5.6 mol), mono hidrato de hidróxido de litio (284mg, 6.77mmol) se mezclan en THF y H_2O a 0° C. Se vacía THF, y la solución se acidifica por dilución de H_2SO_4, se extrae por EtOAc dos veces. Las capas orgánicas se combinan, se secan yse evaporan.

Ejemplo 6 tetrahidropiranilglicina

Se compra tetrahidropiranilglicina de NovaBiochem, o se sintetiza de acuerdo a la literatura: Ghosh, A. K.; Thompson, W. J.; holloway, M. K.; McKee, S. P.; Duong, T. T.; Lee, H. Y.; Munson, P. M.; Smith, A. M.; Wai, J. M; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleife, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem*, 1993, 36, 2300-2310.

Ejemplo 7 piperidinilglicina

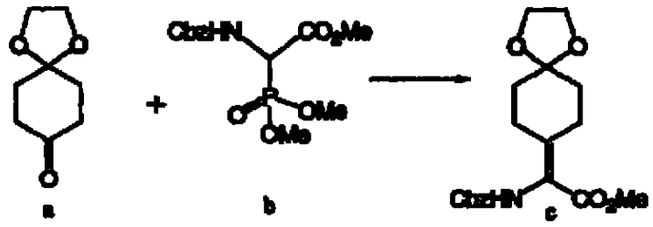
Se sintetiza piperidinilglicina de acuerdo a la literatura: Shieh, W-C; Xue, S.; Reel, N.; Wu, R.; Fitt, J.; Repic, O. *Tetrahedron: Asymmetry*, 2001, 12, 2421-2425.

Ejemplo 8 4,4-difluorociclohexilglicina

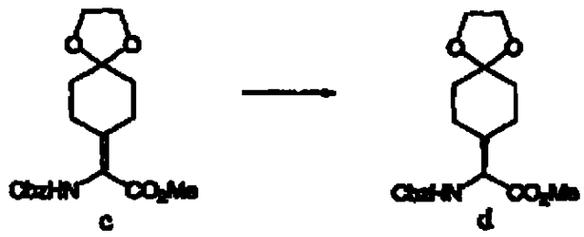
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Se hace 4,4-difluorociclohexilglicina de acuerdo a los procedimientos descritos en US 2003/0216325.

Ejemplo 9 ácido Boc (S)-2-amino-2-(4-hidroxiciclohexil)acético

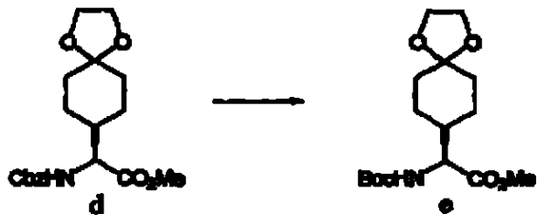


Siguiendo el procedimiento de Sheih, (*Tetrahedron: Asymmetry*, 2001, 12, 2421-2425), una solución de cetona **a** (8.4 g) y EtOAc (30 mL) se agrega a una solución de éster de metilo de N-Cbz-fosfonoglicina **b**, TMG (4.5 mL) y EtOAc (30 mL). La solución se mantiene así durante 48 h, entonces se lava con HCl 1N (3x50 mL), solución salina (1x50 mL) se seca (Na_2SO_4), se filtra, y se concentra. El residuo se adsorbe en Celita, y se purifica por cromatografía, entonces se purifica adicionalmente por re-cristalización de EtOAc/Hexanos para proporcionar 5.2 g del producto **c**.

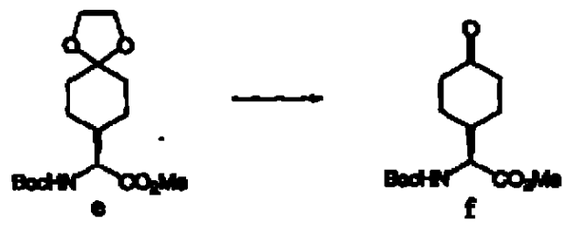


Siguiendo el procedimiento de Sheih, (*Tetrahedron: Asymmetry*, 2001, 12, 2421-2425), una solución de eneamida **c** (5.0 g), (S,S)-Me-BPE-Rh(I) (1.5g, Strem Chemicals, Newburyport, MA), y MeOH

(100 mL) se sacude vigorosamente bajo 70 psi de H_2 durante 48 h. Se remueve el solvente bajo presión reducida. El residuo se pone en EtOAc, y se filtra a través de SiO_2 con más EtOAc. Se remueve el solvente bajo presión reducida para proporcionar 4.0 g del producto **d** como un sólido incoloro.



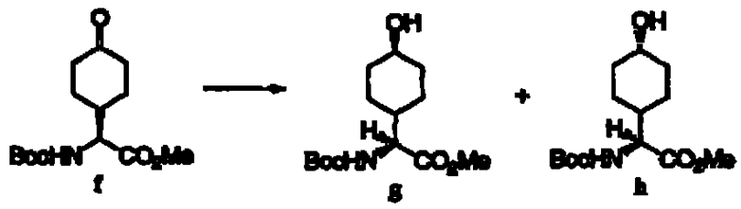
Una mezcla de Cbz-carbamato d, (4.0 g) BoC_2O, (2.9 g), 20% de $Pd(OH)_2 \cdot C$ (1.0 g) y MeOH (30 mL) se mantiene bajo una atmósfera de H_2 durante 6h. La mezcla se filtra a través de Celita con MeOH. Se remueve el solvente bajo presión reducida para proporcionar 4.5 g del residuo **e**, el cual se toma directamente.



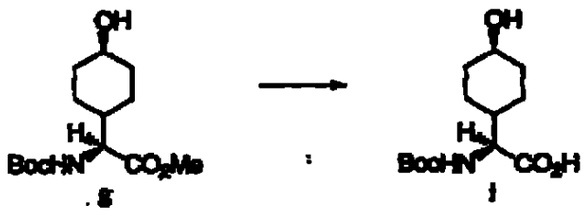
El residuo **e** anterior se disuelve en H_2O (10 mL), AcOH (30 mL), THF (5 mL), y ácido dicloroacético (3 mL) y se mantiene a ta durante la noche. Se agrega agua (5 mL) y la solución y se mantiene hasta que se completa la hidrólisis, se monitorea por HPLC-MS. Se agrega Na_2CO_3 sólido cautelosamente hasta que cesa la evolución del gas, la mezcla se diluye con $NaHCO_3$ ac, y se extrae con 10% de EtOAc/DCM. Las fases orgánicas combinadas se lavan una

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vez con solución salina, se secan (Na_2SO_4), se filtran, y se concentran. El residuo se purifica por cromatografía para proporcionar 2.9 g del producto **f**.

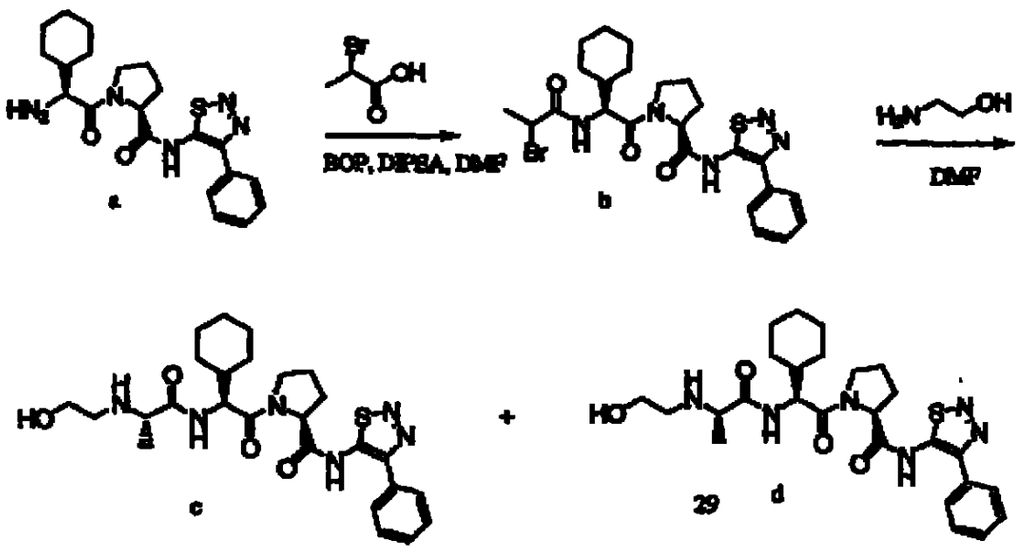


Una mezcla de cetona **f** (1.5g) MeOH (50 ml) se trata con $NaBH_4$ (290 mg) a 0° C durante 20 min. La mezcla se acidifica a ~pH 1 con 10% de ácido cítrico ac. y el MeOH se remueve bajo presión reducida. El residuo se diluye con agua y se extrae con 20% de EtOAc/DCM. Las fases orgánicas combinadas se lavan una vez con solución salina, se secan (Na_2SO_4), se filtran, y se concentran. El residuo se purifica por cromatografía para proporcionar 1.17 g del producto **g** y 0.23 g del producto **h**.



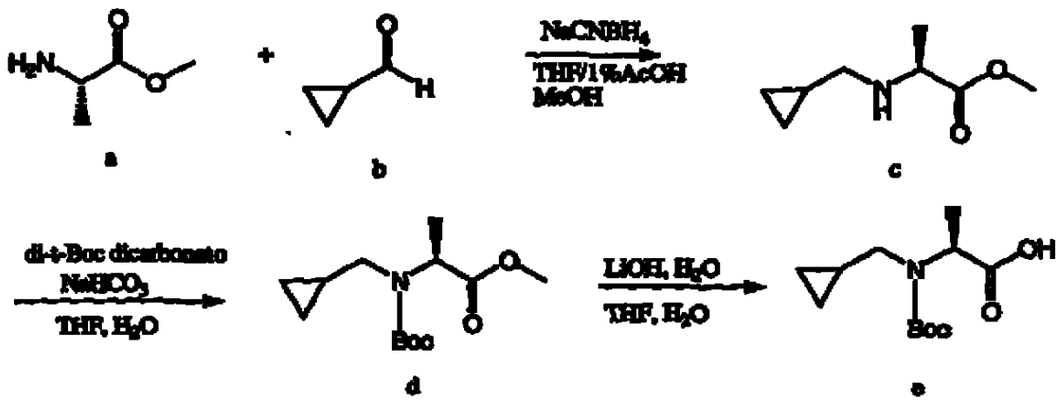
Una mezcla de éster **g** (1.17g) $LiOH \cdot H_2O$ (160 mg), THF (3 mL) y agua (4.5 mL) se agita vigorosamente a t.a. durante la noche. La mezcla se diluye con solución salina y se extrae exhaustivamente con EtOAc. Las fases orgánicas combinadas se lavan una vez con solución salina, se secan (Na_2SO_4), se filtran, y se concentran para proporcionar el ácido **i** (525 mg).

Ejemplo 10 compuesto 29



Una mezcla de amina **a** (1.56 mmol), ácido 2-Bromopropiónico (0.72 g, 4.68 mmol), BOP (2.1 g, 4.68 mmol) y DIPEA (1.6 ml, 9.36 mmol) en 10 ml de DMF se agita a temperatura ambiente durante 2 horas. El análisis LCMS indica que la reacción se completa. Se agrega 100 ml de EtOAc a la reacción y la capa orgánica se lava con $NaHCO_3$ saturado seguido por solución salina, se seca sobre Na_2SO_4 y se concentra hasta sequedad. El material crudo se purifica por cromatografía utilizando 50% de EtOAc/Hexano para obtener el compuesto **b**. El compuesto **b** (0.832 g, 1.5 mmol) se trata con etanolamina (200 ul, 2.73 mmol) en 3 ml DMF y se agita durante la noche para terminación. La mezcla de reacción se purifica por HPLC de fase reversa para obtener dos diastereómeros **c** (53mg) y **d** (compuesto 29) (150 mg).

Ejemplo 11 N-Boc-N-ciclopropilmetil-1-alanine



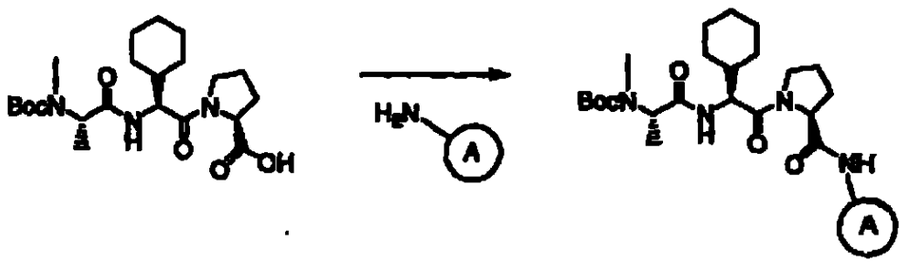
Clorhidrato de éster de metilo L-alanina **a** (5 g, 35.8 mmol) y ciclopropanocarboxaldehído **b** (2.67 ml, 35.8 mmol) se suspenden en 50 ml de THF p/1% de AcOH. La adición de 5 ml de CH_3OH hace que la solución nublada se torne clara. Se agrega $NaCNBH_4$ (2.25 g, 35.8 mmol) y la mezcla de reacción se agita durante la noche. La reacción se apaga por la adición de NaOH 1N ac., se extrae por EtOAc dos veces, las capas orgánicas se secan sobre Na_2SO_4 y se concentran hasta sequedad. El material crudo se purifica por cromatografía utilizando 30% de EtOAc/Hexano (se mancha por ninhidrina) para obtener el compuesto **c** (1 g, 18%).

El compuesto **c** (1 g, 6.37 mmol) y di-t-bocdicarbonato (2.1g, 9.55 mmol) se diluyen en THF (20 ml) y H_2O (20 ml), se agrega $NaHCO_3$ (1.3 g, 15.9 mmol). La mezcla de reacción se agita durante la noche para terminación. Se remueve THF bajo presión reducida, y la capa acuosa se extrae por EtOAc 3 veces. Las capas orgánicas combinadas se lavan con NaOH 1N, sat, NH_4Cl seguido por solución salina, se concentran hasta sequedad. El compuesto Boc-protegido **d** (1.39 g, 5.40 mmol) se agita con $LiOH-H_2O$ (1.1 4g, 27 mmol) en THF (20 ml) y H_2O (20 ml) durante la noche a temperatura ambiente. Se retira el THF, y la capa acuosa se ajusta a pH=4 por

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adición de 10% de ácido cítrico, entonces se extrae por EtOAc 3 veces. Las capas orgánicas combinadas se lavan con solución salina y se concentran. El crudo se purifica por columna C-18 de fase reversa se eluye por 0%-50% de Acetonitrilo/H_2O para dar el compuesto puro e como un sólido blanco (794 mg).

Ejemplo 12 proceso de acoplamiento de fluoruro ácido

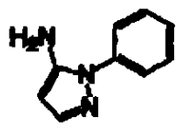


Una solución de Boc-MeAla-Chg-Pro-OH (2.3 mmol) y piridina (6.9 umol) en diclorometano anhidro (23 ml) se enfría a 0° C y fluoruro cianúrico (2.3 mmol) se agrega gota a gota durante 30 seg. La mezcla se agita a 0° C durante 15 min, a temperatura ambiente durante 5 hr, y entonces se apaga con agua. La mezcla se extrae tres veces con diclorometano (total 100 ml), y las fases orgánicas combinadas se lavan con solución salina y se secan sobre sulfato de sodio anhidro. La filtración y concentración *in vacuo* producen el péptido fluoruro ácido como un aceite incoloro, claro que se utiliza directamente sin purificación adicional.

Una solución del fluoruro ácido crudo (0.50 mmol) y piridina (1.5 mmol) en diclorometano (2.5 ml) se agrega a la amina sólida (0.50 mmol), y la mezcla resultante se agita a temperatura ambiente o a 50° C (vaso sellado). La mezcla se vierte en bicarbonato de sodio

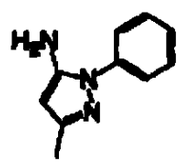
acuoso y se extrae tres veces con diclorometano (total 100 ml). Las fases orgánicas combinadas se lavan con solución salina, se seca sobre sulfato de sodio anhidro, se filtra y se concentra *in vacuo*. El péptido de amida crudo se utiliza directamente sin purificación adicional.

Ejemplo 13 1-fenil-1H-pirazol-5-amina



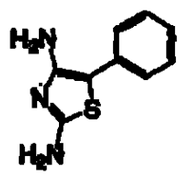
1-fenil-1H-pirazol-5-amina está comercialmente disponible de TCI America (catalog# A0174).

Ejemplo 14 3-metil-1-fenil-1H-pirazol-5-amina



3-metil-1-fenil-1H-pirazol-5-amina está comercialmente disponible de TCI America (catalog# A1311).

Ejemplo 15 5-feniltiazol-2,4-diamina



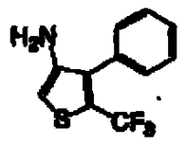
206

5-feniltiazol-2,4-diamina está comercialmente disponible de Acros Organics (catalog# 11234- 0010).

Ejemplo 16 5-(trifluorometil)-4-feniltiofen-3-amina

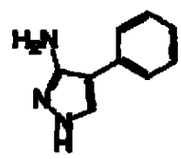
5-(trifluorometil)-4-feniltiofen-3-amina está comercialmente disponible de Acros Organics (catalog# SEW03133DA).

Ejemplo 17 4-fenil-1H-pirazol-3-amina



4-fenil-1H-pirazol-3-amina se prepara de acuerdo a los procedimientos descritos en E. L. Anderson *et al; J. Med. Chem.*, 1964, 7, 259-268.

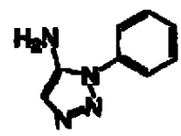
Ejemplo 18 5-metil-4-fenil-1H-pirazol-3-amina



5-metil-4-fenil-1H-pirazol-3-amina se prepara de acuerdo a los procedimientos descritos en E. L. Anderson *et al; J. Med. Chem.*, 1964, 7, 259-268.

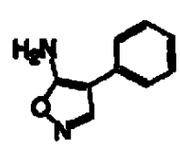
Ejemplo 19 3-fenil-3H-1,2,3-triazol-4-amina

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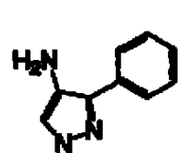
3-fenil-3H-1,2,3-triazol-4-amina se prepara de acuerdo a los procedimientos descritos en K. M. Baines, T. W. Rourke, K. Vaughan; *J. Org. Chem.*, 1981, 46, 856-859.

Ejemplo 20 4-fenilisoxazol-5-amina



4-fenilisoxazol-5-amina se prepara de acuerdo a los procedimientos descritos en H. Peeters, W. Vogt; EP 43024.

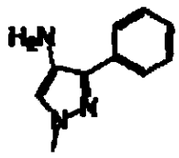
Ejemplo 21 3-fenil-1H-pirazol-4-amina



3-fenil-1H-pirazol-4-amina se prepara de acuerdo a los procedimientos descritos en C. Chen, K. Wilcoxen, J. R. McCarthy; *Tetrahedron Lett.*, 1988, 39, 8229-8232.

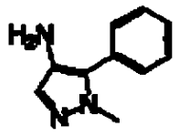
Ejemplo 22 1-metil-3-fenil-1H-pirazol-4-amina

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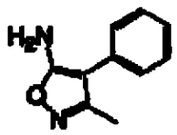
1-metil-3-fenil-1H-pirazol-4-amina se prepara de acuerdo a los procedimientos descritos en C. Chen, K. Wilcoxen, J. R. McCarthy; *Tetrahedron Lett.*, 1988, 39, 8229-8232.

Ejemplo 23 1-metil-5-fenil-1H-pirazol-4-amina



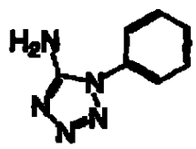
1-metil-5-fenil-1H-pirazol-4-amina se prepara de acuerdo a los procedimientos descritos en C. Chen, K. Wilcoxen, J. R. McCarthy; *Tetrahedron Lett.*, 1988, 39, 8229-8232.

Ejemplo 24 3-metil-4-fenilisoxazol-5-amina



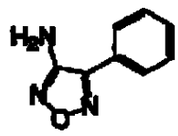
3-metil-4-fenilisoxazol-5-amina se prepara de acuerdo a los procedimientos descritos en H. Peeters, W. Vogt; EP 43024.

Ejemplo 25 1 -fenil-1H-tetrazol-5-amina



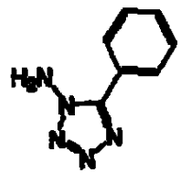
1-fenil-1H-tetrazol-5-amina se prepara de acuerdo a los procedimientos descritos en R. A. Batey, D. A. Powell; *Org. Lett.*, 2000, 2, 3237-3240.

Ejemplo 26 4-fenil-1,2,5-oxadiazol-3-amina



4-fenil-1H,2,5-oxadiazol-3-amina se prepara de acuerdo a los procedimientos descritos en R. Lakhan, O. P. Singh; *Ind. J. Chem.*, 1987, *26B*, 690-692.

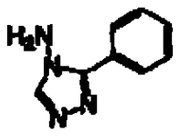
Ejemplo 27 1-amino-5-fenil-1H-tetrazol



1-amino-5-fenil-1H-tetrazol se prepara de acuerdo a los procedimientos descritos en T. L. Gilchrist, G. E. Gymer, C. W. Rees; *J. Chem. Soc, Perkin Trans.* 1, 1975, 1747-1750.

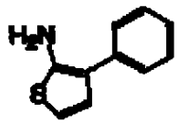
Ejemplo 28 4-amino-3-fenil-4H-1,2,4-triazol

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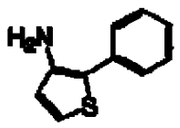
4-amino-3-fenil-4H-1,2,4-triazol se prepara de acuerdo a los procedimientos descritos en A. A. Ikizler, N. Yildirim; *J. Heterocyclic Chem.*, 1998, 35, 377-380.

Ejemplo 29 3-feniltiofen-2-amina



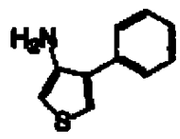
3-feniltiofen-2-amina se prepara de acuerdo a los procedimientos descritos en Y. Yoshikawa *et al.*; EP 737682 (US 5747518).

Ejemplo 30 2-feniltiofen-3-amina



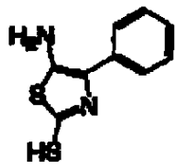
2-feniltiofen-3-amina se prepara de acuerdo a los procedimientos descritos en Y. Yoshikawa *et al.*; EP 737682 (US 5747518).

Ejemplo 31 4-feniltiofen-3-amina



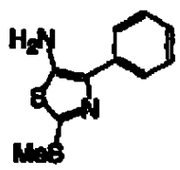
4-feniltiofen-3-amina se prepara de acuerdo a los procedimientos descritos en G. Kirsch, D. Cagniant, P. Cagniant; *J. Heterocyclic Chem.*, 1982, 19, 443-445.

Ejemplo 32 5-amino-4-feniltiazol-2-tiol



5-amino-4-feniltiazol-2-tiol se prepara de acuerdo a los procedimientos descritos en A. H. Cook, I. Heilbron, A. L. Levy; *J. Chem. Soc*, 1947, 1598-1609.

Ejemplo 33 2-(metiltio)-4-feniltiazol-5-amina



2-(metiltio)-4-feniltiazol-5-amina se prepara de acuerdo a los procedimientos descritos en A. H. Cook, I. Heilbron, A. L. Levy; *J. Chem. Soc*, 1947, 1598-1609.

Ejemplo 34 5-amino-2-(metilsulfinil)-4-feniltiazol



A 5-amino-2-(metilsulfanil)-4-feniltiazol (305 mg, 1.37 mmol) en ácido acético (3.0 ml) se agrega peróxido de hidrógeno acuoso (660 µl, 30% en peso, 6.9 mmol) gota a gota a temperatura ambiente. Después de 4 hr la mezcla se particiona entre diclorometano (60 ml) y agua (60 ml). La fase orgánica se separa, se lava con solución salina, se seca sobre sulfato de sodio, se filtra y se concentra *in vacuo*. Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) producen 5-amino-2-(metilsulfinil)-4-feniltiazol puro (285 mg, 87%).

Ejemplo 35 5-amino-2-(metilsulfonil)-4-feniltiazol



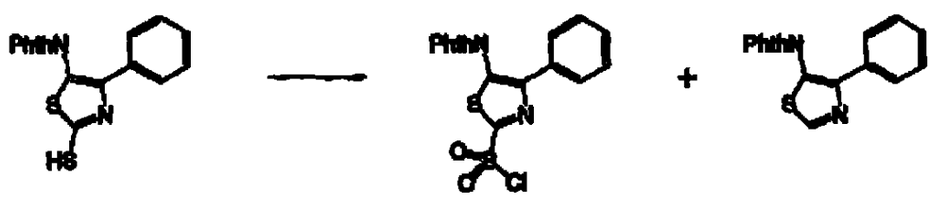
A 5-amino-2-(metilsulfanil)-4-feniltiazol (302 mg, 1.36 mmol) en diclorometano (5.0 ml) se agrega en forma de porción ácido 3-cloroperbenzoico (638 mg, 77% en peso, 2.9 mmol) con enfriamiento a 0° C. La mezcla se diluye con diclorometano (3.0 ml) y después de 5 min se le permite calentar a temperatura ambiente. Después de 3 hr se agrega una cantidad adicional de ácido 3-cloroperbenzoico (305 mg, 77% en peso, 1.4 mmol) en forma de

porción. Después de 20 hr la mezcla se trata con tiosulfato de sodio (2 ml, 1.0 M), se vierte en bicarbonato de sodio acuoso saturado y se extrae tres veces en diclorometano (total 100 ml). Las fases orgánicas combinadas se lavan con bicarbonato de sodio acuoso saturado y solución salina, se secan sobre sulfato de sodio y se concentran *in vacuo* para dar una espuma café oscuro. Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) producen 5-amino-2-(metilsulfonil)-4-feniltiazol puro (90 mg, 26%).

Ejemplo 36 5-amino-2-(aminosulfonil)-4-feniltiazol y 5-amino-4-feniltiazol



5-Amino-2-mercapto-4-feniltiazol (1.01 g, 4.83 mmol) y anhídrido ftálico (716 mg, 4.84 mmol) en ácido acético (20 ml) se calienta a 100° C durante 64 hr y se le permite enfriar. La mezcla se diluye en agua helada (150 ml) y el precipitado se recolecta por filtración, se lava con agua (50 ml) y se seca bajo alto vacío (1.46 g, 90%). La ftalimida se contamina con una menor cantidad de disulfuro pero utilizado sin purificación adicional.



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2-Mercapto-4-fenil-5-ftalimido-tiazol (203 mg, 600 µmol) en ácido acético (4.5 ml) y agua (0.5 ml) a 0° C se trata con N-clorosuccinimida (243 mg, 1.82 mmol) en una porción. La mezcla se agita a 0° C durante 10 min, se le permite calentar a temperatura ambiente durante 1 hr y entonces se particiona entre diclorometano (50 ml) y agua (50 ml). La fase acuosa se extrae dos veces más con diclorometano (2 x 25 ml), y las fases orgánicas combinadas se lavan con solución salina y se secan sobre sulfato de sodio. La filtración y concentración *in vacuo* producen una mezcla (231 mg) de 2-(clorosulfonil)-4-fenil-5-ftalimido-tiazol (componente principal) con 4-fenil-5-ftalimido-tiazol (ca. 2:1), utilizado sin purificación.



La mezcla cruda de cloruro de sulfonilo con 4-fenil-5-ftalimido-tiazol (231 mg) en diclorometano (10 ml) se trata con amoniaco en metanol (900 µl, 2.0 M) gota a gota a temperatura ambiente. Después de 10 min la mezcla se concentra *in vacuo*. El residuo se suspende en etanol (10 ml), se trata con hidrázina etanólica (660 µl, 1.0 M, 660 µmol) y se calienta a reflujo. Después de 1.5 hr se agrega una porción de hidrázina etanólica (660 µl, 1.0 M, 660 µmol) y se continúa reflujo durante 15 hr. La mezcla fría se filtra y se concentra *in vacuo*. Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) producen 5-amino-2-

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(aminosulfonil)-4-feniltiazol (56 mg, 36% durante 3 etapas) puro y 5-amino-4-feniltiazol (17 mg, 16% durante 3 etapas).

Ejemplo 37 5-amino-2-(terc-butilsulfanil)-4-feniltiazol



A una suspensión de 5-amino-2-mercapto-4-feniltiazol (210 mg, 1.01 mmol) en agua (1.0 ml) y terc-butanol (82 mg, 1.1 mmol) se agrega se concentra ácido sulfúrico (3.0 ml) con enfriamiento a ca. 20° C. Después de 1.5 hr a temperatura ambiente se agrega una porción de terc-butanol en agua (300 µl, 1.0 M, 300 µmol). Después de 1.5 hr la mezcla se vierte en exceso de bicarbonato de sodio acuoso y se extrae tres veces en diclorometano (total 120 ml). Las fases orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de sodio, se filtran y se concentran *in vacuo*. Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) producen 5-amino-2-(terc-butilsulfanil)-4-feniltiazol (220 mg, 82%).

Ejemplo 38 5-amino-2-(*terc*-butilsulfinil)-4-feniltiazol



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A 5-amino-2-(*terc*-butilsulfanil)-4-feniltiazol (102 mg, 385 µmol) en ácido acético (5.0 ml) se agrega peróxido de hidrógeno acuoso (218 µl, 30% en peso, 1.9 mmol) gota a gota a temperatura ambiente. Después de 5 hr la mezcla se particiona entre diclorometano (50 ml) y agua (50 ml). La fase acuosa se separa y se extrae con diclorometano (20 ml). Las fases orgánicas combinadas se lavan con bicarbonato de sodio acuoso saturado, se secan sobre sulfato de sodio, se filtran y se concentran *in vacuo* para producir esencialmente 5-amino-2-(*terc*-butilsulfinil)-4-feniltiazol puro (110 mg, cuant.).

Ejemplo 39 5-amino-4-fenil-2-(trifluorometilsulfanil)tiazol



Una suspensión de 5-amino-2-mercapto-4-feniltiazol (503 mg, 2.41 mmol) en ácido acético (5.0 ml) se trata con hexano-2,5-diona (290 µl, 2.47 mmol) a temperatura ambiente durante 14 hr y entonces se calienta a reflujo durante 3 hr. La mezcla llega a ser homogénea en reflujo y en congelamiento se deposita un precipitado el cual se recupera por filtración, se lava con ácido acético (3 X 1.0 ml) y se seca *in vacuo* para producir el pirrolidino-tiazol puro (624 mg, 90%) como un sólido microcristalino amarillo brillante.

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Una solución del mercapto-tiazol (201 mg, 701 µmol) y carbonato de potasio (291 mg, 2.11 mmol) en DMF (2.0 ml) se satura con yoduro de trifuorometilo por burbujeo durante 5 min, y el vaso se sella y se calienta a 50° C durante 30 min. La mezcla fría nuevamente se satura con yoduro de trifuorometilo, y se calienta a 100° C durante 1.5 hr. La mezcla una vez más se satura con yoduro de trifuorometilo, se regresa a 100° C (total 24 hr) y se le permite enfriarse. La mezcla se vierte en agua y se extrae tres veces en acetato de etilo (total 100 ml). Las fases orgánicas combinadas se lavan con agua y solución salina, se secan sobre sulfato de magnesio, se filtran y se concentran *in vacuo*. Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) producen el (trifluorometilsulfanil)-tiazol puro (72 mg, 29%) como una película cristalina incolora.



Una suspensión del tiazol (72 mg) y clorhidrato hidroxilamina (71 mg, 1.0 mmol) en etanol (5.0 ml) se calienta a reflujo durante 17 hr, se diluye con ácido acético (3 ml), se refluye adicionalmente durante 2 hr, y se concentra a ca. 3 ml. La mezcla fría se trata

con hidroxilamina acuosa (1.0 ml, 50% en peso) y se regresa a reflujo durante 42 hr. La mezcla se trata con agua (50 ml) y bicarbonato de sodio acuoso saturado (50 ml) y se extrae tres veces en diclorometano (total 100 ml). Las fases orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de sodio, se filtran y se concentran *in vacuo*. Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) producen 5-amino-4-fenil-2-(trifluorometilsulfanil)tiazol puro (12.5 mg, 22%).

Ejemplo 40 5-amino-4-fenil-2-(trifluorometil)tiazol



α-Aminofenilacetamida (2.00 g, 13.3 mmol) en metanol (50 ml) a 0° C se trata con trifluoroacetato etilo (3.2 ml, 27 mmol) durante 30 min y se le permite calentar a temperatura ambiente durante 18 hr. La mezcla se concentra *in vacuo*, se hace homogénea con metanol y otra vez la trifluoroacetamida pura se concentra primero para la producción (3.27g, cuant.).



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La trifluoroacetamida (881 mg, 3.58 mmol) y Reactivo de Lawesson (1.45g, 3.59 mmol) se tratan junto con piridina anhidra (7.2 ml) y la mezcla se calienta a 100° C durante 20 hr. La mezcla fría se vierte en bicarbonato de sodio acuoso saturado y se extrae tres veces en cloroformo (total 120 ml). Las fases orgánicas combinadas se lavan con agua que contiene un décimo de volumen de bicarbonato de sodio acuoso saturado, y solución salina, y se secan sobre sulfato de sodio. La filtración y concentración *in vacuo* producen un aceite café-rojo(829 mg). El crudo se trata con hidróxido de sodio acuoso (25 ml, 1.0 N) durante 15 min y se extrae tres veces en diclorometano (total 100 ml). Las fases orgánicas combinadas se lavan con hidróxido de sodio acuoso (25 ml, 1.0 N) y solución salina, se secan sobre sulfato de sodio, se filtran y se concentran *in vacuo*. Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) produce 5-amino-4-fenil-2-(trifluorometil)tiazol puro (65 mg, 7.5%).

Ejemplo 41 3-amino-4-fenil-1,2,5-tiadiazol



A una solución de monocloruro de azufre (24.0 g, 178 mmol) en DMF (30 ml) a 0° C se agrega clorhidrato de α-aminofenilacetonitrilo (10.0 g, 59.3 mmol) en forma de porción durante 20 min. Después de 40 min la mezcla se le permite calentar a temperatura ambiente durante 20 min, se diluye con DMF (20 ml) y se agita adicionalmente durante 20 hr antes se vierte en agua helada. La

mezcla se extrae con éter (200 ml), se filtra, y se extrae dos veces más con éter (2 X 50 ml). Las fases orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de magnesio y se concentran *in vacuo* para dar 3- cloro-4-fenil-1,2,5-tiadiazol como un aceite naranja móvil (10.1 g, 87%). Destilación de trayecto corto de este aceite (9.35 g) a presión reducida produce un aceite incoloro, claro (7.75 g, 83%) el cual se cristaliza en reposo.



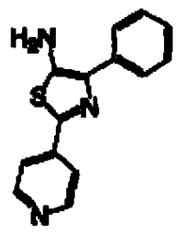
3-Cloro-4-fenil-1,2,5-tiadiazol (3.19 g, 16.2 mmol) en THF (32 ml) t 0° C se trata gota a gota con una solución de bis(trimetilsilil)amida de litio en THF (17.0 ml, 1.0 M, 17.0 mmol). Después de 10 min la mezcla se le permite calentar a temperatura ambiente durante 1.5 hr, se trata con ácido clorhídrico 1N, y se extrae tres veces en éter (total 300 ml). Las fases orgánicas combinadas se lavan con bicarbonato de sodio acuoso saturado y solución salina, y se secan sobre sulfato de magnesio y se concentran *in vacuo*. El residuo se disuelve en metanol (50 ml) y trietilamina (0.5 ml) se calienta a reflujo durante 15 hr y de nuevo se concentra *in vacuo*. Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) produce 3-amino-4-fenil-1,2,5-tiadiazol (1.96 g, 68%) como un sólido incoloro.

Ejemplo 42 5-amino-2-metil-4-feniltiazol



A una suspensión de clorhidrato de α-aminofenilacetonitrilo (3.37 g, 20.0 mmol) y azufre en polvo (641 mg, 20.0 mmol) en etanol (20 ml) a 0° C se agrega trietilamina (4.18 ml, 30.0 mmol) y entonces acetaldehído (2.3 ml, 41 mmol). El vaso se sella y se calienta a 60-70° C durante 1 hr. La mezcla fría se filtra y se concentra *in vacuo*, y el residuo se trata con etanol (20 ml) y ácido clorhídrico (20 ml, 1N) durante 15 hr. La mezcla se trata con carbonato de sodio acuoso y se extrae tres veces en acetato de etilo (total 300 ml). Las fases orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de sodio y se concentran *in vacuo* para dar un aceite café oscuro. Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) produce 5-amino-2-metil-4-feniltiazol (1.31 g, 34%), el cual se cristaliza de tolueno.

Ejemplo 43 5-amino-2-metil-4-feniltiazol

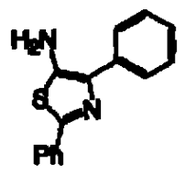


Una suspensión de clorhidrato de α-aminofenilacetonitrilo (1.69 g, 10.0 mmol), azufre en polvo (321 mg, 10.0 mmol) y 4-

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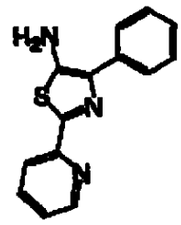
piridinacarboxaldehído (1.91 ml, 20.0 mmol) en etanol (10 ml) se trata con trietilamina (2.09 ml, 15.0 mmol), y la mezcla se agita a 50° C durante 80 min. La mezcla fría se diluye con etanol (5 ml) y se trata con hidroxilamina acuosa (700 µl, 50% en peso, 11 mmol) a temperatura ambiente durante 15 hr, y se diluye con diclorometano (50 ml). Se agrega bicarbonato de sodio acuoso saturado y la fase acuosa separada se extrae dos veces más con diclorometano (total 100 ml). Las fases orgánicas combinadas se secan sobre sulfato de sodio y se concentran *in vacuo* para dar una espuma aceitosa café oscura (3.23 g). Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) produce 5-amino-2-(4-piridil)-4-feniltiazol (1.41 g, 56%).

Ejemplo 44 2,4-difeniltiazol-5-amina



2,4-difeniltiazol-5-amina se prepara de acuerdo a los procedimientos descritos en K. Gewald, H. Schonfelder, U. Hain; *J. Prakt. Chem.*, 1974, 361, 299-303.

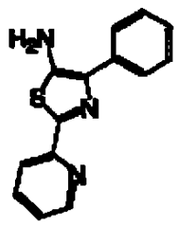
Ejemplo 45 4-fenil-2-(piridin-2-il)tiazol-5-amina



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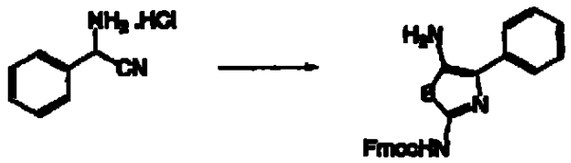
4-fenil-2-(piridin-2-il)tiazol-5-amina se prepara de acuerdo a los procedimientos descritos en K. Gewald, H. Schonfelder, U. Hain; *J. Prakt. Chem.*, 1974, 361, 299-303

Ejemplo 46 4-fenil-2-(piridin-3-il)tiazol-5-amina



4-fenil-2-(piridin-3-il)tiazol-5-amina se prepara de acuerdo a los procedimientos descritos en K. Gewald, H. Schonfelder, U. Hain; *J. Prakt. Chem.*, 1974, 361, 299-303

Ejemplo 47 5-amino-2-(Fmoc-amino)-4-feniltiazol

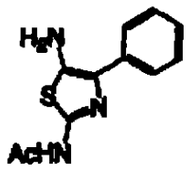


Una suspensión de clorhidrato de α-aminofenilacetonitrilo (3.19 g, 18.9 mmol) y Fmoc-isotiocianato (5.31 g, 18.9 mmol) en DCM se trata con etildiisopropilamina (3.62 ml, 20.8 mmol) a 0° C durante 1 hr y entonces a temperatura ambiente durante 3 hr. La mezcla se vierte en bicarbonato de sodio acuoso saturado y se extrae tres veces en acetato de etilo. Las fases orgánicas combinadas se lavan con agua y solución salina, y se secan sobre

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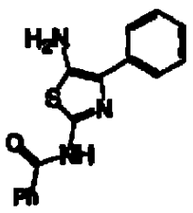
sulfato de sodio y se concentran *in vacuo*. Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) producen 5-amino-2-(Fmoc-amino)-4-feniltiazol (3.75 g, 48%).

Ejemplo 48 N-(5-amino-4-feniltiazol-2-il)acetamida



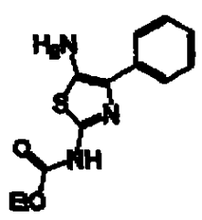
N-(5-amino-4-feniltiazol-2-il)acetamida se prepara de acuerdo a procedimientos similares a aquellos descritos en el ejemplo 47.

Ejemplo 49 N-(5-amino-4-feniltiazol-2-il)benzamida



N-(5-amino-4-feniltiazol-2-il)benzamida se prepara de acuerdo a procedimientos similares a aquellos descritos en el ejemplo 47.

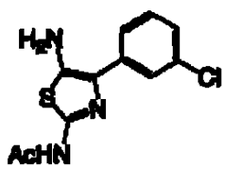
Ejemplo 50 etil 5-amino-4-feniltiazol-2-ilcarbamato



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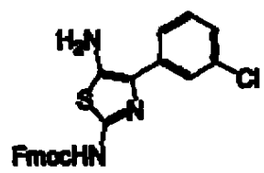
5-amino-4-feniltiazol-2-ilcarbamato de etilo se prepara de acuerdo a procedimientos similares a aquellos descritos en el ejemplo 47.

Ejemplo 51 N-(5-amino-4-(2-clorofenil)tiazol-2-il)acetamida



N-(5-amino-4-(2-clorofenil)tiazol-2-il)acetamida se prepara de acuerdo a procedimientos similares a aquellos descritos en el ejemplo 47.

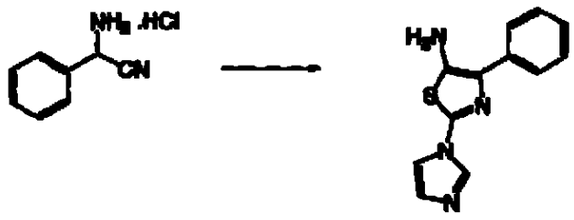
Ejemplo 52 5-amino-4-(2-clorofenil)tiazol-2-ilcarbamato de (9H-fluoren-9-il)metilo



(5-amino-4-(2-clorofenil)tiazol-2-ilcarbamato de 9H-fluoren-9-il)metilo se prepara de acuerdo a procedimientos similares a aquellos descritos en el ejemplo 47.

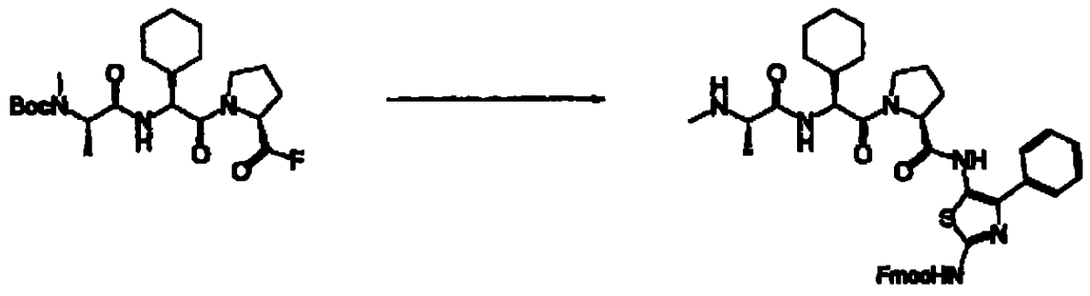
Ejemplo 53 5-amino-2-(1-imidazolil)-4-feniltiazol

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Una suspensión de clorhidrato de α-aminofenilacetonitrilo (5.01 g, 29.7 mmol) y tiocarbonil diimidazol (5.30 g, 29.7 mmol) en DCM (100 ml) se trata con etildiisopropilamina (5.69 ml, 32.7 mmol) a 0° C durante 15 min y entonces a temperatura ambiente durante 3 hr. La mezcla se vierte en bicarbonato de sodio acuoso saturado (50 ml) y agua (150 ml), y se extrae tres veces en diclorometano (total 300 ml). Las fases orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de magnesio y se concentran *in vacuo* para dar un aceite café oscuro (8.18 g). Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) producen 5-amino-2-(1-imidazolil)-4- feniltiazol (2.47 g, 34%).

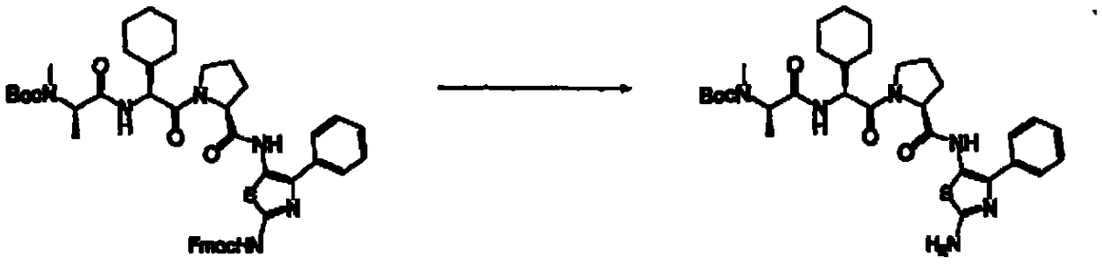
Ejemplo 54 amida de péptido de MeAla-Chg-Pro de 2,5-diamino-4-feniltiazol



5-Amino-2-(Fmoc-amino)-4-feniltiazol (250 mg, 605 µmol) se trata con el fluoruro ácido (730 µmol; derivado de Boc-MeAla-Chg-Pro-

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OHcomo se describió previamente) y piridina (147 µl, 1.82 mmol) en diclorometano (2.0 ml) a temperatura ambiente durante 6 días. La mezcla se vierte en bicarbonato de sodio acuoso saturado y se extrae tres veces en diclorometano (total 100 ml). Las fases orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de magnesio y se concentran *in vacuo* para producir el péptido de amida crudo como un aceite amarillo (525 mg), utilizado posteriormente sin purificación adicional.



El péptido de amida crudo en DMF (9.0 ml) se trata con piperidina (1.0 ml) a temperatura ambiente durante 20 min y entonces se concentra *in vacuo*. Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) producen el péptido amida 2,5-diamino-4-feniltiazol (228 mg, 61% durante 2 etapas).

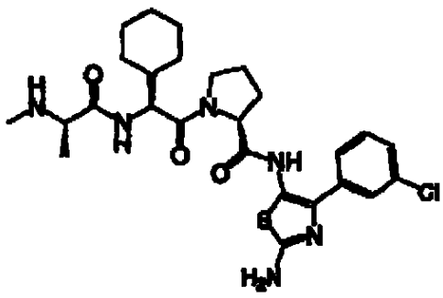


El péptido de amida crudo (48 mg, 78 µmol) en diclorometano (2.0 ml) se trata con ácido trifluoroacético (2.0 ml) a temperatura ambiente durante 30 min. La mezcla se concentra *in vacuo*, se hace homogénea con diclorometano y de nuevo se concentra. El residuo

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se purifica por HPLC preparativo de fase reversa (acetonitrilo/agua) para producir la sal de ácido trifluoroacético amida de péptido completamente desprotegido de (42 mg, 73%) como un sólido amorfo blanco.

Ejemplo 55 amida de péptido de MeAla-Chg-Pro 2,5-diamino-4-(3-clorofenil)tiazol



MeAla-Chg-Pro péptido de amida de 2,5-diamino-4-(3-clorofenil)tiazol se prepara utilizando el mismo procedimiento descrito en el ejemplo 55.

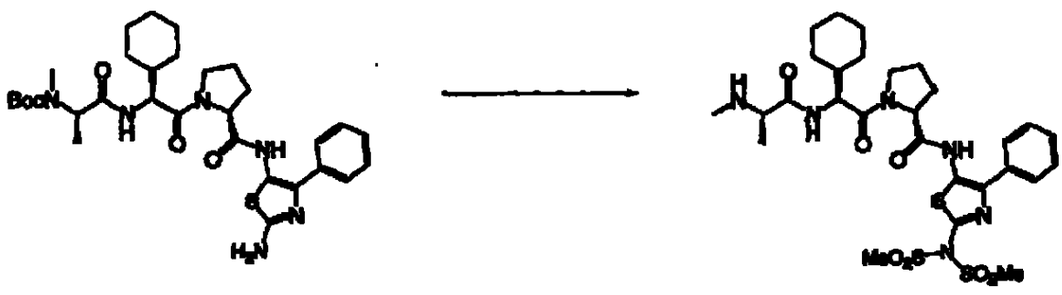
Ejemplo 56 amida MeAla-Chg-Pro de 5-amino-2-(pivaloilamino)-4-feniltiazol



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El Boc-péptido amino-tiazol (48 mg, 78 µmol) y etildiisopropilamina (140 µl, 0.80 mmol) en diclorometano (2.0 ml) se tratan con cloruro de pivaloilo (50 µl, 0.40 mmol) a temperatura ambiente durante 3 hr, y entonces con bicarbonato de sodio acuoso saturado y se extrae tres veces en diclorometano (total 60 ml). Las fases orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de magnesio y se concentran *in vacuo*. El aceite crudo se trata con ácido trifluoroacético (5.0 ml) en diclorometano (5.0 ml) a temperatura ambiente durante 20 min. La mezcla se concentra *in vacuo*, se hace homogénea con diclorometano y otra vez se concentra. El residuo se disuelve en ácido acético acuoso (50%) para purificación por HPLC preparativo de fase reversa (acetonitrilo/agua) para producir el péptido de amida puro de sal de ácido trifluoroacético (38 mg, 68% durante 2 etapas) como un sólido amorfo blanco.

Ejemplo 57 MeAla-Chg-Pro amida de 5-amino-2-(pivaloilamino)-4-feniltiazol



El Boc-péptido amino-tiazol (38 mg, 62 µmol) y etildiisopropilamina (107 µl, 0.61 mmol) en diclorometano (2.0 ml) se tratan con cloruro de metanosulfonilo (24 µl, 0.31 mmol) a

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temperatura ambiente durante 20 min, y entonces con bicarbonato de sodio acuoso saturado y se extrae tres veces en diclorometano. Las fases orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de magnesio y se concentran *in vacuo*. El aceite crudo se trata con ácido trifluoroacético (4 ml) en diclorometano (4 ml) a temperatura ambiente durante 20 min. La mezcla se concentra *in vacuo*, se hace homogénea con diclorometano y de nuevo se concentra. El residuo se disuelve en ácido acético acuoso (50%) para purificación por HPLC preparativo de fase reversa (acetonitrilo/agua) para producir el péptido de amida puro sal de ácido trifluoroacético (11 mg, 23% durante 2 etapas) como un sólido amorfo blanco.

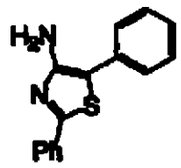
Ejemplo 57 2-(acetilamino)-4-amino-5-feniltiazol



α-Bromofenilacetonitrilo (1.08 g, 5.48 mmol) en etanol (10 ml) se trata con N-acetiltiourea (649 mg, 5.49 mmol) a temperatura ambiente durante 4 hr, y entonces se calienta a reflujo durante 3.5 hr. La mezcla fría se concentra *in vacuo* y entonces se particiona entre diclorometano y bicarbonato de sodio acuoso saturado. La fase orgánica se lava con solución salina, se seca sobre sulfato de sodio, se filtra y se concentra *in vacuo*. Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) produce 2-(acetilamino)-4-amino-5-feniltiazol (295 mg, 23%).

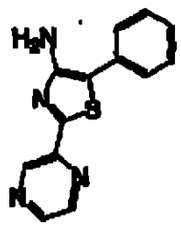
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Ejemplo 58 2,5-difeniltiazol-4-amina



2,5-difeniltiazol-4-amina se prepara utilizando el mismo procedimiento descrito en el ejemplo 57.

Ejemplo 59 5-fenil-2-(pirazin-2-il)tiazol-4-amina



5-fenil-2-(pirazin-2-il)tiazol-4-amina se prepara utilizando el mismo procedimiento descrito en el ejemplo 57.

Ejemplo 60 5-amino-1-(3'-nitrofenil)pirazol



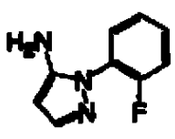
Clorhidrato de 3-Nitrofenilhidrazina (7.03 g, 36.3 mmol), diisopropiletilamina (9.5 ml, 54.5 mmol), y etanol (60 ml) se agitan bajo nitrógeno a temperatura ambiente durante 2 h. Se

agrega etoximetilenomalononitrilo (4.52 g, 36.3 mmol), después de lo cual la reacción se refluye durante 1 h. La reacción se enfría a temperatura ambiente. El solvente se remueve bajo presión reducida hasta que el precipitado choca afuera. El sólido se filtra para producir 6.54 g del producto ciclizado (78% de rendimiento).



5-amino-1-(3'-nitrofenil)-4-cianopirazol (559 mg, 2.44 mmol) y ácido fosfórico (86%, 6 ml) se refluyen a 170° C durante 15 h. La reacción se enfría a temperatura ambiente y se neutraliza con hidróxido de amonio. Los orgánicos se extraen tres veces con dietil éter (total 40 ml), se lava con solución salina, y se seca sobre sulfato de magnesio. La remoción del solvente da 5-amino-1-(3'-nitrofenil)-pirazol como un polvo amarillo (398 mg, 80% de rendimiento).

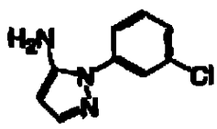
Ejemplo 61 1-(2-fluorofenil)-1H-pirazol-5-amina



1-(2-fluorofenil)-1H-pirazol-5-amina se prepara utilizando el mismo procedimiento descrito en el ejemplo 60.

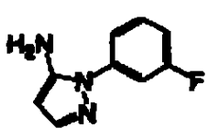
Ejemplo 62 1-(3-clorofenil)-1H-pirazol-5-amina

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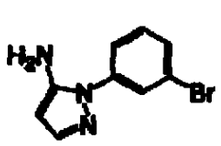
1-(3-clorofenil)-1H-pirazol-5-amina se prepara utilizando el mismo procedimiento descrito en el ejemplo 60.

Ejemplo 63 1-(3-fluorofenil)-1H-pirazol-5-amina



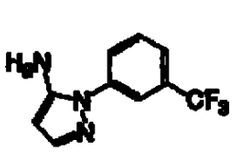
1-(3-fluorofenil)-1H-pirazol-5-amina se prepara utilizando el mismo procedimiento descrito en el ejemplo 60.

Ejemplo 64 1-(3-bromofenil)-1H-pirazol-5-amina



1-(3-bromofenil)-1H-pirazol-5-amina se prepara utilizando el mismo procedimiento descrito en el ejemplo 60.

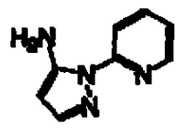
Ejemplo 65 1-(3-triclorometilfenil)-1H-pirazol-5-amina



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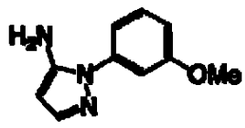
1-(3-triclorometilfenil)-1H-pirazol-5-amina se prepara utilizando el mismo procedimiento descrito en el ejemplo 60.

Ejemplo 66 1-(piridin-2-il)-1H-pirazol-5-amina



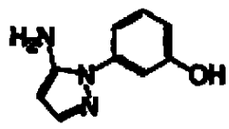
1-(piridin-2-il)-1H-pirazol-5-amina se prepara utilizando el mismo procedimiento descrito en el ejemplo 60.

Ejemplo 67 1-(3-metoxifenil)-1H-pirazol-5-amina



1-(3-metoxifenil)-1H-pirazol-5-amina se aísla siguiendo la descianación de 5-amino-4-ciano-1-(3'-metoxifenil)pirazol en el ejemplo 60.

Ejemplo 67 1-(3-hidroxifenil)-1H-pirazol-5-amina



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1-(3-hidroxifenil)-1H-pirazol-5-amina se prepara utilizando el mismo procedimiento descrito en el ejemplo 60.

Ejemplo 68 4-amino-5-fenil-1,2,3-tiadiazol



Ácido fenilpirúvico (25 g, 149 mmol) y carbazato de etilo (16 g, 149 mmol) se refluyen en benceno (225 ml) durante 2 hr, y la mezcla se concentra *in vacuo*. El crudo se disuelve en un mínimo de diclorometano caliente para producir la hidrazona como un precipitado sobre enfriamiento a temperatura ambiente, se aísla por filtración (30.4 g, 81%) y se utiliza sin purificación adicional.

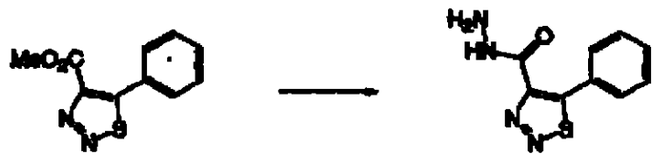


Se genera Diazometano por adición de una solución de Diazald (N-metil-N-nitroso-*p*-toluenosulfonamida; 18.6 g, 86.9 mmol) en dietil éter (180 ml) a una solución de hidróxido de potasio (18.2 g, 325 mmol) en agua (37 ml) y 2-(2-etoxietoxi)-etanol (37 ml) a 65° C, gota a gota durante 45 min. La destilación así produce una solución etereal de diazometano a la cual se agrega directamente una solución de la hidrazona (10.9 g, 43.5 mmol) en metanol (150 ml) a 0° C. El sistema se aclara con exceso de dietil éter hasta

que el destilado llega a ser claro, la mezcla se trata con ácido acético (1 ml), y se concentra *in vacuo*. El aceite resultante se particiona entre acetato de etilo (200 ml) y bicarbonato de sodio (200 ml), y la fase orgánica se seca sobre sulfato de sodio. La filtración y concentración *in vacuo* produce el éster de metilo como un sólido amarillo (10.2 g, 89%).

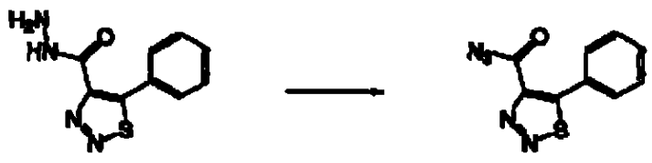


El éster de hidrazona-metilo (10.2 g, 38.6 mmol) se trata con cloruro de tionilo (25 ml, 343 mmol) a temperatura ambiente durante 24 hr, y la mezcla se concentra *in vacuo*. La cristalización de Hexanos produce el éster de tiadiazol-metilo (4.81 g, 56%).



El éster de tiadiazol-metilo (2.79 g, 12.7 mmol) se trata con hidrato de hidrazina (1.09 ml, 93.9 mmol) en metanol (50 ml) a temperatura ambiente durante 24 hr, y el precipitado blanco resultante se recupera por filtración. La recristalización de isopropanol produce the tiadiazol-hydrazide (3.99 g, 83%).

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La hidrazida de tiadiazol (3.99 g, 18.1 mmol) en agua (40 ml) y ácido clorhídrico concentrado (1.8 ml, 21.9 mmol) se trata gota a gota con una solución de nitrito de sodio (1.52 g, 21.3 mmol) en agua (15 ml) a 0° C durante 2 hr. El precipitado resultante se recupera por filtración para producir el tiadiazol-ácido de azida como un sólido blancuzco (3.95 g, 94%).



De acuerdo a los procedimientos descritos en K. Masuda *et al.; Chem. Pharm. Bull.*, 1981, 29, 1743-1747, la azida de ácido tiadiazol- (3.95 g, 17.1 mmol) se refluye en etanol (40 ml) durante 45 min, y la mezcla se concentra *in vacuo*. La cristalización de benceno produce el carbamato de etilo (3.37 g, 74%).



El carbamato de etilo (399 mg, 1.60 mmol) y bromuro de hidrógeno en ácido acético (3 ml, 30% en peso) se calientan en un vaso sellado a 80° C durante 18 hr. La mezcla fría se particiona entre

acetato de etilo (15 ml) y agua (15 ml), y la fase orgánica se concentra *in vacuo*. Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) produce 4-amino-5-fenil-1,2,3-tiadiazol (136 mg, 49%).

Ejemplo 69 4-amino-5-fenilisoxazol



Ácido 5-Fenil-4-isoxazolcarboxílico (460 mg, 2.36 mmol) y cloruro de tionilo (1.71 ml, 23.6 mmol) se calientan a reflujo durante 3 hr, y la mezcla se concentra *in vacuo* para producir el cloruro ácido el cual se utiliza sin purificación.



El cloruro ácido crudo en acetona (7 ml) se trata con una solución de azida de sodio (165 mg, 2.62 mmol) en agua (2 ml) a 0° C durante 1.5 hr, y se le permite calentar a temperatura ambiente y se concentra *in vacuo*. El sólido blanco resultante se lava con agua y se seca *in vacuo*, y se utiliza sin purificación.



La azida de ácido (409 mg, 1.91 mmol) se calienta a reflujo en metanol durante 6 hr, y la mezcla se concentra *in vacuo* para producir el carbamato de metilo como un sólido blanco, que se utiliza sin purificación.



El carbamato de metilo (378 mg, 1.73 mmol) se trata con ácido hidrobrómico (13 ml, 48% en peso, 115 mmol), se hace homogéneo con ácido acético (2 ml), y se calienta a 65° C durante 48 hr, y se le permite enfriar. La mezcla se neutraliza con hidróxido de sodio acuoso y se extrae con acetato de etilo (2 X 125 ml). Las fases orgánicas combinadas se secan sobre sulfato de sodio y se concentran *in vacuo* para producir 4-amino-5-fenilisoxazol como un sólido blanco (193 mg, 70%).

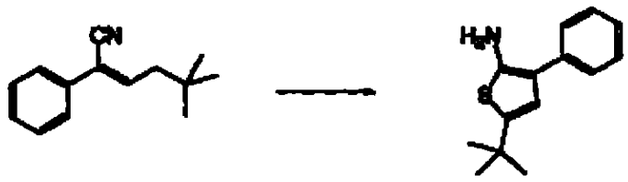
Ejemplo 70 Síntesis de 5-alquil-2-amino-3-feniltiofenos



Cianuro de bencilo (2.33 ml, 20 mmol) se trata con base Verkade (2,8,9-trimetil-2,5,8,9-tetraaza-1-fosfabiciclo[3.3.3]undecano; 441 mg, 2.0 mmol) y 3,3-dimetilbutiraldehído (2.64 ml, 200 mmol) en metanol (4 ml) y la mezcla se calienta en un vaso sellado a 45° C durante 16 hr. La mezcla fría se concentra *in vacuo* para

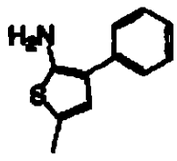
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producir el nitrilo insaturado como un aceite incoloro, que se utiliza sin purificación.



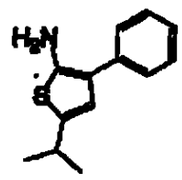
El nitrilo (10.0 mmol), carbonato de potasio (2.34 g, 23.4 mmol) y azufre en polvo (330 mg, 10.3 mmol) en etanol (2 ml) se calientan en un vaso sellado a 160° C durante 24 hr. La mezcla fría se diluye con agua, se extrae dos veces en dietil éter y los orgánicos combinados se concentran *in vacuo*. Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) produce 5-amino-2-*terc*-butil-4-feniltiazol (75%).

Ejemplo 71 5-metil-3-feniltiofen-2-amina



5-metil-3-feniltiofen-2-amina se prepara utilizando el mismo procedimiento descrito en el ejemplo 70.

Ejemplo 72 5-isopropil-3-feniltiofen-2-amina



5-isopropil-3-feniltiofen-2-amina se prepara utilizando el mismo procedimiento descrito en el ejemplo 70.

Ejemplo 73 2-amino-5-cloro-3-feniltiofeno



2-Amino-3-fenil-tiofeno (12.0 mmol) en THF (7 ml) se trata con dicarbonato de di-*terc*-butilo (2.97 g, 13.3 mmol) y diisopropiletilamina (3.15 ml, 18.1 mmol) a temperatura ambiente durante 60 hr, y la mezcla se concentra *in vacuo*. Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) produce 2-(N-Boc-amino)-3-fenil-tiofeno (1.98 g, 59%).



A 2-(N-Boc-amino)-3-fenil-tiofeno (89 mg, 0.32 mmol) en diclorometano (4 ml) a 0° C se agrega lentamente N-clorosuccinimida (48 mg, 0.36 mmol), y la mezcla se le permite calentar a temperatura ambiente durante 16 hr. La mezcla se diluye con diclorometano, se lava con agua, y la fase orgánica se

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concentra *in vacuo*. Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) produce 2-(N-Boc-amino)-5-cloro-3-fenil-tiofeno (66 mg, 66%).



2-(N-Boc-amino)-5-cloro-3-fenil-tiofeno (66 mg, 0.21 mmol) se trata con ácido trifluoroacético (1 ml) en diclorometano (3 ml) a temperatura ambiente durante 1 hr. La mezcla se diluye con DMF (1 ml) y los materiales más volátiles se remueven bajo presión reducida. La solución DMF resultante de 2-amino-5-cloro-3-feniltiofeno se utiliza en el posterior acoplamiento de la etapa sin purificación.

Ejemplo 74 1-Metil-4-(metilamino)-3-fenilpirazol



A 1-metil-4-amino-3-fenilpirazol (572 mg, 3.30 mmol) y di-*terc*-butil dicarbonato (799 mg, 3.66 mmol) en THF (10 ml) y agua (3 ml) se agrega gota a gota bicarbonato de sodio acuoso saturado (3 ml, 1.2 M, 3.6 mmol). La mezcla se agita a temperatura ambiente durante 7 hr y entonces se vierte en ácido cítrico acuoso (0.5 M) y se extrae tres veces en éter (total 100 ml). Las fases orgánicas combinadas se lavan con bicarbonato de sodio acuoso

saturado y solución salina, se secan sobre sulfato de magnesio y se concentran *in vacuo* para producir El crudo carbamato como un aceite café (920 mg), utilizado posteriormente sin purificación adicional.



Una suspensión de hidruro de sodio en aceite mineral (327 mg, 60% en peso, 8.18 mmol) se lava con THF (2 x 5 ml) y se suspende en THF (3.0 ml) a 0° C. A esta se agrega gota a gota el pirazol (744 mg, 2.72mmol) en THF (5.0 ml), y después de 15 min, yoduro de metilo (187 µl, 3.00 mmol). Después de 30 min adicionales a 0° C la mezcla se le permite calentar a temperatura ambiente durante 18 hr y entonces se trata con cloruro de amonio acuoso saturado y suficiente agua para disolver los sólidos. La mezcla se extrae tres veces en éter (total 120 ml), y las fases orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de magnesio y se concentran *in vacuo* para producir el carbamato de N-metilo crudo como un sólido ámbar (750 mg, 96%), que se utiliza sin purificación.

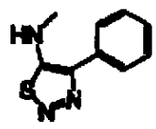


El carbamato de N-metilo crudo en DCM (1.0 ml) se trata con ácido trifluoroacético (1.0 ml) a temperatura ambiente durante 40 min.

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La mezcla se concentra *in vacuo*, se hace homogénea con diclorometano y de nuevo se concentra para producir esencialmente 1-metil-4-(metilamino)-3-fenilpirazol puro (150 mg, cuant.) como un aceite café.

Ejemplo 75 N-metil-4-fenil-1,2,3-tiadiazol-5-amina



N-metil-4-fenil-1,2,3-tiadiazol-5-amina se prepara utilizando el mismo procedimiento descrito en el ejemplo 74.

Ejemplo 76 1-*terc*-Butil-4-amino-3-fenilpirazol y 1-*terc*-butil-4-amino-5- fenilpirazol

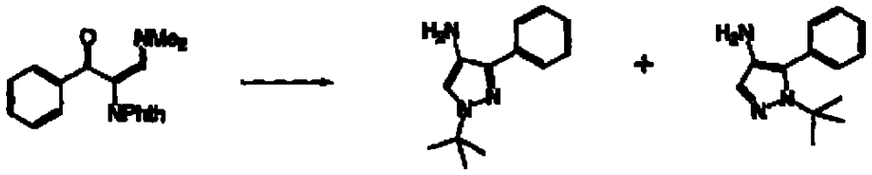


Una solución de 2-bromoacetofenona (30.0 g, 151 mmol) en DMF (120 ml) se trata con ftalamida de potasio (30.8 g, 166 mmol) en forma de porción a temperatura ambiente, y entonces se calienta a 40° C durante 3.5 hr. La mezcla fría se vierte en agua (600 ml) y se extrae con cloroformo (300 ml luego 100 ml). Las fases orgánicas combinadas se lavan con hidróxido de sodio (200 ml, 0.2 N), agua (2 x 100 ml) y solución salina (100 ml), se secan sobre sulfato de magnesio y se concentran *in vacuo*. El sólido crema resultante se suspende en éter (100 ml), se recupera por filtración, se lava

con éter (100 ml) y se seca *in vacuo* para producir 2-ftalimido-acetofenona pura como un sólido blanco (34.3 g, 86%).



De acuerdo a los procedimientos descritos en C. Chen, K. Wilcoxen, J. R. McCarthy; *Tetrahedron Lett*, **1988**, 39, 8229-8232 una suspensión de 2-ftalimidoacetofenona (13.3 g, 50.0 mmol) en dimetilformamida dimetil acetal (26.7 ml, 200 mmol) se calienta a reflujo durante 28 hr y se concentra *in vacuo*. El sólido ámbar resultante se cristaliza para formar isopropanol (100 ml) y se lava con isopropanol (2 x 5 ml) para producir 3-(dimetilamino)-1-fenil-2-ftalimido-2-propen-1-ona como agujas amarillas (13.7 g, 85%).

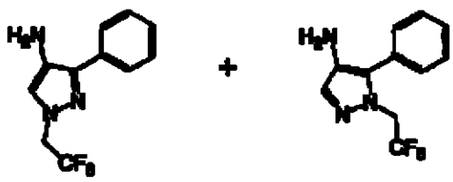


Una mezcla de 3-(dimetilamino)-1-fenil-2-ftalimido-2-propen-1-ona (3.00 g, 9.38 mmol) y clorhidrato de hidazina *terc*-butilo (1.29 g, 10.3 mmol) en etanol (94 ml) y agua (9.4 ml) se agita a temperatura ambiente durante 64 hr y entonces se calienta a reflujo durante 24 hr. La mezcla fría se trata con hidrazina (590 µl, 18.8 mmol) y se regresa a reflujo durante 75 min. En frió y reposo a temperatura ambiente se forma un precipitado. La mezcla se filtra, el sólido se lava con una mezcla de etanol (5 ml) y agua (0.5 ml), y el filtrado se concentra *in vacuo*. El residuo se

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particiona entre éter (250 ml) y bicarbonato de sodio acuoso saturado (50 ml) se diluye con agua (100 ml), y la fase acuosa se extrae dos veces más con éter (2 x 50 ml). Las fases orgánicas combinadas se lavan con solución salina, se secan sobre sulfato de sodio y se concentran *in vacuo* para dar un sólido pálido (1.92 g). Cromatografía flash sobre gel de sílice (acetato de etilo/Hexanos) produce 1-terc-butil-4-amino-3-fenilpirazol (1.52 g, 75% durante 2 etapas) y 1-*terc*-butil-4-amino-5-fenilpirazol (114 mg, 6% durante 2 etapas).

Ejemplo 77 1-(2,2,2-trifluoroetil)-3-fenil-1H-pirazol-4-amina y 1-(2,2,2-trifluoroetil)-5-fenil-1H-pirazol-4-amina



Se preparan 1-(2,2,2-trifluoroetil)-3-fenil-1H-pirazol-4-amina y 1-(2,2,2-trifluoroetil)-5-fenil-1H-pirazol-4-amina similarmente de 2,2,2-trifluoroetilhidrazina de acuerdo a los procedimientos descritos en ejemplo 76.

Ejemplo 78 ensayos de inhibición IAP

En los siguientes experimentos se utiliza un dominio BIR quimérico referido como MLXBIR3SG en el cual 11 de los 110 residuos corresponden a aquellos encontrados en XIAP-BIR3, mientras que el restante corresponde a ML-IAP-BIR. La proteína

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quimérica MLXBIR3SG se muestra por unir e inhibir la caspasa-9 significativamente mejor que cualquiera de los dominios BIR nativos, pero une los péptidos basados en Smac y el Smac maduro con afinidades similares a aquellas del ML-IAP-BIR nativo. La inhibición de la caspasa-9 mejorada del dominio BIR quimérico MLXBIR3SG se ha correlacionado con la inhibición incrementada de la apoptosis inducida por doxorubicina cuando se transfecta en células MCF7.

Secuencia MLXBIR3SG

MGSSHHHHHHSSGLVPRGSHMLETEFEEEEGAGATLSRGPAFPGMGSEELRLASFYDWP
LTAEVPPELLAAAGFFHTGHQDKVRCFFCYGGLQSWKRGDDPWTEHAKWFPGCQFLLR
SKGQEYINNIHLTHSL (SEQ ID NO.: 1)

Ensayo de Unión de Péptido TR-FRET

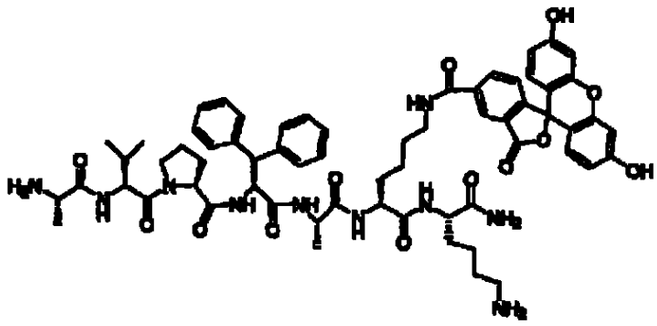
Se desarrollan experimentos de competición de Transferencia de energía de Resonancia de Fluorescencia Resuelta con Tiempo en el Lector Contador de Multietiqueta Wallac Victor2 (Perkin Elmer Life y Analytical Sciences, Inc.) de acuerdo con los procedimientos de Kolb *et al.* (Journal of Biomolecular Screening, 1996, 1(4):203). Un cóctel de reactivo que contiene 300 nM his-etiquetado MLXBIR3SG; 200 nM de péptido SMAC biotinilado (AVPI); 5 µg/mL anti-his aloficocianina (XL665) (CISBio International); y 200 ng/mL de estreptavidina-europio (Perkin Elmer) se prepara en amortiguador de reactivo (50 mM Tris [pH 7.2], 120 mM NaCl, 0.1% de globulinas de bovino, 5 mM de DTT y 0.05% de octilglucosido). (Alternativamente, este cóctel se puede preparar utilizando anti-

His etiquetado con europio (Perkin Elmer) y estreptavidin-aloficocianina (Perkin Elmer) en concentraciones de 6.5 nM y 25 nM, respectivamente). El cóctel de reactivo se incuba a temperatura ambiente durante 30 minutos. Después de incubación, el cóctel se agrega a diluciones seriales 1:3 de un compuesto antagonista (concentración de partida de 50 μM) en 384-pozos de placa FIA negro (Greiner Bio-ona, Inc.). Después de una incubación de 90 minutos a temperatura ambiente, se lee la fluorescencia con filtros para la excitación de europio (340 nm) y para la emisión de longitudes de onda de europio (615 nm) y una aloficocianina (665 nm). Los datos del antagonista se calculan como una proporción de la señal de emisión de aloficocianina en 665 nm para aquella de la emisión de europio en 615 nm (estas proporciones se multiplican por un factor de 10,000 para facilidad de manipulación de datos). Los valores resultantes se grafican como una función de la concentración antagonista y se ajustan a una ecuación de 4 parámetros utilizando software Kaleidograph (Synergy Software, Reading, PA). Se determinan las indicaciones de potencia de antagonista de los valores IC50. Los compuestos de la invención en donde se encuentra que tiene actividad inhibidora IAP que se demuestra en este ensayo.

Ensayo de Unión de Péptido de Polarización de Fluorescencia

Se desarrolla experimentos de polarización en un Analyst HT 96-384 (Molecular Devices Corp.) de acuerdo con el procedimiento de Keating, S.M., Marsters, J, Beresini, M., Ladner, C, Zioncheck, K., Clark, K., Arellano, F., y Bodary., S.(2000) en *Proceedings of SPIE: en Vitro Diagnostic Instrumentation* (Cohn, G.E., Ed.) pp

128-137, Bellingham, WA. Se preparan muestras para mediciones de afinidad de polarizaciones de fluorescencia mediante la adición de diluciones seriales 1:2 partiendo en una concentración final de 5µM de MLXBIR3SG en amortiguador de polarización (50 mM Tris [pH 7.2], 120 mM NaCl, 1% globulinas de bovino 5mM DTT y 0.05% de octilglucosido) a conjugado de 5-carboxiflouresceina AVPdi-Phe-NH_2 (AVP-diPhe-FAM) en concentración final de5 nM final.



sonda AVP-diPhe-FAM

Se leen reacciones después de un tiempo de incubación de 10 minutos a temperatura ambiente con filtros de corte estándar para el fluoróforo de fluoresceína (λ_{ex} = 485 nm; λem = 530 nm) en placas de 96 pozos HE96 negro (Molecular Devices Corp.). Se grafican los valores de fluorescencia como una función de la concentración de proteína se obtienen IC_{50} al ajustar los datos a una ecuación de 4 parámetros utilizando el software Kaleidograph (Synergy software, Reading, PA).Los experimentos de competición se desarrollan mediante la adición del MLXBIR3SG a 30 nM a pozos que contienen 5 nM de a sonda AVP-diPhe-FAM así como también diluciones en serie 1:3 de compuestos antagonistas que parten en una concentración de 300 µM en el amortiguador de polarización. Las muestras se leen después de incubación de 10 minutos. Los

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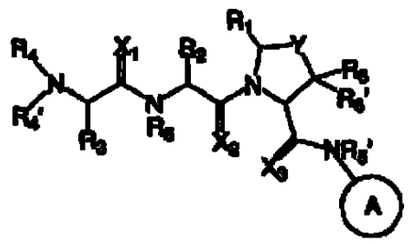
valores de polarización de fluorescencia se grafican como una función de la concentración de antagonista, y los valores IC-50 se obtiene al ajustar los datos a una ecuación de 4 parámetros utilizando el software Kaleidograph (Synergy software, Reading, PA). Las constantes de inhibición (K_i) para los antagonistas se determinan a partir de los valores IC_{50}. Los compuestos de la invención se encuentra que tienen una actividad inhibidora IPA que se demuestra en este ensayo.

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REIVINDICACIONES

REIVINDICAMOS:

1. Un compuesto de fórmula I:



I

en donde X_1, X_2 y X_3 son independientemente O o S;

Y es $(CHR_7)_n$, O o S; en donde n es 1 o 2 y R_7 es H5 halógeno, alquilo, arilo, aralquilo, amino, arilamino, alquilamino, aralquilamino, alcoxi, ariloxi o aralquiloxi;

A es un heterociclo de 5 miembros que comprende 1 a 4 heteroátomos opcionalmente sustituidos con amino, hidroxilo, mercapto, halógeno, carboxilo, amidino, guanidino, alquilo, alcoxi, arilo, ariloxi, acilo, aciloxi, acilamino, alcoxicarbonilamino, cicloalquilo, alquiltio, alquilsulfinilo, alquilsulfonilo, aminosulfonilo, alquilaminosulfonilo, alquilsulfonilamino o un heterociclo; en donde cada sustitución de alquilo, alcoxi, arilo, ariloxi, acilo, aciloxi, acilamino, cicloalquilo y heterociclo es opcionalmente sustituida con hidroxilo, halógeno, mercapto, carboxilo, alquilo, alcoxi,

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haloalquilo, amino, nitro, ciano, cicloalquilo, arilo o un heterociclo;

R_1 es H o R_1 y R_2 juntos forman un anillo de 5 a 8 miembros;

R_2 es alquilo, cicloalquilo, cicloalquilalquilo, arilo, aralquilo, un heterociclo o heterociclilalquilo; cada uno opcionalmente sustituido con hidroxilo, mercapto, halógeno, amino, carboxilo, alquilo, haloalquilo, alcoxi o alquiltio;

R_3 es H o alquilo;

R_4 y R_4' son independientemente H, hidroxilo, amino, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo, o heteroarilalquilo en donde cada alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo y heteroarilalquilo es opcionalmente sustituido con halógeno, hidroxilo, mercapto, carboxilo, alquilo, alcoxi, amino y nitro;

R_5, y R_5' son cada uno independientemente H o alquilo;

R_6, y R_6' son cada uno independientemente H, alquilo, arilo o aralquilo; y sales y solvatos de estos.

2. El compuesto de la reivindicación 1, en donde el anillo A tiene la fórmula IIa o IIb:



IIa

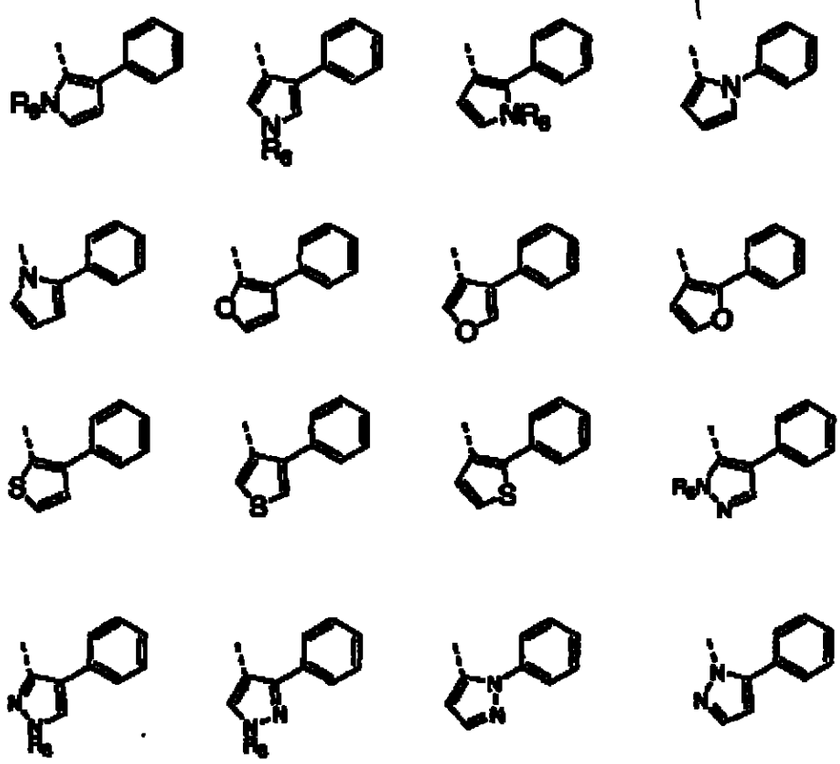


IIb

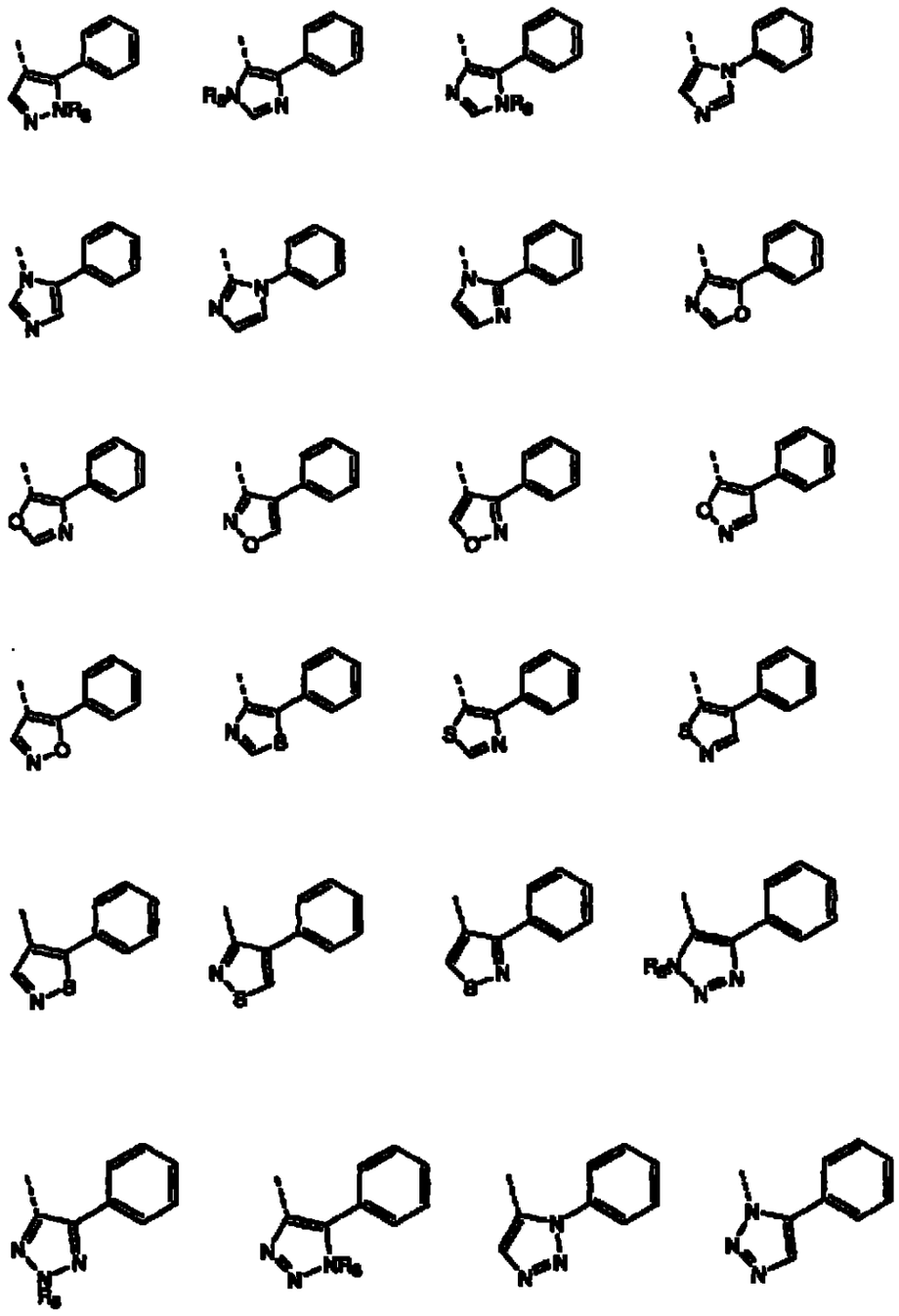
en donde Q_1 es NR_8, O o S; Q_2, Q_3, Q_4, Q_5, Q_6, Q_7, y Q_8, son independientemente CR_9 o N; en donde R_9 es H, amino, hidroxilo, mercapto, halógeno, carboxilo, amidino, guanidino, alquilo, alcoxi, arilo, ariloxi, acilo, aciloxi, acilamino, cicloalquilo o un heterociclo; en donde cada sustitución de alquilo, alcoxi, arilo, ariloxi, acilo, aciloxi, acilamino, cicloalquilo y heterociclo es opcionalmente sustituida con hidroxilo, halógeno, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, cicloalquilo, arilo o un heterociclo; R_8 es H, alquilo, acilo, arilo, cicloalquilo o un heterociclo; en donde cada alquilo, arilo, cicloalquilo y heterociclo es opcionalmente sustituido con hidroxilo, halógeno, mercapto, carboxilo, alquilo, haloalquilo, amino, nitro, cicloalquilo, arilo o un heterociclo; y Q_9 es CH o N..

3. El compuesto de la reivindicación 1, en donde el anillo A se selecciona del grupo que consiste de:

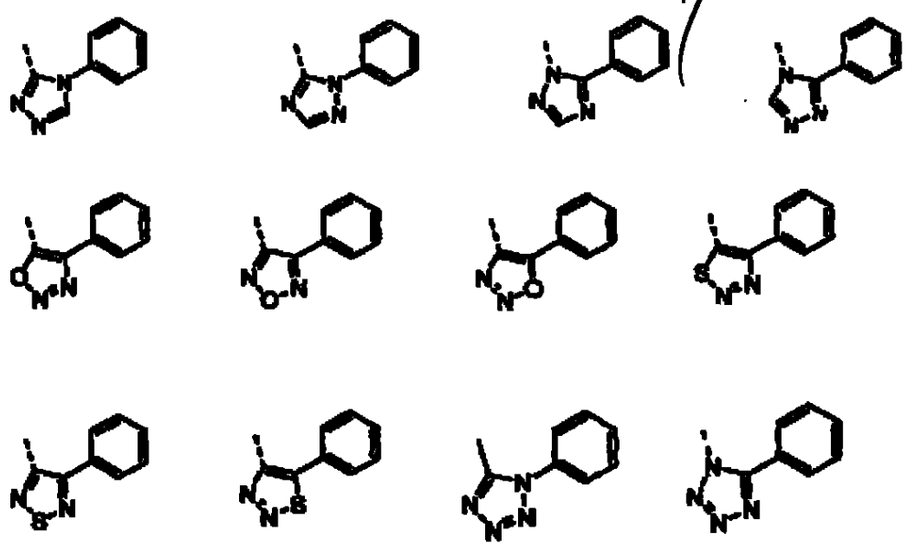
254



255



256



en donde R_8 es H, alquilo o acilo.

4. El compuesto de la reivindicación 3, en donde R_8 es H.

5. El compuesto de la reivindicación 1, en donde R_1 y R_2 juntos forman un anillo de 5 a 8 miembros.

6. El compuesto de la reivindicación 1, en donde R_1 es H.

7. El compuesto de la reivindicación 1, en donde R_2 es alquilo o cicloalquilo.

8. El compuesto de la reivindicación 1, en donde R_2 es isopropilo, t-butilo, o ciclohexilo.

9. El compuesto de la reivindicación 1, en donde R_3 es metilo.

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10. El compuesto de la reivindicación 1, en donde R_4 es H o metilo, y R4' es H.

11. El compuesto de la reivindicación 1, en donde R_5 y R_5' son independientemente H o metilo. 12. El compuesto de la reivindicación 1, en donde R_6 y R_6' son independientemente H o metilo.

13. El compuesto de la reivindicación 1, en donde cada uno de X_1, X_2 y X_3 son O.

14. El compuesto de la reivindicación 2, en donde R_1 es H; R_2 es isopropilo, t-butilo, o ciclohexilo; R_3 es metilo; R_4 es H o metilo, y R_4' es H, R_5 y R_5' son H o metilo; X_1, X_2 y X_3 son O.

15. Un método para inducir apoptosis en una célula comprende introducir en dicha célula un compuesto de la reivindicación 1.

16. Un método para sensibilizar una célula para una señal apoptótica comprende introducir en dicha célula un compuesto de la reivindicación 1.

17. El método de la reivindicación 16, en donde dicha señal apoptótica se induce al poner en contacto dicha célula con un compuesto seleccionado del grupo que consiste de citarabina, fludarabina, 5-fluoro-2'-deoxiuiridina, gemcitabina, metotrexato, bleomicina, cisplatina,

ciclofosfamida, adriamicina (doxorubicina), mitoxantrona, camptotecina, topotecan, colcemid, colchicina, paclitaxel, vinblastina, vincristina, tamoxifen, finasterida, taxoter y mitomicina C.

18. El método de la reivindicación 16, en donde dicha señal apoptótica se induce al poner en contacto dicha célula con Apo2L/TRAIL.

19. Un método para inhibir la unión de una proteína IAP una proteína caspasa que comprende poner en contacto dicha proteína IAP con un compuesto de la reivindicación 1.

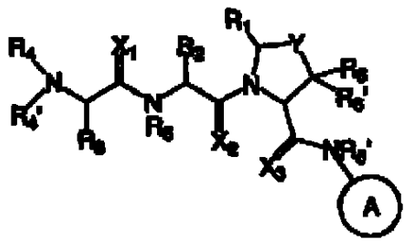
20. Un método para tratar una enfermedad o condición asociada con la sobreexpresión de un LAP en un mamífero, comprende administrar a dicho mamífero una cantidad efectiva del compuesto de la reivindicación 1.

21. Un método para tratar cáncer, que comprende administrar a dicho mamífero una cantidad efectiva del compuesto de la reivindicación 1.

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RESUMEN

La invención suministra inhibidores novedosos de IAP que son útiles como agentes terapéuticos para el tratamiento de malignidades en donde los compuestos tienen la fórmula general I:



I

en donde X, Y, A, R_1, R_2, R_3, R_4, R_4', R_5, R_5', R_6 Y R_6' son como se describe aquí.

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Listado de secuencias

<110> COHEN, FREDERICK
DESHAYES, KART
FAIRBROTHER, WAYNE J.
FENG, BAINIAN
FLYGARE, JOHN A.
GAZZARD, LEWIS J. TSUI,
VICKIE HSIAO-WEI

<120> INHIBIDORES DE IAP

<130> P2154R1

<140> US 11/174,784
<141> 2005-07-05

<150> US 60/585,501
<151> 2004-07-02

<160> 1

<210> 1
<211> 133
<212> PRT
<213> Homo sapiens

<400> 1

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            20                  25                  30
Gly Ala Gly Ala Thr Leu Ser Arg Gly Pro Ala Phe Pro Gly Met
        35                  40                  45
Gly Ser Glu Glu Leu Arg Leu Ala Ser Phe Tyr Asp Trp Pro Leu
    50                  55                  60
Thr Ala Glu Val Pro Pro Glu Leu Leu Ala Ala Ala Gly Phe Phe
65                  70                  75
His Thr Gly His Gln Asp Lys Val Arg Cys Phe Phe Cys Tyr Gly
                80                  85                  90
Gly Leu Gln Ser Trp Lys Arg Gly Asp Asp Pro Trp Thr Glu His
            95                 100                 105
Ala Lys Trp Phe Pro Gly Cys Gln Phe Leu Leu Arg Ser Lys Gly
        110                 115                 120
Gln Glu Tyr Ile Asn Asn Ile His Leu Thr His Ser Leu
    125                 130
```

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PATENT COOPERATION TREATY

DE/LS

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

CALENDARED/LS
Respond to ISR/Consider Chapter II Deadline - 5 Feb 06

DUE DATE (PCT Rule 44.1)

To:
GENENTECH, INC.
Attn. Evans, David W.
1 DNA Way
South San Francisco, CA 94080-4990
UNITED STATES OF AMERICA

Date of mailing (day/month/year): 05/12/2005

Applicant's or agent's file reference: P2154R1

RECEIVED
DEC 0 5 2005
GENENTECH, INC.
LEGAL DEPT.

FOR FURTHER ACTION: See paragraphs 1 and 4 below

International application No.: PCT/US2005/023564

International filing date (day/month/year): 05/07/2005

CALENDARED/LS
IDS Due - 30 Day Deadline
P2154R1 US 4 JAN 06

Applicant: GENENTECH, INC.

DUE DATE

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes, 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

   Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stefan Brell

Form PCT/ISA/220 (January 2004) *(See notes on accompanying sheet)*

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 48.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P2154R1	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2005/023564	International filing date *(day/month/year)* 05/07/2005	(Earliest) Priority Date *(day/month/year)* 02/07/2004
Applicant GENENTECH, INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.
2. [ ] Certain claims were found unsearchable (See Box II).
3. [ ] Unity of invention is lacking (see Box III).
4. With regard to the title,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:
5. With regard to the abstract,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
   a. the figure of the drawings to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/023564

A. CLASSIFICATION OF SUBJECT MATTER
C07K5/08 A61K38/06 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHAI JIJIE ET AL: "STRUCTURAL AND BIOCHEMICAL BASIS OF APOPTOTIC ACTIVATION BY SMAC/DIABLO" NATURE, NATURE PUBLISHING GROUP, LONDON, GB, vol. 406, no. 6798, 24 August 2000 (2000-08-24), pages 855-862, XP002200489 ISSN: 0028-0836 cited in the application page 860, Smac 7 and Smac 10 -/-	1-21

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 2005	05/12/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schmid, A

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/023564

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LIU Z ET AL: "STRUCTURAL BASIS FOR BINDING OF SMAC/DIABLO TO THE XIAP BIR3 DOMAIN" NATURE, NATURE PUBLISHING GROUP, LONDON, GB, vol. 408, no. 6815, 21 December 2000 (2000-12-21), pages 1004-1008, XP001153400 ISSN: 0028-0836 cited in the application page 1007, table 1, sequences starting with "AVP"	1-21

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/023564

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

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

Although claims 15-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

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

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

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

Remark on Protest

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

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

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/US2005/023564	International filing date *(day/month/year)* 05.07.2005
Priority date *(day/month/year)* 02.07.2004	
International Patent Classification (IPC) or both national classification and IPC C07K5/08, A61K38/08, A61P35/00	
Applicant GENENTECH, INC.	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Schmid, A Telephone No. +49 89 2399-8591

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/023564

Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/023564

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 15-21

because:

☒ the said international application, or the said claims Nos. 15-21 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/023564

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/US2005/023564

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1) Claims 15-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) Reference is made to the following documents:

D1: CHAI JIJIE ET AL: "STRUCTURAL AND BIOCHEMICAL BASIS OF APOPTOTIC ACTIVATION BY SMAC/DIABLO" NATURE, NATURE PUBLISHING GROUP, LONDON, GB, vol. 406, no. 6798, 24 August 2000 (2000-08-24), pages 855-862, XP002200489 ISSN: 0028-0836

D2: LIU Z ET AL: "STRUCTURAL BASIS FOR BINDING OF SMAC/DIABLO TO THE XIAP BIR3 DOMAIN" NATURE, NATURE PUBLISHING GROUP, LONDON, GB, vol. 408, no. 6815, 21 December 2000 (2000-12-21), pages 1004-1008, XP001153400 ISSN: 0028-0836

2) The present peptides differ from the prior art represented by D1 and D2 essentially in the heterocyclic ring "A" which does not exist neither in D1 nor in D2. On the contrary D1 and D2 disclose peptides which have additional amino acids instead of the heterocycle, which means that the present peptides are also shorter.

Accordingly, the present subject-matter is novel pursuant to Article 33(2) PCT.

3) A skilled person looking for alternative IAP inhibitors would surely not try to shorten

the known peptides and to add a heterocyclic ring instead with a reasonable expectation of success in order to obtain IAP inhibitors which is alleged by the applicant.

However, looking at pages 96 and 97, below the applicant simply alleges that the present compounds show the desired activity without putting forward any specifc test results in order to prove this allegation.

Therefore, for the time being, no inventive step with regard to Article 33(3) PCT can be acknoweledged for the present subject-matter.

4) For the assessment of the present claims 15-21on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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RECEIVED PATENT COOPERATION TREA... PCT/US2005/023564

NOV 16 2005

GENENTECH, INC.
LEGAL DEPT.

DE/LS

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

EVANS, David, W.
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)* 03 November 2005 (03.11.2005)	
Applicant's or agent's file reference P2154R1	IMPORTANT NOTIFICATION
International application No. PCT/US2005/023564	International filing date *(day/month/year)* 05 July 2005 (05.07.2005)
International publication date *(day/month/year)*	Priority date *(day/month/year)* 02 July 2004 (02.07.2004)
Applicant GENENTECH, INC. et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)* An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
02 July 2004 (02.07.2004)	60/585,601	US	12 August 2005 (12.08.2005)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Fiona DOHERTY
Facsimile No. (41-22) 338.87.40
Telephone No. +41 22 338 9495

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* P2154R1

Box No. I TITLE OF INVENTION

INHIBITORS OF IAP

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

GENENTECH, INC.
1 DNA Way
South San Francisco, CA 94080-4990
US

Telephone No.
650-225-1000

Facsimile No.
650-952-9881

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality:
US

State *(that is, country)* of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

COHEN, Frederick
2001 McAllister Street, #143
San Francisco, CA 94118
US

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:
US

State *(that is, country)* of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

EVANS, David W.
GENENTECH, INC.
1 DNA Way
South San Francisco, CA 94080-4990
US

Telephone No.
650-225-1739

Facsimile No.
650-952-9881

Teleprinter No.

Agent's registration No. with the Office
L0035

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent

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Sheet No. ...2...

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
DESHAYES, Kurt
138 Southwood Drive
San Francisco, CA 94112
US

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
FAIRBROTHER, Wayne J.
1008 Toyon Drive
Burlingame, CA 94080
US

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
FENG, Bainian
1018 Avalon Avenue
Foster City, CA 94404
US

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
FLYGARE, John
1419 Vancouver Avenue
Burlingame, CA 94010
US

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

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Sheet No. ...3...

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

GAZZARD, Lewis J.
2552 Belmont Canyon Road
Belmont, CA 94002
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* **of nationality:** US

State *(that is, country)* **of residence:** US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

TSUI, Vickie Hsiao-Wei
650 Chestnut Street, #108
San Francisco, CA 94133
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* **of nationality:** CA

State *(that is, country)* **of residence:** US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* **of nationality:**

State *(that is, country)* **of residence:**

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* **of nationality:**

State *(that is, country)* **of residence:**

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Sheet No. ...4...

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No...." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

(i) If more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;

(ii) If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

(iii) If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

(iv) If, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) If, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.

2. If the applicant intends to make an indication of the wish that the international application be treated, in certain designated States, as an application for a patent of addition, certificate of addition, inventor's certificate of addition or utility certificate of addition: in such a case, write the name or two-letter code of each designated State concerned and the indication "patent of addition," "certificate of addition," "inventor's certificate of addition" or "utility certificate of addition," the number of the parent application or parent patent or other parent grant and the date of grant of the parent patent or other patent grant or the date of filing of the parent application (Rules 4.11(a)(iii) and 49bis.1(a) or (b)).

3. If the applicant intends to make an indication of the wish that the international application be treated, in the United States of America, as a continuation or continuation-in-part of an earlier application: in such a case, write "United States of America" or "US" and the indication "continuation" or "continuation-in-part" and the number and the filing date of the parent application (Rules 4.11(a)(iv) and 49bis.1(d)).

Continuation of Box No. IV: Applicants also appoint:

ANDRUS, Alex	AGARWAL, Atulya R.
BARNES, Elizabeth M.	NAIK, Paul
CARPENTER, David A.	COBURN, Cara M.
CONLEY, Deirdre L.	CUI, Steven X.
HASAK, Janet E.	JOHNSTON, Sean A.
KALINOWSKI, Grant	KRESNAK, Mark T.
KUBINEC, Jeffrey S.	LEE, Wendy M.
MARSCHANG, Diane L.	PLEASURE, Irene T.
SCHWARTZ, Timothy R.	SHERMAN, Daniel E.
SHIN, Elinor K.	SVOBODA, Craig G.
TAN, Lee K.	YEUNG, Bonny G.

all of:

GENENTECH, INC.
1 DNA Way
South San Francisco, CA 94080-4990
US

Box No. V DESIGNATIONS

The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

☐ DE Germany is not designated for any kind of national protection

☐ KR Republic of Korea is not designated for any kind of national protection

☐ RU Russian Federation is not designated for any kind of national protection

(The check-boxes above may be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law, of an earlier national application from which priority is claimed. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 02 July 2004 (02.07.04)	60/585,501	US		
item (2)				
item (3)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

** Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):*

.....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA / EP.....

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*:		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor :	
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent :	
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application :	
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America) :	
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty :	

Sheet No. 6

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:		
(a) on paper, the following number of sheets:		
request (including declaration sheets)	:	6
description (excluding sequence listing and/or tables related thereto)	:	97
claims	:	5
abstract	:	1
drawings	:	0
Sub-total number of sheets	:	109
sequence listing	:	
tables related thereto	:	
(for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below)		
Total number of sheets	:	109
(b) ☐ only in electronic form (Section 801(a)(i))		
(i) ☐ sequence listing		
(ii) ☐ tables related thereto		
(c) ☐ also in electronic form (Section 801(a)(ii))		
(i) ☐ sequence listing		
(ii) ☐ tables related thereto		
Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the		
☐ sequence listing:		
☐ tables related thereto:		
(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)		

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:	Number of items
1. ☐ fee calculation sheet	:
2. ☐ original separate power of attorney	:
3. ☐ original general power of attorney	:
4. ☐ copy of general power of attorney; reference number, if any:	:
5. ☐ statement explaining lack of signature	:
6. ☐ priority document(s) identified in Box No. VI as item(s):	:
7. ☐ translation of international application into *(language)*:	:
8. ☐ separate indications concerning deposited microorganism or other biological material	:
9. ☐ sequence listing in electronic form *(indicate type and number of carriers)*	
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:
(ii) ☐ *(only where check-box (b)(i) or (c)(i) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column	:
10. ☐ tables in electronic form related to sequence listing *(indicate type and number of carriers)*	
(i) ☐ copy submitted for the purposes of international search under Section 802(b-*quater*) only (and not as part of the international application)	:
(ii) ☐ *(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-*quater*)	:
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column	:
11. ☐ other *(specify)*:	:

Figure of the drawings which should accompany the abstract:	Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

David W. EVANS
Agent for Applicants

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

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DWE/LL

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

PR2154

OCTOBER 14, 2004

PTAS "700122428A"

GENENTECH, INC.
DAVID W EVANS
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

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RECORDATION DATE: 10/12/2004 REEL/FRAME: 015238/0960
NUMBER OF PAGES: 4

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).
DOCKET NUMBER: PR2154

ASSIGNOR:
COHEN, FREDERICK DOC DATE: 09/20/2004

ASSIGNOR:
DESHAYES, KURT DOC DATE: 09/20/2004

ASSIGNOR:
FAIRBROTHER, WAYNE DOC DATE: 09/21/2004

ASSIGNOR:
FENG, BAINIAN DOC DATE: 10/06/2004

ASSIGNOR:
FLYGARE, JOHN DOC DATE: 10/06/2004

ASSIGNOR:
GAZZARD, LEWIS J. DOC DATE: 10/06/2004

015238/0960 PAGE 2

ASSIGNOR:
TSUI, VICKIE HSIAO-WEI DOC DATE: 10/06/2004

ASSIGNEE:
GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CALIFORNIA

94080-4990

SERIAL NUMBER: 60585501 FILING DATE: 07/02/2004
PATENT NUMBER: ISSUE DATE:
TITLE: INHIBITORS OF IAP

JEFFREY OLSEN, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

283

10/12/2004
700122426

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

RECORDATION FORM COVER SHEET
PATENTS ONLY

Atty Dkt No P8216

Assistant Commissioner of Patents: Please record the attached original document or copy thereof

1. Name of conveying party(ies):
Frederick Cohen
Kurt Deshayes
Wayne Fairbrother
Sabalan Farag
John Flygare
Lewis J. Gazzard
Victdie Hsiao-Wei Tsui
Additional name(s) of conveying party(ies) attached? _ Yes X No

2. Name and address of receiving party(ies):
Name: GENENTECH, INC.
Internal Address:
Street Address: 1 DNA Way
City: South San Francisco State: California
ZIP: 94080-4990
Additional name(s) & address(es) attached? _ Yes X No

3. Nature of conveyance:
X Assignment Merger
Security Agreement
Change of Name
Other:
Execution Date: 9/20/04; 9/20/04; 9/21/04; 10/06/04; 10/06/04; 10/06/04; 10/06/04; 10/06/04

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is:
A. Patent Application No.(s)
60/585,501
B. Patent No.(s)
Additional number(s) attached? _ Yes X No

5. Name and address of party to whom correspondence concerning document should be mailed:
DAVID W EVANS
GENENTECH, INC.
1 DNA Way
South San Francisco, CA 94080

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41): $ 40.00
_ Enclosed
X Authorized to be charged to deposit account

8. Deposit account number:
07-0610

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9. Statement and signature
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

DAVID W EVANS
Name of Person Signing
Registration No.

Signature

October 13, 2004
Date

Total number of pages comprising cover sheet, attachments and document: 5

*A copy of a document pursuant to 37 C.F.R. § 10.930 is retained as part of the authorization of the above to prosecute the attached application. The original of the document is on file in the Office of Enrollment and Discipline.

Revised 10/01/2003

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Docket No. PR2154

ASSIGNMENT

WHEREAS, Frederick Cohen, a citizen of United States of America, residing at 2001 McAllister Street, San Francisco, CA 94118, and Kurt Deshayes, a citizen of United States of America, residing at 138 Southwood Drive, San Francisco, CA 94112, and Wayne Fairbrother, a citizen of New Zealand, residing at 1008 Toyon Drive, Burlingame, CA 94010, and Bainian Feng, a citizen of United States of America, residing at 1018 Avalon Avenue, Foster City, CA 94404, and John Flygare, a citizen of United States of America, residing at 1419 Vancouver Avenue, Burlingame, CA 94010, and Lewis J. Gazzard, a citizen of Great Britain, residing at 2552 Belmont Canyon Road, Belmont, CA 94002, and Vickie Hsiao-Wei Tsui, a citizen of Canada, residing at 650 Chestnut Street #108, San Francisco, CA 94133, (hereinafter "ASSIGNORS"), have invented a new and useful invention in

INHIBITORS OF IAP

for which a provisional application Serial No. 60/585,501 (Docket No. PR2154) has been filed by them on JULY 2, 2004; and

WHEREAS, GENENTECH, INC., a corporation organized and existing under and by virtue of the laws of the State of Delaware, having a place of business at 1 DNA Way, South San Francisco, California 94080-4490, is desirous of acquiring an interest in and to said invention, and in and to the Letters Patents to be obtained therefor;

NOW, THEREFORE, be it known by all whom it may concern;

That for good and valuable consideration the receipt of which is hereby acknowledged, the said ASSIGNORS have and do hereby sell, assign, transfer and set over unto the said GENENTECH, INC., its successors and assigns, the full and exclusive right, title and interest including all rights under the Paris Convention for the Protection of Industrial Property, in and to said invention, and in and to any and all Letters Patents to be granted and issued therefor or any continuation, division, renewal, or substitute thereof, and as to Letters Patents any reissue or re-examination thereof, not only for, to, and in the United States of America, its territories and possessions, but for, to and in all other countries; and it has been and is hereby authorized and requested that the appropriate government agencies issue said Letters Patents to said GENENTECH, INC., in accordance with this Assignment.

Said ASSIGNORS covenant and agree to cooperate with GENENTECH, INC., to enable said GENENTECH, INC. to enjoy to the fullest extent the right, title and interest herein conveyed in the United States and foreign countries. Such cooperation by said ASSIGNORS includes prompt production of pertinent facts and documents, giving of testimony, execution of petitions, oaths, specifications, declarations or other papers, and other assistance all to the extent deemed necessary or desirable by said GENENTECH, INC., (a) for perfecting the right, title and interest herein conveyed; (b) for prosecuting any of said applications; (c) for filing and prosecuting applications for reissuance of any of said patents; (d) for interference or other priority proceedings involving said invention; and (e) for legal proceedings involving said invention and any applications therefor and any patents granted thereon, including without limitation opposition proceedings, cancellation proceedings, priority contests, public use proceedings, infringement actions and court actions; provided, however, that the expense incurred by said ASSIGNORS in providing such cooperation shall be paid for by said GENENTECH, INC.

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Serial No. 60/585,501 Docket No. PR2154

The terms and covenants of this assignment shall inure to the benefit of said GENENTECH, INC., its successors, assigns and other legal representatives, and shall be binding upon said ASSIGNORS, their respective heirs, legal representatives and assigns.

Said ASSIGNORS hereby warrant and represent that they have not entered and will not enter into any assignment, contract, or understanding in conflict herewith.

IN WITNESS WHEREOF we undersign as follows;

South San Francisco
Dated: 9/20/04

Frederick Cohen

South San Francisco
Dated: 9/20/04

Kurt Deshayes

South San Francisco
Dated: 9/21/04

Wayne Fairbrother

South San Francisco
Dated: 10/06/04

Bainian Feng

South San Francisco
Dated: 10/6/04

John Flygare

South San Francisco
Dated: 10/6/04

Lewis J. Gazzard

South San Francisco
Dated: 10/6/04

Vickie Hsiao-Wei

286

State of California

SECRETARY OF STATE

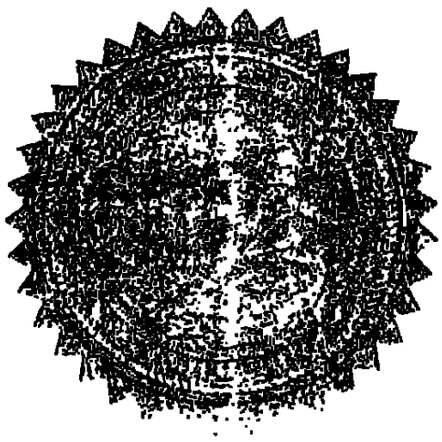
APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *Country: United States of America*
   This public document
2. *has been signed by AIDA MICLAT GUIAM*
3. *acting in the capacity of Notary Public, State of California*
4. *bears the seal/stamp of AIDA MICLAT GUIAM, Notary Public, State of California*

CERTIFIED

5. *At Sacramento, California*
6. *the 15th day of December 2005*
7. *by Deputy Secretary of State, State of California*
8. *No. 267083*
9. *Seal/Stamp:*



10. *Signature*

Secretary of State

BY

NP-84 A (REV. 4-05)

OSP 05 90772

22 NOV 2006

OSCAR ALARCON NUÑEZ
NOTARIO CUARENTA Y

287 287

CALIF RNIA ALL-PURPOSE ACKN WLEDGMENT

State of California
County of San Mateo } ss.

On December 6, 2005 (Date) before me, Aida Miclat Guiam (Name and Title of Officer (e.g., "Jane Doe, Notary Public"))

personally appeared Timothy R. Schwartz (Name(s) of Signer(s))

☐ personally known to me
☒ proved to me on the basis of satisfactory evidence

to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

AIDA MICLAT GUIAM
Commission # 1456662
Notary Public - California
San Mateo County
My Comm. Expires Dec 9, 2007

WITNESS my hand and official seal.

Aida Miclat Guiam
Signature of Notary Public

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☐ Individual
☐ Corporate Officer — Title(s): _____
☐ Partner — ☐ Limited ☐ General
☐ Attorney-In-Fact
☐ Trustee
☐ Guardian or Conservator
☐ Other: _____

Signer Is Representing: _____

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BOGOTA D.C. REPUBLICA DE COLOMBIA
22 NOV 2006
OSCAR ALARCON NUÑEZ
NOTARIO CUARENTA Y SEIS

Brigard & Castro

BOGOTA - COLOMBIA

~~287~~ 288

PODER

Yo (nosotros)

domiciliado(s) en

Nombro(amos) a: **JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO y/o CARLOS H. PALACIO EASTMAN y/o HECTOR GOMEZ MEJIA**, de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO y/o CARLOS H. PALACIO EASTMAN y/o HECTOR GOMEZ MEJIA**,, domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y/o designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

hoy . de de 200

Firma

Nombre

Cargo

POWER OF ATTORNEY

I (We) **Genentech, Inc.**
1 DNA Way

domiciled in **South San Francisco, California 94080-4990 USA**

Hereby appoints **JUAN PABLO CADENA SARMIENTO** and/or **BEATRIZ JARAMILLO** and/or **CARLOS H. PALACIO EASTMAN** and/or **HECTOR GOMEZ MEJIA**, of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; criminal proceedings, actions for payment of damages: claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures and in other actions or similar proceedings.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoints **JUAN PABLO CADENA SARMIENTO** and/or **BEATRIZ JARAMILLO** and/or **CARLOS H. PALACIO EASTMAN** and/or **HECTOR GOMEZ MEJIA**, domiciled in Carrera 7 No. 16-56, Piso 9, my attorney(s) in fact, with powers to receive and to designate judicial and extrajudicial

Granted and signed in **South San Francisco, California USA**

22 NOV 2006

NOTARIA CUARENTA Y UNO

day of December 2005

Signature

Name Timothy R. Schwartz, Ph.D.

Title Section Patent Counsel
Authorized Corporate Signatory
Genentech, Inc.

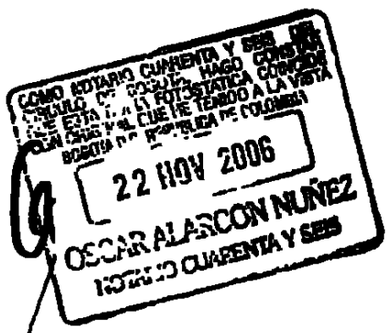
289

AUTHORIZATION

Genentech, Inc. hereby authorizes any of Janet E. Hasak, Mark T. Kresnak, Jeffrey S. Kubinec and Timothy R. Schwartz, for so long as they remain employees of Genentech, Inc., to execute, on its behalf, any submissions associated with the filing, prosecution, granting, and extension and maintenance of grant of patent and trademark applications in the U.S. and foreign countries, contracts relating to biological deposits with the American Type Culture Collection, and assignments to publishers of copyrights covering works authored by Genentech employees.

August 27, 2002
Dated

Sean Johnston
Sean A. Johnston
Vice President, Intellectual Property
Genentech, Inc.



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ESTADO DE CALIFORNIA
SECRETARIA DE ESTADO

APOSTILLA
(Convención de La Haya del 5 de Octubre de 1961)

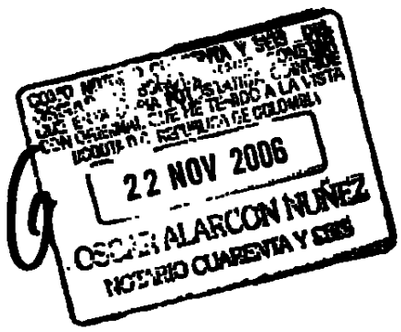
1 País: Estados Unidos de América
Esta documento público
2. ha sido firmado por AIDA MICLAT GUIAM
3. actuando en capacidad de Notario Público, Estado de California
4. lleva el sello/timbre de AIDA MICLAT GUIAM, Notario Público
Estado de California

CERTIFICADO

5. en Sacramento, California
6. el 15 de diciembre de 2005
7. por el Secretario de Estado Delegado, Estado de California
8. No. 267083
9. Sello/Timbre

10. Firma

(Firma)
Secretario de Estado



24 291

RECONOCIMIENTO TODO-PROPOSITO DE CALIFORNIA

Estado de California)
} ss.
Condado de San Mateo)

El 6 de diciembre de 2005, ante mi, AIDA MICLAT GUIAM, apareció personalmente Thimoty R. Schwartz

☐ a quien conozco personalmente

☒ quien demostró ante mi en base a evidencia satisfactoria ser la persona cuyo nombre esta suscrito en el instrumento y quien reconoció ante mi que ejecutó el mismo en su capacidad autorizada, y que por su firma en el instrumento la persona o la entidad a nombre de la cual la persona actuó, ejecutó el instrumento.

Hay un sello que dice:
AIDA MICLAT GUIAM
COMISIÓN # 14556612
Notario Público-California
Condado de San Mateo
Mi comisión expira Dic. 9 de 2007

Atestigua mi firma y sello oficial,

AIDA MICLAT GUIAM

----------OPCIONAL----------

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☐ Funcionario Corporativo – Título(s): _____
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☐ Otro: _____

El firmante representa: _____

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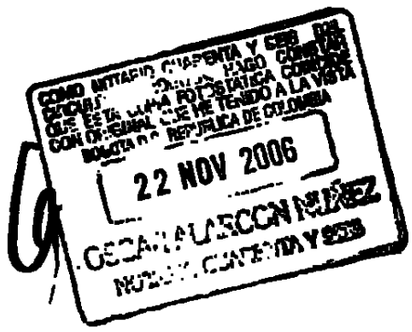
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AUTORIZACION

Genentech, Inc. por la presente autoriza a cualquiera de Janet E. Hasak, Mark T. Kresnak, Jeffrey S. Kubinec y Thomity R. Schwartz, mientras permanezcan como empleados de Genentech, Inc., a ejecutar, a su nombre, cualquier solicitud asociada con presentación, procesamiento, consecución, y extensión y mantenimiento de concesión de solicitudes de patente y marca registrada en los Estados Unidos y países extranjeros, contratos relacionados con depósitos biológicos con la Colección Americana de Tipo de Cultivo, y cesiones a publicistas de derechos de autor que cubran los trabajos de autoría de los empleados de Genentech.

27 de Agosto de 2002
Fechado

(Firma)
Sean A. Johnston
Vicepresidente, Propiedad Intelectual
Genentech, Inc.



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Apostille

(Convention de La Haye du 5 Octobre 1961)

1. Country: United States of America

This public document:

2. has been signed by Harriet Smith Windsor

3. acting in the capacity of Secretary of State of Delaware

4. bears the seal/stamp of Office of Secretary of State

Certified

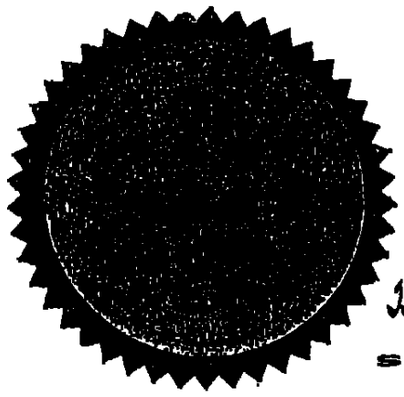
5. at Dover, Delaware

6. the twenty-fourth day of May, A.D. 2005

7. by Secretary of State, Delaware Department of State

8. No. 0254030

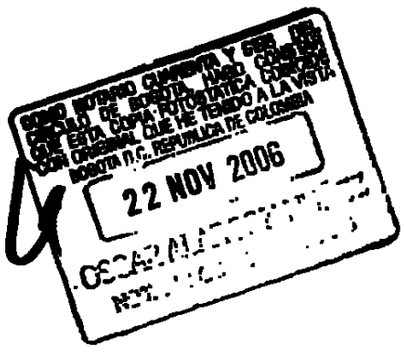
9. Seal/Stamp:



10. Signature:

Harriet Smith Windsor

Secretary of State



294

Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE RESTATED CERTIFICATE OF "GENENTECH, INC.", FILED IN THIS OFFICE ON THE TWENTY-SECOND DAY OF JULY, A.D. 1999, AT 9 O'CLOCK A.M.

2112549

050426506

Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

AUTHENTICATION: 3900384

05-24-05

DECIMO NOTARIO CUARENTA Y SEIS DEL CIRCULO DE BOGOTA. HAGO CONSTAR QUE ESTA COPIA FOTOSTATICA CORRESPONDE CON ORIGINAL QUE HE TENIDO A LA VISTA BOGOTA D.C. REPUBLICA DE COLOMBIA

22 NOV 2006

OSCAR A... NOTARIO

295

AMENDED AND RESTATED

CERTIFICATE OF INCORPORATION

GENENTECH, INC.

Genentech, Inc. (the "**Corporation**"), a corporation organized and existing under and by virtue of the General Corporation Law of the State of Delaware, does hereby amend the Certificate of Incorporation of the Corporation, which was originally filed on December 23, 1986 under the name "Genentech Delaware, Inc.", and subsequently amended.

The Certificate of Incorporation of the Corporation is hereby restated and further amended to read in its entirety as follows:

ARTICLE 1

The name of the Corporation is: Genentech, Inc.

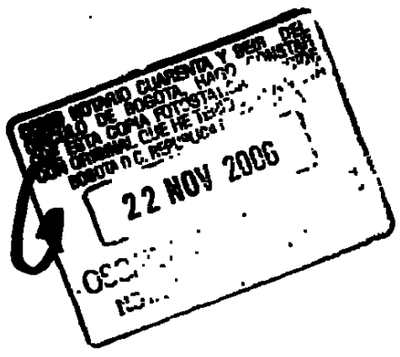
ARTICLE 2

The address of the registered office of the Corporation in the State of Delaware is Corporation Service Company, 1013 Centre Road, City of Wilmington, County of New Castle, Delaware 19805. The name of its registered agent at such address is Corporation Service Company.

ARTICLE 3

The purpose of the Corporation is to engage in any lawful act or activity for which corporations may be organized under the General Corporation Law of the State of Delaware as the same exists or may hereafter be amended ("Delaware Law").

STATE OF DELAWARE
SECRETARY OF STATE
DIVISION OF CORPORATIONS
FILED 09:00 AM 07/22/1999
991302331 – 2112549



ARTICLE 4

SECTION 4.01. *Capital Stock.* (a) The Corporation is authorized to issue two classes of stock to be designated, respectively, preferred stock and common stock. The total number of shares which the Corporation is authorized to issue is four hundred million (400,000,000) shares. One hundred million (100,000,000) shares shall be designated preferred stock, par value $0.02 per share ("Preferred Stock"). Three hundred million (300,000,000) shares shall be designated common stock, par value $0.02 per share ("Common Stock") The Common Stock of the Corporation shall be all of one class.

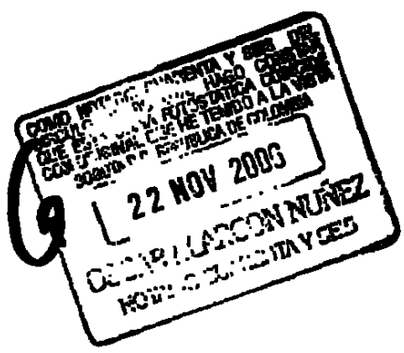
(b) The number of authorized shares of any class or classes of stock may be increased or decreased (but not below the number of shares thereof then outstanding) by the affirmative vote of a majority in voting power of the outstanding stock of the Corporation entitled to vote thereon irrespective of the provisions of Section 242(b)(2) of Delaware Law.

SECTION 4.02. *Common Stock.* (a) *Issuance and Consideration.* Any unissued or treasury shares of the Common Stock may be issued for such consideration as may be fixed in accordance with applicable law from time to time by the Board of Directors.

(b) *Dividends.* Subject to the rights of holders of the Preferred Stock, the holders of the Common Stock shall be entitled to receive, when and as declared by the Board of Directors, out of the assets of the Corporation which are by law available therefor, dividends payable either in cash, in property, or in shares of stock and the holders of the Preferred Stock shall not be entitled to participate in any such dividends (unless otherwise provided by the Board of Directors in any resolution providing for the issue of a series of Preferred Stock).

SECTION 4.03. *Preferred Stock.*

(a) *Series and Limits of Variations between Series.* Any unissued or treasury shares of the Preferred Stock may be issued from time to time in one or more series for such consideration as may be fixed from time to time by the Board of Directors. Before any shares of Preferred Stock of any particular series shall be issued, a certificate shall be filed with the Secretary of State of Delaware setting forth the designation, rights, privileges, restrictions, and conditions to be attached to the Preferred Stock of such series and such other matters as may be required, and the Board of Directors shall fix and determine, and is hereby expressly empowered to fix and determine, in the manner provided by law, the particulars of



the shares of such series (so far as not inconsistent with the provisions of this Article 4 applicable to all series of Preferred Stock), including, but not limited to, the following:

(i) the distinctive designation of such series and the number of shares which shall constitute such series, which number may be increased (except where otherwise provided by the Board of Directors in creating such series) or decreased (but not below the number of shares thereof then outstanding) from time to time by like action of the Board of Directors;

(ii) the annual rate of dividends payable on shares of such series, the conditions upon which such dividends shall be payable and the date from which dividends shall be cumulative in the event the Board of Directors determines that dividends shall be cumulative;

(iii) whether such series shall have voting rights, in addition to the voting rights provided by law and, if so, the terms of such voting rights;

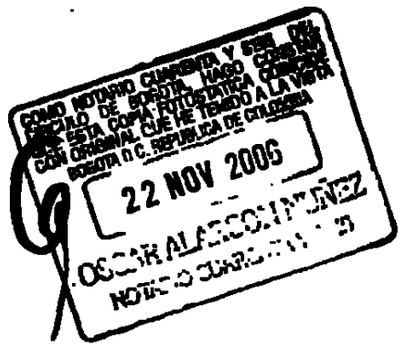
(iv) whether such series shall have conversion privileges and, if so, the terms and conditions of such conversion, including, but not limited to, provision for adjustment of the conversion rate upon such events and in such manner as the Board of Directors shall determine;

(v) whether or not the shares of such series shall be redeemable and, if so, the terms and conditions of such redemption, including the date or dates upon or after which they shall be redeemable, and the amount per share payable in case of redemption, which amount may vary under different conditions and at different redemption dates;

(vi) whether such series shall have a sinking fund for the redemption or purchase of shares of that series and, if so, the terms and amount of such sinking fund;

(vii) the rights of the shares of such series in the event of voluntary or involuntary liquidation, dissolution or winding up of the Corporation, and the relative rights of priority, if any, of payment of shares of that series; and

(viii) any other relative rights, preferences and limitations of such series.



ARTICLE 5

SECTION 5.01. *Amendment of Bylaws by Directors.* (a) In furtherance and not in limitation of the powers conferred by statute, the Board of Directors is expressly authorized to make, alter, amend, repeal and rescind the bylaws of the Corporation, subject to Sections 5.01(b) and 5.01(c) hereof.

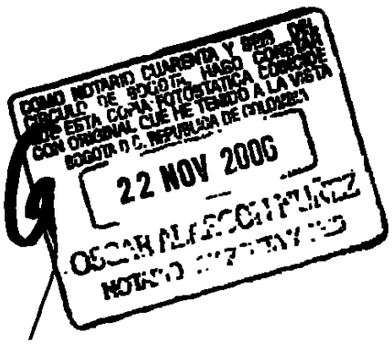
(b) Sections 2.02, 3.02, 3.03(a), 3.03(b), 3.04, 3.05, 3.14, and 5.06 of the bylaws may only be altered, amended, repealed, or rescinded by the affirmative vote of holders of capital stock entitled to vote thereon representing more than 60% of the shares entitled to be voted thereon.

(c) Sections 3.03(c) and 3.15 of the bylaws may only be altered, amended, repealed, or rescinded by the affirmative vote of holders of capital stock entitled to vote thereon representing more than 90% of the shares entitled to be voted thereon.

SECTION 5.02. *Amendment of Certificate of Incorporation.* Section 5.01(b) of this Certificate of Incorporation may only be altered, amended, repealed, or rescinded by the affirmative vote of holders of capital stock entitled to vote thereon representing more than 60% of the shares entitled to be voted thereon. Section 5.01(c) and Articles 8 and 9 of this Certificate of Incorporation may only be altered, amended, repealed, or rescinded by the affirmative vote of holders of capital stock entitled to vote thereon representing more than 90% of the shares entitled to be voted thereon.

ARTICLE 6

SECTION 6.01. *Election of Directors by Holders of Preferred Stock.* During any period when the holders of any Preferred Stock or any one or more series thereof, voting as a class, shall be entitled to elect a specified number of directors, by reason of dividend arrearages or other provisions giving them the right to do so, then and during such time as such right continues (i) the then otherwise authorized number of directors shall be increased by such specified number of directors, and the holders of such Preferred Stock or such series thereof, voting as a class, shall be entitled to elect the additional directors so provided for, pursuant to the provisions of such Preferred Stock or series; (ii) each such additional director shall serve for such term, and have such voting powers, as shall be stated in the provisions pertaining to such Preferred Stock or series; and (iii) whenever the holders of any such Preferred Stock or series thereof are



divested of such rights to elect a specified number of directors, voting as a class, pursuant to the provisions of such Preferred Stock or series, the terms of office of all directors elected by the holders of such Preferred Stock or series, voting as a class pursuant to such provisions or elected to fill any vacancies resulting from the death, resignation or removal of directors so elected by the holders of such Preferred Stock or series, shall forthwith terminate and the authorized number of directors shall be reduced accordingly.

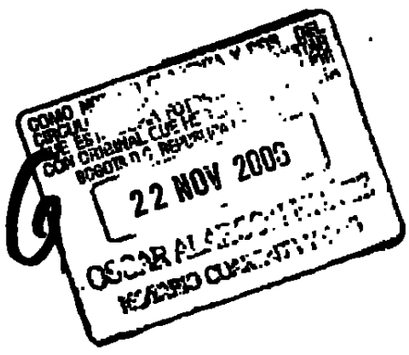
SECTION 6.02. *Ballots.* Elections of directors at an annual or special meeting of stockholders need not be by written ballot unless the bylaws of the Corporation shall provide otherwise.

SECTION 6.03. *Elimination of Certain Personal Liability of Directors.* (a) A director of the Corporation shall not be liable to the Corporation or its stockholders for monetary damages for breach of fiduciary duty as a director to the fullest extent permitted by Delaware Law.

(b) Each person (and the heirs, executors or administrators of such person) who was or is a party or is threatened to be made a party to, or is involved in any threatened, pending or completed action, suit or proceeding, whether civil, criminal, administrative or investigative, by reason of the fact that such person is or was a director of the Corporation or is or was serving at the request of the Corporation as a director of another corporation, partnership, joint venture, trust or other enterprise, shall be indemnified and held harmless by the Corporation to the fullest extent permitted by Delaware Law. The right to indemnification conferred in this Section 6.03 shall also include the right to be paid by the Corporation the expenses incurred in connection with any such proceeding in advance of its final disposition to the fullest extent authorized by Delaware Law. The right to indemnification conferred in this Section 6.03 shall be a contract right.

(c) The Corporation may, by action of its Board of Directors, provide indemnification to such of the officers, employees and agents of the Corporation to such extent and to such effect as the Board of Directors shall determine to be appropriate and authorized by Delaware Law.

(d) The Corporation shall have power to purchase and maintain insurance on behalf of any person who is or was a director, officer, employee or agent of the Corporation, or is or was serving at the request of the Corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise against any expense, liability or loss incurred by such person in any such capacity or arising out of his status as such, whether or



not the Corporation would have the power to indemnify him against such liability under Delaware Law.

(e) The rights and authority conferred in this Section 6.03 shall not be exclusive of any other right which any person may otherwise have or hereafter acquire.

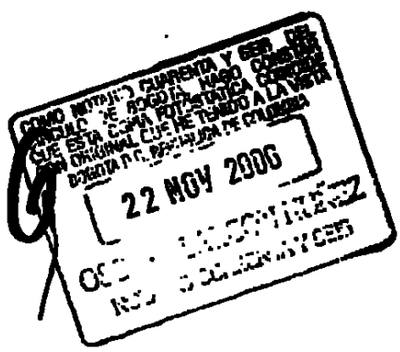
(f) Neither the alteration, amendment, repeal or recission of this Section 6.03, nor the adoption of any provision of this Certificate of Incorporation or the bylaws of the Corporation, nor, to the fullest extent permitted by Delaware Law, any modification of law, shall eliminate or reduce the effect of this Section 6.03 in respect of any acts or omissions occurring prior to such alteration, amendment, repeal, recission, adoption or modification.

ARTICLE 7

SECTION 7.01. *Section 203 of Delaware Law.* The Corporation hereby elects not to be governed by Section 203 of Delaware Law.

ARTICLE 8

SECTION 8.01. *Relationship With Roche.* In anticipation that the Corporation will cease to be a wholly owned subsidiary of Roche Holdings, Inc., but that Roche (as defined in Section 8.05) will remain a stockholder of the Corporation, and in anticipation that the Corporation (as defined in Section 8.05) and Roche may engage in the same or similar activities or lines of business and have an interest in the same areas of corporate opportunities, and in recognition of (i) the benefits to be derived by the Corporation through its continued contractual, corporate and business relations with Roche (including service of officers and directors of Roche as directors of the Corporation) and (ii) the difficulties attendant to any director, who desires and endeavors fully to satisfy such director's fiduciary duties, in determining the full scope of such duties in any particular situation, the provisions of this Article 8 are set forth to regulate, define and guide the conduct of certain affairs of the Corporation as they may involve Roche and its officers and directors, and the powers, rights, duties and liabilities



of the Corporation and its officers, directors and stockholders in connection therewith.

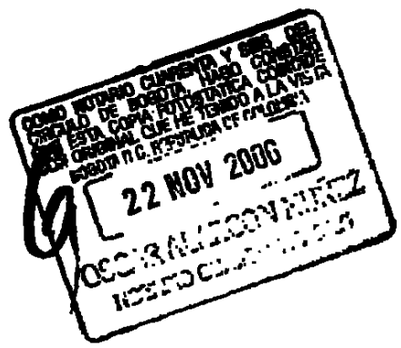
SECTION 8.02. *Similar Business Activities.* Except as Roche Holdings, Inc. may otherwise agree in writing,

(a) Roche shall not have a duty to refrain from engaging directly or indirectly in the same or similar business activities or lines of business as the Corporation, and

(b) neither Roche nor any officer or director thereof shall be liable to the Corporation or its stockholders for breach of any fiduciary duty by reason of any such activities of Roche or of such person's participation therein.

In the event that Roche acquires knowledge of a potential transaction or matter that may be a corporate opportunity for both Roche and the Corporation, Roche shall have no duty to communicate or offer such corporate opportunity to the Corporation and shall not be liable to the Corporation or its stockholders for breach of any fiduciary duty as a stockholder of the Corporation or controlling person of a stockholder by reason of the fact that Roche pursues or acquires such corporate opportunity for itself, directs such corporate opportunity to another person or entity, or does not communicate information regarding, or offer, such corporate opportunity to the Corporation.

SECTION 8.03. *Corporate Opportunities.* In the event that a director, officer or employee of the Corporation who is also a director, officer or employee of Roche acquires knowledge of a potential transaction or matter that may be a corporate opportunity for the Corporation and Roche (whether such potential transaction or matter is proposed by a third-party or is conceived of by such director, officer or employee of the Corporation), such director, officer or employee shall be entitled to offer such corporate opportunity to the Corporation or Roche as such director, officer or employee deems appropriate under the circumstances in his sole discretion, and no such director, officer or employee shall be liable to the Corporation or its stockholders for breach of any fiduciary duty or duty of loyalty or failure to act in (or not opposed to) the best interests of the Corporation or the derivation of any improper personal benefit by reason of the fact that (i) such director, officer or employee offered such corporate opportunity to Roche (rather than the Corporation) or did not communicate information regarding such corporate opportunity to the Corporation or (ii) Roche pursues or acquires such corporate opportunity for itself or directs such corporate opportunity to another person or does not communicate information regarding such corporate opportunity to the Corporation.



SECTION 8.04. *Deemed Consent of Stockholders.* Any person or entity purchasing or otherwise acquiring any interest in any shares of capital stock of the Corporation shall be deemed to have notice of and to have consented to the provisions of this Article 8.

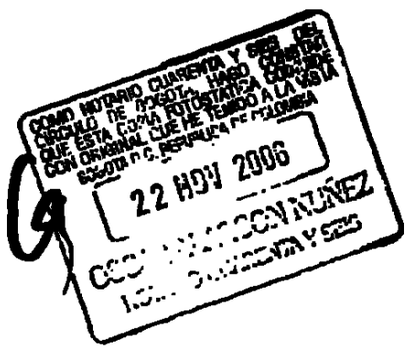
SECTION 8.05. *Definitions.* For purposes of this Article 8 and Article 9 only, (i) the term "**Corporation**" shall mean the Corporation and all corporations, partnerships, joint ventures, associations and other entities in which the Corporation beneficially owns (directly or indirectly) fifty percent or more of the outstanding voting stock, voting power or similar voting interests, and (ii) the term "**Roche**" shall mean Roche Holdings, Inc. and all corporations, partnerships, joint ventures, associations and other entities (other than the Corporation, defined in accordance with clause (i) of this Section 8.05) that are "affiliates" (as defined in Rule 12b-2 under the Securities Exchange Act of 1934, as amended) of Roche Holdings, Inc.

SECTION 8.06. *Termination; Binding Effect.* Notwithstanding anything in this Certificate of Incorporation to the contrary, the foregoing provisions of this Article 8 shall expire on the date that Roche ceases to own beneficially Common Stock representing at least 5% of the number of outstanding shares of Common Stock of the Corporation and no person who is a director or officer of the Corporation is also a director or officer of Roche. Neither such expiration, nor the alteration, amendment, change or repeal of any provision of this Article 8 nor the adoption of any provision of this Amended and Restated Certificate of Incorporation inconsistent with any provision of this Article 8 shall eliminate or reduce the effect of this Article 8 in respect of any matter occurring, or any cause of action, suit or claim that, but for this Article 8, would accrue or arise, prior to such expiration, alteration, amendment, repeal or adoption.

SECTION 8.07. *Article 9.* The provisions of this Article 8 are in addition to the provisions of Article 9.

ARTICLE 9

SECTION 9.01. *Contracts Not Void.* No contract, agreement, arrangement or transaction (or any amendment, modification or termination thereof) between the Corporation and Roche shall be void or voidable solely for the reason that Roche is a party thereto, or solely because any directors or officers of the Corporation who are affiliated with Roche are present at or participate in the



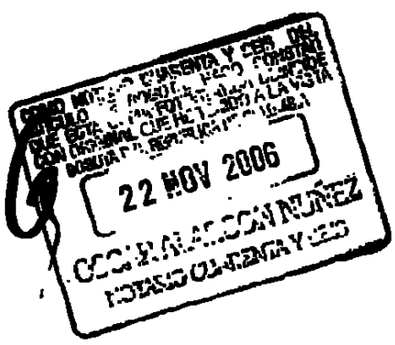
meeting of the Board of Directors or committee thereof which authorizes the contract, agreement, arrangement, transaction, amendment, modification or termination or solely because his or their votes are counted for such purpose, but any such contract, agreement, arrangement or transaction (or any amendment, modification or termination thereof) shall be governed by the provisions of this Amended and Restated Certificate of Incorporation, the Corporation's Bylaws, Delaware Law and other applicable law. For purposes of this Article 9, the terms the "Corporation" and "Roche" have the meanings set forth in Section 8.05.

SECTION 9.02. *Quorum.* Directors of the Corporation who are also directors or officers of Roche may be counted in determining the presence of a quorum at a meeting of the Board of Directors or of a committee that authorizes or approves any such contract, agreement, arrangement or transaction (or amendment, modification or termination thereof). Outstanding shares of Common Stock owned by Roche may be counted in determining the presence of a quorum at a meeting of stockholders that authorizes or approves any such contract, agreement, arrangement or transaction (or amendment, modification or termination thereof).

SECTION 9.03. *No Liability For Good Faith Actions.* Neither Roche nor any officer or director thereof shall be liable to the Corporation or its stockholders for breach of any fiduciary duty or duty of loyalty or failure to act in (or not opposed to) the best interests of the Corporation or the derivation of any improper personal benefit by reason of the fact that Roche or an officer of director thereof in good faith takes any action or exercises any rights or gives or withholds any consent in connection with any agreement or contract between Roche and the Corporation. No vote cast or other action taken by any person who is an officer, director or other representative of Roche, which vote is cast or action is taken by such person in his capacity as a director of this Corporation, shall constitute an action of or the exercise of a right by or a consent of Roche for the purpose of any such agreement or contract.

SECTION 9.04. *Deemed Consent by Stockholders.* Any person or entity purchasing or otherwise acquiring any interest in any shares of capital stock of the Corporation shall be deemed to have notice of and to have consented to the provisions of this Article 9.

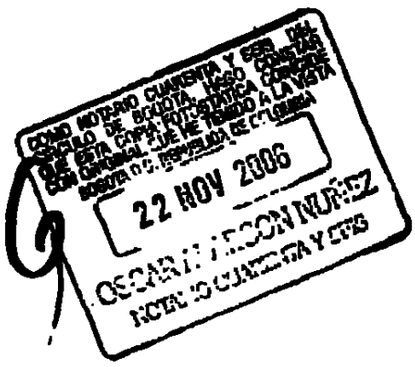
SECTION 9.05. *Contracts Covered.* For purposes of this Article 9, any contract, agreement, arrangement or transaction with the Corporation or any corporation, partnership, joint venture, association or other entity in which the Corporation beneficially owns (directly or indirectly) fifty percent or more of the outstanding voting stock, voting power or similar voting interests shall be deemed to be a contract, agreement, arrangement or transaction with the Corporation.



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SECTION 9.06. *Binding Effect.* Neither the alteration, amendment, change or repeal of any provision of this Article 9 nor the adoption of any provision inconsistent with any provision of this Article 9 shall eliminate or reduce the effect of this Article 9 in respect of any matter occurring, or any cause of action, suit or claim that, but for this Article 9, would accrue or arise, prior to such alteration, amendment, change, repeal or adoption.

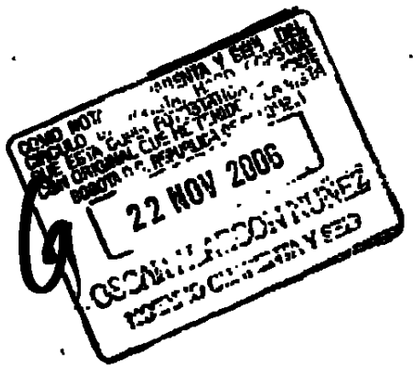
SECTION 9.07. *Article 8.* The provisions of this Article 9 are in addition to the provisions of Article 8.



IN WITNESS WHEREOF, this Amended and Restated Certificate of Incorporation, having been duly adopted in accordance with Sections 242 and 245 of the General Corporation Law of the State of Delaware and by the written consent of the sole stockholder of the Corporation in accordance with Section 228 of the General Corporation Law of the State of Delaware, has been executed this 22nd day of July, 1999.

GENENTECH, INC.

By: /s/ Stephen G. Juelsgaard
Name: Stephen G. Juelsgaard
Title: Senior Vice President,
General Counsel and Secretary



TRADUCCION AL ESPAÑOL del Certificado de Incorporación de Genentech, Inc.

APOSTILLA

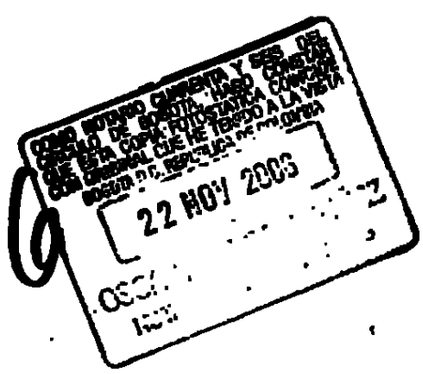
(Convención de La Haya del 5 de Octubre de 1961)

1. País: Estados Unidos de América
   Este documento público
2. ha sido firmado por Harriet Smith Windsor
3. actuando en capacidad de Secretaria de Estado de Delaware
4. lleva el sello/timbre de la Oficina del Secretario de Estado

Certificado

5. en Dover, Delaware
6. el veinticuatro de mayo, A. D. 2005
7. por el Secretario de Estado, Departamento de Estado de Delaware
8. No. 0254030
9. Sello/timbre
10. Firma

Harriet Smith Windsor (Firma)
Secretaria de Estado



preferenciales, por un valor de $0.02 por acción ("**Acción Preferencial**"). Trecientos millones (300,000,000) de acciones serán designadas acciones comunes, por un valor de $0.02 por acción ("**Acción Común**"). La acción común de la Corporación será toda de una misma clase.

(b) El número de acciones autorizadas de cualquier clase o clases de acciones puede incrementarse o disminuirse (pero no por debajo del número del número de acciones de las mismas que en su momento están vigentes) por el voto afirmativo de una mayoría con poder de votación de las acciones vigentes de la Corporación con derecho a votar por la misma independiente de las consideraciones de la Sección 242(b)(2) de la Ley de Delaware.

SECCION 4.02. *Acción Común.* (a) *Emisión y Consideración.* Cualquier acción sin emitir o del tesoro del las Acciones Comunes puede emitirse para tal consideración como pueda fijarse de acuerdo con la ley aplicable cada cierto tiempo por la Junta Directiva.

(b) *Dividendos.* Sujeto a los derechos de los accionistas de las Acciones Preferenciales, los accionistas de Acciones Comunes deberán tener el derecho a recibir, cuando y como se declare por la Junta Directiva, de los activos de la Corporación los cuales están disponibles para ello por ley, dividendos pagables ya sea en dinero, propiedad, o acciones y los accionistas de la Acción Preferencial no tendrán derecho a participar en tales dividendos (a menos que la Junta Directiva determine lo contrario en cualquier resolución que condiciona la emisión de una serie de Acciones Preferenciales).

SECCIÓN 4.03. *Acción Preferencial*

(a) *Series y Límites de Variaciones entre Series.* Cualquier acción no emitida o del tesoro de las Acciones Preferenciales puede emitirse cada cierto tiempo en una o más series para tal consideración como pueda ser fijada cada cierto tiempo por la Junta Directiva. Antes de que se emita cualquier acción de las Acciones Preferenciales de cualquier serie particular, se deberá presentar un certificado ante el Secretario de Estado de Delaware estableciendo las designaciones, derechos, privilegios, restricciones, y condiciones que irán anexas a las Acciones Preferenciales de tal serie y tales otras cuestiones como puedan requerirse, y la Junta Directiva deberá fijar y determinar, y por la presente está expresamente autorizada para fijar y determinar, en la forma provista por la ley, los

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CORREGIDO Y VUELTO A REDACTAR
CERTIFICADO DE INCORPORACIÓN
GENENTECH, INC.

Genentech, Inc (la "**Corporación**"), una corporación organizada y existente bajo y por virtud de la Ley General de Corporación del Estado de Delaware, por la presente corrige el Certificado de Incorporación, el fue presentado originalmente el 23 de diciembre de 1986, bajo el nombre "Genentech Delaware, Inc.", y corregido subsiguientemente.

Por la presente se vuelve a redactar el certificado de incorporación de la Corporación y se corrige aun más para que diga en su totalidad lo que sigue:

ARTICULO 1

El nombre de la Corporación es: Genentech, Inc.

ARTICULO 2

La dirección de la oficina registrada de la Corporación en el Estado de Delaware es Corporation Service Company, 1013 Centre Road, Ciudad de Wilmington, Condado de New castle, Delaware 19805. El nombre de su agente registrado en tal dirección es Corporation Service Company.

ARTICULO 3

El propósito de a Corporación es el de participar en cualquier acto o actividad legal para las cuales las corporaciones pueden ser organizadas bajo la Ley General de Corporación del Estado de Delaware como existe o puede se modificada la misma en adelante ("**Delaware Law**").

ARTICULO 4

SECCION 4.01. *Acciones de Capital.* (a) la Corporación está autorizada a emitir dos clases de acciones que deben designarse, respectivamente, acciones preferenciales y acciones comunes. El número total de acciones que la Corporación esta autorizada a emitir es de cuatrocientos millones (400,000,000) de acciones. Cien millones (100,000,000) de acciones serán designadas acciones

particulares de las acciones de tal serie (siempre y cuando no sean inconsistentes con las condiciones de este Artículo 4 aplicables a todas las series de Acciones Preferenciales), incluyendo, pero sin limitarse a, las siguientes:

(i) la designación distintiva de tal serie y el número de las acciones que han de constituir tal serie, numero que puede incrementarse (excepto cuando lo determine de otro modo la Junta Directiva al crear tal serie) o reducida (pero no por debajo del número de acciones de las mismas que están vigentes) cada cierto tiempo por una acción semejante de la Junta Directiva;

(ii) la tasa anual de dividendos a pagar sobre las acciones de tal serie, las condiciones sobre las cuales se pagarán tales dividendos y le fecha a partir de la cual los dividendos serán acumulativos en el evento que la Junta Directiva determine que los dividendos serán acumulativos;

(iii) si la serie tendrá o no derechos de voto, además de los derechos de voto provistos por la ley, y de ser así, los términos de tales derechos de voto;

(iv) si tal serie tendrá o no privilegios de conversión y, de ser así, los términos y condiciones de tal conversión, incluyendo, pero sin estar limitado a, la condición para ajuste de la tasa de conversión en tales eventos y de tal forma como la Junta Directiva lo determine;

(v) si las acciones de tal serie serán o no redimibles y, de ser así, los términos y condiciones de tal redención, incluyendo la fecha o fechas en las cuales o después de las cuales pueden ser redimibles, y la cantidad a pagar por acción en caso de redención, cantidad que variará bajo diferentes condiciones y en diferentes fechas de redención;

(vi) si tal serie tendrá o no un fondo de inversión para la redención o compra de acciones de esa serie y, de ser así, los términos y la cantidad de tal fondo de inversión;

(vii) los derechos de las acciones de tal serie en caso de una liquidación, disolución o cierre voluntaria o involuntaria de la corporación, y

los derechos relativos de prioridad, de haber, de pago de acciones de esa serie; y

(viii) cualquier otro derecho relativo, preferencia y limitación de tal serie.

ARTICULO 5

SECCION 5.01. *Enmiendas a los estatutos por los Directores.* (a) En adición y no limitando los poderes conferidos por estatutos, la Junta Directiva esta expresamente autorizada para hacer, alterar, enmendar, rechazar y rescindir los estatutos de la Corporación, sujetos a las secciones 5.01(b) y 5.01(c) a continuación.

(b) Las secciones 2.02, 3.02, 3.03(a), 3.04, 3.05, 3.14 y 5.06 de los estatutos solo pueden alterarse, enmendarse, repelerse, o rescindirse por el voto afirmativo de los accionistas de capital con derecho a votar las mismas que representen más del 60% de las acciones con derecho a votar las mismas.

(c) Las secciones 3.03(c) y 3.15 de los estatutos solo pueden ser alteradas, enmendadas, repelidas, o rescindidas por le voto afirmativo de los accionistas de capital con derecho a votar las mismas que representen más del 90% de las acciones con derecho a votar las mismas.

o

SECCION 5.02. *Enmienda del Certificado de Incorporación.* La sección 5.01 (b) de este Certificado de Incorporación solo puede ser alterada, enmendada, repelida, o rescindida por el voto afirmativo de los accionistas de capital con derecho a voto sobre la misma que representen a más del 60% de las acciones con derecho a votar la misma. La sección 5.01(c) y los Artículos 8 y 9 de este Certificado de Incorporación solo pueden alterarse, enmendarse, repelerse, o rescindirse por el voto afirmativo de los accionistas de capital con derecho a votar la misma que representen más del 90% de las acciones con derecho a votar la misma.

ARTICULO 6

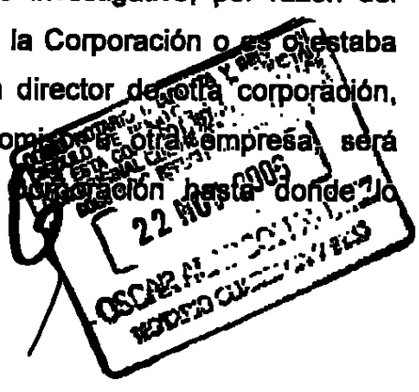
SECCION 6.01. *Elección del Director por los Accionistas de Acción Preferencial.* Durante cualquier periodo en el cual los accionistas de cualquier

acción preferencial cualquiera de una o más series de las mismas, que voten como una clase, tengan derecho a elegir un número específico de directores, por razón a atrasos en los dividendos u otras condiciones que les dan el derecho a hacerlo, entonces y durante el tiempo que continúe el derecho (i) el número de directores autorizado de otro modo será incrementado por tal número de directores especificado, y los accionistas de tales Acciones Preferenciales o tales series de las mismas, que votan como una clase, tendrán derecho a elegir los directores adicionales para lo que se provee, de acuerdo con las condiciones de tales Acciones Preferenciales o series; (ii) cada uno de tales directores adicionales servirá durante tal termino, y tendrá tales poderes de voto, como se han de otorgar en las provisiones pertinentes a tales Acciones Preferenciales o series; y (iii) siempre que los accionistas de cualquiera de tales Acciones Preferenciales o series de las mismas están desprovistos de tales derechos a elegir un número específico de directores, votando como clase, de acuerdo con las condiciones de tales Acciones preferenciales o series, los términos de oficio de todos los directores elegidos por los accionistas de tales Acciones preferenciales o series, que votan como clase, de acuerdo con las condiciones o elegidos para llenar cualquier vacante resultante de la muerte, renuncia o remoción de directores así elegidos por los accionistas de tales Acciones Preferenciales o series, terminarán en adelante y el número autorizado de directores será reducido en concordancia.

SECCION 6.02. *Votaciones.* Las elecciones de directores en una reunión anual o especial de accionistas necesaria no serán por votos escritos a menos que los estatutos de la Corporación digan lo contrario.

SECCION 6.03. *Eliminación de cierta responsabilidad personal de los directores.* (a) Un director de la Corporación no será responsable ante la Corporación o sus accionistas por daños monetarios por violación del deber fiduciario como director hasta donde lo permita la Ley de Delaware.

(b) Cada persona (y sus herederos, ejecutores o administradores de tal persona) quien fue o es una parte o esta amenazado de ser parte de, o esta involucrado en cualquier acción, demanda o proceso amenazado, pendiente, o completado, ya sea civil, criminal, administrativo o investigativo, por razón del hecho de que esa persona es o fue un director de la Corporación o es o estaba sirviendo por solicitud de la Corporación como un director de otra corporación, sociedad, sociedad de riesgo compartido, fideicomiso de otra empresa, será indemnizado y completamente protegido por la Corporación hasta donde lo



permita la Ley de Delaware. El derecho a la indemnización concedido en esta sección 6.03 también debe incluir el derecho a que la Corporación le pague los gastos incurridos en conexión cuna cualquiera de tales procesos por adelantado de su decisión final hasta donde los autoriza la Ley de Delaware. El derecho a indemnización conferido en esta sección 6.03 será un derecho contractual.

(c) La Corporación puede, por acción de su Junta Directiva, proporcionar indemnización a tales funcionarios, empleados y agentes de la Corporación hasta tal punto y a tal efecto como lo determine apropiado la Junta Directiva y lo autorice la Ley de Delaware.

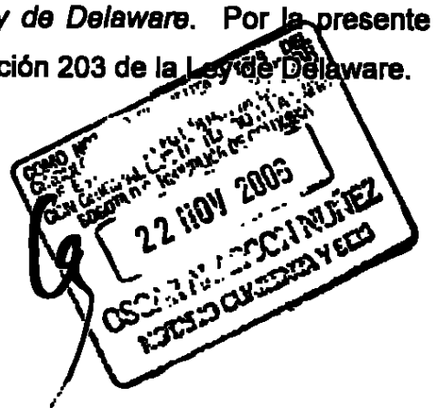
(d) La Corporación tendrá el poder de comprar y mantener un seguro a nombre de cualquier persona quien es o fue director, funcionario, empleado o agente de la corporación, o esta o estuvo en servicio por pedido de la Corporación como director, funcionario, empleado o agente de otra corporación, sociedad, sociedad de riesgo compartido, fideicomiso u otra empresa contra cualquier gasto, responsabilidad o pérdida incurrida por tal persona en cualquier capacidad o que surge de su estado como tal, ya sea si la Corporación tiene o no el poder de indemnizarlo contra tal responsabilidad bajo la ley de Delaware.

(e) Los derechos y autoridad conferidos en esta Sección 6.03 no serán exclusivos de ningún otro derecho el cual cualquier otra persona pueda tener o adquirir de aquí en adelante.

(f) Ni la alteración, enmienda, rechazo o rescisión de esta Sección 6.03, ni la adopción de ninguna condición de este Certificado de Incorporación o de los Estatutos de la Corporación, ni, hasta donde lo permite la Ley de Delaware, ninguna modificación de la ley, debe eliminar o reducir el efecto de esta Sección 6.03 respecto a ninguno de los actos u omisiones que ocurran antes de tal alteración, enmienda, rechazo, rescisión, adopción o modificación.

ARTICULO 7

SECCION 7.01, *Sección 203 de la Ley de Delaware*. Por la presente la Corporación elige no ser gobernada por la Sección 203 de la Ley de Delaware.



ARTICULO 8

SECCION 8.01. *Relación con Roche.* Anticipándose a que la Corporación cese de ser un subsidiaria completamente de propiedad de Roche Holdings, Inc., pero que Roche (como se define en la sección 8.05) permanezca siendo un accionista de la Corporación, y anticipándose a que la Corporación (como se define en la Sección 8.05) y Roche puede entrar en actividades o líneas de negocios semejantes o similares y tener un interés en las mismas áreas de oportunidades corporativas, y en reconocimiento de (i) los beneficios a ser derivados por la Corporación a través de sus relaciones contractuales, corporativas y de negocios con Roche (incluyendo el servicio de funcionarios y directores de Roche como directores de la Corporación) y (ii) las dificultades concomitantes a cualquier director, quien desea y se propone satisfacer completamente tales deberes fiduciarios del director, al determinar el alcance completo de tales deberes en cualquier situación particular, las condiciones de este artículos 8 se establecen para regular, definir y guiar la conducta de ciertas cuestiones de la Corporación ya que pueden involucrar a Roche y sus funcionaros y directores, y los poderes, derechos, deberes y responsabilidades de la Corporación y sus funcionarios, directores y accionistas en conexión con éste.

SECCION 8.02. *Actividades en Negocios Similares.* Excepto que Roche Holdings, Inc. pueda de otra forma acordarlo por escrito,

(a) Roche no tendrá el deber de abstenerse de entrar directamente o indirectamente en actividades de negocios o líneas de negocios semejantes o similares a las de la Corporación, y

(b) ni Roche ni ninguno de sus funcionarios o director de la misma será responsable a la Corporación o sus accionistas por violar cualquier deber fiduciario por razón de alguna de tales actividades de Roche o de la participación de tal persona en las mismas.

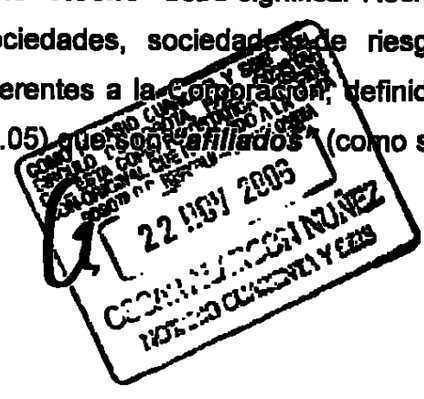
En el evento que Roche adquiera conocimientos de una transacción o materia potencial que pueda ser una oportunidad corporativa tanto para Roche como para la Corporación, Roche no tendrá el deber de comunicar u ofrecer tal oportunidad corporativa a la Corporación y no será responsable ante la Corporación o sus accionistas por violar ningún deber fiduciario como accionista de la Corporación o la persona que controla a un accionista por razón del hecho

que Roche prosigue o adquiere tal oportunidad corporativa para si misma, dirige tal oportunidad corporativa a otra persona o entidad, o no comunica información respecto, u ofrece, tal oportunidad corporativa a la Corporación.

SECCION 8.03. *Oportunidades Corporativas.* En el evento que un director, funcionario o empleado de la Corporación quien también es director, funcionario o empleado de Roche adquiera conocimiento de una transacción o materia potencial que pueda ser una oportunidad corporativa para la Corporación y Roche (ya se si esta transacción o materia potencial es propuesta por un tercero o es concebida por tal director, funcionario o empleado de la Corporación o no), tal director, funcionario o empleado debe tener el derecho a ofrecer tal oportunidad corporativa a la Corporación o Roche como tal director, funcionario o empleado los considere apropiado bajo las circunstancias de su discreción, y tal director, funcionario o empleado no será responsable a la Corporación o sus accionistas por violar ningún deber fiduciario o deber de lealtad o faltar en actuar en (o no oponerse a) los mejores intereses de la Corporación o la derivación de ningún beneficio personal inapropiado por razón del hecho que (i) tal director, funcionario o empleado ofreció tal oportunidad corporativa a Roche (en lugar de a la Corporación) o no comunicó información respecto a tal oportunidad corporativa a la Corporación o (ii) Roche busca o adquiere tal oportunidad corporativa para si misma o dirige tal oportunidad corporativa a otra persona o no comunica información respecto a tal oportunidad corporativa a la Corporación.

SECCION 8.04. *Consentimiento estimado de los accionistas.* Se considerará que cualquier persona o entidad que compre o de otro modo adquiera algún interés en cualquiera de las acciones de capital de la Corporación ha tenido noticia o ha estado de acuerdo con las condiciones de este Artículo 8.

SECCION 8.05, *Definiciones.* Para propósitos de este Artículo 8 y el Artículo 9 solamente, (i) el término ***"Corporación"*** debe significar la Corporación y todas las corporaciones, sociedades, sociedades de riesgo compartido y otras entidades en las cuales la Corporación posee con beneficio (directa o indirectamente) cincuenta por ciento o más de las acciones con voto, poder de voto o intereses de voto similares, y (ii) el término ***"Roche"*** debe significar Roche Holdings, Inc y todas las corporaciones, sociedades, sociedades de riesgo compartido, asociaciones y otras entidades (diferentes a la Corporación, definida de acuerdo con la cláusula (i) de esta sección 8.05) que son ***afiliados*** (como se



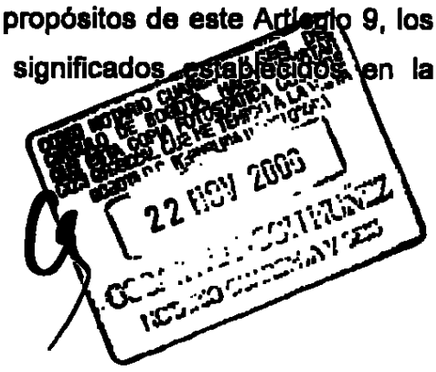
define en la Regla 12b-2 bajo el Acta de Intercambio de Valores de 1934, como se enmendó) de Roche Holdings, Inc.

SECCION 8.06, *Finalización: Efecto Obligante.* Son consideración con nada en este Certificado de Incorporación que lo contradiga, las condiciones anteriores de este Artículo 8 deberán expirar en la fecha que Roche cese de poseer con beneficios Acciones Comunes que representen al menos 5% del número de acciones vigentes de las Acciones Comunes de la Corporación y nadie que se director o funcionario de la Corporación sea también director o funcionario de Roche. Ni tal vencimiento, ni la alteración, enmienda, cambio o rechazo de alguna de las condiciones de este Artículo 8 así como tampoco ninguna condición de este Certificado de Incorporación Enmendado y Vuelto a Redactar inconsistente con alguna de las condiciones de este Artículo 8 eliminará o reducirá el efecto de este Artículo 8 respecto a cualquier materia, o cualquier causa de acción, demanda o reclamo que, excepto por este Artículo 8, pueda acaecer o surgir, antes de tal vencimiento, alteración, enmienda o adopción.

SECCION 8.07. *Artículo 9.* Las condiciones de este Artículo son adicionales a las condiciones del Artículo 9.

ARTICULO 9

SECCION 9.01. *Contratos no nulos.* Ningún contrato, acuerdo, arreglo o transacción (o cualquier enmienda, modificación o finalización de los mismos) entre la Corporación y Roche será nulo u anulable solamente por razón de que Roche es parte del mismo, o solamente porque cualquiera de los directores o funcionarios de la Corporación quienes están afiliados a Roche están presentes en o participan en la reunión de la Junta Directiva o comité de la misma que autoriza el contrato, acuerdo, arreglo, transacción, enmienda, modificación o finalización o solamente porque su o sus votos se cuentan para tal propósito, pero cualquiera de tal contrato, acuerdo, arreglo o transacción (o cualquier enmienda, modificación o finalización del mismo) estará gobernado por las condiciones de este Cerificado de Incorporación Enmendado y vuelto a Redactar, los Estatutos de la Corporación, la Ley de Delaware y otras leyes aplicables. Para propósitos de este Artículo 9, los términos "***Corporación***" y "***Roche***" tienen los significados establecidos en la Sección 8.05.

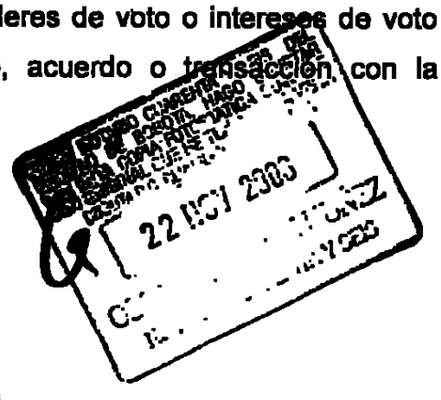


SECCION 9.02. *Quórum.* Los Directores de la Corporación que son también directores o funcionarios de Roche pueden contarse al determinar la presencia de un quórum en una reunión de la Junta Directiva o de un comité que autoriza o aprueba cualquiera de tal contrato, acuerdo, arreglo o transacción (o cualquier enmienda, modificación o finalización del mismo). Las acciones vigentes de las Acciones Comunes de propiedad de Roche pueden contarse al determinar la presencia de un quórum en una reunión de accionistas que autorice o apruebe tal contrato, acuerdo, arreglo o transacción (o cualquier enmienda, modificación o finalización del mismo).

SECCION 9.03. *No responsabilidad por acciones de buena fe.* Ni Roche ni ningún funcionario o director de la misma será responsable ante la Corporación o sus accionistas por violar cualquiera de los deberes fiduciarios o deberes de lealtad o por fallar en actuar en (o no oponerse a) los mejores intereses de la Corporación o por derivación de cualquier beneficio personal por razón del hecho que Roche o un funcionario o director de la misma de buena fe tome cualquier acción o ejerza cualquier derecho o de o retenga cualquier consentimiento en conexión con cualquier acuerdo o contrato entre Roche y la Corporación. Ningún voto dado u otra acción tomada por cualquier persona que es un funcionario, director o representante de Roche, donde el voto o acción es tomado por tal persona en su capacidad como director de esta Corporación, constituirá una acción de o el ejercicio de un derecho o un consentimiento de Roche para los propósitos de cualquiera de tal acuerdo o contrato.

SECCION 9.04. *Consentimiento estimado de los accionistas.* Se considerará que cualquier persona o entidad que compre o de otro modo adquiera algún interés en cualquiera de las acciones de capital de la Corporación ha tenido noticia o ha estado de acuerdo con las condiciones de este Artículo 9.

SECCION 9.05. *Contratos cubiertos.* Para propósitos de este Artículo 9, cualquier contrato, acuerdo, arreglo o transacción con la Corporación o cualquier corporación, sociedad, sociedad de riesgo conjunto, asociación u otra entidad en la cual la Corporación posee con beneficio (directa o indirectamente) el cincuenta por ciento o más de las acciones con voto, poderes de voto o intereses de voto similares vigentes se considerará un contrato, acuerdo o transacción con la Corporación.



SECCION 9.06. *Efecto obligante.* Ni la alteración, enmienda, cambio o rechazo de alguna de las condiciones de este Artículo 9 ni la adopción de alguna condición inconsistente con cualquier condición de este Artículo 9 eliminará o reducirá el efecto de este Artículo 9 respecto a cualquier materia que ocurra, o cualquier causa de acción, demanda o reclamo que, a no ser por este Artículo 9, pueda acaecer o surgir, antes de tal alteración, enmienda, cambio, rechazo o adopción.

SECCION 9.07. *Artículo 8.* Las condiciones de este Artículo 9 son adicionales a las condiciones del Artículo 8.

EN TESTIMONIO DE LO CUAL, este Certificado de Incorporación Enmendado y vuelto a Redactar, el cual ha sido adoptado de acuerdo con las secciones 242 y 245 de la Ley General de Corporación del Estado de Delaware y por consentimiento escrito de el único accionista de la Corporación de acuerdo con la sección 228 de Ley General de Corporación del Estado de Delaware, ha sido ejecutado este 22 de Julio de 1999.

GENENTECH, INC.
Por: /s/ Stephen G. Juelsgaard
Nombre: Stephen G. Juelsgaard
Título: Vicepresidente
Consejo General y Secretaría



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Apostille

(Convention de La Haye du 5 Octobre 1961)

1. Country: United States of America

This public document:

2. has been signed by Harriet Smith Windsor

3. acting in the capacity of Secretary of State of Delaware

4. bears the seal/stamp of Office of Secretary of State

Certified

5. at Dover, Delaware

6. the twenty-fourth day of May, A.D. 2005

7. by Secretary of State, Delaware Department of State

8. No. 0254032

9. Seal/Stamp:

10. Signature:

Harriet Smith Windsor

Secretary of State



Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "GENENTECH, INC.", FILED IN THIS OFFICE ON THE TENTH DAY OF MAY, A.D. 2001, AT 2:05 O'CLOCK P.M.

2112549

050426506

Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

AUTHENTICATION: 3900386

DATE: 05-24-05



STATE OF DELAWARE
SECRETARY OF STATE
DIVISION OF CORPORATIONS
FILED 02:05 PM 05/10/2001
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S ///STATE/OF/DELAWARE///// V
T ///SECRETARY/OF/STATE///// O
A DIVISION/OF/CORPORATIONS// I
M FILED/02/05/PM/05/10/2001/ D
P ///SRV222225/+/2112549////
BY Sandy Miller

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CERTIFICATE OF AMENDMENT OF AMENDED AND RESTATED CERTIFICATE OF INCORPORATION

Genentech, Inc. a corporation organized and existing under and by virtue of the General Corporation Law of the State of Delaware.

DOES HEREBY CERTIFY:

FIRST: That at a meeting of the Board of Directors of Genentech, Inc. resolutions were duly adopted setting forth a proposed amendment of the Amended and Restated Certificate of Incorporation of said corporation, declaring said amendment to be advisable and calling a meeting of the stockholders of said corporation for consideration thereof. The resolution setting forth the proposed amendment is as follows:

RESOLVED, that the Amended and Restated Certificate of Incorporation of this corporation be amended by changing "Section 4.01(a)" of the Article thereof numbered "4" so that, as amended, said Section of said Article shall be and read as follows:

> "Section 4.01. *Capital Stock.* (a) The Corporation is authorized to issue two classes of stock to be designated, respectively, preferred stock and common stock. The total number of shares which the Corporation is authorized to issue is one billion three hundred million (1,300,000,000) shares. One hundred million (100,000,000) shares shall be designated preferred stock, par value $0.02 per share ("Preferred Stock"). One billion two hundred million (1,200,000,000) shares shall be designated common stock, par value $0.02 per share ("Common Stock"). The Common Stock of the Corporation shall be all of one class."

SECOND: That thereafter, pursuant to resolution of its Board of Directors, the regular meeting of the stockholders of said corporation was duly called and held upon notice in accordance with Section 222 of the General Corporation Law of the State of Delaware at which meeting the necessary number of shares as required by statute were voted in favor of the amendment.

THIRD: That said amendment was duly adopted in accordance with the provisions of Section 242 of the General Corporation Law of the State of Delaware.

FOURTH: That the capital of said corporation shall not be reduced under or by reason of said amendment.

IN WITNESS WHEREOF, said Genentech, Inc. has caused this Certificate of Amendment to be signed by Stephen G. Juelsgaard, an Authorized Officer, this 10th day of May, 2001.

GENENTECH, INC.

By: _____
Name: Stephen G. Juelsgaard
Title: Senior Vice President, General Counsel and Secretary

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TRADUCCION AL ESPAÑOL del Certificado de Enmienda de Genentech, Inc.

APOSTILLA

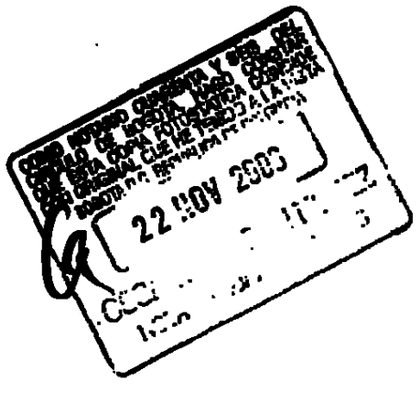
(Convención de La Haya del 5 de Octubre de 1961)

1. País: Estados Unidos de América
   Este documento público
2. ha sido firmado por Harriet Smith Windsor
3. actuando en capacidad de Secretaria de Estado de Delaware
4. lleva el sello/timbre de la Oficina del Secretario de Estado

Certificado

5. en Dover, Delaware
6. el veinticuatro de mayo, A. D. 2005
7. por el Secretario de Estado, Departamento de Estado de Delaware
8. No. 0254032
9. Sello/timbre
10. Firma

Harriet Smith Windsor (Firma)
Secretaria de Estado



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DELAWARE

EL PRIMER ESTADO

YO, HARRIET SMITH WINDSOR, SECRETARIA DE ESTADO DEL ESTADO DE DELAWARE, CERTIFICO POR LA PRESENTE QUE EL ANEXO ES UNA COPIA AUTÉNTICA Y CORRECTA DEL CERTIFICADO DE ENMIENDA DE "GENENTECH, INC", PRESENTADO EN ESTA OFICINA EL DECIMO DIA DE MAYO, A. D. 2001, A LAS 2:05 EN PUNTO DE LA TARDE.

Harriet Smith Windsor (Firma)
Harriet Smith Windsor, Secretaria de Estado
AUTENTIFICACIÓN: 3900386

FECHA: 05 – 24 – 05

CERTIFICADO DE TERCERA ENMIENDA DEL CERTIFICADO DE INCORPORACIÓN CORREGIDO Y VUELTO A REDACTAR

Genentech, Inc. una corporación organizada y existente bajo y por virtud de la Ley General de Corporación del Estado de Delaware.

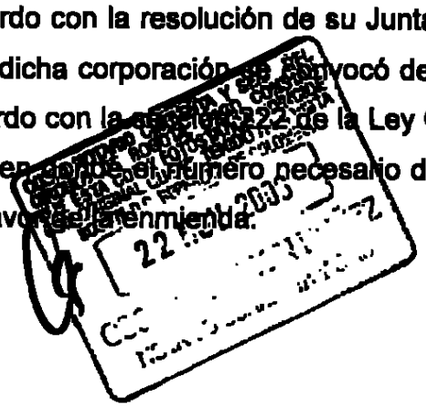
CERTIFICA POR LA PRESENTE:

PRIMERO: Que en una reunión de la Junta Directiva de Genentech, Inc. se adoptaron debidamente resoluciones que establecen una enmienda propuesta del certificado de Incorporación Corregido y vuelto a Redactar de dicha corporación, declarando dicha enmienda como aconsejable y llamando a una reunión de accionistas de dicha corporación para consideración de la misma. La resolución establece la enmienda propuesta de la siguiente manera:

RESUELVE, que el Certificado de Incorporación Corregido y vuelto a Redactar de esta corporación se enmiende cambiando "la Sección 4.01(a)" del Artículo allí numerado "4" tal que, como se enmienda, dicha Sección de dicho Artículo se lea de la siguiente manera:

> SECCION 4.01. *Acciones de Capital.* (a) la Corporación está autorizada a emitir dos clases de acciones que deben designarse, respectivamente, acciones preferenciales y acciones comunes. El número total de acciones que la Corporación esta autorizada a emitir es de mil trescientos millones (1,300,000,000) de acciones. Cien millones (100,000,000) de acciones serán designadas acciones preferenciales, por un valor de $0.02 por acción ("**Acción Preferencial**"). Mil doscientos millones (1,200,000,000) de acciones serán designadas acciones comunes, por un valor de $0.02 por acción ("**Acción Común**"). La acción común de la Corporación será toda de una misma clase.

SEGUNDO: Que por lo tanto, de acuerdo con la resolución de su Junta Directiva, la reunión ordinaria de accionistas de dicha corporación se convocó debidamente y se sostuvo al ser anunciada de acuerdo con la sección 222 de la Ley General de Corporación del Estado de Delaware, en donde el número necesario de acciones requerido por los estatutos votaron a favor de la enmienda.



TERCERO: Que dicha enmienda se adoptó debidamente de acuerdo con lo previsto en la Sección 242 de la Ley General de Corporación del Estado de Delaware.

CUARTO: Que el capital de dicha corporación no será reducido bajo o por razón de dicha enmienda

EN TESTIMONIO DE LO CUAL, dicha Genentech, Inc. ha causado este Certificado de Enmienda para que sea firmado por Stephen G. Juelsgaard, un Funcionario Autorizado, este 10 de Mayo de 2001.

GENENTECH, INC.

Por: (Firma)
Nombre: Stephen G. Juelsgaard
Título: Vicepresidente, Consejo
y Secretaría General.



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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-129467- -00000-0000
Fec: 2006-12-27 16:41:42 Dep: 2020 NUEGREACIONES
Tra: 11 PATENTEYM
Fre: 378 FASENACIONALI
Act 411 PRESENTACION Folios: 324

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [4] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [1]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [1]
- Descripción de la invención [1]
- Dibujos de ser estos pertinentes [1]
- Comprobante de pago de las tasas establecidas [1]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha 27 DIC. 2006

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

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REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
GENENTECH INC

REFERENCIA	Radicación No.	06 129487
	Solicitud internacional	PCT/US2005/023564
	Fecha inicio fase nacional	02/02/2007
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	1931

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 09 FEB. 2007
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