(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 August 2008 (21.08.2008)

PCT

(10) International Publication Number
WO 2008/100448 A3

(51) International Patent Classification:
A61K 31/435 (2006.01)

(21) International Application Number:
PCT/US2008/001748

(22) International Filing Date: 8 February 2008 (08.02.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/901,609 13 February 2007 (13.02.2007) US

(71) Applicant *(for all designated States except US)*: **SAPPHIRE THERAPEUTICS, INC.** [—/US]; 1160 U.S. Highway 22, Suite 104, Bridgewater, NJ 08807 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **POLVINO, Williams, J.** [US/US]; 10 Churchill Downs, Tinton Falls, NJ 07724 (US).

(74) Agents: **SPARKS, Jonathan, M.** et al.; Edwards Angell Palmer & Dodge LLP, P.O. Box 55874, Boston, MA 02205 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
23 October 2008

(54) Title: METHOD OF TREATING CELL PROLIFERATIVE DISORDERS USING GROWTH HORMONE SECRETAGOGUES

(57) Abstract: The present invention relates to a method of treating cell proliferative disorders by administering to a subject an effective amount of a growth hormone secretagogue compound or a pharmaceutically acceptable salt, hydrate or solvate thereof.

WO 2008/100448 A3

METHOD OF TREATING CELL PROLIFERATIVE DISORDERS USING GROWTH HORMONE SECRETAGOGUES

RELATED APPLICATIONS

This application claims the benefit of United States provisional patent application number 60/901,609, filed February 13, 2007. The entire contents of the aforementioned application are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

[0001] Cancer is a leading cause of death in developed countries. Despite continuing advances in both diagnosis and treatment regimens, most existing treatments have undesirable side effects and limited efficacy. Progress in this field has been hindered because a number of different cellular events contribute to the formation of tumors, and many of these events are still not well understood. Chemotherapy is one of the major options available for the treatment of cancers. However, effective chemotherapeutic agents are still needed to treat the increasing numbers of subjects developing cancer.

[0002] Insulin-like growth factor binding protein-3 (IGFBP-3) is the major circulating carrier protein for IGFs and is also active in the cellular environment as a potent antiproliferative agent (Baxter, R.C. (2001) Mol Pathol. 54(3):145–148). Accordingly, therapeutics that are able to differentially increase the levels of IGFBP-3 would be valuable anticancer agents.

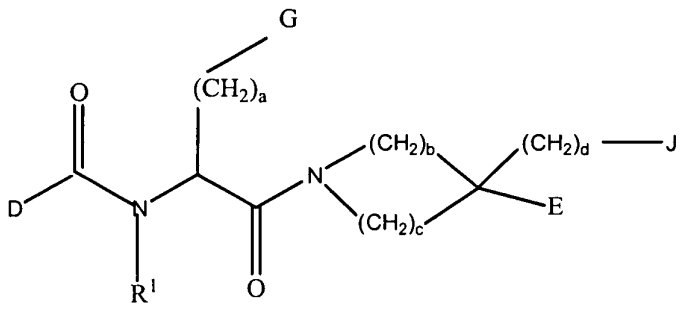
[0003] In view of the above, an effective treatment of cell proliferative disorders, e.g., cancer, is highly desirable.

SUMMARY OF THE INVENTION

[0004] The present invention relates to methods of treating subjects having cell proliferative disorders, e.g., cancer. The methods comprise administering to a subject in need thereof a therapeutically effective amount of a growth hormone secretagogue compound or a pharmaceutically acceptable salt, hydrate or solvate thereof.

[0005] The invention provides a method for treating a cell proliferative disorder in a subject in need thereof, by administering to the subject an effective amount of a growth hormone secretagogue. The invention also provides methods for treating a subject having cancer cachexia by administering to the subject an effective amount of a growth hormone secretagogue. Exemplary growth hormone secretagogues are represented by Formulas I-V, or a pharmaceutically acceptable salt, hydrate, amides or solvate thereof.

[0006] One growth hormone secretagogue is represented by the structural Formula I:



I

wherein:

R^1 is hydrogen, or C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl;

a and d are independently 0, 1, 2 or 3;

b and c are independently 0, 1, 2, 3, 4 or 5, provided that b+c is 3, 4 or 5;

D is R^2 —NH—$(CR^3 R^4)_e$ —$(CH_2)_f$—M—$(CHR^5)_g$—$(CH_2)_h$ —

wherein:

R^2, R^3, R^4 and R^5 are independently hydrogen or C_{1-6} alkyl optionally substituted with one or more halogen, amino, hydroxyl, aryl or hetaryl; or

R^2 and R^3 or R^2 and R^4 or R^3 and R^4 can optionally form —$(CH_2)_i$ —U—$(CH_2)_j$ —, wherein i and j are independently 1 or 2 and U is —O—, —S— or a valence bond;

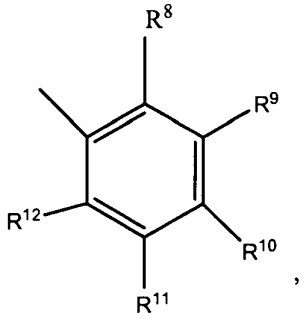
h and f are independently 0, 1, 2, or 3;

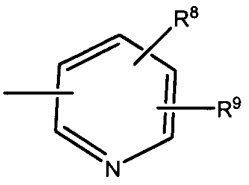
g and e are independently 0 or 1;

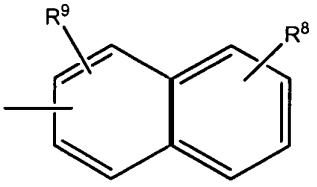
M is a valence bond, —CR^6==CR^7 —, arylene, hetarylene, —O— or —S—;

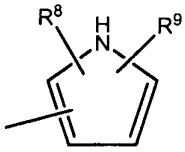
R^6 and R^7 are independently hydrogen, or C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl;

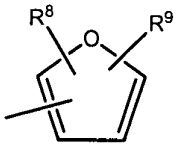
G is —O—$(CH_2)_k$—R^8,

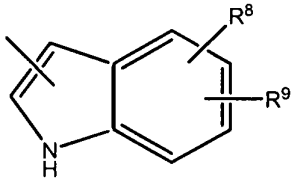


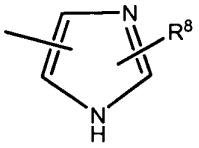
,


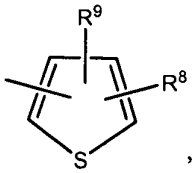
,


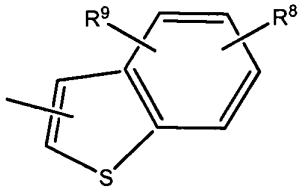
,


,


,


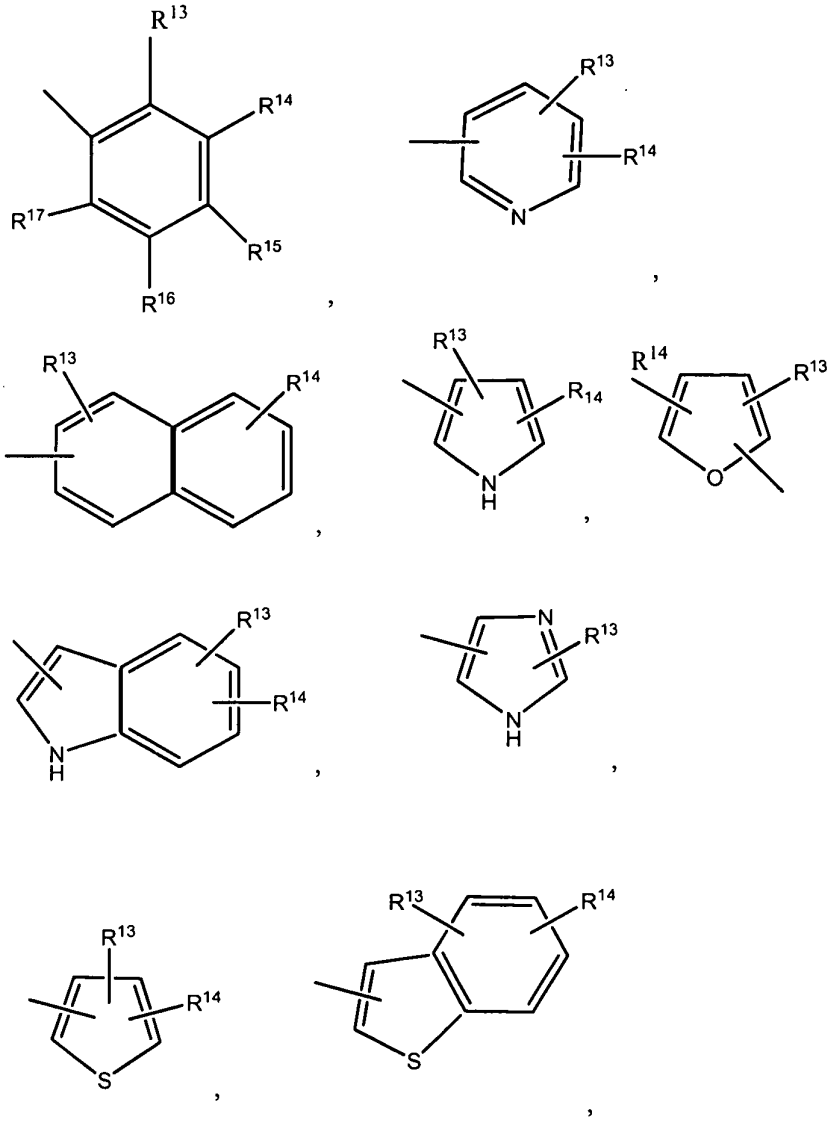
,


,


,


;

J is —O—$(CH_2)_l$—R^{13},



wherein:

R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} independently are hydrogen, halogen, aryl, hetaryl, C_{1-6} -alkyl or C_{1-6} -alkoxy;

k and l are independently 0, 1 or 2;

E is —$CONR^{18}$ R^{19}, —$COOR^{19}$, —$(CH_2)_m$ —NR^{18} SO_2 R^{20}, —$(CH_2)_m$ —NR^{18} — COR^{20}, —$(CH_2)_m$ —OR^{19}, —$(CH_2)_m$ —$OCOR^{20}$, —$CH(R^{18})R^{19}$, —$(CH_2)_m$ —NR^{18} —CS—NR^{19} R^{21} or —$(CH_2)_m$ —NR^{18} —CO—NR^{19} R^{21} ; or

E is —$CONR^{22}$ NR^{23} R^{24}, wherein R^{22} is hydrogen, C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl, or aryl or hetaryl optionally substituted with one or more C_{1-6} -alkyl; R^{23} is C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl, or C_{1-7} -acyl; and R^{24} is hydrogen, C_{1-6} -alkyl optionally substituted

with one or more aryl or hetaryl; or aryl or hetaryl optionally substituted with one or more C_{1-6} -alkyl; or

R^{22} and R^{23} together with the nitrogen atoms to which they are attached can form a heterocyclic system optionally substituted with one or more C_{1-6} -alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

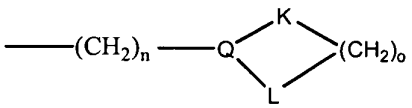
R^{22} and R^{24} together with the nitrogen atoms to which they are attached can form a heterocyclic system optionally substituted with one or more C_{1-6} -alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

R^{23} and R^{24} together with the nitrogen atom to which they are attached can form a heterocyclic system optionally substituted with one or more C_{1-6} -alkyl, halogen, amino, hydroxyl, aryl or hetaryl;

wherein m is 0, 1, 2 or 3,

R^{18}, R^{19} and R^{21} independently are hydrogen or C_{1-6} -alkyl optionally substituted with halogen, —$N(R^{25})R^{26}$, wherein R^{25} and R^{26} are independently hydrogen or C_{1-6} alkyl; hydroxyl, C_{1-6} -alkoxy, C_{1-6} -alkoxycarbonyl, C_{1-6} -alkylcarbonyloxy or aryl;

or R^{19} is



wherein

Q is —CH< or —N<,

K and L are independently —CH_2 —, —CO—, —O—, —S—, —NR^{27} — or a valence bond, where R^{27} is hydrogen or C_{1-6} alkyl;

n and o are independently 0, 1, 2, 3 or 4;

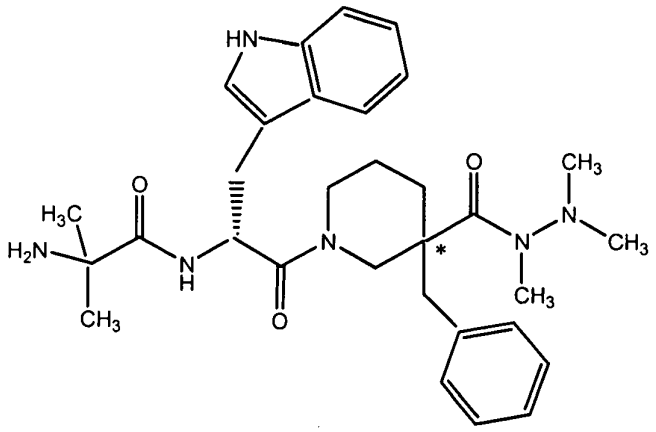
R^{20} is C_{1-6} alkyl, aryl or hetaryl;

or a pharmaceutically acceptable salt thereof;

with the proviso that if M is a valence bond then E is —$CONR^{22}$ NR^{23} R^{24}.

[0007] The compounds of Formula I are fully described in U.S. Patent No. 6,303,620 to Hansen, *et al.*, the entire content of which is hereby incorporated by reference.

[0008] One growth hormone secretagogue of Formula I is more specifically represented by the structural Formula II:

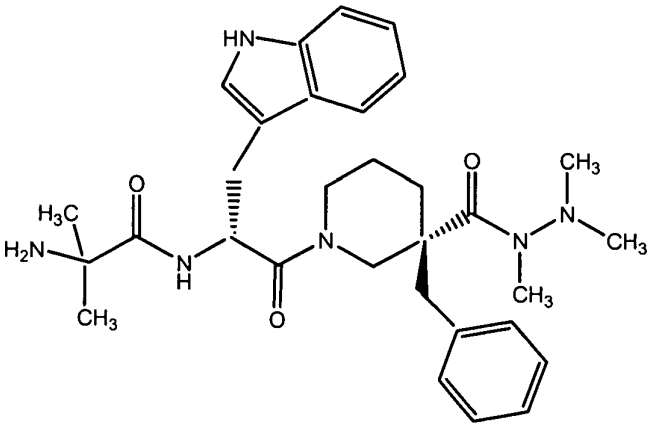


II

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0009] The compounds of Formula II are fully described in U.S. Patent No. 6,303,620 to Hansen, *et al.*, the entire content of which is hereby incorporated by reference.

[0010] Another growth hormone secretagogue is represented by the structural Formula III:



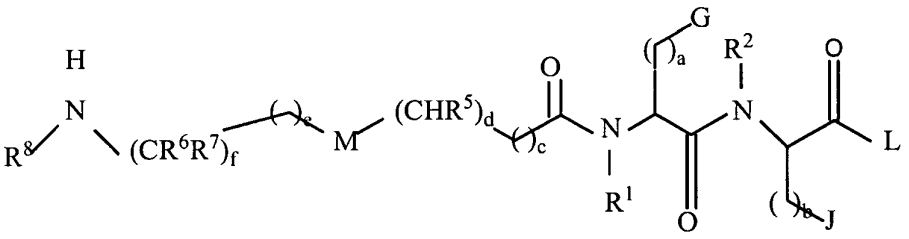
III

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0011] The compound of Formula III is fully described in U.S. Patent No. 6,576,648 to Hansen, *et al.*, the entire content of which is hereby incorporated by reference. The chemical name of the compound of Formula III is 2-Amino-N-{(1R)- 2-[3-benzyl- 3-(N,N',N'-trimethylhydrazinocarbonyl)piperidin-1 -yl]-1-((1H-indol-3-yl)- 2-oxoethyl}-2-methylpropionamide, and is referred to as RC-1291 and anamorelin.

[0012] Another growth hormone secretagogue is represented by the structural Formula IV:

IV

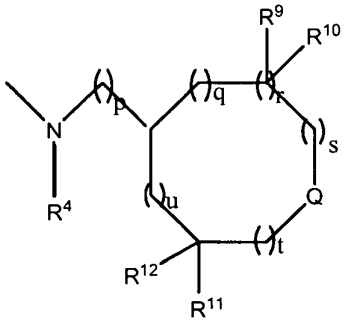


wherein

R^1 is hydrogen or C_{1-6}-alkyl;

R^2 is hydrogen or C_{1-6}-alkyl;

L is



wherein

R^4 is hydrogen or C_{1-6} alkyl;

p is 0 or 1;

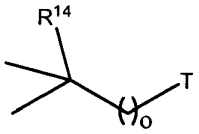
q, s, t, u are independently 0, 1, 2, 3, or 4;

r is 1;

the sum q + r + s + t + u is 0, 1, 2, 3, or 4;

R^9, R^{10}, R^{11}, and R^{12} are independently hydrogen or C_{1-6} alkyl;

Q is > N-R^{13} or



wherein:

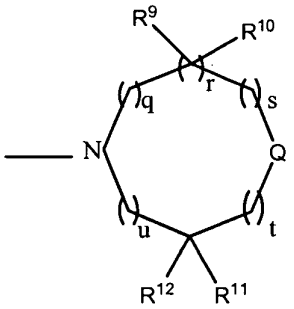
o is 0, 1 or 2;

T is $-N(R^{15})(R^{16})$ or hydroxyl;

R^{13}, R^{15}, and R^{16} are independently hydrogen or C_{1-6} alkyl;

R^{14} is hydrogen, aryl or hetaryl;

Or L is



wherein

p is 0 or 1;

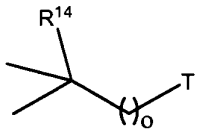
q, s, t, u are independently 0, 1, 2, 3, or 4;

r is 0 or 1;

the sum q + r + s + t + u is 0, 1, 2, 3, or 4;

R^9, R^{10}, R^{11}, and R^{12} are independently hydrogen or C_{1-6} alkyl;

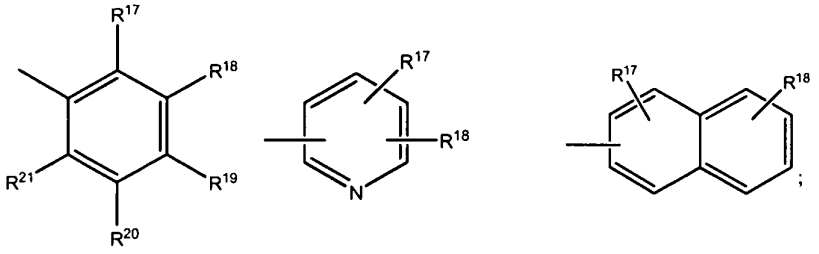
Q is $>N-R^{13}$ or



wherein

o is 0, 1, or 2;

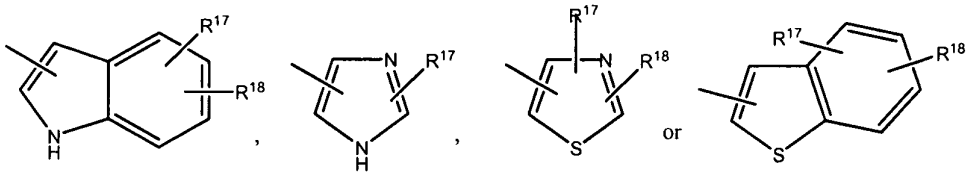
T is $-N(R^{15})(R^{16})$ or hydroxyl;



R^{13}, R^{15}, and R^{16} are independently from each other hydrogen or C_{1-6} alkyl;

R^{14} is hydrogen, aryl, or hetaryl;

G is $-O-(CH_2)-R^{17}$,

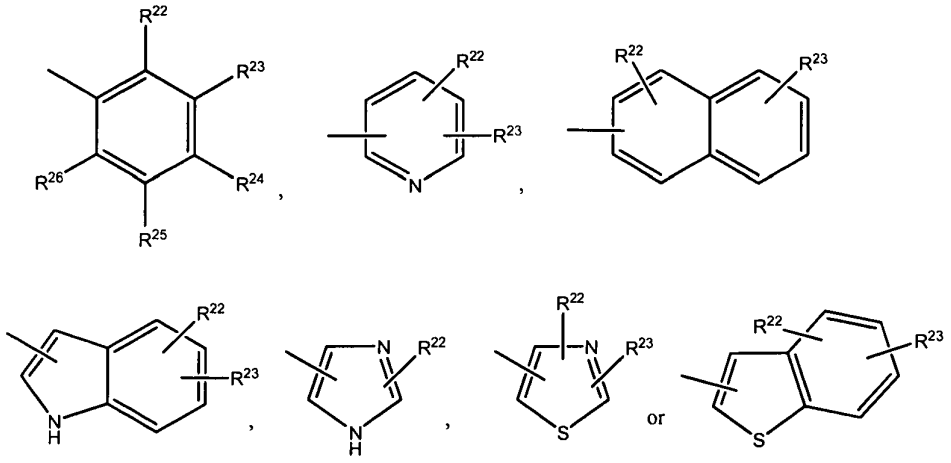


wherein:

R^{17}, R^{18}, R^{19}, R^{20} and R^{21} independently are hydrogen, halogen, aryl, hetaryl, C_{1-6}-alkyl or C_{1-6}-alkoxy;

K is 0, 1 or 2;

J is $-O-(CH_2)_l-R^{22}$,



wherein:

R^{22}, R^{23}, R^{24}, R^{25} and R^{26} independently are hydrogen, halogen, aryl, hetaryl, C_{1-6}-alkyl or C_{1-6}-alkoxy;

l is 0, 1 or 2;

a is 0, 1, or 2;

b is 0, 1, or 2;

c is 0, 1, or 2;

d is 0 or 1;

e is 0, 1, 2, or 3;

f is 0 or 1;

R^5 is hydrogen or C_{1-6}-alkyl optionally substituted with one or more hydroxyl, aryl or hetaryl;

R^6 and R^7 are independently hydrogen or C_{1-6}-alkyl, optionally substituted with one or more halogen, amino, hydroxyl, aryl, or hetaryl;

R^8 is hydrogen or C_{1-6}-alkyl, optionally substituted with one or more halogen, amino, hydroxyl, aryl, or hetaryl;

R^6 and R^7 or R^6 and R^8 or R^7 and R^8 can optionally form $-(CH_2)_i-U-(CH_2)_j-$, wherein i and j independently are 1, 2 or 3 and U is -O-, -S-, or a valence bond;

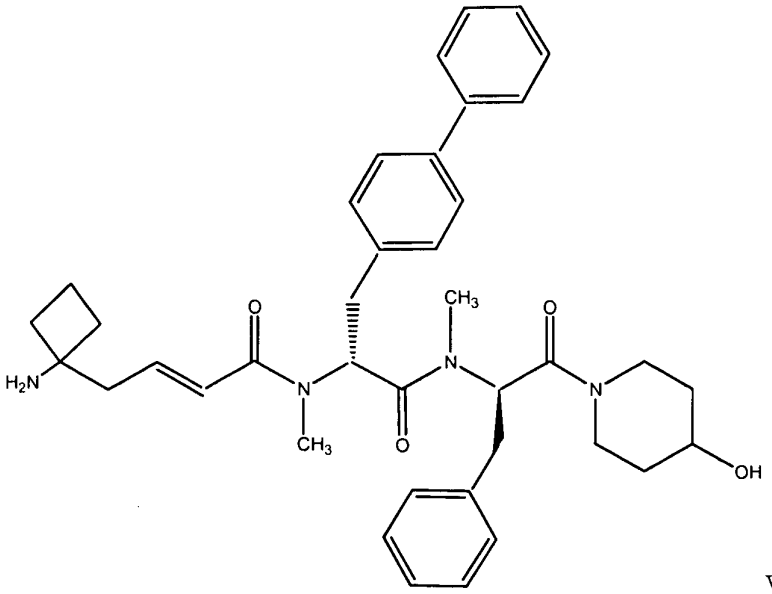
M is arylene, hetarylene, -O-, -S- or-$CR^{27}=CR^{28}$-;

R^{27} and R^{28} are independently hydrogen or C_{1-6}-alkyl, optionally substituted with one or more aryl or hetaryl;

or a pharmaceutically acceptable salt thereof.

[0013] The compounds of Formula IV are fully described in U.S. Patent No. 6,919,315 to Peschke, *et al.*, the entire content of which is hereby incorporated by reference.

[0014] Another growth hormone secretagogue of Formula IV is more specifically represented by the structural Formula VI:



VI

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0015] The chemical name of the compound of Formula VI is: (2E)-4-(1-aminocyclobutyl)but-2-enoic acid N-((1R)-1-{N-[(1R)-1-benzyl-2-(4-hydroxypiperidin-1-yl)-2-oxoethyl]-N-methylcarbomoyl}-2-(biphenyl-4-yl)ethyl)-N-methylamide.

[0016] The compound of Formula VI is fully described in U.S. Patent No. 6,919,315 to Peschke, *et al.*, the entire content of which is hereby incorporated by reference.

[0017] The invention further provides kits and pharmaceutical compositions comprising the growth hormone secretagogues of the invention for the treatment of cell proliferative disorders, e.g., cancer. The kits and pharmaceutical compositions may further comprise one or more additional anti-cancer agents.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] FIG. 1 depicts the results of a twelve week study indicating administration of the growth hormone secretagogue of Formula III results in significantly increased levels of IGFBP-3 and IGF-1.

[0019] FIG. 2 depicts the results of a study demonstrating the increase in levels of IGF-1 in subjects administered RC-1291 as compared to a placebo.

[0020] FIG. 3 depicts the results of a study demonstrating the increase in levels of IGFBP-3 in subjects administered RC-1291 as compared to a placebo.

[0021] Figure 4 sets forth Table 4, a summary of IGF-1 baseline levels and levels at day 7.

[0022] Figure 5 sets forth Table 5, a summary of IGF-1 levels for day 14 and week 4.

[0023] Figure 6 sets forth Table 6, a summary of IGF-1 levels at weeks 4, 8 and 12.

[0024] Figure 7 sets forth Table 7, a summary of IGFBP-3 baseline levels and levels at day 7.

[0025] Figure 8 sets forth Table 8, a summary of IGFBP-3 levels for day 14 and week 4.

[0026] Figure 9 sets forth Table 9, a summary of IGFBP-3 levels at weeks 4, 8 and 12.

[0027] Figure 10 depicts the change in total body mass for subjects administered RC-1291 and a placebo.

[0028] Figure 11 depicts the change in lean body mass for subjects administered RC-1291 and a placebo.

[0029] Figure 12 depicts the change in body weight for subjects administered 50 and 100mg dosages of RC-1291 and a placebo.

[0030] The foregoing and other objects, features and advantages of the invention will be apparent from the following more particular description of preferred embodiments of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0031] The present invention relates to methods of treating subjects having cell proliferative disorders, e.g., cancer. The methods comprise administering to a subject in need thereof a therapeutically effective amount of a growth hormone secretagogue compound or a pharmaceutically acceptable salt, hydrate or solvate thereof. The growth hormone secretagogue is a compound represented by any of Formulas I - XVI, or a pharmaceutically acceptable salt, hydrate, amine or solvate thereof.

[0032] The invention also provides methods of treating cell proliferative disorders by administering a therapeutically effective amount of a growth hormone secretagogue compound or a pharmaceutically acceptable salt, hydrate or solvate thereof, further comprise administering one or more additional anticancer agents. The additional anticancer agent or agents may be selected from, but not limited to, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cisplatin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dactinomycin; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin

hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofosine; interleukin II (including recombinant interleukin II, or rIL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-I a; interferon gamma-I b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine, mechlorethamine oxide hydrochloride rethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; paclitaxel; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, improsulfan, benzodepa, carboquone, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, trimethylolomelamine, chlornaphazine, novembichin, phenesterine, trofosfamide, estermustine, chlorozotocin, gemzar, nimustine, ranimustine, dacarbazine, mannomustine, mitobronitol,aclacinomycins, actinomycin F(1), azaserine, bleomycin, carubicin, carzinophilin, chromomycin, daunorubicin, daunomycin, 6-diazo-5-oxo-1-

norleucine, doxorubicin, olivomycin, plicamycin, porfiromycin, puromycin, tubercidin, zorubicin, denopterin, pteropterin, 6-mercaptopurine, ancitabine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, enocitabine, pulmozyme, aceglatone, aldophosphamide glycoside, bestrabucil, defofamide, demecolcine, elfornithine, elliptinium acetate, etoglucid, flutamide, hydroxyurea, lentinan, phenamet, podophyllinic acid, 2-ethylhydrazide, razoxane, spirogermanium, tamoxifen, taxotere, tenuazonic acid, triaziquone, 2,2',2"-trichlorotriethylamine, urethan, vinblastine, vincristine, vindesine and related agents. 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlns; chloroquinoxaline sulfonamide; cicaprost; cisporphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur;

epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; taxel; taxel analogues; taxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin;

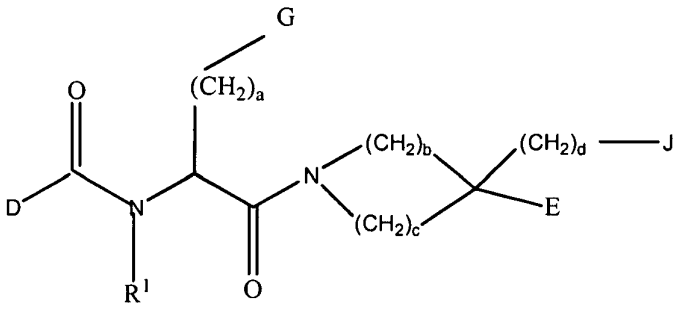
pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer. Additional cancer therapeutics include monoclonal antibodies such as rituximab, trastuzumab and cetuximab.

[0033] GROWTH HORMONE SECRETAGOGUES/GHRELIN AGONISTS

[0034] As used herein, "growth hormone secretagogue" refers to a substance (e.g., a molecule, a compound) which promotes (induces or enhances) at least one function characteristic of a growth hormone secretagogue receptor (GHS receptor). Exemplary growth hormones secretagogues are ghrelins mimetics such as ghrelin agonists. In one embodiment, the growth hormone secretagogue compound or ghrelin agonist binds the GHS receptor or ghrelin receptor (i.e., is a ghrelin or GHS receptor agonist) and induces the secretion of growth hormone. A compound having GHS receptor agonist activity (e.g., a GHS receptor or ghrelin receptor agonist) can be identified and activity assessed by any suitable method. For example, the binding affinity of a GHS receptor agonist to the GHS receptor can be determined employing receptor binding assays and growth hormone stimulation can be assessed as described in U.S. Patent No. 6,919,315, incorporated herein by reference.

[0035] GHS receptors and ghrelin receptors are expressed in the hypothalamus, pituitary and pancreas, among other tissues. Activation of these receptors in the pituitary induces the secretion of growth hormone. In addition to inducing the secretion of growth hormone, recent studies have shown the growth hormone secretagogues can increase appetite and body weight. At typical doses, growth hormone secretagogues are also known to induce the secretion of IGF-1. Exemplary growth hormone secretagogue compounds are those described in U.S. Patent Nos. 6,303,620, 6,576,648, 5,977,178, 6,566,337, 6,083,908, 6,274,584 and U.S. Patent No. 6,919,315, the entire content of all of which are incorporated herein by reference.

[0036] Another the growth hormone secretagogue is represented by the structural Formula I:



I

wherein:

R^1 is hydrogen, or C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl;

a and d are independently 0, 1, 2 or 3;

b and c are independently 0, 1, 2, 3, 4 or 5, provided that b+c is 3, 4 or 5;

D is R^2 —NH—$(CR^3\ R^4)_e$ —$(CH_2)_f$—M—$(CHR^5)_g$—$(CH_2)_h$ —

wherein:

R^2, R^3, R^4 and R^5 are independently hydrogen or C_{1-6} alkyl optionally substituted with one or more halogen, amino, hydroxyl, aryl or hetaryl; or

R^2 and R^3 or R^2 and R^4 or R^3 and R^4 can optionally form

—$(CH_2)_i$ —U—$(CH_2)_j$ —, wherein i and j are independently 1 or 2 and U is —O—, —S— or a valence bond;

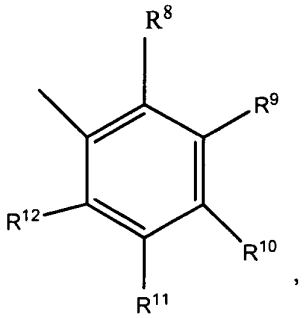
h and f are independently 0, 1, 2, or 3;

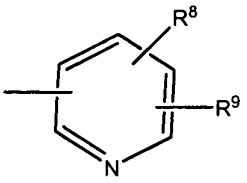
g and e are independently 0 or 1;

M is a valence bond, —CR^6==CR^7 —, arylene, hetarylene, —O— or —S—;

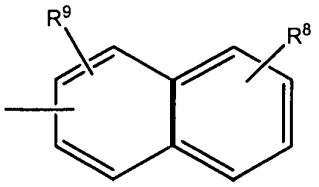
R^6 and R^7 are independently hydrogen, or C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl;

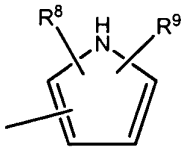
G is —O—$(CH_2)_k$—R^8,

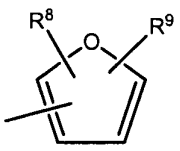


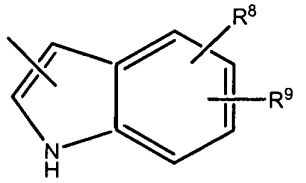
,


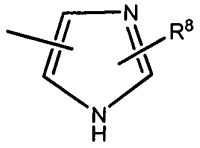
,



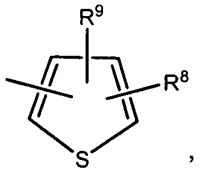
,


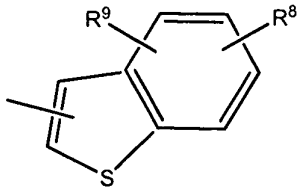
,




,


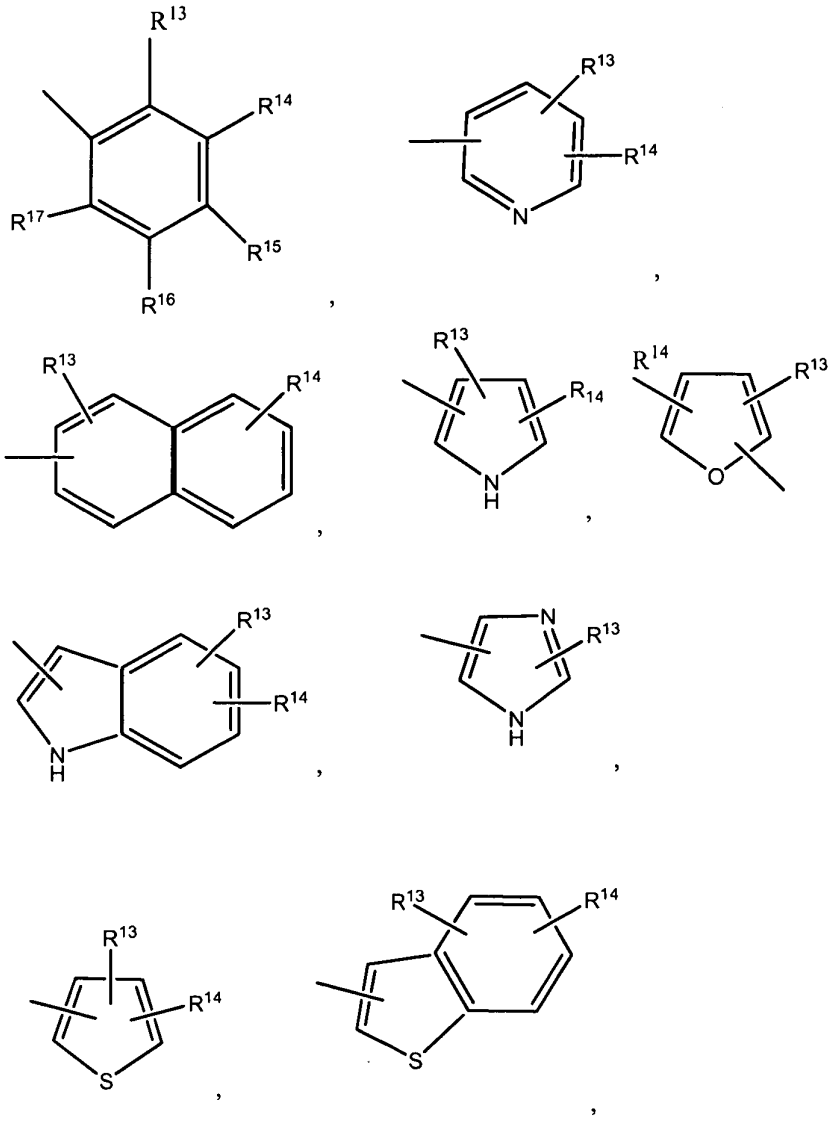
,



,


;

J is —O—$(CH_2)_t$—R^{13},



wherein:

R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} independently are hydrogen, halogen, aryl, hetaryl, C_{1-6} -alkyl or C_{1-6} -alkoxy;

k and l are independently 0, 1 or 2;

E is —$CONR^{18}$ R^{19}, —$COOR^{19}$, —$(CH_2)_m$ —NR^{18} SO_2 R^{20}, —$(CH_2)_m$ —NR^{18} — COR^{20}, —$(CH_2)_m$ —OR^{19}, —$(CH_2)_m$ —$OCOR^{20}$, —$CH(R^{18})R^{19}$, —$(CH_2)_m$ —NR^{18} —CS—NR^{19} R^{21} or —$(CH_2)_m$ —NR^{18} —CO—NR^{19} R^{21} ; or

E is —$CONR^{22}$ NR^{23} R^{24}, wherein R^{22} is hydrogen, C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl, or aryl or hetaryl optionally substituted with one or more C_{1-6} -alkyl; R^{23} is C_{1-6} -alkyl optionally substituted with one or more

aryl or hetaryl, or C_{1-7} -acyl; and R^{24} is hydrogen, C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl; or aryl or hetaryl optionally substituted with one or more C_{1-6} -alkyl; or

R^{22} and R^{23} together with the nitrogen atoms to which they are attached can form a heterocyclic system optionally substituted with one or more C_{1-6} -alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

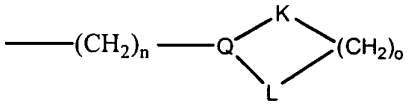
R^{22} and R^{24} together with the nitrogen atoms to which they are attached can form a heterocyclic system optionally substituted with one or more C_{1-6} -alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

R^{23} and R^{24} together with the nitrogen atom to which they are attached can form a heterocyclic system optionally substituted with one or more C_{1-6} -alkyl, halogen, amino, hydroxyl, aryl or hetaryl;

wherein m is 0, 1, 2 or 3,

R^{18}, R^{19} and R^{21} independently are hydrogen or C_{1-6} -alkyl optionally substituted with halogen, —$N(R^{25})R^{26}$, wherein R^{25} and R^{26} are independently hydrogen or C_{1-6} alkyl; hydroxyl, C_{1-6} -alkoxy, C_{1-6} -alkoxycarbonyl, C_{1-6} -alkylcarbonyloxy or aryl;

or R^{19} is



wherein

Q is —CH< or —N<,

K and L are independently —CH_2 —, —CO—, —O—, —S—, —NR^{27} — or a valence bond, where R^{27} is hydrogen or C_{1-6} alkyl;

n and o are independently 0, 1, 2, 3 or 4;

R^{20} is C_{1-6} alkyl, aryl or hetaryl;

or a pharmaceutically acceptable salt thereof;

with the proviso that if M is a valence bond then E is —$CONR^{22}$ NR^{23} R^{24}.

[0037] R^1 may be C_{1-6} -alkyl. a may be 1.

[0038] d may be 1, or, b+c is 4.

[0039] D is

$$R^2 —NH —(CR^3 R^4)_e —(CH_2)_f —M—(CHR^5)_g —(CH_2)_h —$$

wherein

R^2, R^3, R^4 and R^5 are independently hydrogen or C_{1-6} alkyl optionally substituted with a halogen, amino, hydroxyl, aryl or hetaryl; or

R^2 and R^3 or R^2 and R^4 or R^3 and R^4 can optionally form $—(CH_2)_i —U—(CH_2)_j —$, wherein i and j are independently 1 or 2 and U is —O—, —S— or a valence bond;

h and f are independently 0, 1, 2, or 3;

g and e are independently 0 or 1;

M is $—CR^6=CR^7 —$, arylene, hetarylene, —O— or —S—; and

R^6 and R^7 are independently hydrogen, or C_{1-6} -alkyl.

[0040] In a further embodiment, D is

$$R^2 —NH—(CR^3 R^4)_e —(CH_2)_f —M—(CHR^5)_g —(CH_2)_h —$$

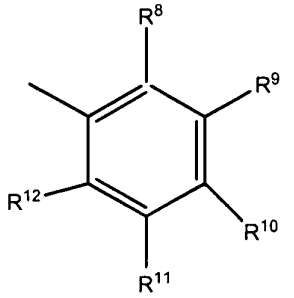
wherein:

R^2, R^3, R^4 and R^5 are independently hydrogen or C_{1-6} alkyl optionally substituted with a halogen, amino, hydroxyl, aryl or hetaryl; or

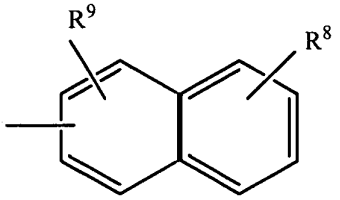
R^2 and R^3 or R^2 and R^4 or R^3 and R^4 can optionally form $—(CH_2)_i —U—(CH_2)_j —$, wherein i and j are independently 1 or 2 and U is —O—, —S— or a valence bond;

h and f are independently 0, 1, 2, or 3; g and e are independently 0 or 1; M is a valence bond.

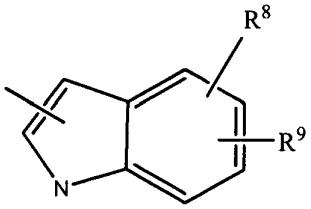
[0041] G may be



,



or

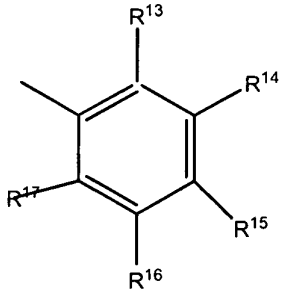


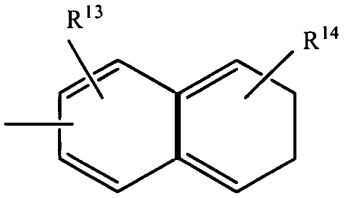
,

wherein:

R^8, R^9, R^{10}, R^{11} and R^{12} independently are hydrogen, halogen, aryl, hetaryl, C_{1-6} -alkyl or C_{1-6} alkoxy; and k is 0, or 2.

[0042] J may be





wherein:

R^{13}, R^{14}, R^{15} R^{16} and R^{17} independently are hydrogen, halogen, aryl, hetaryl, C_{1-6} -alkyl or C_{1-6} -alkoxy.

[0043] E may be —$CONR^{18}$ R^{19}, —$COOR^{19}$ or —$(CH_2)_m$ —OR^{19}, wherein:

m is 0, 1, 2 or 3;

R^{18} and R^{19} independently are hydrogen or C_{1-6} -alkyl optionally substituted by halogen, —$N(R^{25})R^{26}$ wherein R^{25} and R^{26} are independently hydrogen or C_{1-6} alkyl; hydroxyl, C_{1-6} -alkoxy, C_{1-6} -alkoxycarbonyl, C_{1-6} -alkylcarbonyloxy or aryl.

[0044] E may also be —$CONR^{22}$ NR^{23} R^{24}

wherein:

R^{22} is hydrogen, C_{1-6} -alkyl optionally substituted with an aryl or hetaryl, or aryl or hetaryl optionally substituted with a C_{1-6} -alkyl;

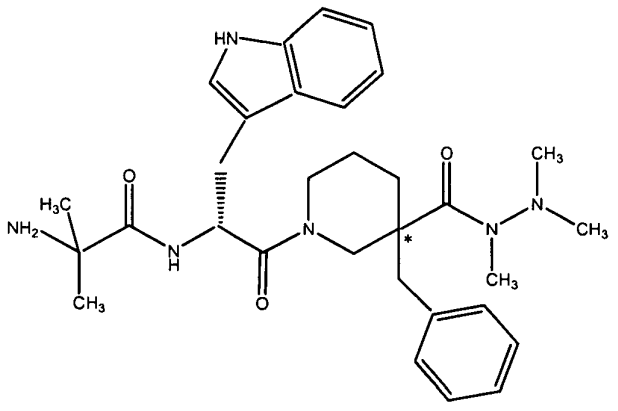
R^{23} is C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl, or C_{1-7} -acyl; and

R^{24} is hydrogen, C_{1-6} -alkyl optionally substituted with an aryl or hetaryl; or aryl or hetaryl optionally substituted with a C_{1-6} -alkyl; or

R^{22} and R^{23} together with the nitrogen atoms to which they are attached can form a heterocyclic system optionally substituted with a C_{1-6} -alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or R^{22} and R^{24} together with the nitrogen atoms to which they are attached can form a heterocyclic system optionally substituted with a C_{1-6} -alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

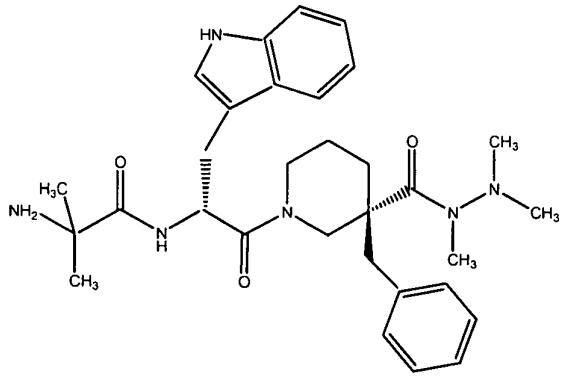
R^{23} and R^{24} together with the nitrogen atom to which they are attached can form a heterocyclic system optionally substituted with a C_{1-6} -alkyl, halogen, amino, hydroxyl, aryl or hetaryl.

[0045] Another growth hormone secretagogue is represented by the structural Formula II:



II

[0046] One exemplary compound of Formula II has the (R) configuration at the chiral carbon designated by the asterisk (*) in Formula II. The chemical name of the compound of Formula II having the (R) configuration at the designated chiral carbon is: 2-Amino-N-{(1R)-2-[3-benzyl-3- (N,N',N'-trimethylhydrazinocarbonyl)piperidin-1 -yl]-1- ((1H-indol-3-yl)-2-oxoethyl}-2-methylpropionamide, represented by structural Formula III:

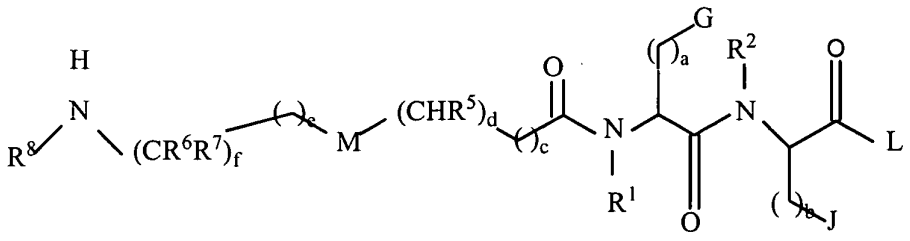


III

and pharmaceutically acceptable salts thereof.

[0047] Another growth hormone secretagogue is represented by the structural Formula IV:

IV

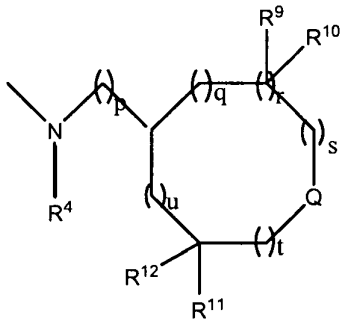


wherein

R^1 is hydrogen or C_{1-6}-alkyl;

R^2 is hydrogen or C_{1-6}-alkyl;

L is



wherein

R^4 is hydrogen or C_{1-6} alkyl;

p is 0 or 1;

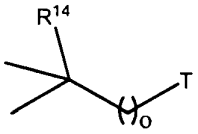
q, s, t, u are independently 0, 1, 2, 3, or 4;

r is 1;

the sum q + r + s + t + u is 0, 1, 2, 3, or 4;

R^9, R^{10}, R^{11}, and R^{12} are independently hydrogen or C_{1-6} alkyl;

Q is > N-R^{13} or



wherein:

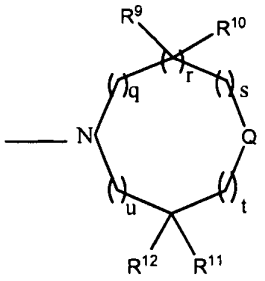
o is 0, 1 or 2;

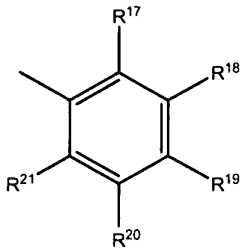
T is -N(R^{15})(R^{16}) or hydroxyl;

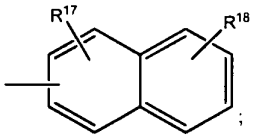
R^{13}, R^{15}, and R^{16} are independently hydrogen or C_{1-6} alkyl;

R^{14} is hydrogen, aryl or hetaryl;

Or L is







wherein

p is 0 or 1;

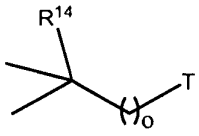
q, s, t, u are independently 0, 1, 2, 3, or 4;

r is 0 or 1;

the sum q + r + s + t + u is 0, 1, 2, 3, or 4;

R^9, R^{10}, R^{11}, and R^{12} are independently hydrogen or C_{1-6} alkyl;

Q is >N-R^{13} or



wherein

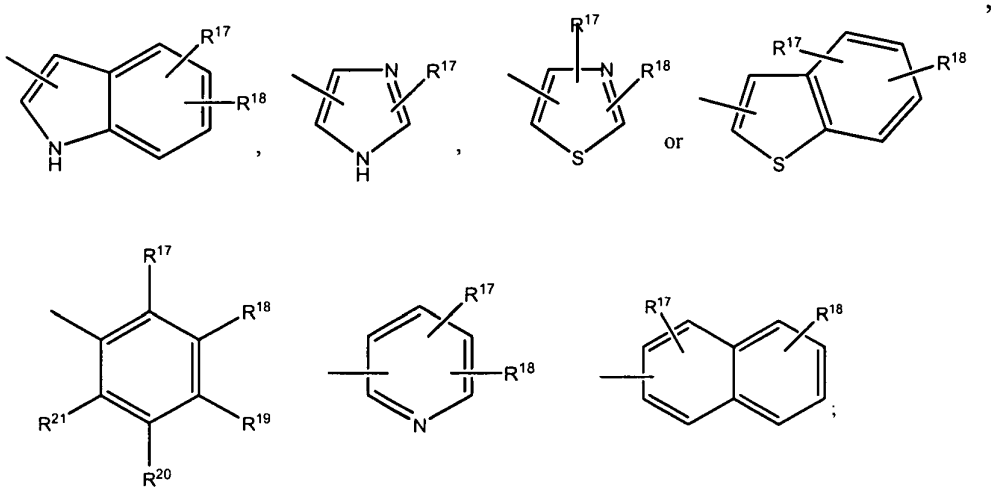
o is 0, 1, or 2;

T is –N(R^{15})(R^{16}) or hydroxyl;

R^{13}, R^{15}, and R^{16} are independently from each other hydrogen or C_{1-6} alkyl;

R^{14} is hydrogen, aryl, or hetaryl;

G is -O-(CH_2)-R^{17},

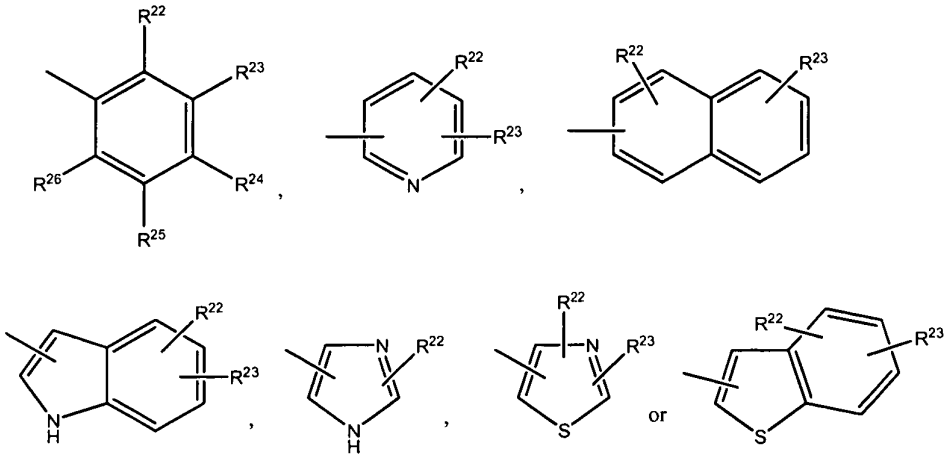


wherein:

R^{17}, R^{18}, R^{19}, R^{20} and R^{21} independently are hydrogen, halogen, aryl, hetaryl, C_{1-6}-alkyl or C_{1-6}-alkoxy;

K is 0, 1 or 2;

J is -O-$(CH_2)_l$-R^{22},



wherein:

R^{22}, R^{23}, R^{24}, R^{25} and R^{26} independently are hydrogen, halogen, aryl, hetaryl, C_{1-6}-alkyl or C_{1-6}-alkoxy;

l is 0, 1 or 2;

a is 0, 1, or 2;

b is 0, 1, or 2;

c is 0, 1, or 2;

d is 0 or 1;

e is 0, 1, 2, or 3;

f is 0 or 1;

R^5 is hydrogen or C_{1-6}-alkyl optionally substituted with one or more hydroxyl, aryl or hetaryl;

R^6 and R^7 are independently hydrogen or C_{1-6}-alkyl, optionally substituted with one or more halogen, amino, hydroxyl, aryl, or hetaryl;

R^8 is hydrogen or C_{1-6}-alkyl, optionally substituted with one or more halogen, amino, hydroxyl, aryl, or hetaryl;

R^6 and R^7 or R^6 and R^8 or R^7 and R^8 can optionally form $-(CH_2)_i-U-(CH_2)_j-$, wherein i and j independently are 1, 2 or 3 and U is -O-, -S-, or a valence bond;

M is arylene, hetarylene, -O-, -S- or-$CR^{27}=CR^{28}$-;

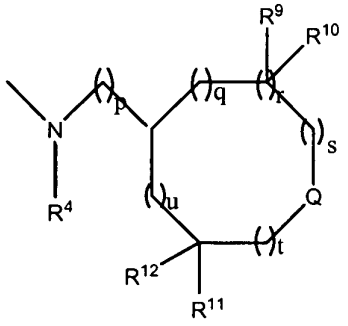
R^{27} and R^{28} are independently hydrogen or C_{1-6}-alkyl, optionally substituted with one or more aryl or hetaryl;

or a pharmaceutically acceptable salt thereof.

[0048] R^1 may be C_{1-6}-alkyl.

[0049] R^2 may be C_{1-6}-alkyl.

[0050] L may be



wherein R^4 is hydrogen or C_{1-6} alkyl;

p is 0 or 1;

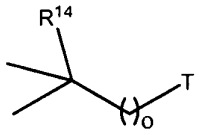
q, s, t, u are independently from each other 0, 1, 2, 3 or 4;

r is 0 or 1;

the sum q + r + s + t + u is 0 , 1, 2, 3, or 4;

R^9, R^{10}, R^{11}, and R^{12} are independently from each other hydrogen or C_{1-6} alkyl;

Q is >N-R^{13} or



wherein:

o is 0, 1 or 2;

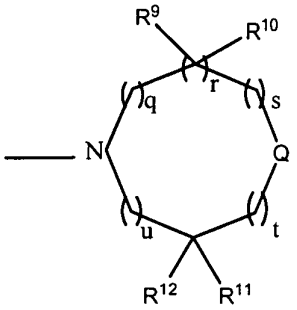
T is -N(R^{15})(R^{16}) or hydroxyl;

R^{13}, R^{15}, and R^{16} are independently from each other hydrogen or C_{1-6} alkyl;

and

R^{14} is hydrogen, aryl or hetaryl.

[0051] L may be



wherein:

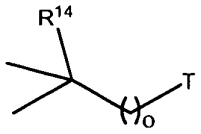
q, s, t, u are independently from each other 0, 1, 2, 3 or 4;

r is 0 or 1;

the sum q + r + s + t + u is 0, 1 , 2, 3, or 4;

R^9, R^{10}, R^{11}, and R^{12} are independently from each other hydrogen or C_{1-6} alkyl;

Q is >N-R^{13} or



wherein:

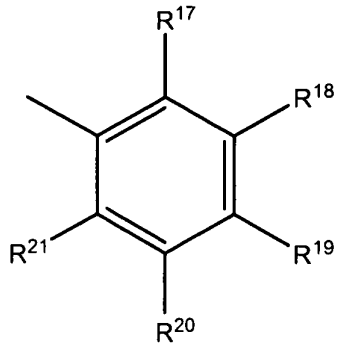
o is 0,1 or 2;

T is -N(R^{15})(R^{16}) or hydroxyl;

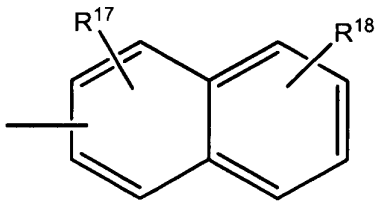
R^{13}, R^{15}, and R^{16} are independently from each other hydrogen or C_{1-6} alkyl;

and R^{14} is hydrogen, aryl or hetaryl.

[0052] G may be



or

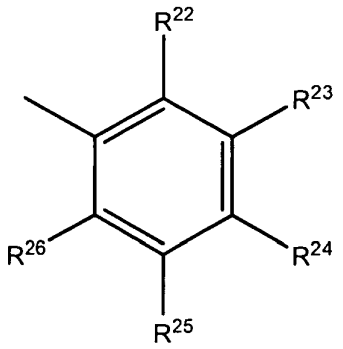


,

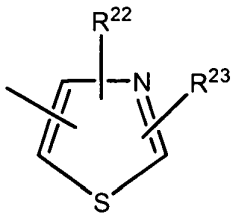
wherein:

R^{17}, R^{18}, R^{19}, R^{20} and R^{21} independently from each other are hydrogen, halogen, aryl, hetaryl, C_{1-6}-alkyl or C_{1-6}-alkoxy.

[0053] J may be



or



,

wherein:

R^{22}, R^{23}, R^{24}, R^{25} and R^{26} independently from each other are hydrogen, halogen, aryl, hetaryl, C_{1-6}-alkyl or C_{1-6}-alkoxy.

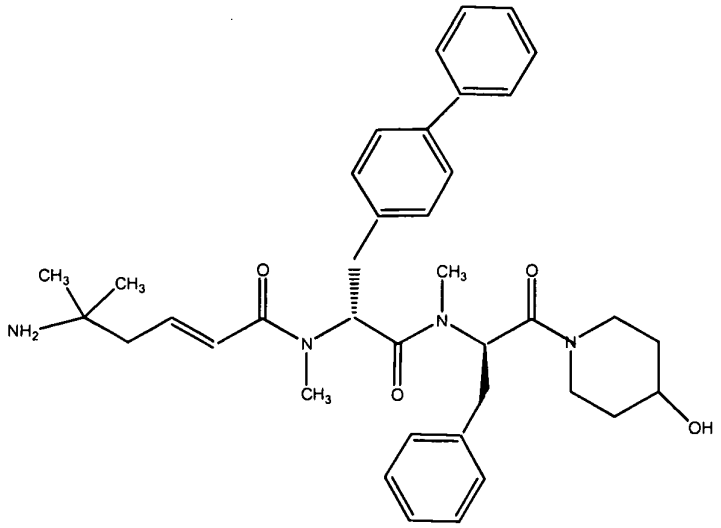
[0054] M may be arylene or $-CR^{27} = CR^{28}-$, wherein R^{27} and R^{28} independently from each other hydrogen or C_{1-6}-alkyl, optionally substituted with aryl or hetaryl.

[001] R^6 and R^7 independently from each other may be hydrogen or C_{1-6}-alkyl.

[002] R^6 and R^7 can also form $-(CH_2)_i-U-(CH_2)_j-$, wherein i and j independently from each other are 1, 2 or 3 and U is -O-, -S-, or a valence bond.

[003] R^8 may be hydrogen or C_{1-6}-alkyl.

[004] Another growth hormone secretagogue compound is represented by the structural Formula V. The chemical name of the compound of Formula V is (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-{N-[(1R)-1-benzyl-2-(4-hydroxypiperidin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(biphenyl-4-yl)ethyl)-N-methylamide and is represented by structural Formula V:



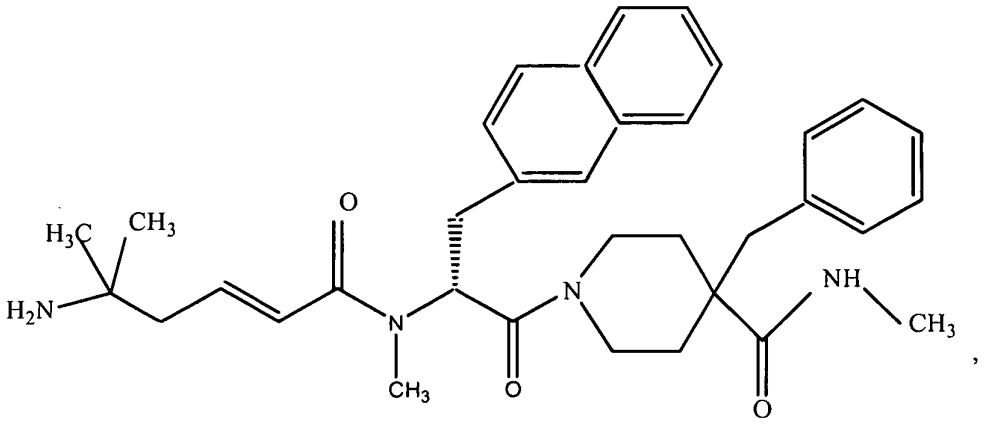
V

and pharmaceutically acceptable salts thereof.

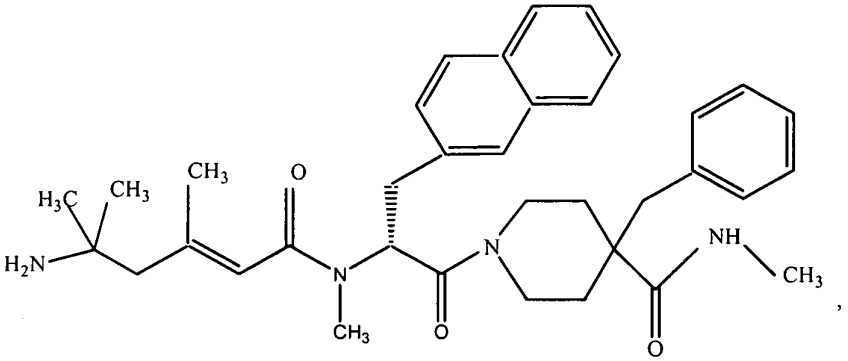
[005] Other compounds of interest include the following:

1-{(2R)-2-[N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino]

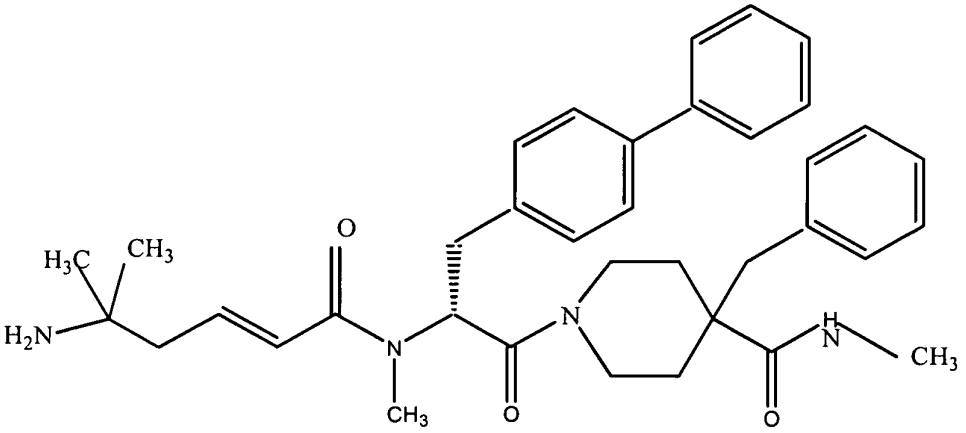
-3-(2-naphthyl)propionyl}-4-benzylpiperidine-4-carboxylic acid methylamide,



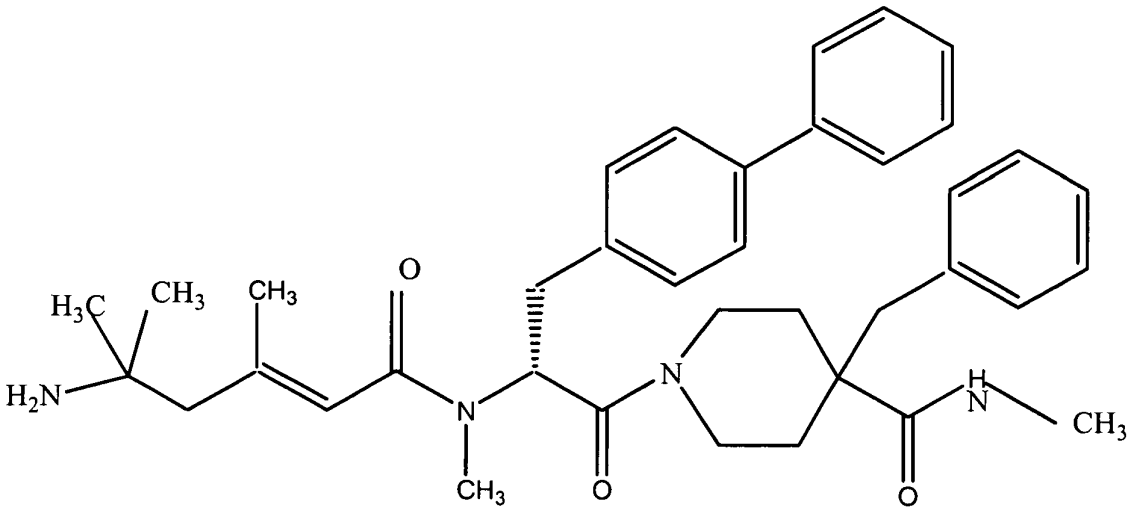
1-{(1R)-2-[N-((2E)-5-Amino-3,5-dimethylhex-2-enoyl)-N-methylamino]-3-(2-naphthyl)propionyl}-4-benzylpiperidine-4-carboxylic acid methylamide



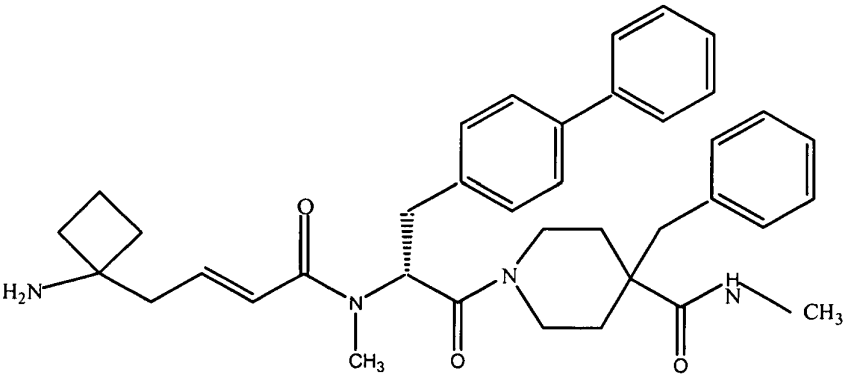
1-{(2R)-2-[N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino]-3-(biphenyl- 4-yl)propionyl}4-benzylpiperidine-4-carboxylic acid methylamide



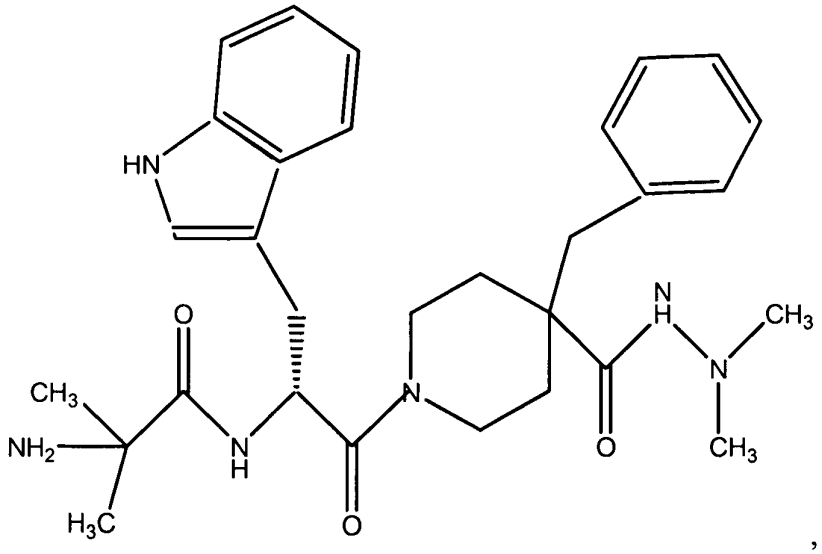
1-{(2R)-2-[N-((2E)-5-Amino-3,5-dimethylhex-2-enoyl)-N-methylamino]-3-(biphenyl-4-yl)propionyl}4-benzylpiperidine-4-carboxylic acid methylamide



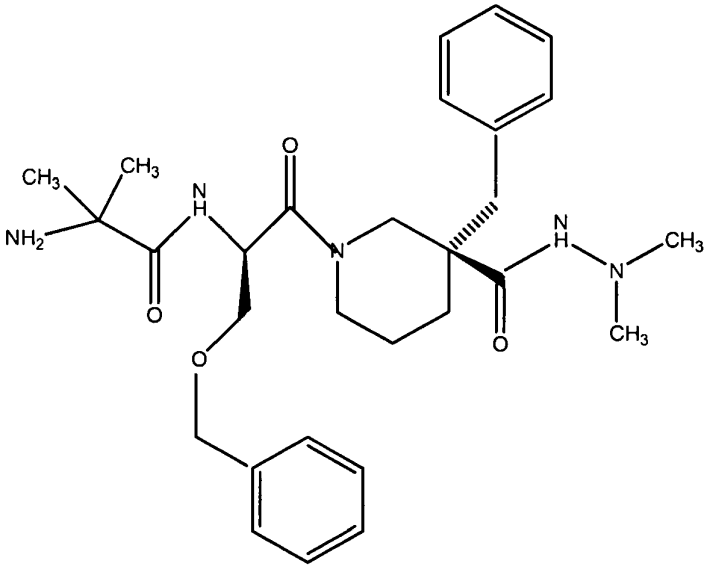
1-((2R)-2-{N-[(2E)4-(1-Aminocyclobutyl)but-2-enoyl]-N-methylamino}-3-(biphenyl-4-yl)propionyl)4-benzylpiperidine-4-carboxylic acid methylamide



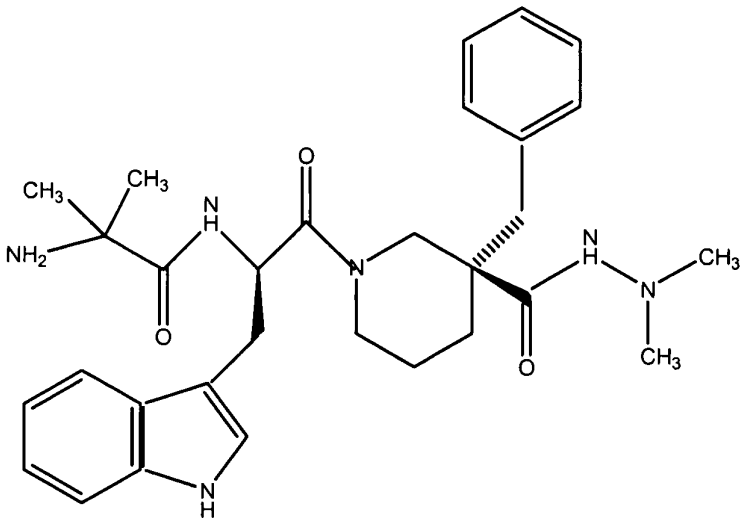
2-Amino-N-[(1R)-2-[4-benzyl-4-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-((1H-indol-3-yl)methyl)-2-oxoethyl]-2-methylpropionamide



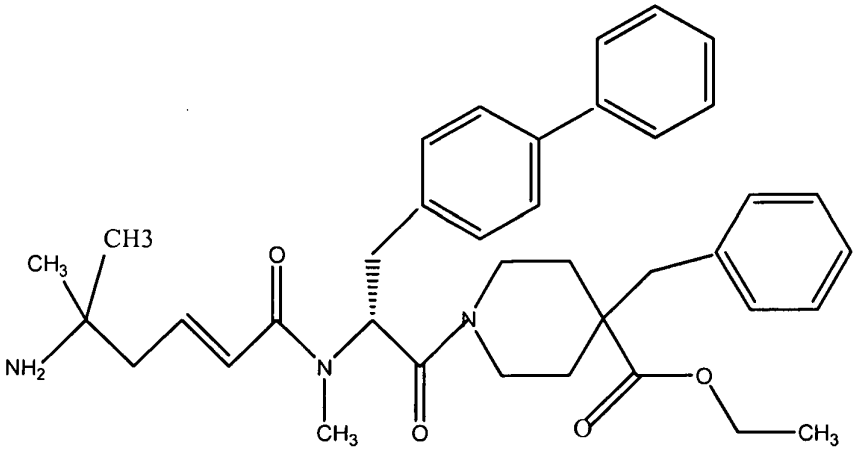
2-Amino-N-{(1R)-2-[(3R)-3-benzyl-3-(N',N'-dimethyl-hydrazinocarbonyl)-piperidin-1-yl]-1-benzyloxymethyl-2-oxo-ethyl}-2-methyl-propionamide



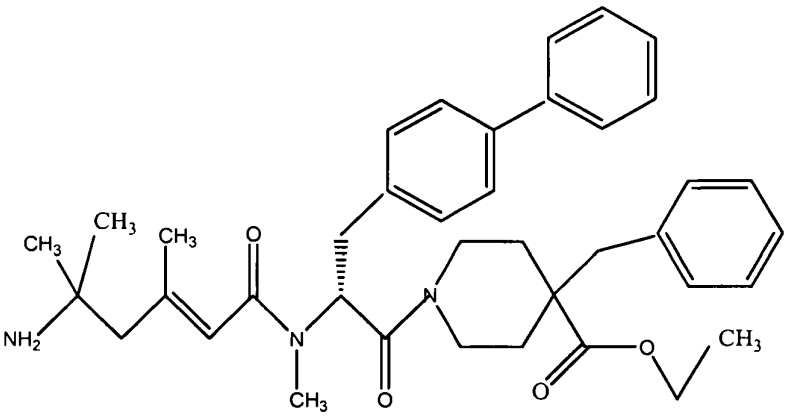
2-Amino-N-[(1R)-2-[(3R)-3-benzyl-3-(N'N'-dimethylhydrazinocarbonyl)-piperidin-1-yl]-1-((1H-indol-3-yl)methyl)-2-oxoethyl]-2-methylpropionamide



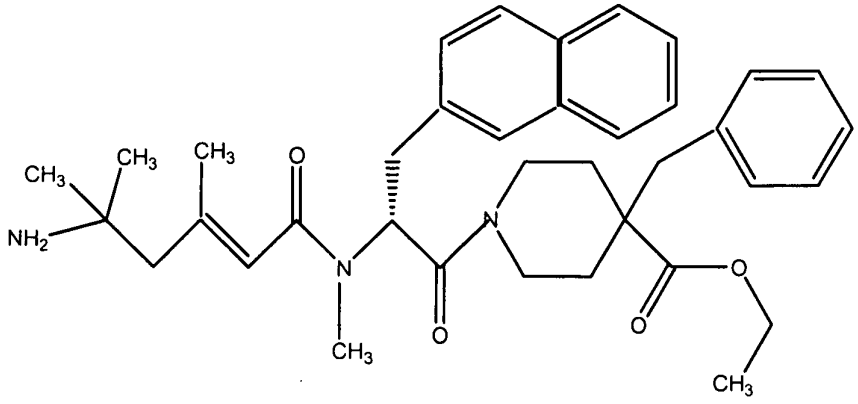
1-{(2R)-2-[N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino]-3-(biphenyl- 4-yl)propionyl}-4-benzylpiperidine-4-carboxylic acid ethyl ester



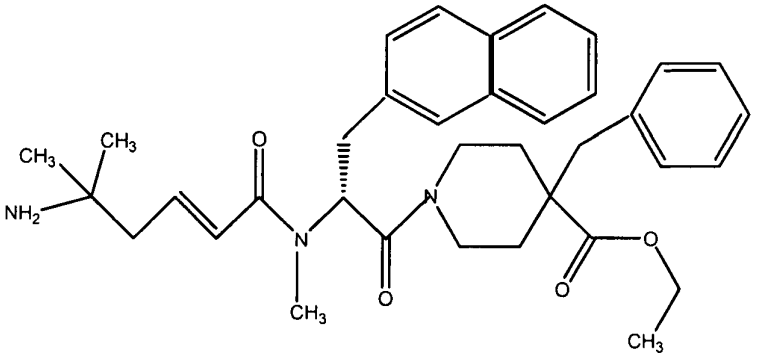
1-{(2R)-2-[N-((2E)-5-Amino-3,5-dimethylhex-2-enoyl)-N-methylamino]-3-(biphenyl-4-yl)propionyl}-4-benzylpiperidine-4-carboxylic acid ethyl ester



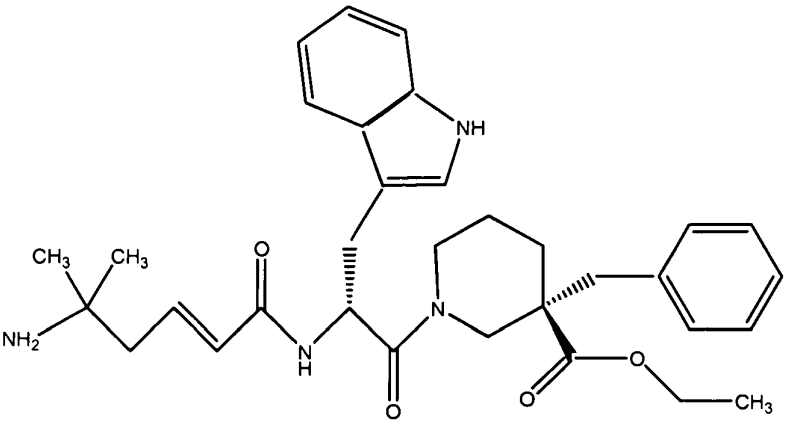
1-{(2R)-2-[N-((2E)-5-Amino-3,5-dimethylhex-2-enoyl)-N-methylamino]-3-(2-naphthyl)propionyl}-4-benzylpiperidine-4-carboxylic acid ethyl ester



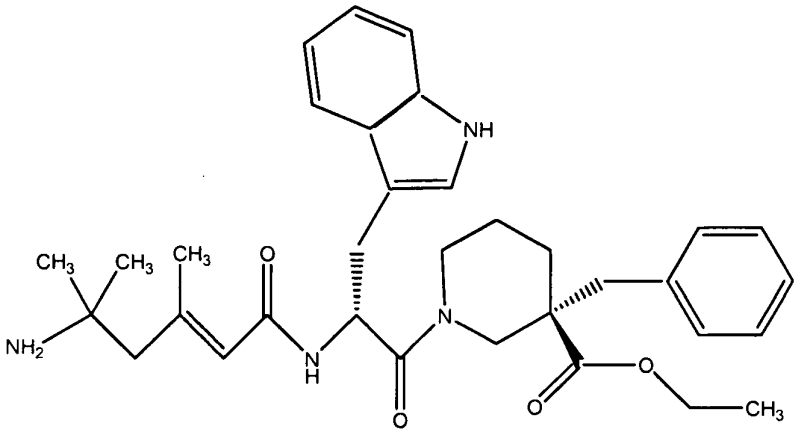
1-{(2R)-2-[N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino]-3-(2-naphthyl)propionyl}-4-benzylpiperidine-4-carboxylic acid ethyl ester



(3S)-1-[(2R)-2-((2E)-5-Amino-5-methylhex-2-enoylamino)-3-(1H-indol-3-yl) propionyl]-3-benzylpiperidine-3-carboxylic acid ethyl ester

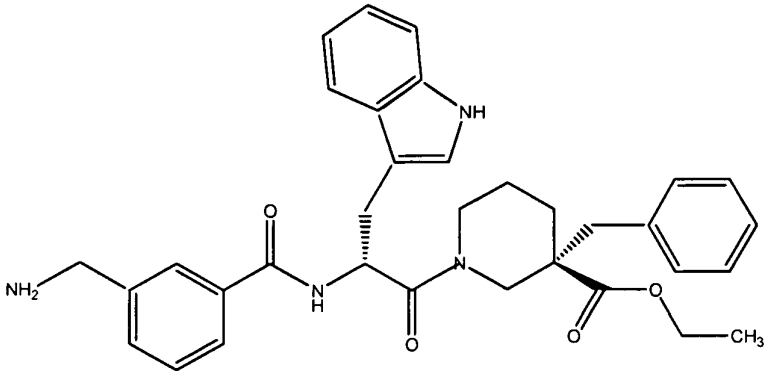


(3S)-1-[(2R)-2-((2E)-5-Amino-3,5-dimethylhex-2-enoylamino)-3-(1H-indol-3-yl) propionyl]-3-benzylpiperidine-3-carboxylic acid ethyl ester

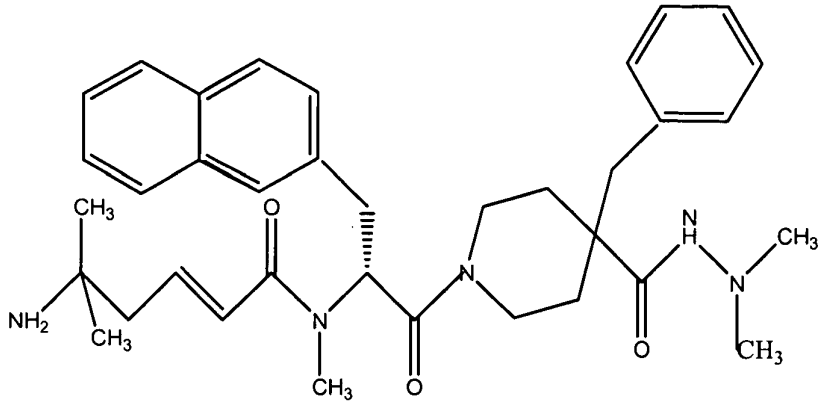


,

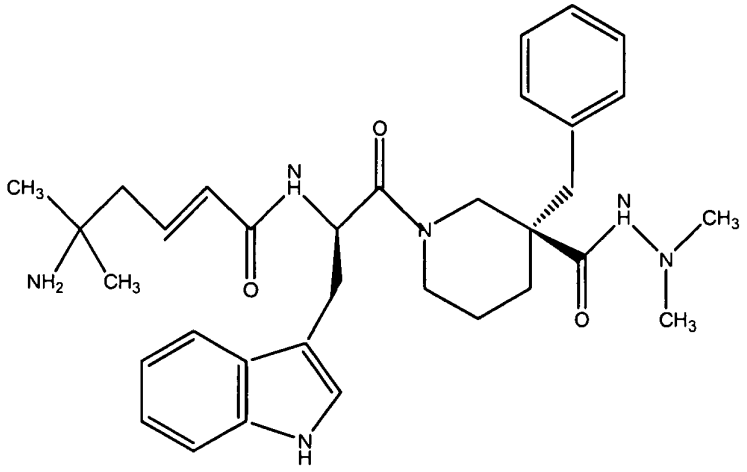
(3S)-1-[(2R)-2-(3-(Aminomethyl)benzoylamino)-3-(1H-indol-3-yl)propionyl]-3-benzylpiperidine-3-carboxylic acid ethyl ester



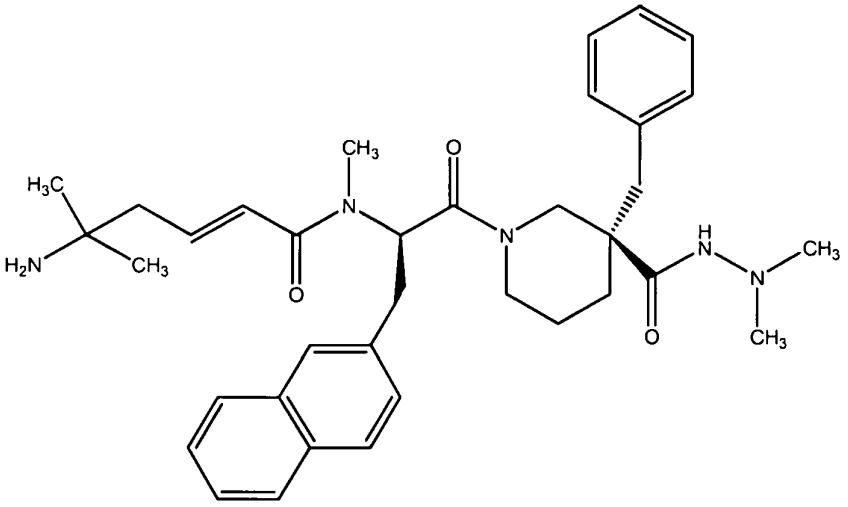
(2E)-5-Amino-5-methylhex-2-enoic acid N-{(1R)-2-[4-benzyl-4- (N',N'-dimethyl-hydrazinocarbonyl)piperidin-1-yl]-1-((2-naphthyl)methyl)-2-oxoethyl}-N-methylamide



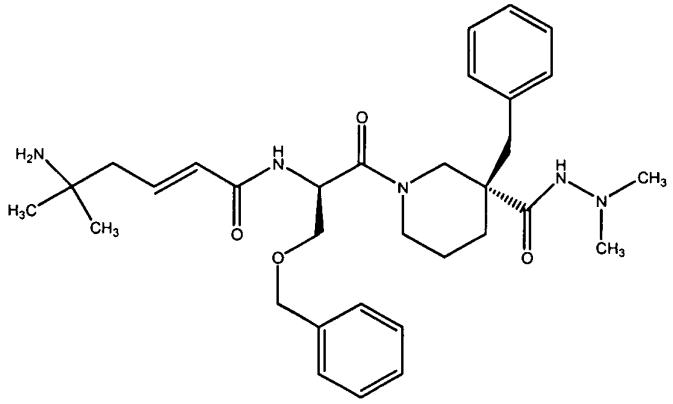
(2E)-5-Amino-5-methylhex-2-enoic acid N-[(1R)-2-[3-benzyl-3- (N',N'-dimethyl-hydrazinocarbonyl)-piperidin-1-yl]-1- ((1H-indol-3-yl)methyl) -2-oxoethyl]amide



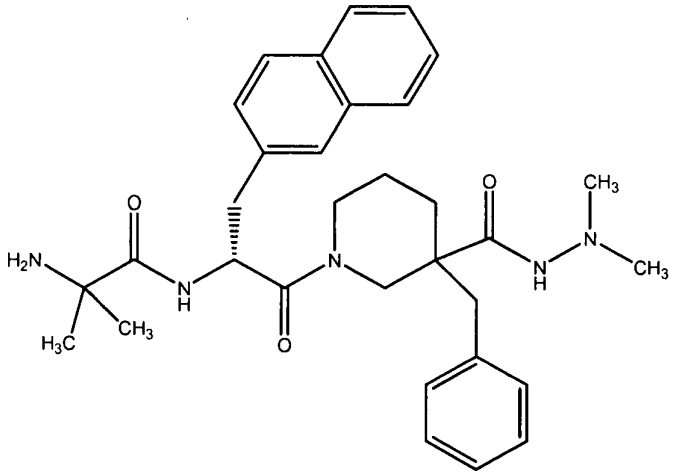
(2E)-5-Amino-5-methylhex-2-enoic acid N-{(1R)-2-[3-benzyl-3-(N',N'-dimethyl-hydrazinocarbonyl)-piperidin-1-yl]-1-((2-naphthyl)methyl)-2-oxoethyl}-N-methyl-amide



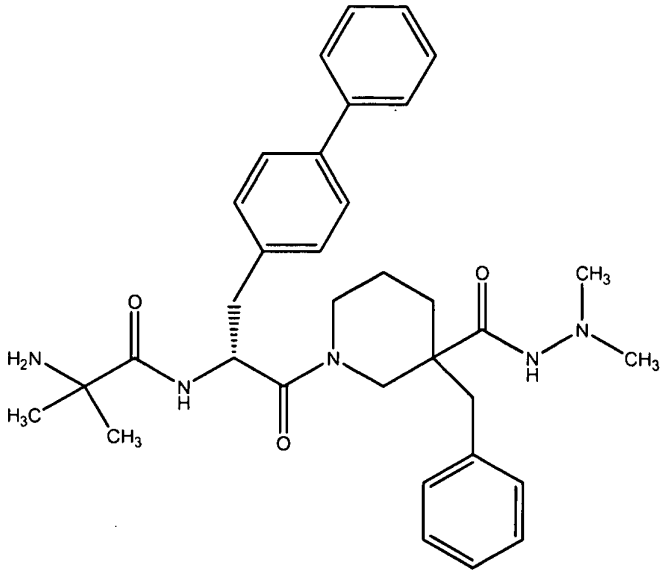
2E)-5-Amino-5-methylhex-2-enoic acid{(1R)-2-[3-benzyl-3-N',N'-dimethyl-hydrazinocarbonyl)piperidin-1-yl]-1-(benzyloxymethyl)-2-oxoethyl}amide



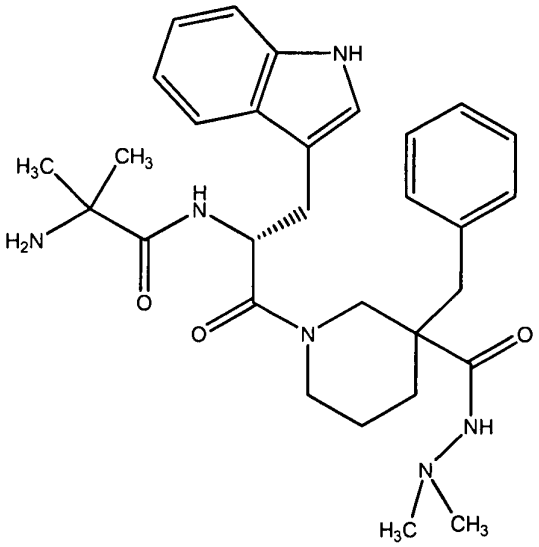
2-Amino-N-{2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1 -((2-naphthyl)methyl)-2-oxo-ethyl}-2-methyl-propionamide



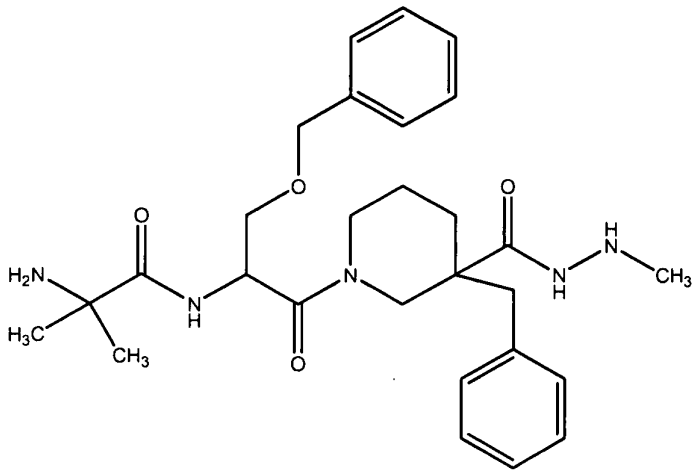
2-Amino-N-{(1R)-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1- yl]-1-((biphenyl-4-yl)methyl)-2-oxoethyl}-2-methylpropionamide



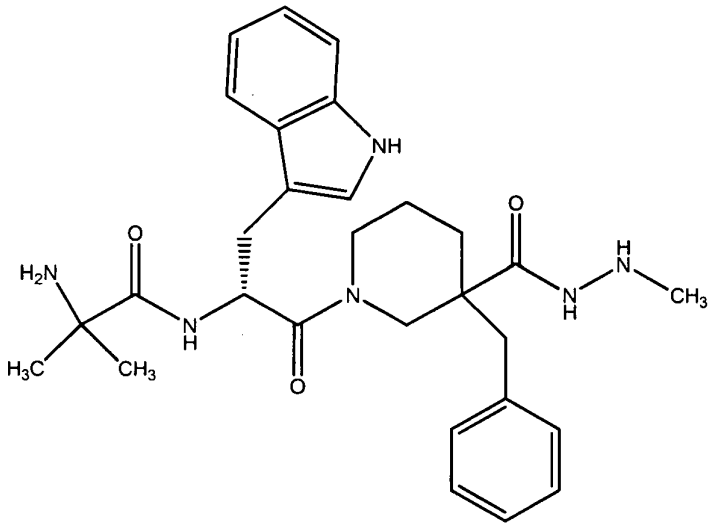
2-Amino-N-{(1R)-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1- yl]-1-((1H-indol-3-yl)methyl)-2-oxoethyl}-2-methylpropionamide



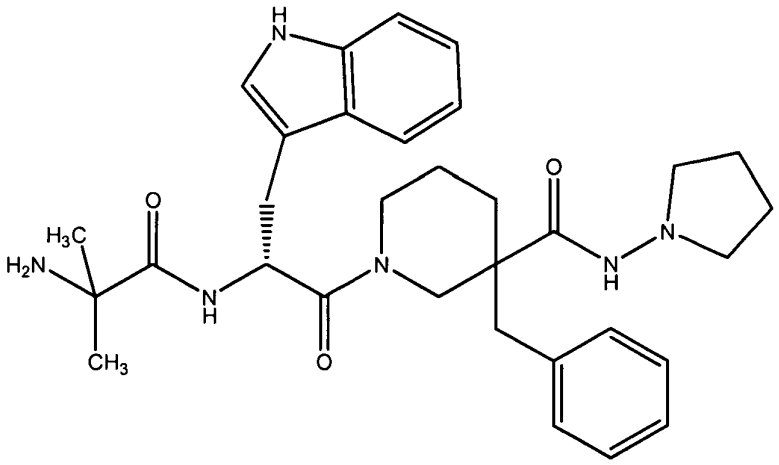
2-Amino-N-{2-[3-benzyl-3-(N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-(benzyloxymethyl)-2-oxoethyl}-2-methylpropionamide



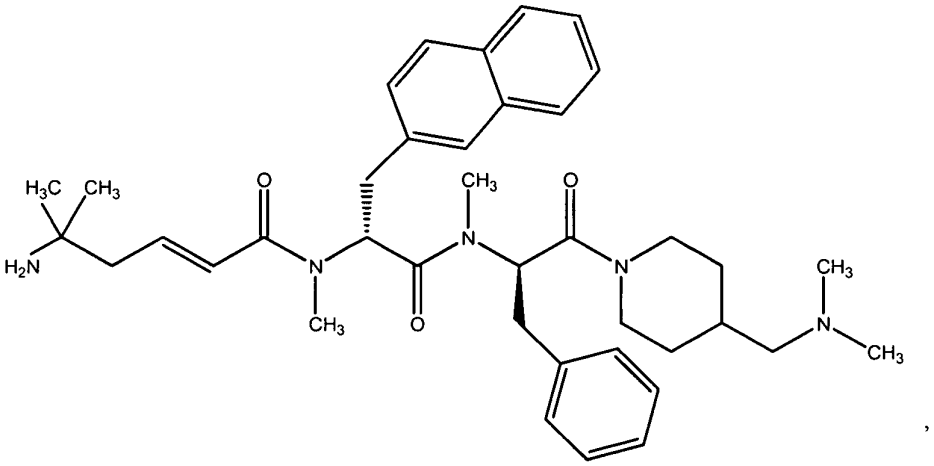
2-Amino-N-{(1R-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-y l]-1-(benzyloxymethyl)-2-oxoethyl}-2-methylpropionamide



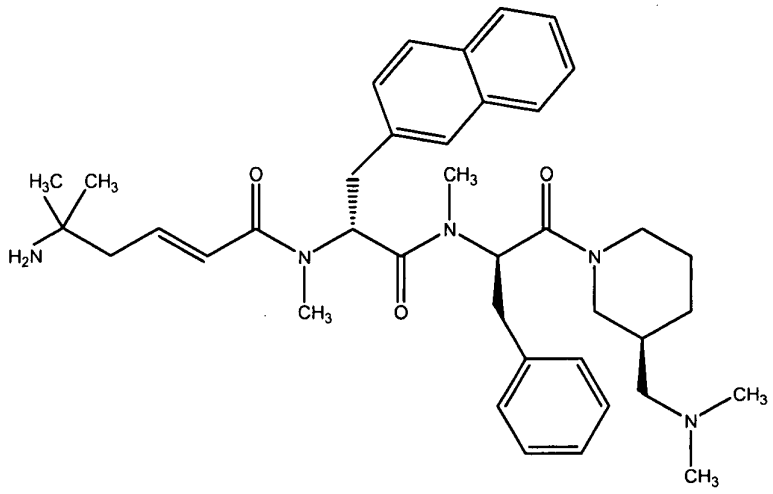
1-[(2R)-2-(2-Amino-2-methylpropionylamino)-3-(1-H-indol-3-yl)propionyl]-3-benzylpiperidine-3-carboxylic acid (pyrrolidin-1-yl)amide



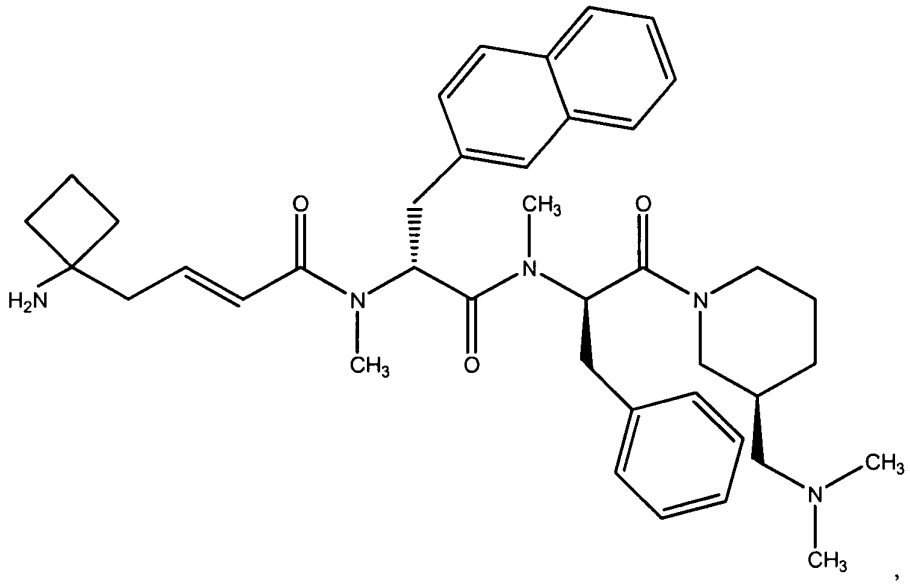
(2E)-5-Amino-5-Methylhex-2-enoic acid N-((1R) -1- {N-[(1R) -1-benzyl-2-(4-((dimethylamino)methyl)piperidin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide



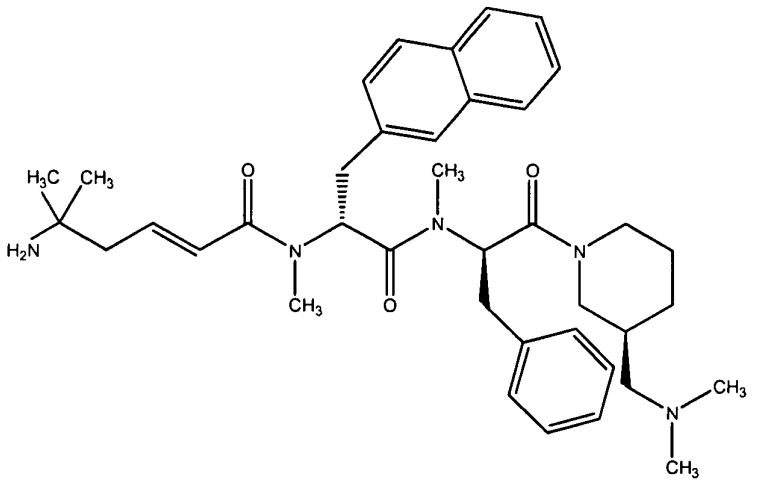
(2E)-5-Amino-5-Methylhex-2-enoic acid N-((1R)-1-{N-[(1R)-1-benzyl-2-((3S)-3-(dimethylaminomethyl)piperidin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N- methylamide



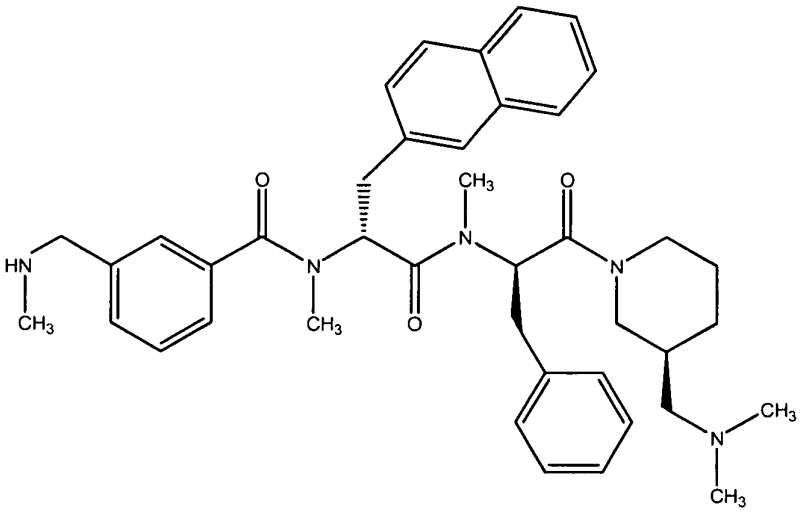
(2E)-4-(1-Aminocyclobutyl)but-2-enoic acid N-((1R)-1-{N-[(1R)-1-benzyl-2-((3S)-3-(dimethylaminomethyl)piperidin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide



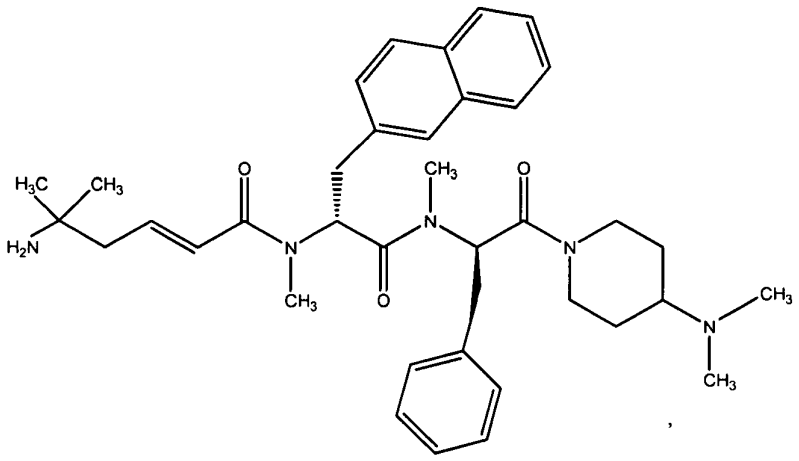
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-{N-[(1R)-1-benzyl-2-((2S)-2-((dimethylamino)methyl)pyrrolidin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide



N-((1R)-1-{N-[(1R)-1-Benzyl-2-((2S)-2-((dimethylamino)methyl)pyrrolidin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methyl-3-((methylamino)methyl)benzamide

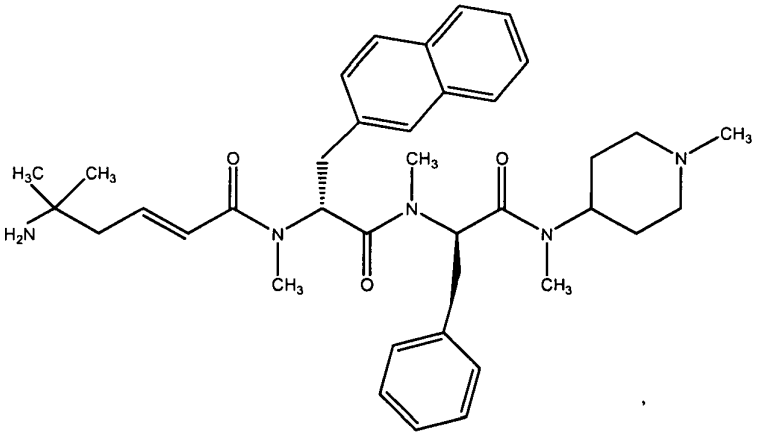


(2E)-5-Amino-5-methylhex-2enoic acid N-((1R-1-{N-[(1R)-1-benzyl-2-(4-(dimethylamino)piperidin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide.

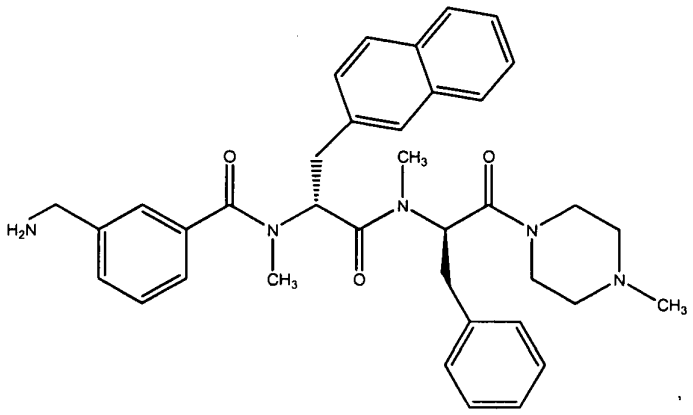


5

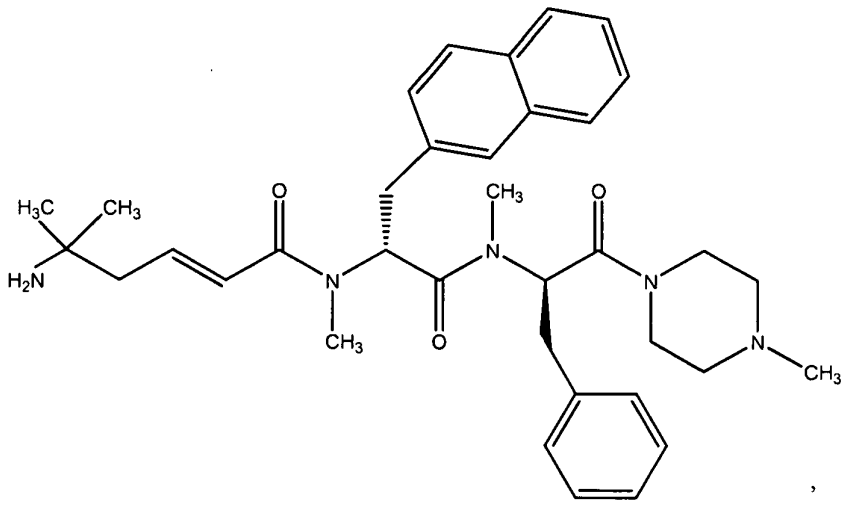
10 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-[(1R)-1-(N-methyl-N-{(1R)-1-[N-methyl-N-(1-methylpiperidin-4-yl)carbamoyl]-2-phenylethyl}carbamoyl)-2-(2-naphthyl) ethyl]amide



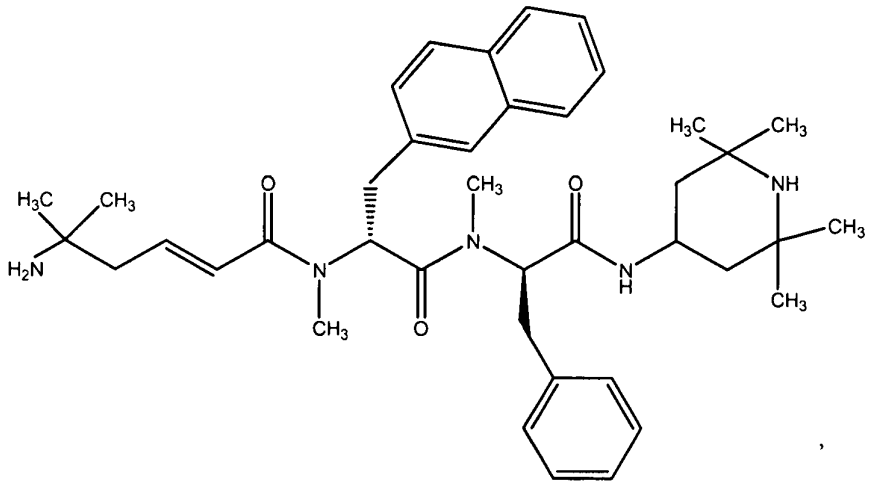
3-Aminomethyl-N-((1R)-1-{N-[(1R)-1-benzyl-2-(4-methylpiperazin-1-yl)-2-oxoethyl]—methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylbenzamide



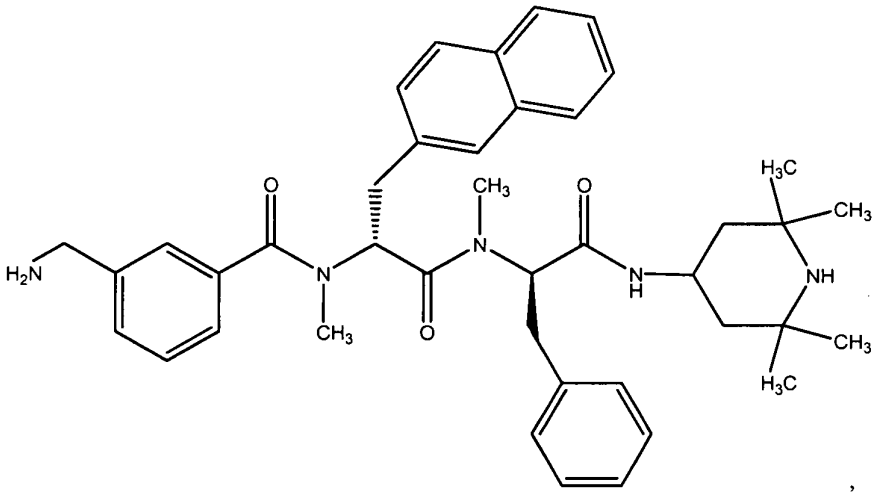
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-{N-[(1R)-1-benzyl-2-(4-methylpiperazin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(2-naphthyl)-N-methylamide



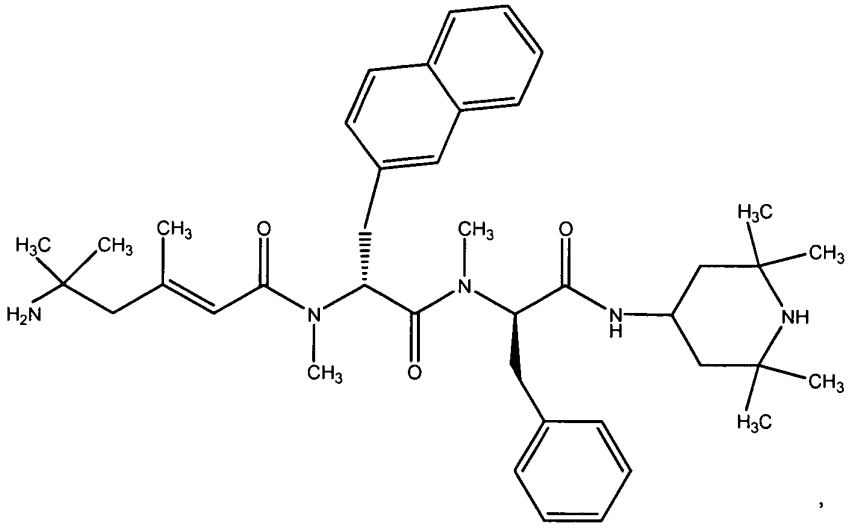
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-methyl-N-[(1R)-2-phenyl-1-((2,2,6,6-tetramethylpiperidin-4-yl)carbamoyl)ethyl]carbamoyl}-2-(2-naphthyl)ethyl)amide



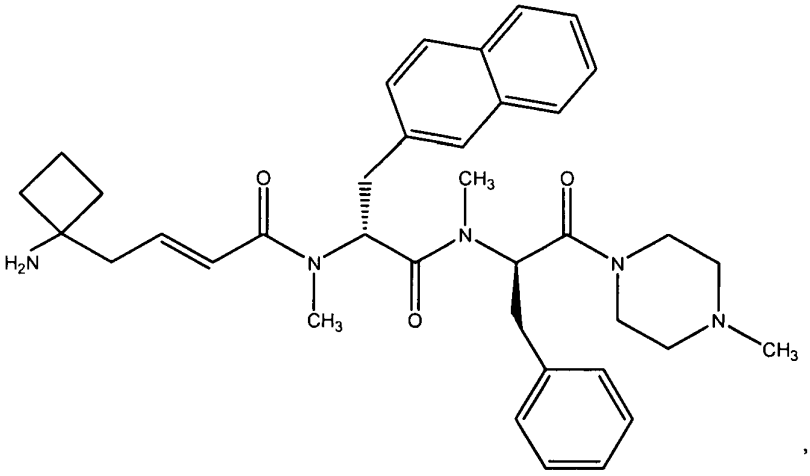
3-Aminomethyl-N-methyl-N-((1R)1-{N-methyl-N-[(1R)-2-phenyl-1-((2,2,6,6-tetramethylpiperidin-4-yl) carbamoyl)ethyl]carbamoyl}-2-(2-naphthyl) ethyl)benzamide



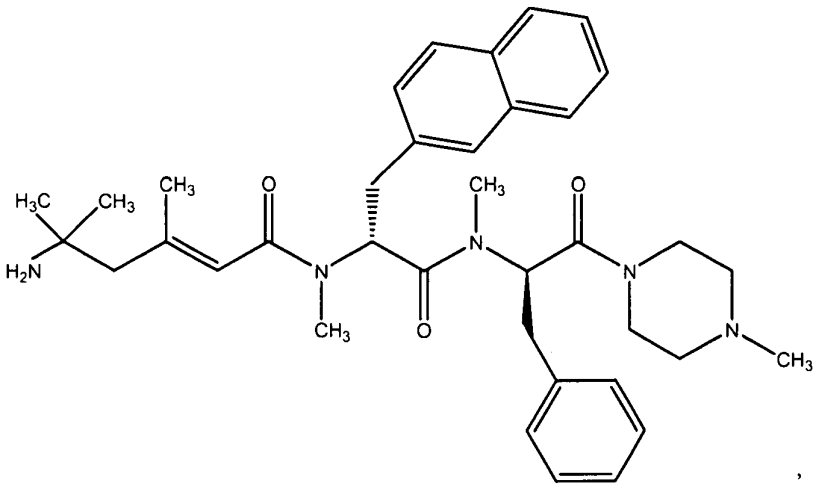
(2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-methyl-N-((1R-1-{N-methyl-N-[(1R)-2-phenyl-1-((2,2,6,6-tetramethylpiperidin-4-yl)carbamoyl)ethyl]carbamoyl}-2-(2-naphthyl)ethyl)amide



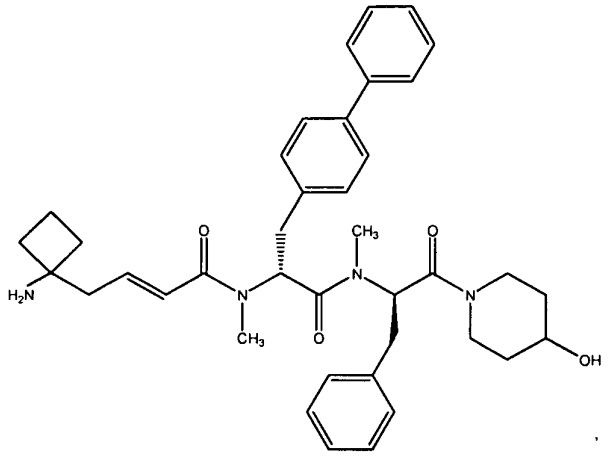
(2E)-4-(1-Aminocyclobutyl)but-2-enoic acid N-((1R)1-{N-[(1R)1-benzyl-2-(4-methylpiperazin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide



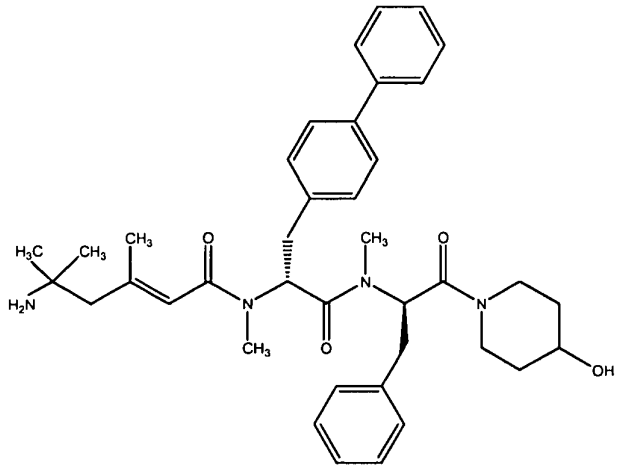
(2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-((1R)1-{N-[(1R)1-benzyl-2-(4-methylpiperazin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide



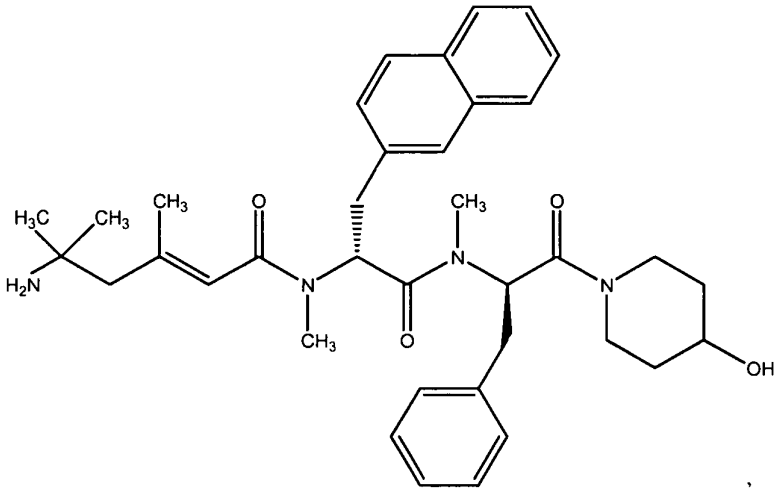
(2E)-4-(1-Aminocyclobutyl)but-2-enoic acid N-((1R)-1-{N-[(1R)-1-benzyl-2-(4-hydroxypiperidin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(biphenyl-4-yl) ethyl)-N-methylamide



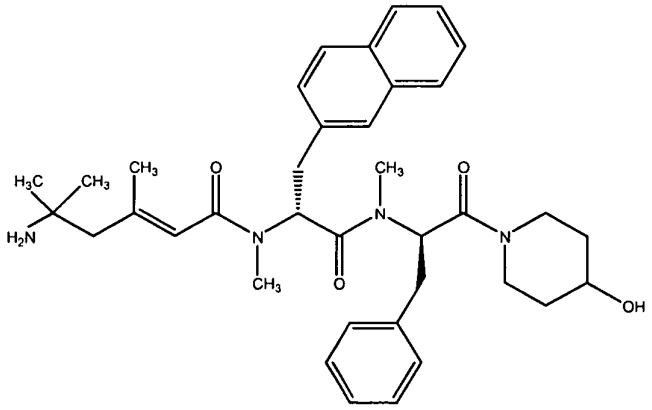
(2E)-5-Amino-3,5-dimethylhex-2enoic acid N-((1R)-1-{N-[(1R)-1-benzyl-2-(4-hydroxypiperidin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(biphenyl-4-yl)ethyl)-N-methylamide



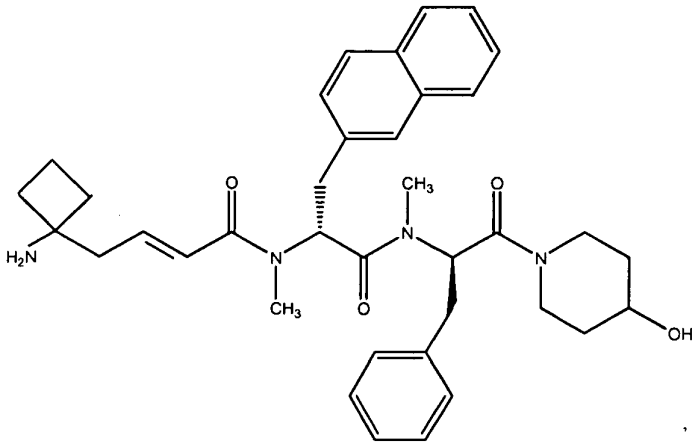
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1 R)-1-{N-[(1R)-1-benzyl-2-(4-hydroxypiperidin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide



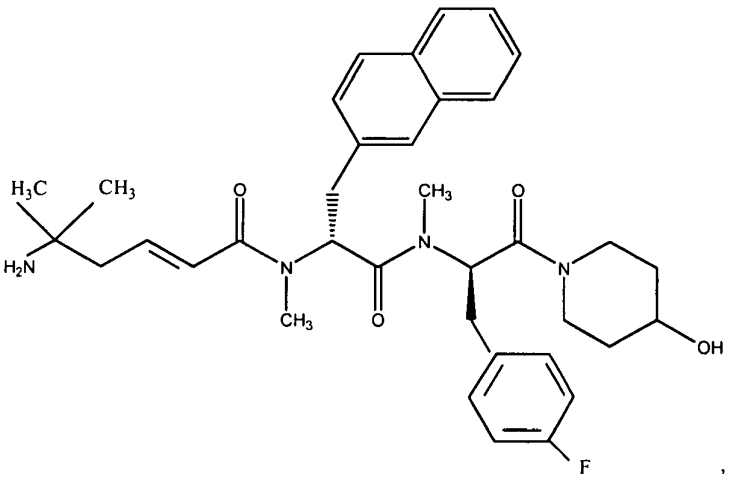
(2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-((1R)-1-{N-[(1R)-1-benzyl-2-(4-hydroxypiperidin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(2-naphthyl) ethyl)-N-methylamide



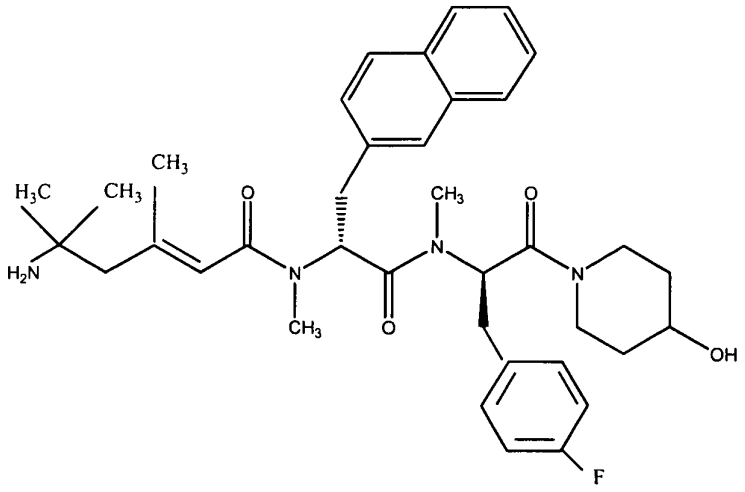
(2E)-4-(1-Aminocyclobutyl)but-2-enoic acid N-((1R)-1-{N-[(1R)-1-benzyl-2-(4-hydroxypiperidin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide



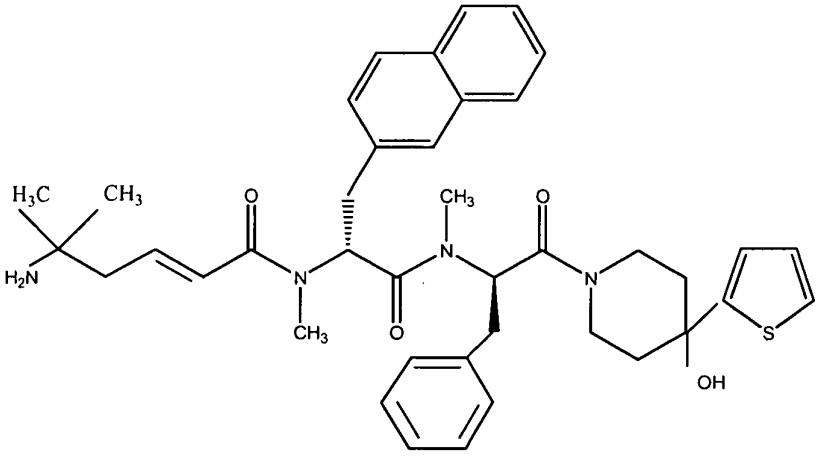
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-{N-[(1R)-1-(4-fluorobenzyl)-2-(4-hydroxypiperidin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide



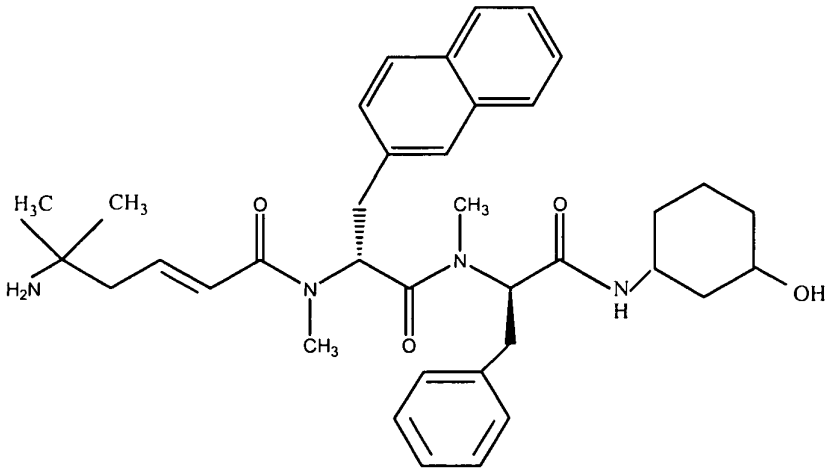
(2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-((1R)-1-{N-[(1R)-1-(4-fluorobenzyl)-2-(4-hydroxypiperidin-1-yl)-2-oxoethyl)-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide



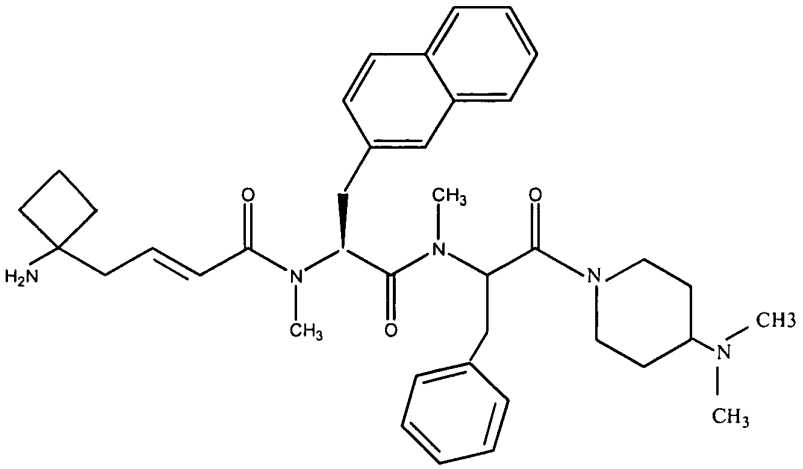
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-{N-[(1R)-1-benzyl-2-(4-hydroxy-4-(2- thienyl)piperidin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide



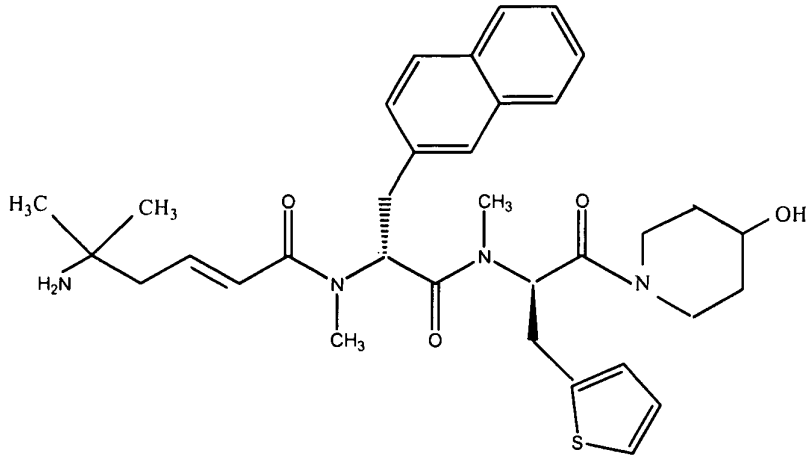
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-{N-[(1R)-1-(3-hydroxycyclohexylcarbamoyl)-2-phenylethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide



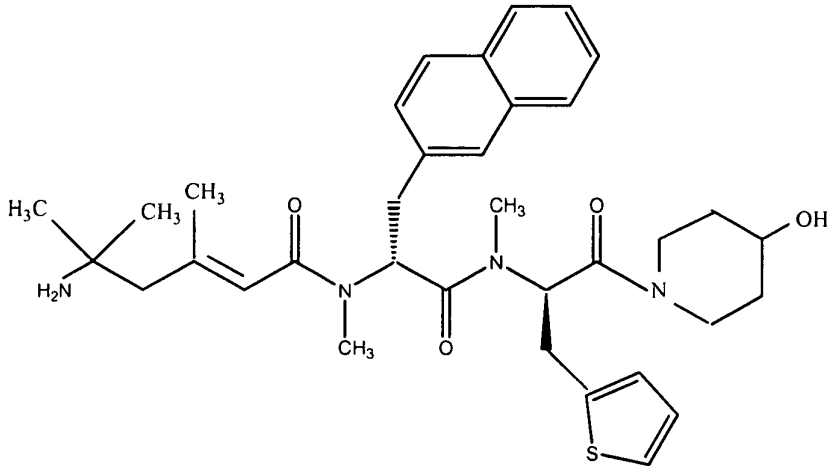
(2E)4-(1-Aminocyclobutyl)but-2-enoic acid N-((1R)-1-{N-[(1R)-1-benzyl-2-(4-(dimethylamino)piperidin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N- methylamide



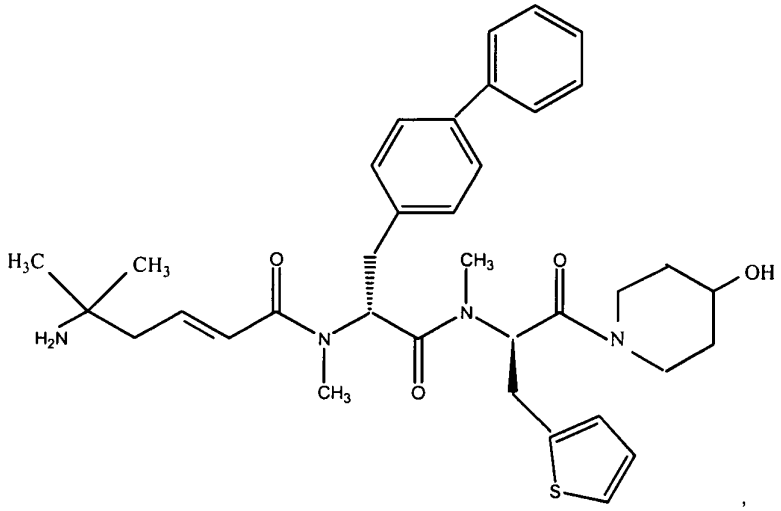
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-{N-[(2R)-2-(4--hydroxypiperidin-1-yl)-2-oxo-1-((2-thienyl)methyl)ethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide



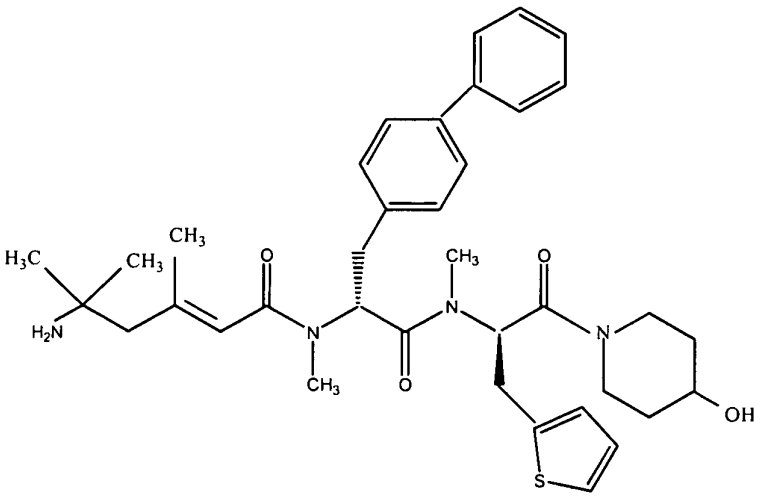
(2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-((1R)-1-{N-[(2R)-2-(4-hydroxypiperidin-1-yl)-2-oxo-1-((2-thienyl)methyl)ethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide



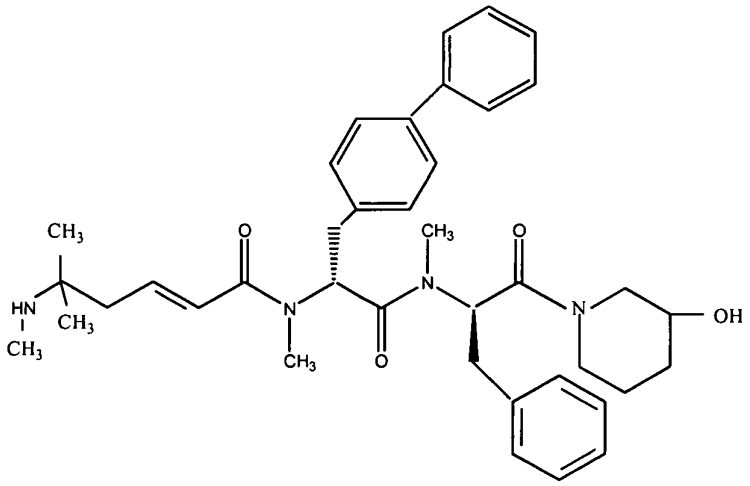
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-2-(biphenyl-4-yl)-1-{N-[(2R)-2-(4-hydroxypiperidin-1-yl)-2-oxo-1-((2-thienyl)methyl)ethyl]-N-methylcarbamoyl}ethyl)-N-methylamide



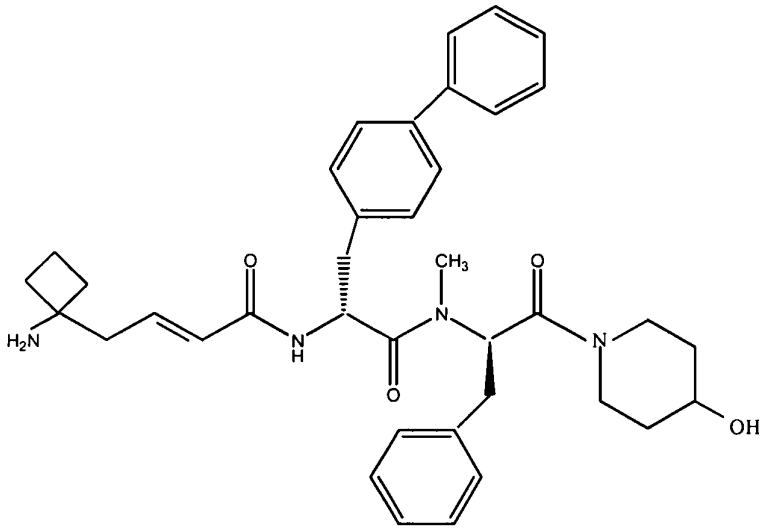
(2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-((1R)-2-(biphenyl-4-yl)-1-{N-[(1R)-2-(4-hydroxypiperidin-1-yl)-2-oxo-1-((2-thienyl)methyl)ethyl]-N-methylcarbamoyl}ethyl)-N-methylamide



(2E)-5-Methyl-5-(methylamino)hex-2-enoic acid N-((1R)-1-{N-[(1R)-1-benzyl-2-(4-hydroxypiperidin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(biphenyl-4-yl)ethyl)-N-methylamide

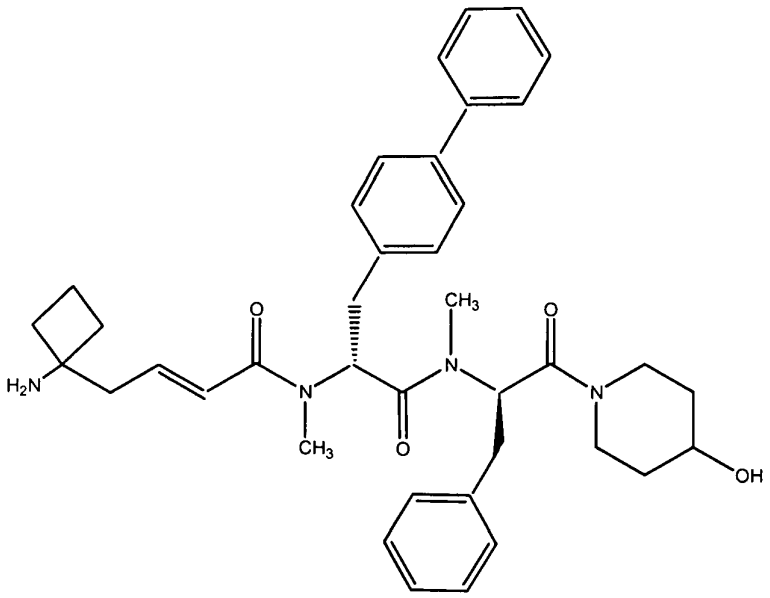


(2E)-4-(1-Aminocyclobutyl)but-2-enoic acid ((1R)-1-{N-[(1R)-1-benzyl-2-(4-hydroxypiperidin-1-yl)-2-oxoethyl]-N-methylcarbamoyl}-2-(biphenyl-4-yl)ethyl)amide



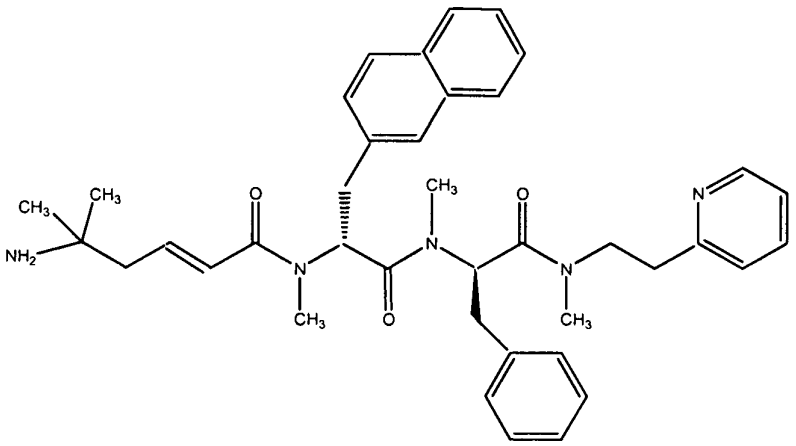
and pharmaceutically acceptable salts thereof.

[006] Another growth hormone secretagogue is represented by structural Formula VI or a pharmaceutically acceptable salt, solvate or hydrate thereof. The chemical name for the compound represented by structural Formula VI is: (2E)-4-(1-aminocyclobutyl) but-2-enoic acid N-((1R)-1-{N-[(1R)-1-benzyl-2-(4-hydroxypiperidin-1-yl)-2-oxoethyl]-N-methylcarbomoyl}-2-(biphenyl-4-yl)ethyl)-N-methylamide.



VI

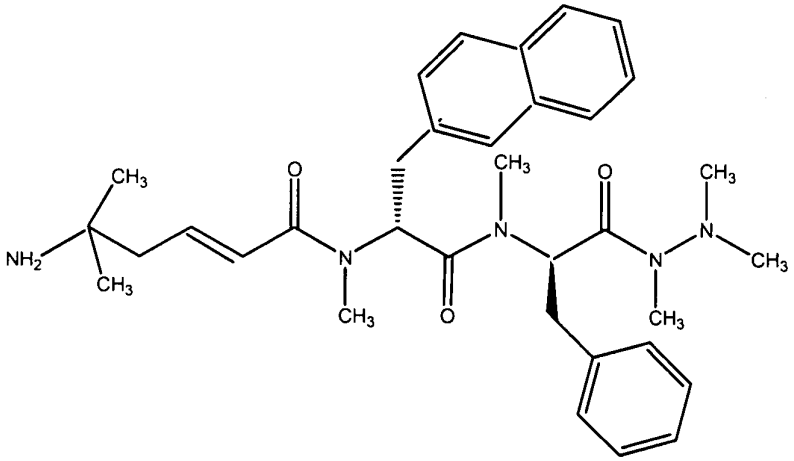
[007] Another growth hormone secretagogue is represented by structural Formula VII or a pharmaceutically acceptable salt, solvate or hydrate thereof. The chemical name of the compound represented by structural Formula VII is: (2E)-5-amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-methyl-N-[(1R)-2-phenyl-1-(N,N',N'-trimethylhydrazinocarbonyl)ethyl]carbamoyl}-2-(2-naphthyl)ethyl)amide.



VII

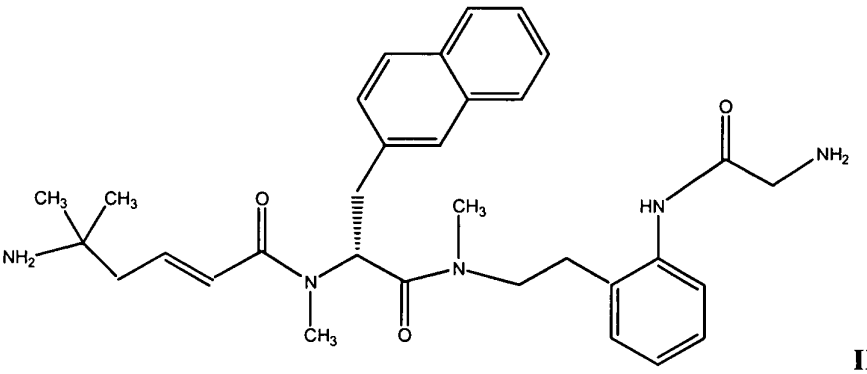
[008] Another growth hormone secretagogue is represented by structural Formula VIII or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[009] The chemical name of the compound represented by structural Formula VIII is: (2E)-5-amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-methyl-N-[(1R)-2-phenyl-1-(N,N',N'-trimethylhydrazinocarbonyl)ethyl]carbamoyl}2-(2-naphthyl)ethyl)amide.



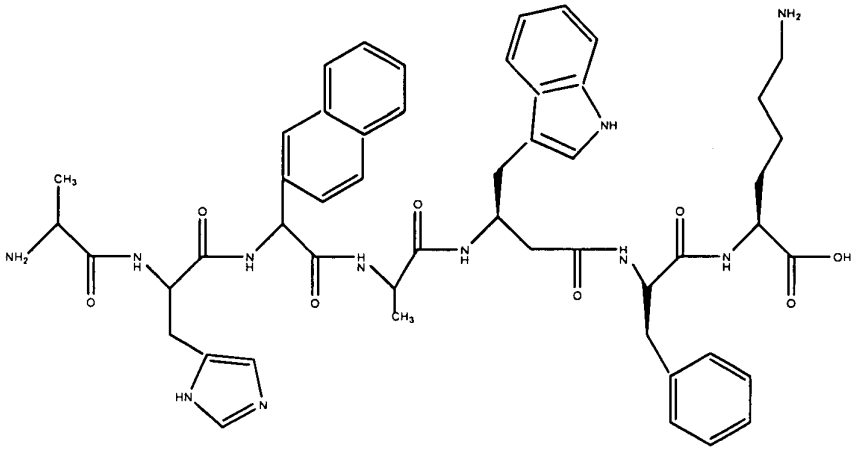
VIII

[010] Another the growth hormone secretagogue is represented by structural Formula IX or a pharmaceutically acceptable salt, solvate or hydrate thereof. The chemical name for the compound represented by structural Formula IX is: 2-amino-N-(2-(2-(N-((2R)-2-(N-((2E)-5-amino-5-methylhex-2-enoyl)-N-methylamino)-3-(2-napthyl)propionyl)-N-methylamino)ethyl)phenyl)acetamide.

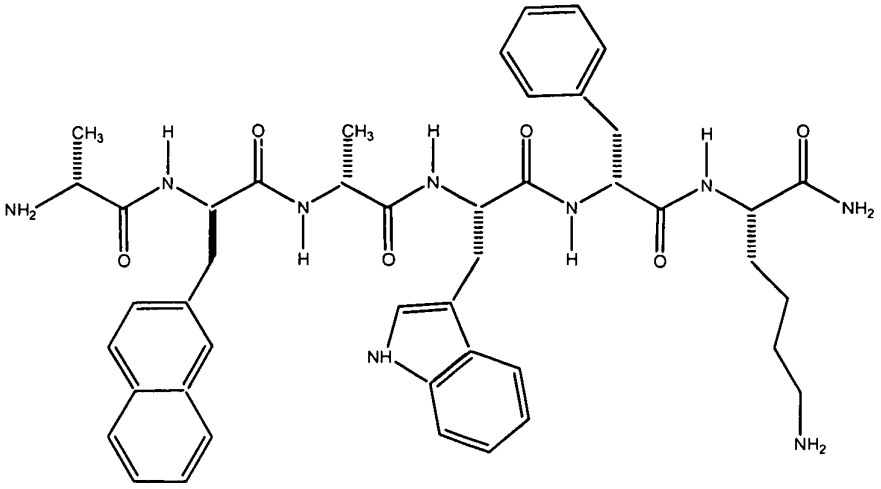


IX

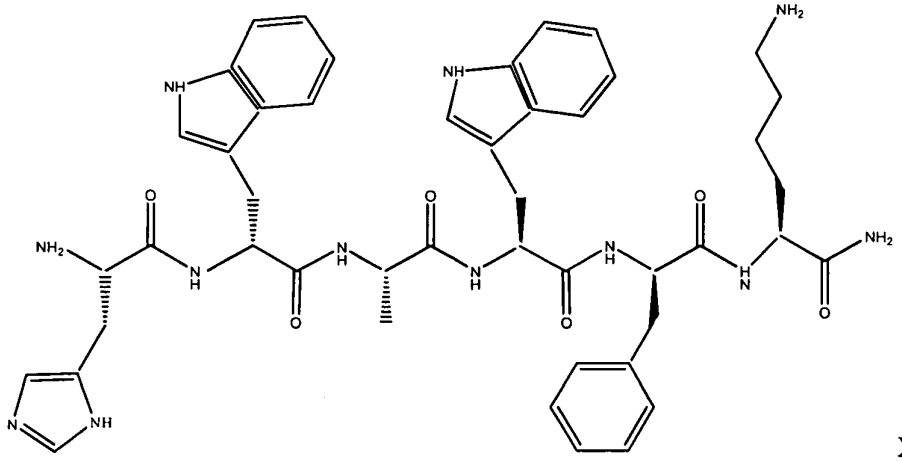
[011] Further exemplary growth hormone secretagogues can be selected from GHRP-1 (Formula X), GHRP-2 (Formula XI), GHRP-6 (Formula XII), NN703 (Formula XIII), Ipamorelin (Formula XIV), Capromorelin (Formula XV) and MK-677 (Formula XVI) and analogs of any of the above.



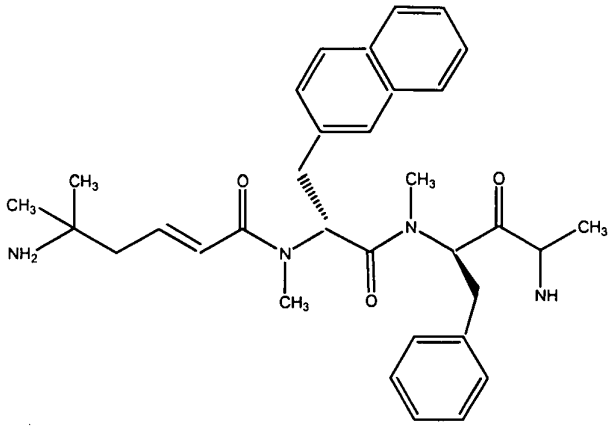
X



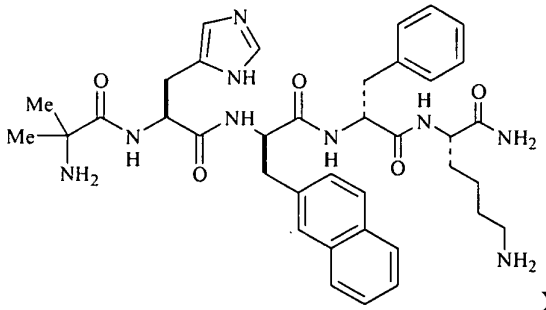
XI



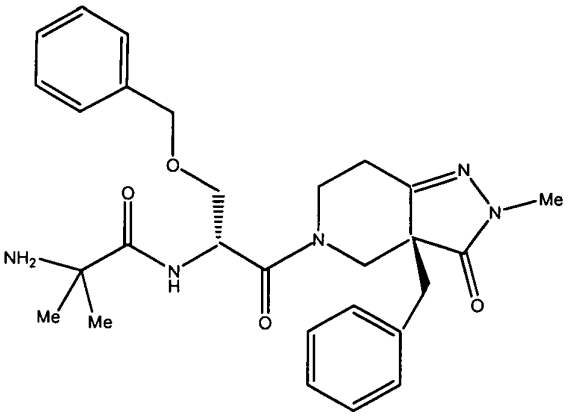
XII



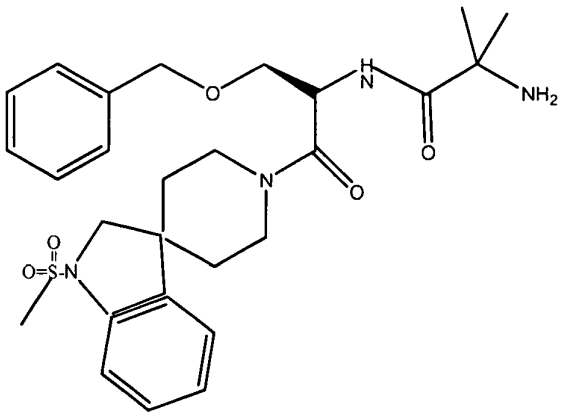
XIII



XIV



XV



XVI

[012] As used herein, the term "cell proliferative disorder" is used to mean a condition in which a cell in a subject's body undergoes abnormal, uncontrolled proliferation. Thus, "cancer" is a type of cell-proliferative disorder. Examples of cancers include, without limitation, solid tumors such as sarcomas and carcinomas (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, nile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodenroglioma, schwannoma, meningioma, melanoma, neuroblastoma, and retinoblastoma). Lymphoproliferative disorders are also considered to be proliferative diseases. Preferred caners include lung, colon, and rectal cancers. The terms "cancer," "neoplasm," and "tumor," are used interchangeably and in either the singular or plural form, refer to cells that have undergone a malignant transformation that makes them pathological to the host organism.

[013] "Subject", as used herein, refers to animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, pigs, dogs, cats, rabbits, guinea pigs, rats, mice or other bovine, ovine, equine, canine, feline, rodent or murine species. In a preferred embodiment, the mammal is a human.

[014] As used herein, "treating" and "treatment" refer to reducing or eliminating cancerous cells from a subject.

[015] As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. In the present invention, the desired biological response is treating cell proliferative disorders, e.g., cancer.

[016] The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. The skilled artisan will be able to determine appropriate dosages depending on these and other factors to achieve the desired biological response.

[017] A suitable dose per day for the growth hormone secretagogue can be in the range of from about 1 ng to about 10,000 mg, about 5 ng to about 9,500 mg, about 10 ng to about 9,000 mg, about 20 ng to about 8,500 mg, about 30 ng to about 7,500 mg, about 40 ng to about 7,000 mg, about 50 ng to about 6,500 mg, about 100 ng to about 6,000 mg, about 200 ng to about 5,500 mg, about 300 ng to about 5,000 mg, about 400 ng to about 4,500 mg, about 500 ng to about 4,000 mg, about 1 μg to about 3,500 mg, about 5 μg to about 3,000 mg, about 10 μg to about 2,600 mg, about 20 μg to about 2,575 mg, about 30 μg to about 2,550 mg, about 40 μg to about 2,500 mg, about 50 μg to about 2,475 mg, about 100 μg to about 2,450 mg, about 200 μg to about 2,425 mg, about 300 μg to about 2,000, about 400 μg to about 1,175 mg, about 500 μg to about 1,150 mg, about .5 mg to about 1,125 mg, about 1 mg to about 1,100 mg, about 1.25 mg to about 1,075 mg, about 1.5 mg to about 1,050 mg, about 2.0 mg to about 1,025 mg, about 2.5 mg to about 1,000 mg, about 3.0 mg to about 975 mg, about 3.5 mg to about 950 mg, about 4.0 mg to about 925 mg, about 4.5 mg to about 900 mg, about 5 mg to about 875 mg, about 10 mg to about 850 mg, about 20 mg to about 825 mg, about 30 mg to about 800 mg, about 40 mg to about 775 mg, about 50 mg to about 750 mg, about 100 mg to about 725 mg, about 200 mg to about 700 mg, about 300 mg to about 675 mg, about 400 mg to about 650 mg, about 500 mg, or about 525 mg to about 625 mg.

[018] Other suitable doses per day for the growth hormone secretagogue include doses of about or greater than 1 ng, about 5 ng, about 10 ng, about 20 ng, about 30 ng, about 40 ng, about 50 ng, about 100 ng, about 200 ng, about 300 ng, about 400 ng, about 500 ng, about 1 μg, about 5 μg, about 10 μg, about 20 μg, about 30 μg, about 40 μg, about 50 μg, about 100 μg, about 200 μg, about 300 μg, about 400 μg, about 500 μg (0.5 mg), about 1 mg, about 1.25 mg, about 1.5 mg, about 2.0 mg, about 2.5 mg,

about 3.0 mg, about 3.5 mg, about 4.0 mg, about 4.5 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1125 mg, about 1150 mg, about 1175 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg, about 2500 mg, about 2525 mg, about 2550 mg, about 2575 mg, about 2600 mg, about 3,000 mg, about 3,500 mg, about 4,000 mg, about 4,500 mg, about 5,000 mg, about 5,500 mg, about 6,000 mg, about 6,500 mg, about 7,000 mg, about 7,500 mg, about 8,000 mg, about 8,500 mg, about 9,000 mg, or about 9,500 mg.

[019] A suitable dose of the growth hormone secretagogue can be in the range of from about 1-150 mg per day, such as from about 10 mg to about 100 mg, for example, from about 20 mg to about 80 mg, such as about 30 mg to about 60 mg per day, such as about 50 mg per day. Preferred dosages are between 50 and 100 mg/day. The dose can be administered in a single dosage or in multiple dosages, for example from 1 to 4 or more times per day. When multiple dosages are used, the amount of each dosage can be the same or different.

[020] A suitable dose for the additional therapeutic agent can be in same range as described above for the growth hormone secretagogue. The dose of growth hormone

secretagogue and additional agent can be the same or different. Suitable doses for the additional agents can be found in the literature.

[021] Cancer Cachexia

[022] Subjects that have cancer also commonly have cachexia. Cachexia is a progressive loss of body weight, which is mainly due to loss of fat and skeletal muscle. Survival of cancer patients is directly related to the total weight loss and also the rate of weight loss. The instant invention provides methods of inhibiting and reversing cachexia in subjects that have cancer. Specifically, the instant invention provides methods for treating a patient with cancer cachexia by administering to the subject a growth hormone secretagogue. As demonstrated in Example 3, both the lean body mass and total body weight increase in subjects administered RC-1291 as compared to a control group.

[023] COMBINATION ADMINISTRATION

[024] Administration of a growth hormone secretagogue can take place prior to, after or at the same time as treatment with an additional therapeutic agent, such as, for example, one or more additional anticancer agents, such as those disclosed herein.

[025] PHARMACEUTICAL COMPOSITIONS AND MODES OF ADMINISTRATION

[026] The growth hormone secretagogue (also referred to herein as "active compounds") of the invention can be incorporated into pharmaceutical compositions. Such compositions typically include the growth hormone secretagogue and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" includes solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible

with pharmaceutical administration. Supplementary active compounds can also be incorporated into the compositions.

[027] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[028] A pharmaceutical composition is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. The compounds for use in the method of the invention can be formulated for administration by any suitable route, such as for oral or parenteral, for example, transdermal, transmucosal (e.g., sublingual, lingual, (trans)buccal), vaginal (e.g., trans- and perivaginally), (intra)nasal and (trans)rectal), subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, inhalation, and topical administration.

[029] Suitable compositions and dosage forms include tablets, capsules, caplets, pills, gel caps, troches, dispersions, suspensions, solutions, syrups, granules, beads, transdermal patches, gels, powders, pellets, magmas, lozenges, creams, pastes, plasters, lotions, discs, suppositories, liquid sprays, dry powders or aerosolized formulations.

[030] It is preferred that the compounds are orally administered. Suitable oral dosage forms include, for example, tablets, capsules or caplets prepared by conventional means with pharmaceutically acceptable excipients such as binding

agents (e.g., polyvinylpyrrolidone or hydroxypropylmethylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrates (e.g., sodium starch glycollate); or wetting agents (e.g., sodium lauryl sulphate). If desired, the tablets can be coated, e.g., to provide for ease of swallowing or to provide a delayed release of active, using suitable methods. Liquid preparation for oral administration can be in the form of solutions, syrups or suspensions. Liquid preparations (e.g., solutions, suspensions and syrups) are also suitable for oral administration and can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agent (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxy benzoates or sorbic acid).

[031] As used herein, the term "pharmaceutically acceptable salt" refers to a salt of a compound to be administered prepared from pharmaceutically acceptable non-toxic acids including inorganic acids, organic acids, solvates, hydrates, or clathrates thereof. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, and phosphoric. Appropriate organic acids may be selected, for example, from aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, camphorsulfonic, citric, fumaric, gluconic, isethionic, lactic, malic, mucic, tartaric, para-toluenesulfonic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic (besylate), stearic, sulfanilic, alginic, galacturonic, and the like.

[032] The growth hormone secretagogues disclosed can be prepared in the form of their hydrates, such as hemihydrate, monohydrate, dihydrate, trihydrate, tetrahydrate and the like and as solvates.

[033] It is understood that growth hormone secretagogue compounds can be identified, for example, by screening libraries or collections of molecules using suitable methods. Another source for the compounds of interest are combinatorial libraries which can comprise many structurally distinct molecular species. Combinatorial libraries can be used to identify lead compounds or to optimize a

previously identified lead. Such libraries can be manufactured by well-known methods of combinatorial chemistry and screened by suitable methods.

[034] STEREOCHEMISTRY

[035] Many of the compounds described herein can have one or more chiral centers and therefore can exist in different enantiomeric forms. If desired, a chiral carbon can be designated with an asterisk (*). When bonds to the chiral carbon are depicted as straight lines in the formulas of the invention, it is understood that both the (R) and (S) configurations of the chiral carbon, and hence both enantiomers and mixtures thereof, are embraced within the formula. As is used in the art, when it is desired to specify the absolute configuration about a chiral carbon, one of the bonds to the chiral carbon can be depicted as a wedge (bonds to atoms above the plane) and the other can be depicted as a series or wedge of short parallel lines is (bonds to atoms below the plane). The Cahn-Inglod-Prelog system can be used to assign the (R) or (S) configuration to a chiral carbon.

[036] When a compound of the present invention has two or more chiral carbons, it can have more than two optical isomers and can exist in diastereoisomeric forms. For example, when there are two chiral carbons, the compound can have up to 4 optical isomers and 2 pairs of enantiomers ((S,S)/(R,R) and (R,S)/(S,R)). The pairs of enantiomers (e.g., (S,S)/(R,R)) are mirror image stereoisomers of one another. The stereoisomers which are not mirror-images (e.g., (S,S) and (R,S)) are diastereomers. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of such compounds and mixtures thereof.

[037] VARIABLE DEFINITIONS

[038] In the above structural formulas and throughout the present specification, the following terms have the indicated meanings:

[039] The C_{1-6}-alkyl, C_{1-6}-alkylene, C_{1-4}-alkyl or C_{1-4}-alkylene groups specified above are intended to include those alkyl or alkylene groups of the designated length in either a linear or branched or cyclic configuration as permitted. Examples of linear alkyl are methyl, ethyl, propyl, butyl, pentyl, and hexyl and their corresponding divalent moieties, such as ethylene. Examples of branched alkyl are isopropyl, sec-butyl, tert-butyl, isopentyl, and isohexyl and their corresponding divalent moieties, such as isopropylene. Examples of cyclic alkyl are C_{3-6}-cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl and their corresponding divalent moieties, such as cyclopropylene.

[040] The C_{1-6}-alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a linear or branched or cyclic configuration. Examples of linear alkoxy are methoxy, ethoxy, propoxy, butoxy, pentoxy, and hexoxy. Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy, and isohexoxy. Examples of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

[041] The C_{1-7}-acyl groups specified above are intended to include those acyl groups of the designated length in either a linear or branched or cyclic configuration. Examples of linear acyl are formyl, acetyl, propionyl, butyryl, valeryl, etc. Examples of branched are isobutyryl, isovaleryl, pivaloyl, etc. Examples of cyclic are cyclopentylcarbonyl, cyclohexylcarbonyl, etc.

[042] In the present context, the term "aryl" is intended to include monovalent carbocyclic aromatic ring moieties, being either monocyclic, bicyclic or polycyclic, e.g., phenyl and napthyl, optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, amino or aryl.

[043] In the present context, the term "arylene" is intended to include divalent carbocyclic aromatic ring moieties, being either monocyclic, bicyclic or polycyclic, e.g. selected from the group consisting of phenylene and napthylene, optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, amino or aryl.

[044] In the present context, the term "hetaryl" is intended to include monovalent heterocyclic aromatic ring moieties, being either monocyclic, bicyclic or polycyclic, e.g. selected from the group consisting of pyridyl, 1-H-tetrazol-5-yl, thiazolyl,

imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thienyl, quinolinyl, pyrazinyl, or isothiazolyl, optionally substituted by one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, amino or aryl.

[045] In the present context, the term "hetarylene" is intended to include divalent heterocyclic aromatic ring moieties, being either monocyclic, bicyclic or polycyclic, e.g. selected from the group consisting of pyridinediyl, 1-H-tetrazolediyl, thiazoldiyl, imidazolediyl, indolediyl, pyrimidinediyl, thiadiazolediyl, pyrazolediyl, oxazolediyl, isoxazolediyl, oxadiazolediyl, thiophenediyl, quinolinediyl, pyrazinediyl, or isothiazolediyl, optionally substituted by one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, amino or aryl.

[046] In the present context, the term "heterocyclic system" is intended to include aromatic as well as non-aromatic ring moieties, which may be monocyclic, bicyclic or polycyclic, and contain in their ring structure at least one, such as one, two or three, nitrogen atom(s), and optionally one or more, such as one or two, other hetero atoms, e.g. sulphur or oxygen atoms. The heterocyclic system is preferably selected from pyrazole, pyridazine, triazine, indazole, phthalazine, cinnoline, pyrazolidine, pyrazoline, aziridine, dithiazine, pyrrol, imidazol, pyrazole, isoindole, indole, indazole, purine, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, indoline, isoindoline, or morpholine.

[047] The term "halogen" is intended to include chlorine (Cl), fluorine (F), bromine (Br) and iodine (I).

[048] EXEMPLIFICATION

[049] The present invention will now be illustrated by the following Examples, which are not intended to be limiting in any way.

[050] Example 1

[051] A double blind, placebo controlled, randomized study was designed to investigate the ability of growth hormone secretagogues to be used for the treatment of cell proliferative disorders.

[052] Subjects were separated in to two groups: the placebo group and the RC-1291 group. The RC-1291 group received 50 mg of RC-1291 in two 25 mg capsules daily. The capsules were microcrystalline cellulose, magnesium stearate and RC-1291 HCl (25 mg) in a hard gelatin capsule. The placebo group received two placebo capsules daily. The placebo capsule was microcrystalline cellulose in a hard gelatin capsule.

[053] One hour before breakfast subjects were administered the two capsules after fasting during the night.

[054] The participants in the study are set forth in Table 1.

	Placebo (PBO) N=28	RC-1291 N=32
Gender M/F	16/12	21/11
Age	64.7	64.8
Caucasian	22(78.6%)	24 (75%)
Lung Cancer	7	6
Colorectal Cancer	6	9
IGF-1 change from baseline (nM) At 4 weeks	-0.56609	6.625703
IGF-1 change from	-0.1595	4.728723

baseline (nM) At 8 weeks		
IGF-1 change from baseline (nM) At 12 weeks	0.130736	5.046411
IGFBP-3 change from baseline (nM) At 4 weeks	-2.62295	26.88525
IGFBP-3 change from baseline (nM) At 8 weeks	-0.32787	17.70492
IGFBP-3 change from baseline (nM) At 12 weeks	-1.31148	20.65574

[055] At various points over the course of the three month study, levels of IGFBP-3 and IGF-1 were measured in both the placebo and RC-1291 groups.

[056] The results are presented in Figure 1 and Table 1. RC-1291 raises the levels of both IGFBP-3 and IGF-1 in a statistically significant manner. The effects of RC-1291 on IFGBP-3 were greater than 3 fold, on a molar basis, than on IGF-1. The increase in the molar ratio of IFGBP-3/IGF-1 suggests that RC-1291 exhibits anti-tumor potential.

[057] Insulin-like growth factor binding protein-3 (IGFBP-3) is the major circulating carrier protein for IGFs and is also active in the cellular environment as a potent antiproliferative agent (Baxter, R.C. (2001) Mol Pathol. 54(3):145–148). Accordingly, the results presented in this Example demonstrate that growth hormone secretagogues such as RC-1291 effectively raise the level of IGFBP-3 when administered to a subject and therefore will be useful for the treatment of cell proliferative disorders, e.g., cancer.

[058] Example 2

[059] A second double blind, placebo controlled, randomized study was designed to investigate the ability of growth hormone secretagogues to be used for the treatment of cell proliferative disorders.

[060] The participants in the study are set forth in Table 2.

	Placebo (PBO) N=16	RC-1291 50 mg N=16	RC-1291 100 mg N=20
Gender M/F	6/10	10/6	15/5
Age	66.0	68.6	64.7
Caucasian	11(68.8%)	15 (93.8%)	14 (70.0%)
Lung Cancer	4	3	5
Colorectal Cancer	3	2	4

[061] Subjects were separated into groups and administered a placebo or RC-1291 (Formula III). Each group was administered the appropriate number of capsules. The capsules were microcrystalline cellulose, magnesium stearate and RC-1291 HCl (25 mg) in a hard gelatin capsule. The placebo capsule was microcrystalline cellulose in a hard gelatin capsule. The RC-1291 groups received 50 mg or 100 mg of RC-1291 daily.

[062] Serum was obtained at office visits, clearly labeled, and stored frozen at -20°C prior to shipment on dry ice to CRL, Lenexa, KS for analysis. Samples were assayed for IGF-1 and IGFBP-3.

[063] The summary of results is set forth in Table 3. Detailed results are presented in Tables 4-9 set forth in Figures 4-9 respectively. The results are presented graphically in Figures 2 and 3.

[064] Table 3

IGF-1						
	ng/mL			nM		
Week	PBO	RC-1291 50 mg	RC-1291 100 mg	PBO	RC-1291 50 mg	RC-1291 100 mg
0	0	0	0	0.00	0.00	0.00
1	-5.86	40.69	80.25	-0.77	5.32	10.49
2	-22.33	57	76.25	-2.92	7.45	9.97
4	-16.82	46.5	73.4	-2.20	6.08	9.60
IGFBP-3						
	ng/mL			nM		
Week	PBO	RC-1291 50 mg	RC-1291 100 mg	PBO	RC-1291 50 mg	RC-1291 100 mg
0	0	0	0	0.00	0.00	0.00
1	-80	580	900	-2.78	20.19	31.32
2	-60	540	670	-2.09	18.79	23.32
4	-80	610	970	-2.78	21.23	33.76

[065] The results presented in this Example demonstrate that RC-1291 raised the levels of both IGFBP-3 and IGF-1 in a statistically significant manner as compared to a placebo. The effects of RC-1291 on IGFBP-3 were 2 to 3 fold greater, on a molar basis, than on IGF-1.

[066] Accordingly, the results presented in these Examples demonstrate that growth hormone secretagogues such as RC-1291 effectively raise the level of IGFBP-3 relative to IGF-1 when administered to a subject and therefore will be useful for the treatment of cell proliferative disorders, e.g., cancer.

[067] Example 3: Treatment of Cancer Cachexia Using Growth Hormone Secretagogues

[068] The placebo controlled, randomized studies described above were used to investigate the ability of growth hormone secretagogues to treat subjects having cancer cachexia.

[069] The results are presented in Figures 10, 11, and 12. Total body mass and lean body mass were measured for subjects described in Example 1 (see figures 10, and

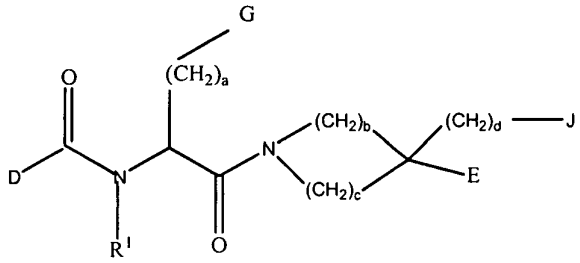
11, respectively.) Lean body mass and total body mass were measured by dual-energy x-ray absorptiometry (DEXA). Total body weight was measured for subjects described in Example 2 (see, Figure 12).

[070] The results presented in Figures 10, 11 and 12 demonstrate that subjects administered RC-1291 (Anamorelin) not only halted the change in lean body mass and total body weight, but that these subjects gained lean body mass and total body weight.

CLAIMS

What is claimed is:

1. A method of treating a subject having a cell proliferative disorder comprising administering to the subject an effective amount of a growth hormone secretagogue, wherein the growth hormone secretagogue is represented by the structural Formula I:



I

wherein:

R^1 is hydrogen, or C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl;

a and d are independently 0, 1, 2 or 3;

b and c are independently 0, 1, 2, 3, 4 or 5, provided that b+c is 3, 4 or 5;

D is R^2 —NH—$(CR^3 R^4)_e$ —$(CH_2)_f$—M—$(CHR^5)_g$—$(CH_2)_h$ —

wherein:

R^2, R^3, R^4 and R^5 are independently hydrogen or C_{1-6} alkyl optionally substituted with one or more halogen, amino, hydroxyl, aryl or hetaryl; or

R^2 and R^3 or R^2 and R^4 or R^3 and R^4 can optionally form —$(CH_2)_i$ —U—$(CH_2)_j$ —, wherein i and j are independently 1 or 2 and U is —O—, —S— or a valence bond;

h and f are independently 0, 1, 2, or 3;

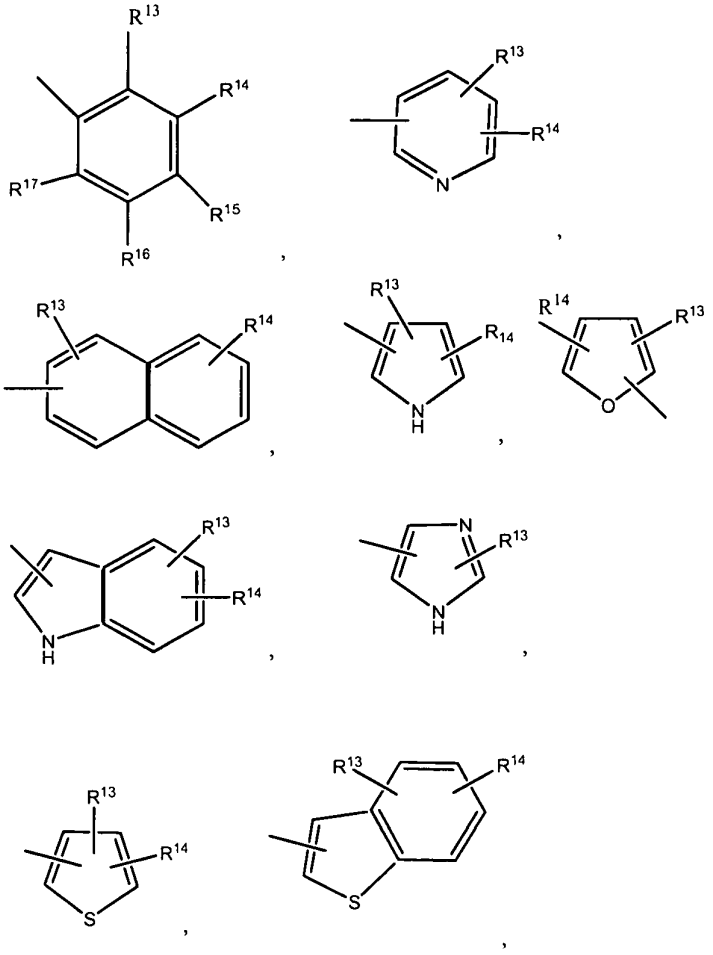
g and e are independently 0 or 1;

M is a valence bond, —CR^6==CR^7 —, arylene, hetarylene, —O— or —S—;

R^6 and R^7 are independently hydrogen, or C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl;

G is —O—$(CH_2)_k$—R^8,

J is —O—$(CH_2)_l$—R^{13} ,



wherein:

R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} independently are hydrogen, halogen, aryl, hetaryl, C_{1-6} -alkyl or C_{1-6} -alkoxy;

k and l are independently 0, 1 or 2;

E is —$CONR^{18}$ R^{19}, —$COOR^{19}$, —$(CH_2)_m$ —NR^{18} SO_2 R^{20}, —$(CH_2)_m$ —NR^{18} — COR^{20}, —$(CH_2)_m$ —OR^{19}, —$(CH_2)_m$ —$OCOR^{20}$, —$CH(R^{18})R^{19}$, —$(CH_2)_m$ —NR^{18} —CS—NR^{19} R^{21} or —$(CH_2)_m$ —NR^{18} —CO—NR^{19} R^{21} ; or

E is —$CONR^{22}$ NR^{23} R^{24}, wherein R^{22} is hydrogen, C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl, or aryl or hetaryl optionally substituted with one or more C_{1-6} -alkyl; R^{23} is C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl, or C_{1-7} -acyl; and R^{24} is hydrogen, C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl; or aryl or hetaryl optionally substituted with one or more C_{1-6} -alkyl; or

R^{22} and R^{23} together with the nitrogen atoms to which they are attached can form a heterocyclic system optionally substituted with one or more C_{1-6} -alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

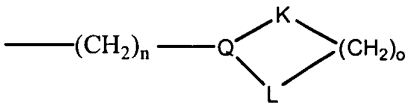
R^{22} and R^{24} together with the nitrogen atoms to which they are attached can form a heterocyclic system optionally substituted with one or more C_{1-6} -alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

R^{23} and R^{24} together with the nitrogen atom to which they are attached can form a heterocyclic system optionally substituted with one or more C_{1-6} -alkyl, halogen, amino, hydroxyl, aryl or hetaryl;

wherein m is 0, 1, 2 or 3,

R^{18}, R^{19} and R^{21} independently are hydrogen or C_{1-6} -alkyl optionally substituted with halogen, —$N(R^{25})R^{26}$, wherein R^{25} and R^{26} are independently hydrogen or C_{1-6} alkyl; hydroxyl, C_{1-6} -alkoxy, C_{1-6} -alkoxycarbonyl, C_{1-6} -alkylcarbonyloxy or aryl;

or R^{19} is



wherein

Q is —CH< or —N<,

K and L are independently —CH_2 —, —CO—, —O—, —S—, —NR^{27} — or a valence bond, where R^{27} is hydrogen or C_{1-6} alkyl;

n and o are independently 0, 1, 2, 3 or 4;

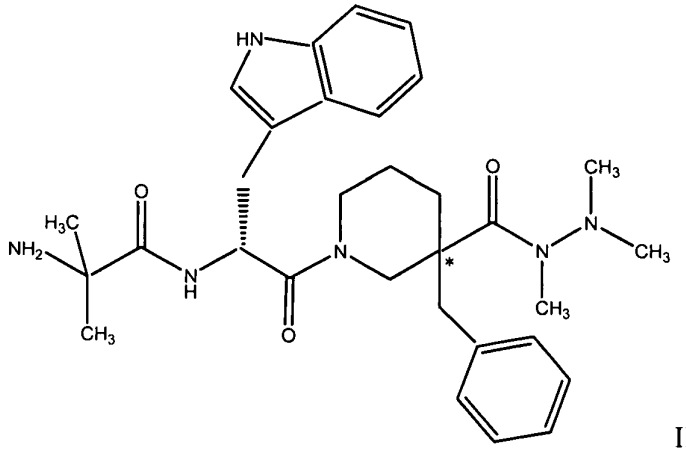
R^{20} is C_{1-6} alkyl, aryl or hetaryl;

or a pharmaceutically acceptable salt thereof;

with the proviso that if M is a valence bond then E is —$CONR^{22}$ NR^{23} R^{24}.

thereby treating the subject.

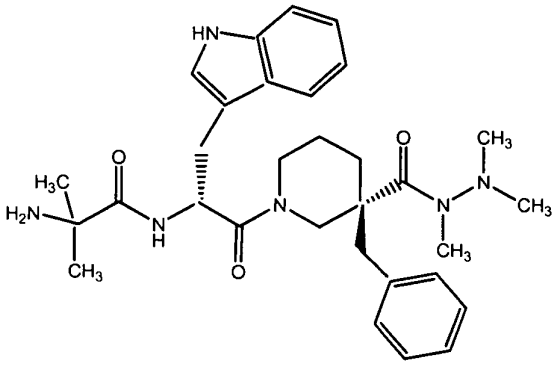
2. The method of Claim 1, wherein the growth hormone secretagogue is represented by the structural Formula II:



II

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

3. The method of Claim 1, wherein the growth hormone secretagogue is represented by the structural Formula III:

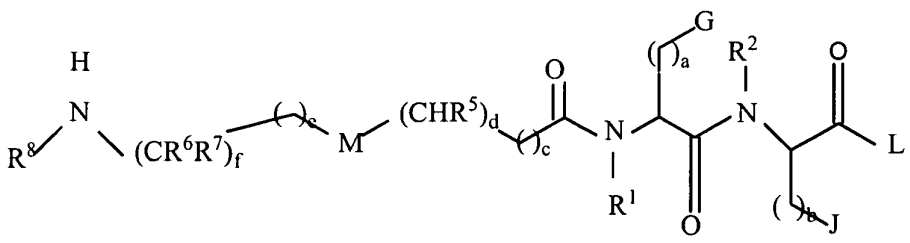


III

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

4. The method of Claim 1, wherein the growth hormone secretagogue is represented by the structural Formula IV:

IV

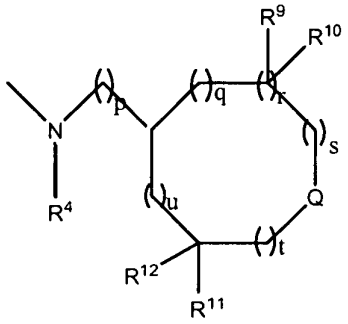


wherein

R^1 is hydrogen or C_{1-6}-alkyl;

R^2 is hydrogen or C_{1-6}-alkyl;

L is



wherein

R^4 is hydrogen or C_{1-6} alkyl;

p is 0 or 1;

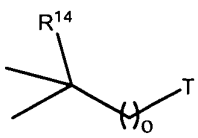
q, s, t, u are independently 0, 1, 2, 3, or 4;

r is 1;

the sum q + r + s + t + u is 0, 1, 2, 3, or 4;

R^9, R^{10}, R^{11}, and R^{12} are independently hydrogen or C_{1-6} alkyl;

Q is > N-R^{13} or



wherein:

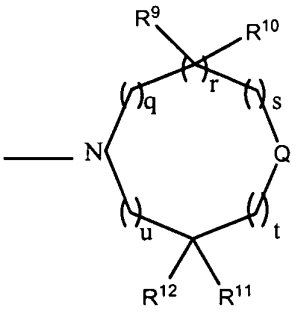
o is 0, 1 or 2;

T is -N(R^{15})(R^{16}) or hydroxyl;

R^{13}, R^{15}, and R^{16} are independently hydrogen or C_{1-6} alkyl;

R^{14} is hydrogen, aryl or hetaryl;

Or L is



wherein

p is 0 or 1;

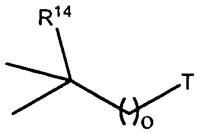
q, s, t, u are independently 0, 1, 2, 3, or 4;

r is 0 or 1;

the sum q + r + s + t + u is 0, 1, 2, 3, or 4;

R^{9}, R^{10}, R^{11}, and R^{12} are independently hydrogen or C_{1-6} alkyl;

Q is >N-R^{13} or



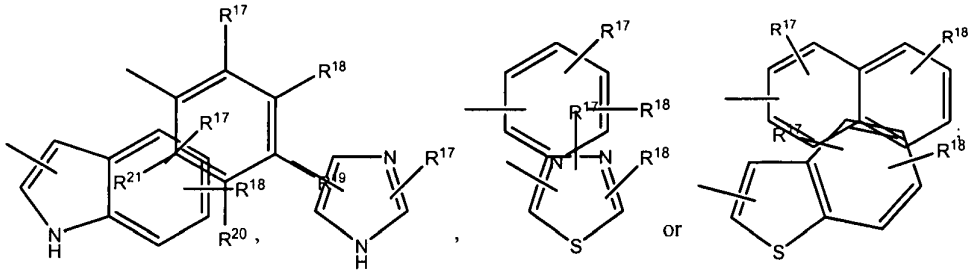
wherein

o is 0, 1, or 2;

T is –N(R^{15})(R^{16}) or hydroxyl;

R^{13}, R^{15}, and R^{16} are independently from each other hydrogen or C_{1-6} alkyl;

R^{14} is hydrogen, aryl, or hetaryl;



G is $-O-(CH_2)-R^{17}$,

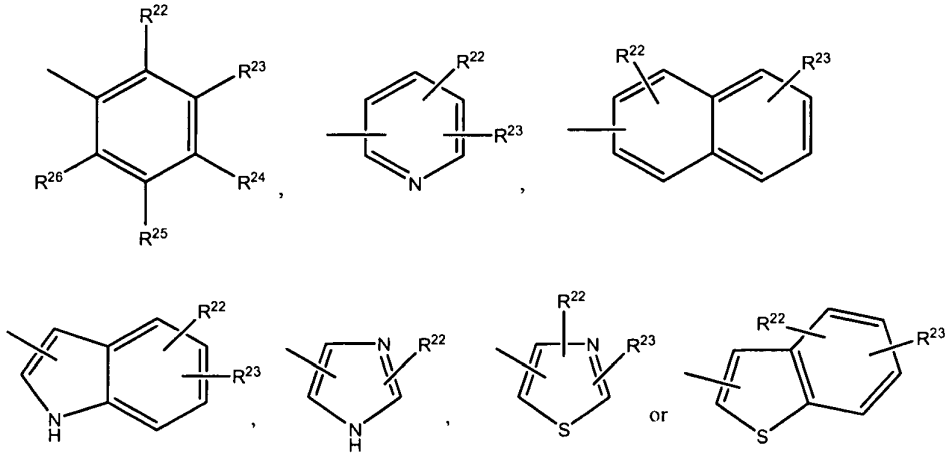
wherein:

R^{17}, R^{18}, R^{19}, R^{20} and R^{21} independently are hydrogen, halogen, aryl, hetaryl,

C_{1-6}-alkyl or C_{1-6}-alkoxy;

K is 0, 1 or 2;

J is $-O-(CH_2)_l-R^{22}$,



wherein:

R^{22}, R^{23}, R^{24}, R^{25} and R^{26} independently are hydrogen, halogen, aryl, hetaryl,

C_{1-6}-alkyl or C_{1-6}-alkoxy;

l is 0, 1 or 2;

a is 0, 1, or 2;

b is 0, 1, or 2;

c is 0, 1, or 2;

d is 0 or 1;

e is 0, 1, 2, or 3;

f is 0 or 1;

R^5 is hydrogen or C_{1-6}-alkyl optionally substituted with one or more hydroxyl, aryl or hetaryl;

R^6 and R^7 are independently hydrogen or C_{1-6}-alkyl, optionally substituted with one or more halogen, amino, hydroxyl, aryl, or hetaryl;

R^8 is hydrogen or C_{1-6}-alkyl, optionally substituted with one or more halogen, amino, hydroxyl, aryl, or hetaryl;

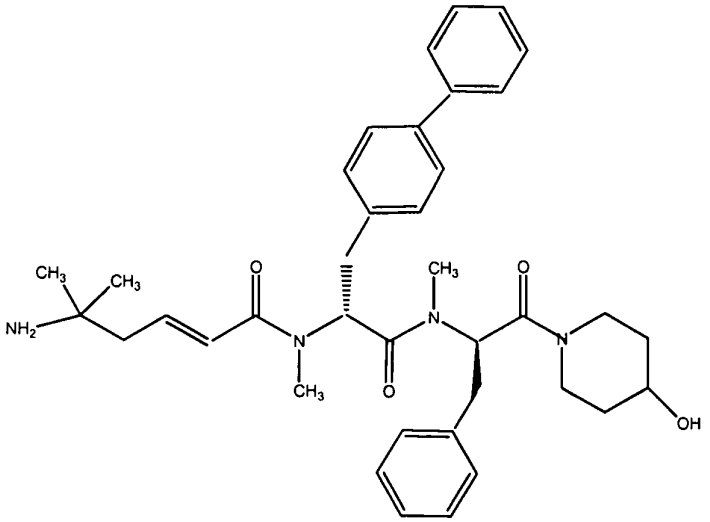
R^6 and R^7 or R^6 and R^8 or R^7 and R^8 can optionally form $-(CH_2)_i-U-(CH_2)_j-$, wherein i and j independently are 1, 2 or 3 and U is -O-, -S-, or a valence bond;

M is arylene, hetarylene, -O-, -S- or-$CR^{27}=CR^{28}$-;

R^{27} and R^{28} are independently hydrogen or C_{1-6}-alkyl, optionally substituted with one or more aryl or hetaryl;

or a pharmaceutically acceptable salt thereof.

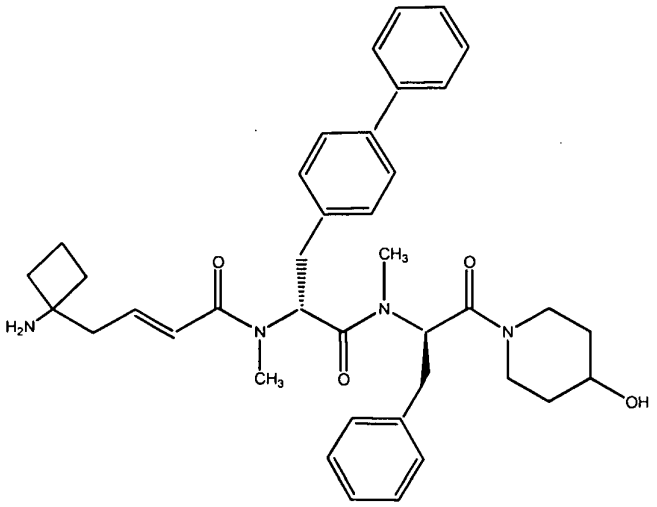
5. The method of Claim 4, wherein the growth hormone secretagogue is represented by the structural Formula V:



V

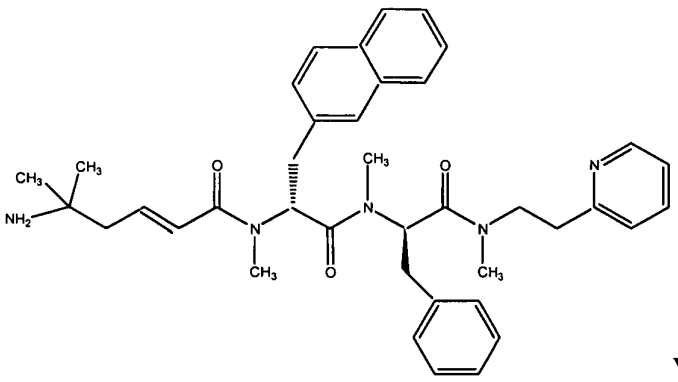
or a pharmaceutically acceptable salt, solvate or hydrate thereof.

6. The method of claim 1, wherein the growth hormone secretagogue is selected from the group consisting of Formula VI,



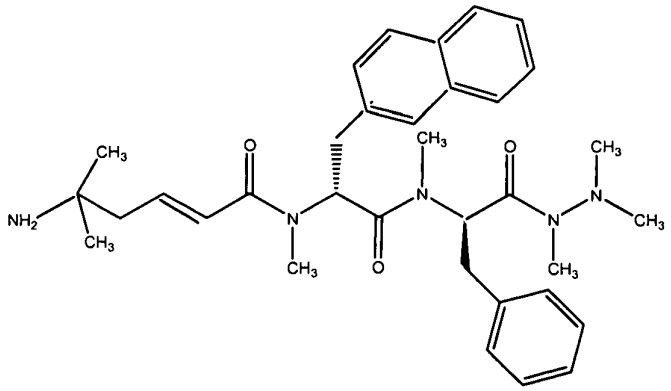
VI

Formula VII,



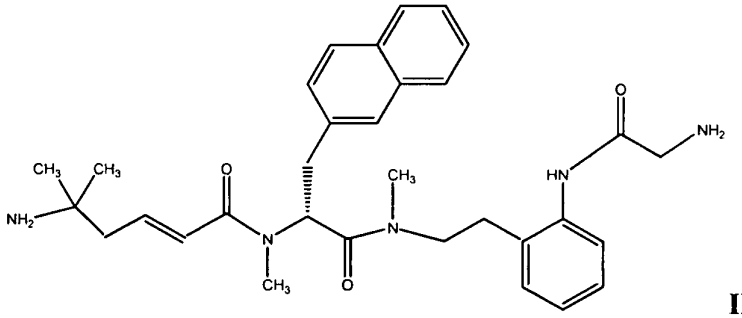
VII

Formula VIII,



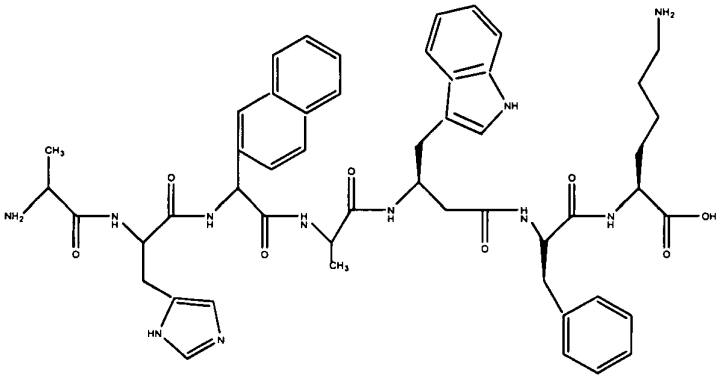
VIII

Formula IX,



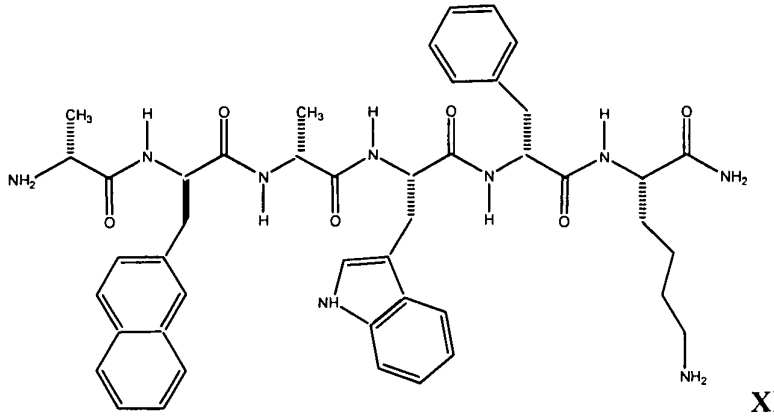
IX

Formula X,



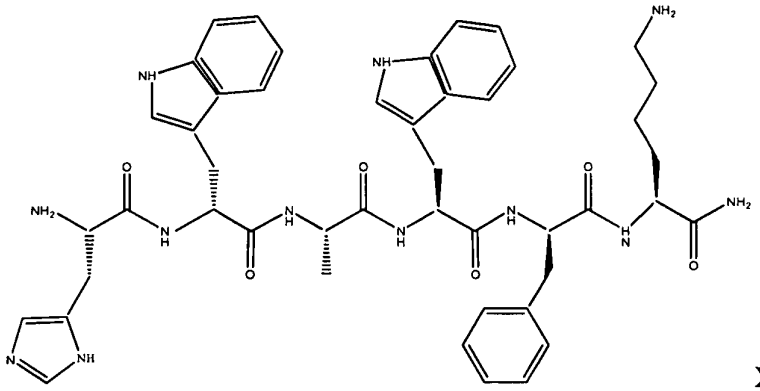
X

Formula XI,



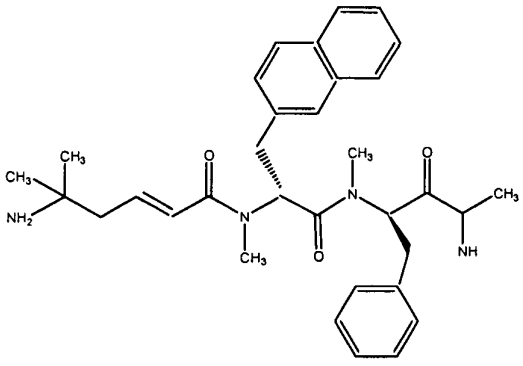
XI

Formula XII,



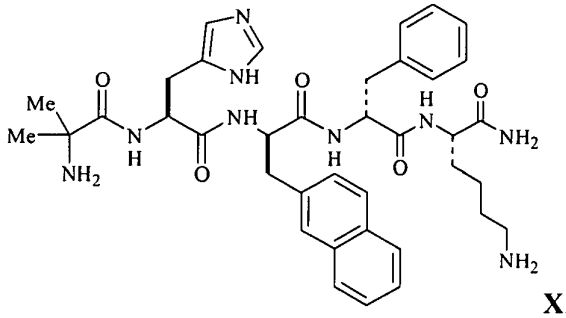
XII

Formula XIII,



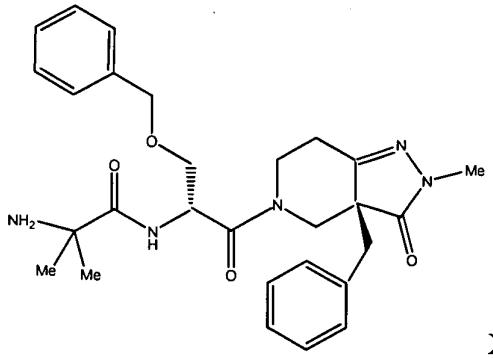
XIII

Formula XIV,



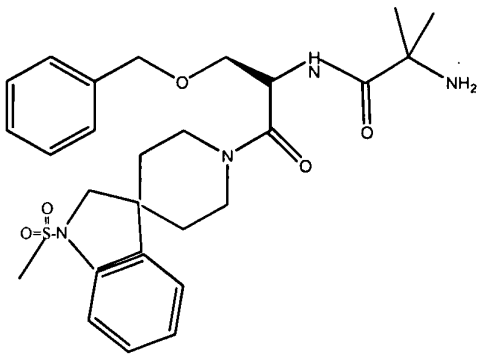
XIV

Formula XV,



XV

and Formula XVI,



XVI

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

7. The method of claim 1, wherein the cell proliferative disorder is cancer.

8. The method of claim 7, wherein the cancer is a solid-tumor cancer.

9. The method of claim 8, wherein the solid tumor cancer is selected from the group consisting of lung, colon and rectal cancer.

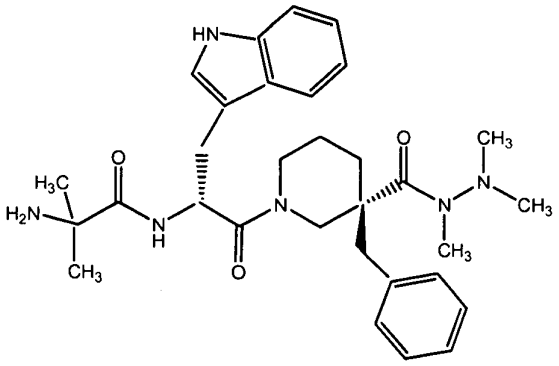
10. The method of claim 7, further comprising administering to the subject one or more additional anti-cancer agents.

11. The method of claim 1, wherein the growth hormone secretagogue is administered at an amount of between about 25 mg/day-150mg/day.

12. The method of claim 11, wherein the growth hormone secretagogue is administered at an amount of between about 50 mg/day-100mg/day.

13. The method of claim 12, wherein the growth hormone secretagogue is administered at an amount of about 50 mg/day.

14. A method of treating a subject having a solid tumor cancer comprising administering to the subject an effective amount of the growth hormone secretagogue represented by structural Formula III:



III

thereby treating the subject.

15. The method of claim 14, wherein the cancer is lung, colon or rectal cancer.

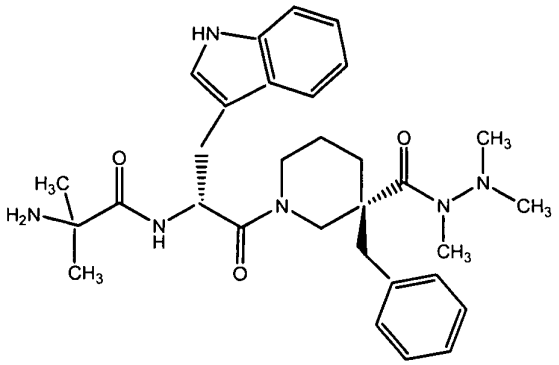
16. The method of claim 14, further comprising administering to the subject one or more additional anti-cancer agents.

17. The method of claim 14, wherein the growth hormone secretagogue is administered at an amount of between about 25 mg/day-150mg/day.

18. The method of claim 17, wherein the growth hormone secretagogue is administered at an amount of between about 50 mg/day-100mg/day.

19. The method of claim 18, wherein the growth hormone secretagogue is administered at an amount of about 50 mg/day.

20. A method of treating a subject having or at risk of developing lung, colon or rectal cancer comprising: administering to the subject an effective amount of the growth hormone secretagogue represented by structural Formula III:



III

threby treating the subject.

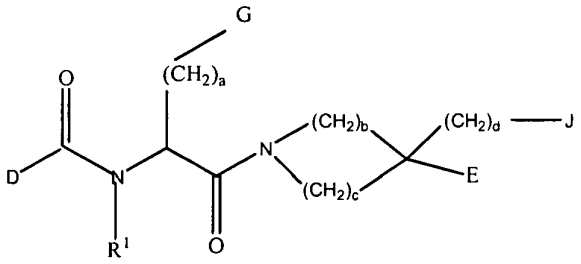
21. The method of claim 20, further comprising administering to the subject one or more additional anti-cancer agents.

22. The method of claim 20, wherein the growth hormone secretagogue is administered at an amount of between about 25 mg/day-150mg/day.

23. The method of claim 22, wherein the growth hormone secretagogue is administered at an amount of between about 50 mg/day-100mg/day.

24. The method of claim 23, wherein the growth hormone secretagogue is administered at an amount of about 50 mg/day.

25. A pharmaceutical composition comprising a growth hormone secretagogue, one or more additional anticancer agents and a pharmaceultically acceptable carrier, wherein the growth hormone secretagogue is represented by the structural Formula I:



I

wherein:

R^1 is hydrogen, or C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl;

a and d are independently 0, 1, 2 or 3;

b and c are independently 0, 1, 2, 3, 4 or 5, provided that b+c is 3, 4 or 5;

D is R^2 —NH—$(CR^3 R^4)_e$ —$(CH_2)_f$—M—$(CHR^5)_g$—$(CH_2)_h$ —

wherein:

R^2, R^3, R^4 and R^5 are independently hydrogen or C_{1-6} alkyl optionallysubstituted with one or more halogen, amino, hydroxyl, aryl or hetaryl; or

R^2 and R^3 or R^2 and R^4 or R^3 and R^4 can optionally form —$(CH_2)_i$ —U—$(CH_2)_j$ —, wherein i and j are independently 1 or 2 and U is —O—, —S— or a valence bond;

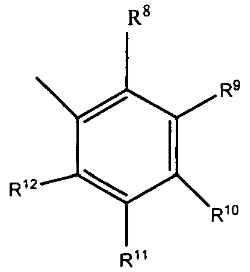
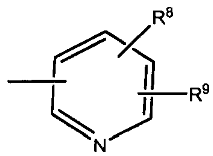
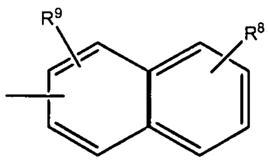
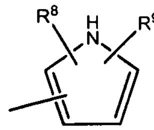
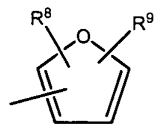
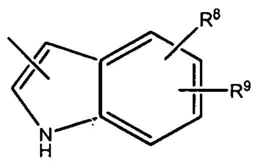
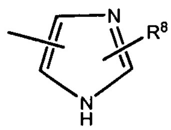
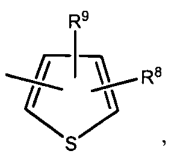
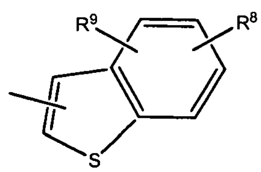
h and f are independently 0, 1, 2, or 3;

g and e are independently 0 or 1;

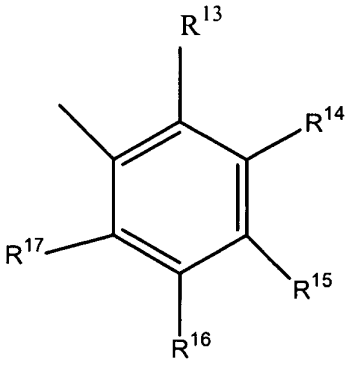
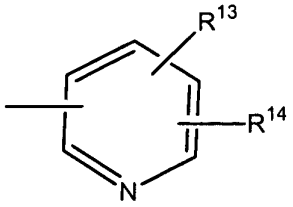
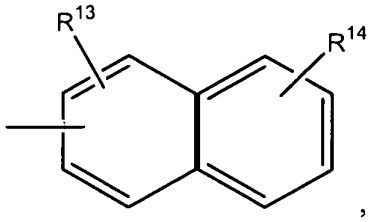
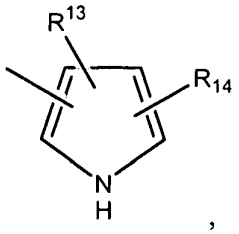
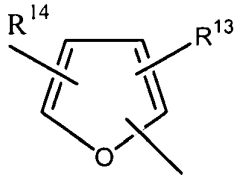
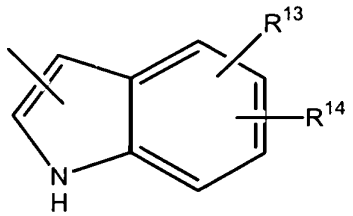
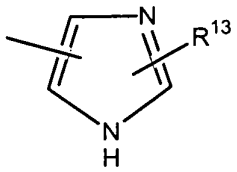
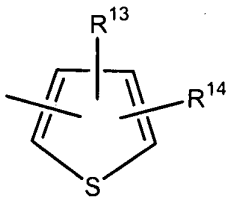
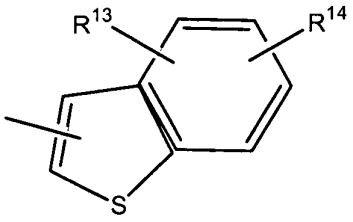
M is a valence bond, —CR^6==CR^7 —, arylene, hetarylene, —O— or —S—;

R^6 and R^7 are independently hydrogen, or C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl;

G is —O—$(CH_2)_k$—R^8,


,

,

,

,

,

,

,

,

;

J is —O—$(CH_2)_t$—R^{13} ,

wherein:

R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} independently are hydrogen, halogen, aryl, hetaryl, C_{1-6} -alkyl or C_{1-6} -alkoxy;

k and l are independently 0, 1 or 2;

E is —$CONR^{18}$ R^{19}, —$COOR^{19}$, —$(CH_2)_m$ —NR^{18} SO_2 R^{20}, —$(CH_2)_m$ —NR^{18} — COR^{20}, —$(CH_2)_m$ —OR^{19}, —$(CH_2)_m$ —$OCOR^{20}$, —$CH(R^{18})R^{19}$, —$(CH_2)_m$ —NR^{18} —CS—NR^{19} R^{21} or —$(CH_2)_m$ —NR^{18} —CO—NR^{19} R^{21} ; or

E is —$CONR^{22}$ NR^{23} R^{24}, wherein R^{22} is hydrogen, C_{1-6} -alkyl

optionally substituted with one or more aryl or hetaryl, or aryl or hetaryl optionally substituted with one or more C_{1-6} -alkyl; R^{23} is C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl, or C_{1-7} -acyl; and R^{24} is hydrogen, C_{1-6} -alkyl optionally substituted with one or more aryl or hetaryl; or aryl or hetaryl optionally substituted with one or more C_{1-6} -alkyl; or

R^{22} and R^{23} together with the nitrogen atoms to which they are attached can form a heterocyclic system optionally substituted with one or more C_{1-6} -alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

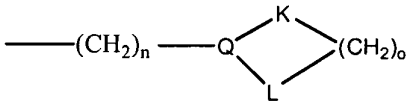
R^{22} and R^{24} together with the nitrogen atoms to which they are attached can form a heterocyclic system optionally substituted with one or more C_{1-6} -alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

R^{23} and R^{24} together with the nitrogen atom to which they are attached can form a heterocyclic system optionally substituted with one or more C_{1-6} -alkyl, halogen, amino, hydroxyl, aryl or hetaryl;

wherein m is 0, 1, 2 or 3,

R^{18}, R^{19} and R^{21} independently are hydrogen or C_{1-6} -alkyl optionally substituted with halogen, —$N(R^{25})R^{26}$, wherein R^{25} and R^{26} are independently hydrogen or C_{1-6} alkyl; hydroxyl, C_{1-6} -alkoxy, C_{1-6} -alkoxycarbonyl, C_{1-6} -alkylcarbonyloxy or aryl;

or R^{19} is



wherein

Q is —CH< or —N<,

K and L are independently —CH_2 —, —CO—, —O—, —S—, —NR^{27} — or a valence bond, where R^{27} is hydrogen or C_{1-6} alkyl;

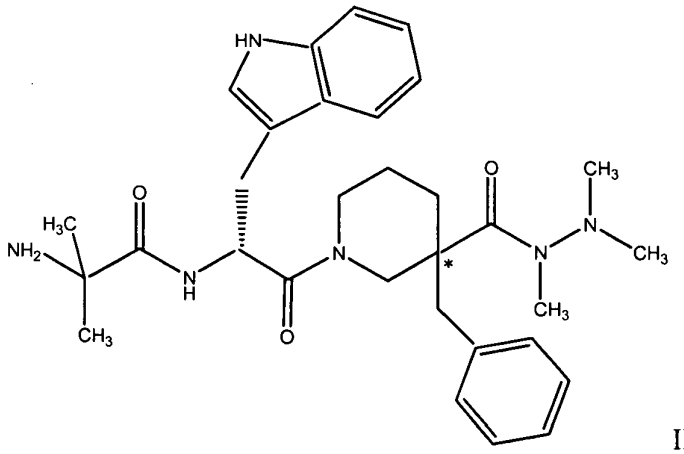
n and o are independently 0, 1, 2, 3 or 4;

R^{20} is C_{1-6} alkyl, aryl or hetaryl;

or a pharmaceutically acceptable salt thereof;

with the proviso that if M is a valence bond then E is —$CONR^{22}$ NR^{23} R^{24}.

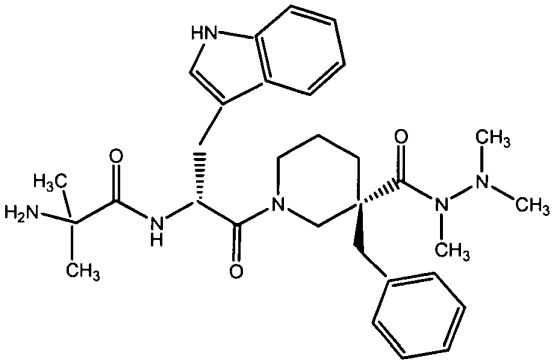
26. The pharmaceutical composition of Claim 25, wherein the growth hormone secretagogue is represented by the structural Formula II:



II

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

27. The pharmaceutical composition of Claim 26, wherein the growth hormone secretagogue is represented by the structural Formula III:

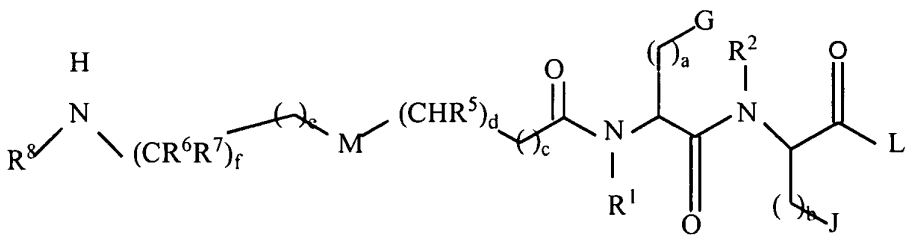


III

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

28. The pharmaceutical composition of Claim 25, wherein the growth hormone secretagogue is represented by the structural Formula IV:

IV

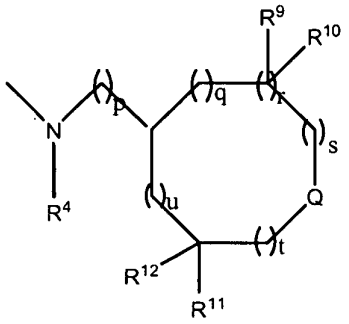


wherein

R^1 is hydrogen or C_{1-6}-alkyl;

R^2 is hydrogen or C_{1-6}-alkyl;

L is



wherein

R^4 is hydrogen or C_{1-6} alkyl;

p is 0 or 1;

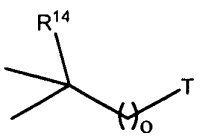
q, s, t, u are independently 0, 1, 2, 3, or 4;

r is 1;

the sum q + r + s + t + u is 0, 1, 2, 3, or 4;

R^9, R^{10}, R^{11}, and R^{12} are independently hydrogen or C_{1-6} alkyl;

Q is > N-R^{13} or



wherein:

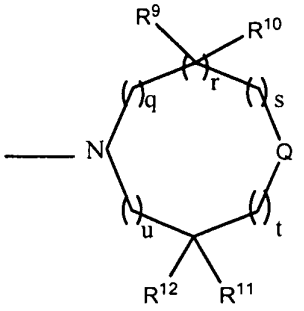
o is 0, 1 or 2;

T is -N(R^{15})(R^{16}) or hydroxyl;

R^{13}, R^{15}, and R^{16} are independently hydrogen or C_{1-6} alkyl;

R^{14} is hydrogen, aryl or hetaryl;

Or L is



wherein

p is 0 or 1;

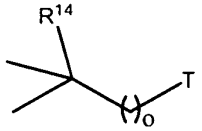
q, s, t, u are independently 0, 1, 2, 3, or 4;

r is 0 or 1;

the sum q + r + s + t + u is 0, 1, 2, 3, or 4;

R^{9}, R^{10}, R^{11}, and R^{12} are independently hydrogen or C_{1-6} alkyl;

Q is >N-R^{13} or



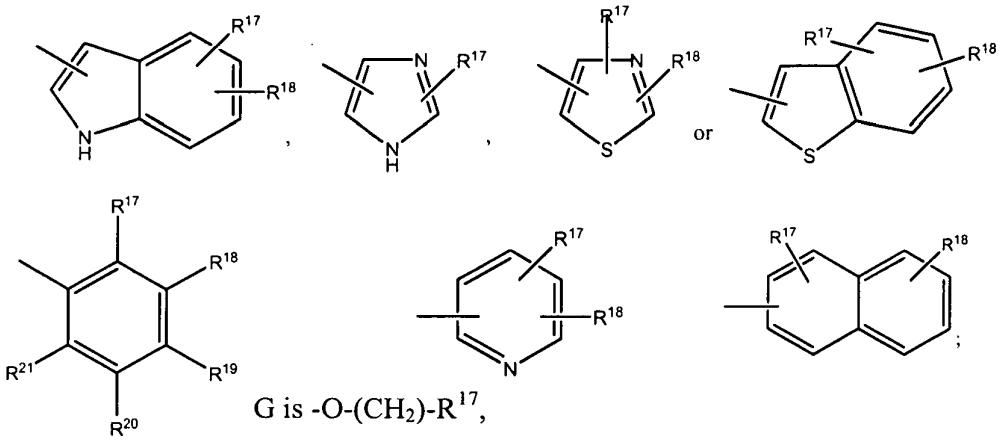
wherein

o is 0, 1, or 2;

T is –N(R^{15})(R^{16}) or hydroxyl;

R^{13}, R^{15}, and R^{16} are independently from each other hydrogen or C_{1-6} alkyl

R^{14} is hydrogen, aryl, or hetaryl;



G is -O-(CH_2)-R^{17},

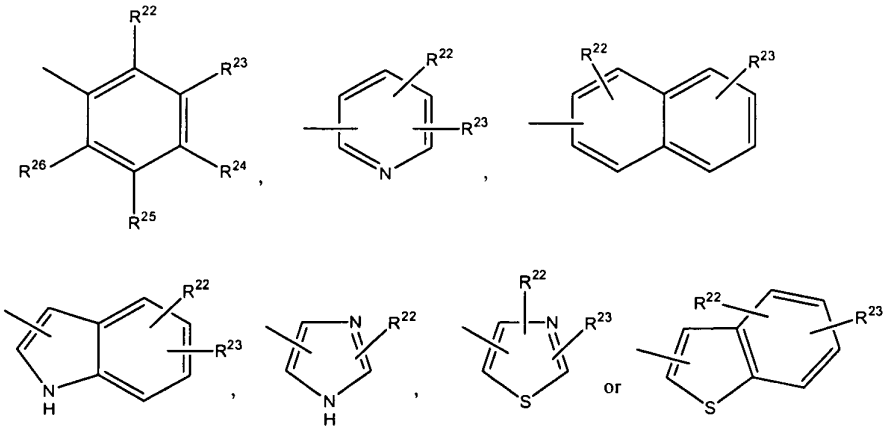
wherein:

R^{17}, R^{18}, R^{19}, R^{20} and R^{21} independently are hydrogen, halogen, aryl, hetaryl,

C_{1-6}-alkyl or C_{1-6}-alkoxy;

K is 0, 1 or 2;

J is -O-$(CH_2)_l$-R^{22},



wherein:

R^{22}, R^{23}, R^{24}, R^{25} and R^{26} independently are hydrogen, halogen, aryl, hetaryl,

C_{1-6}-alkyl or C_{1-6}-alkoxy;

l is 0, 1 or 2;

a is 0, 1, or 2;

b is 0, 1, or 2;

c is 0, 1, or 2;

d is 0 or 1;

e is 0, 1, 2, or 3;

f is 0 or 1;

R^5 is hydrogen or C_{1-6}-alkyl optionally substituted with one or more hydroxyl, aryl or hetaryl;

R^6 and R^7 are independently hydrogen or C_{1-6}-alkyl, optionally substituted with one or more halogen, amino, hydroxyl, aryl, or hetaryl;

R^8 is hydrogen or C_{1-6}-alkyl, optionally substituted with one or more halogen, amino, hydroxyl, aryl, or hetaryl;

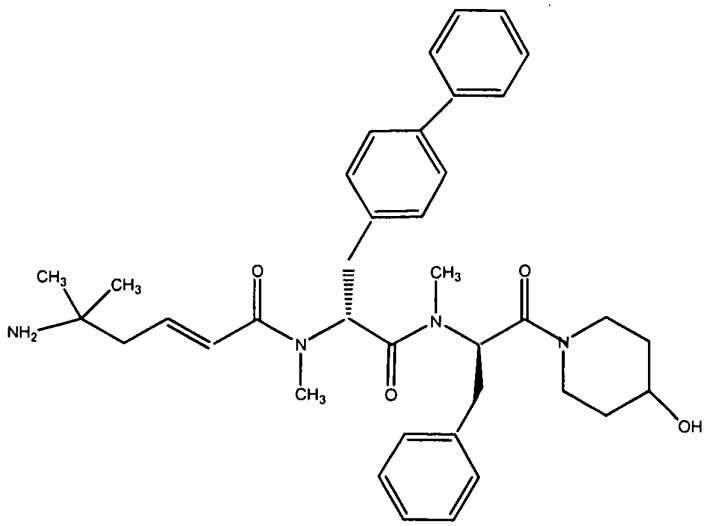
R^6 and R^7 or R^6 and R^8 or R^7 and R^8 can optionally form $-(CH_2)_i-U-(CH_2)_j-$, wherein i and j independently are 1, 2 or 3 and U is -O-, -S-, or a valence bond;

M is arylene, hetarylene, -O-, -S- or-$CR^{27}=CR^{28}$-;

R^{27} and R^{28} are independently hydrogen or C_{1-6}-alkyl, optionally substituted with one or more aryl or hetaryl;

or a pharmaceutically acceptable salt thereof.

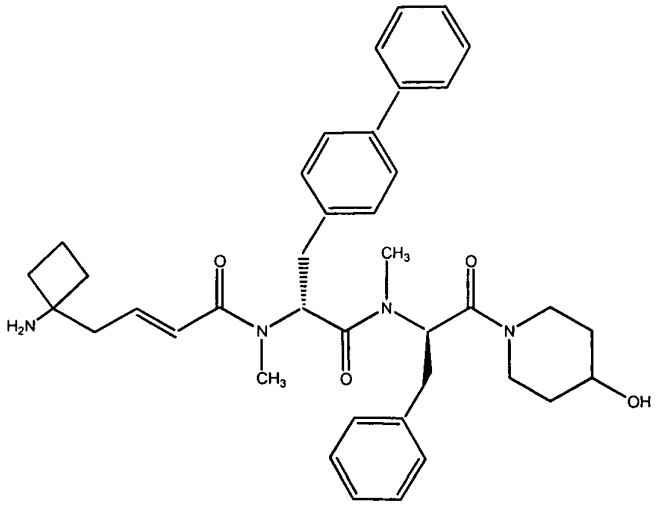
29. The pharmaceutical composition of Claim 28, wherein the growth hormone secretagogue is represented by the structural Formula V:



V

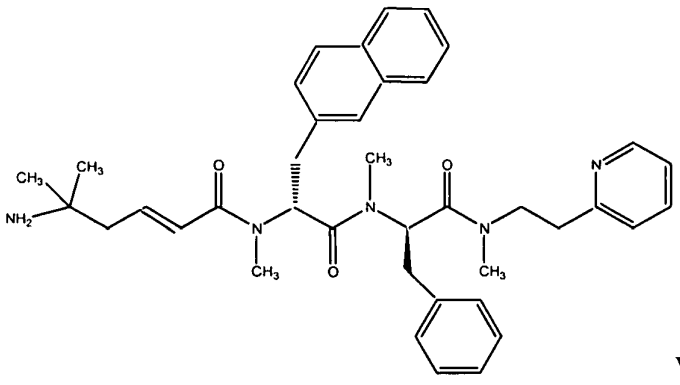
or a pharmaceutically acceptable salt, solvate or hydrate thereof.

30. The pharmaceutical composition of claim 25, wherein the growth hormone secretagogue is selected from the group consisting of Formula VI,



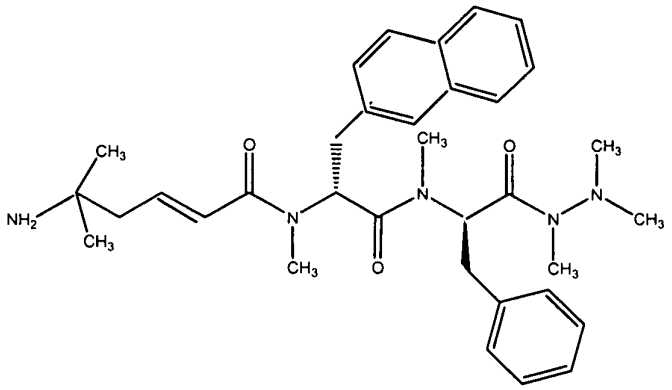
VI

Formula VII,



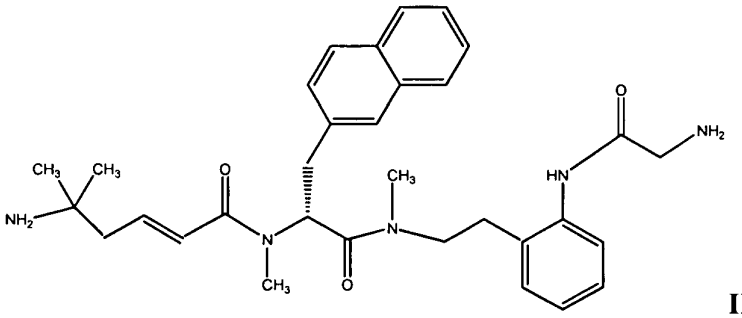
VII

Formula VIII,



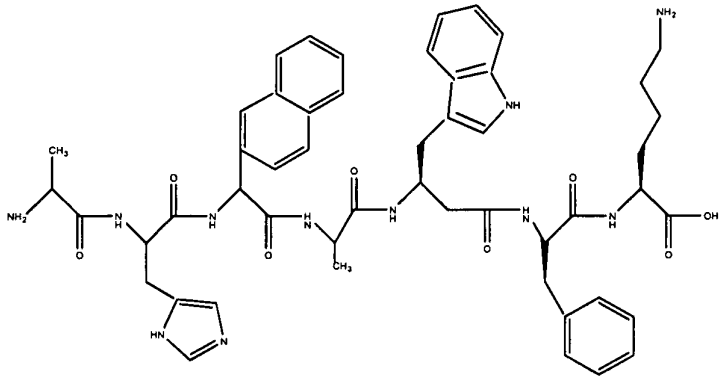
VIII

Formula IX,



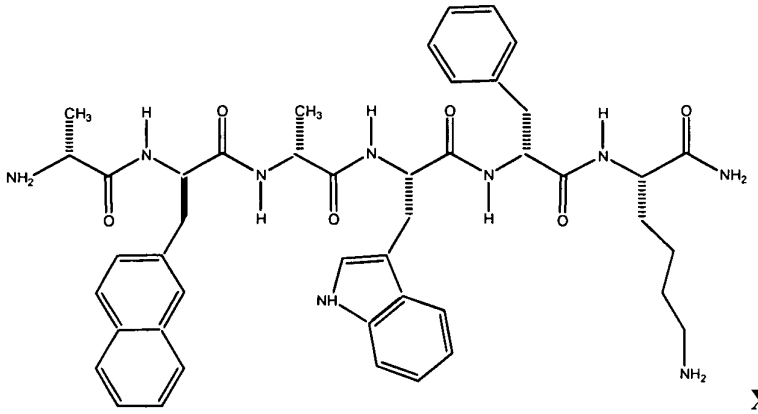
IX

Formula X,



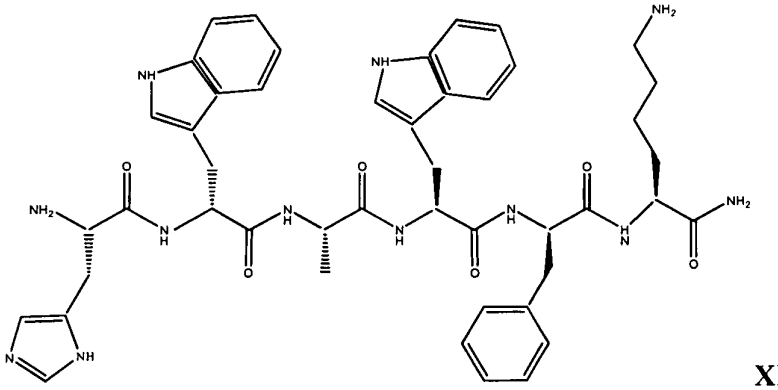
X

Formula XI,



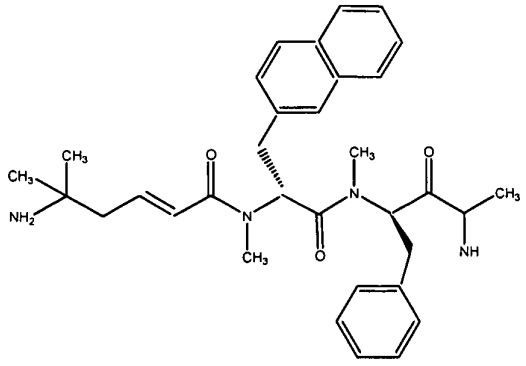
XI

Formula XII,



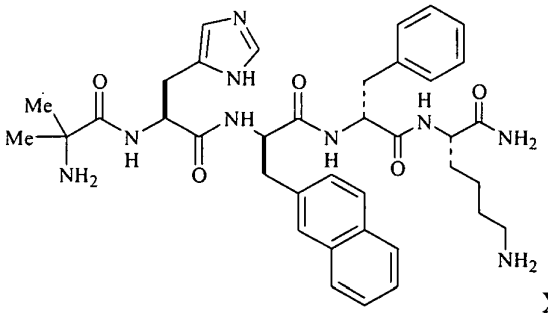
XII

Formula XIII,



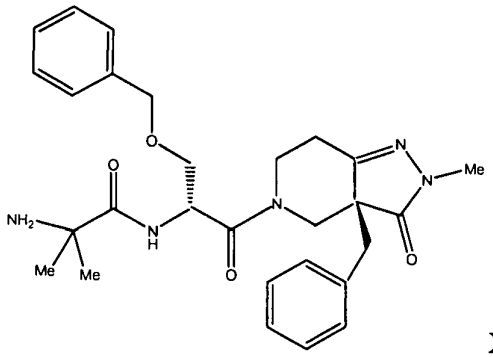
XIII

Formula XIV,



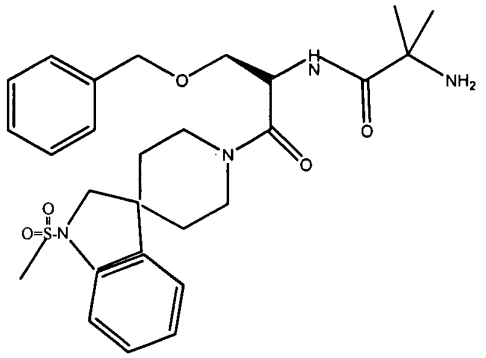
XIV

Formula XV,



XV

and Formula XVI,



XVI

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

31. The pharmaceutical composition of claim 25, further comprising one or more additional anti-cancer agents.

32. The pharmaceutical composition of claim 31, comprising between about 10 mg-150mg of the growth hormone secretagogue.

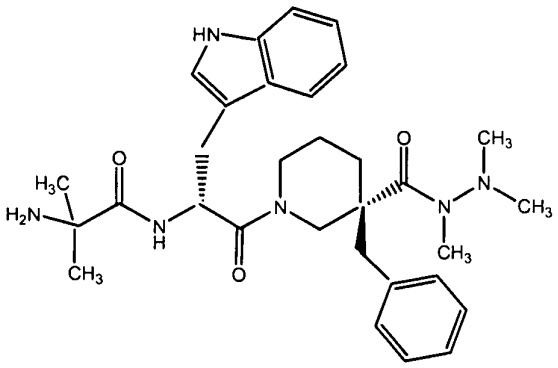
33. The pharmaceutical composition of claim 32, comprising between about 25 mg-125mg of the growth hormone secretagogue.

34. The pharmaceutical composition of claim 33, comprising between about 25mg-100mg of the growth hormone secretagogue.

35. The pharmaceutical composition of claim 34, comprising between about 10 mg-50mg of the growth hormone secretagogue.

36. The pharmaceutical composition of claim 25, comprising about 50mg to about 100 mg of the growth hormone secretagogue.

37. A pharmaceutical composition for the treatment of a cell proliferative disorder comprising a growth hormone secretagogue represented by structural Formula III:



III

or a pharmaceutically acceptable salt, solvate or hydrate thereof, one or more cancer agents, and pharmaceutically acceptable carrier.

38. The pharmaceutical composition of claim 37, comprising between about 10 mg-150mg of the growth hormone secretagogue.

39. The pharmaceutical composition of claim 38, comprising between about 25 mg-125mg of the growth hormone secretagogue.

40. The pharmaceutical composition of claim 39, comprising between about 25mg-100mg of the growth hormone secretagogue.

41. The pharmaceutical composition of claim 40, comprising between about 25 mg-75mg of the growth hormone secretagogue.

42. The pharmaceutical composition of claim 37, comprising about 50 mg-to about 100mg of the growth hormone secretagogue.

43. A kit for the treatment of a cell proliferative disorder comprising the pharmaceutical composition of any one of claims 25-42 and instructions for use.

44. The kit of claim 43, for the treatment of a solid-tumor cancer.

45. The kit of claim 44, wherein the solid-tumor cancer is lung, colon, or rectal cancer.

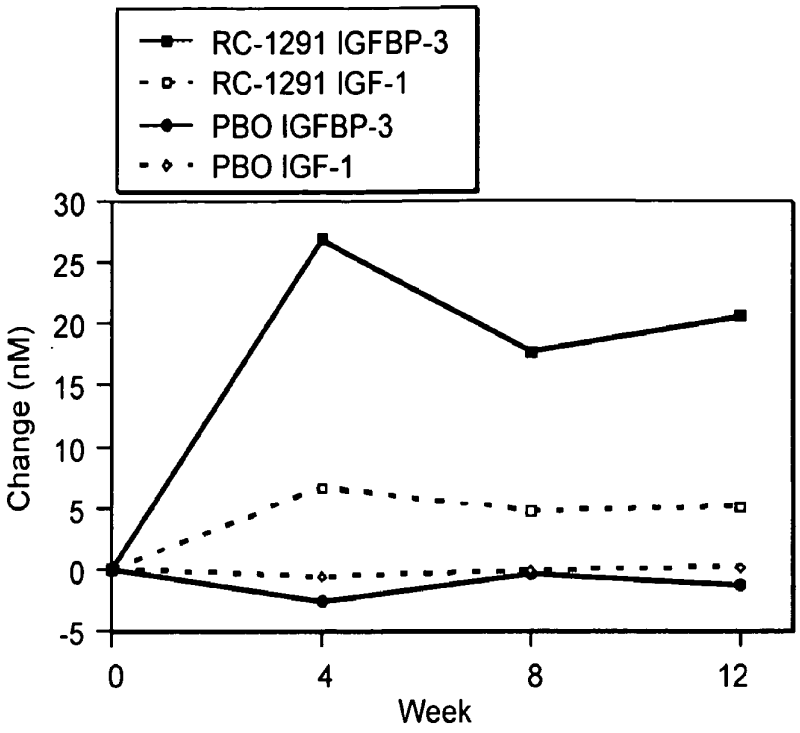

RC-1291 IGFBP-3
RC-1291 IGF-1
PBO IGFBP-3
PBO IGF-1
Change (nM)
30
25
20
15
10
5
0
-5
0
4
8
12
Week

FIG. 1

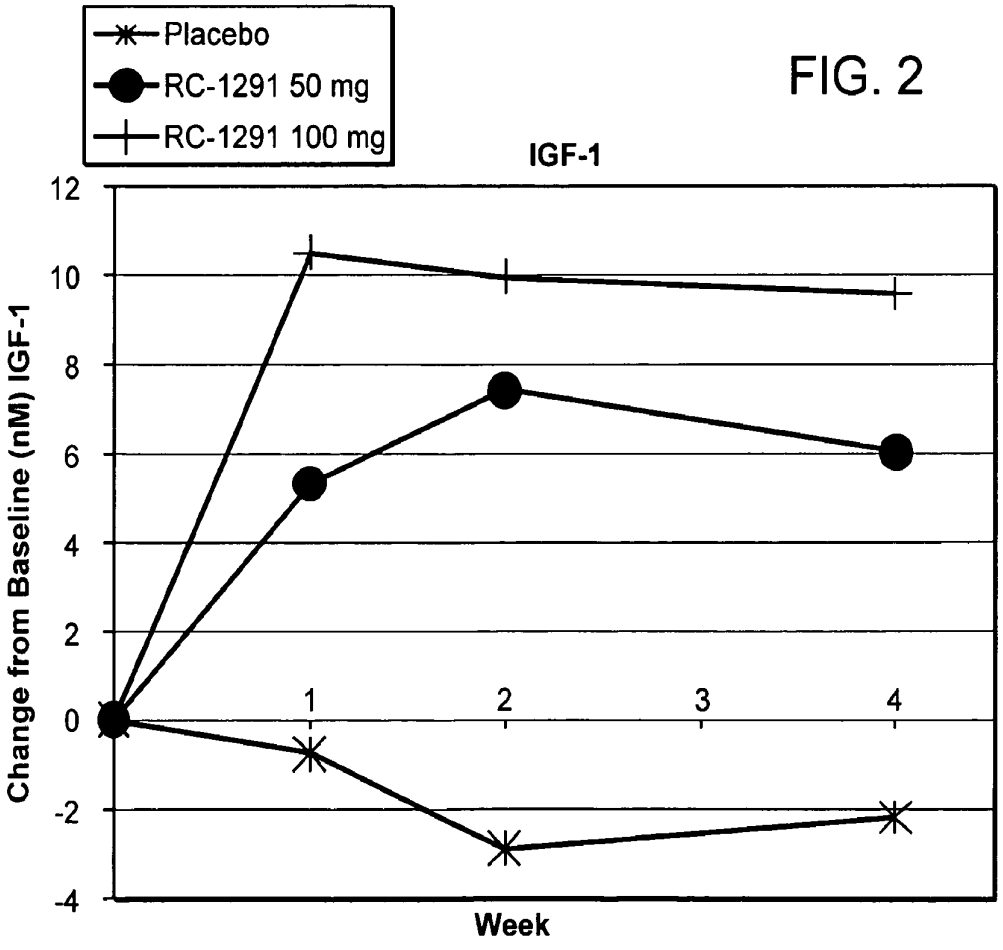

Placebo
RC-1291 50 mg
RC-1291 100 mg
IGF-1
Change from Baseline (nM) IGF-1
12
10
8
6
4
2
0
-2
-4
1
2
3
4
Week

FIG. 2

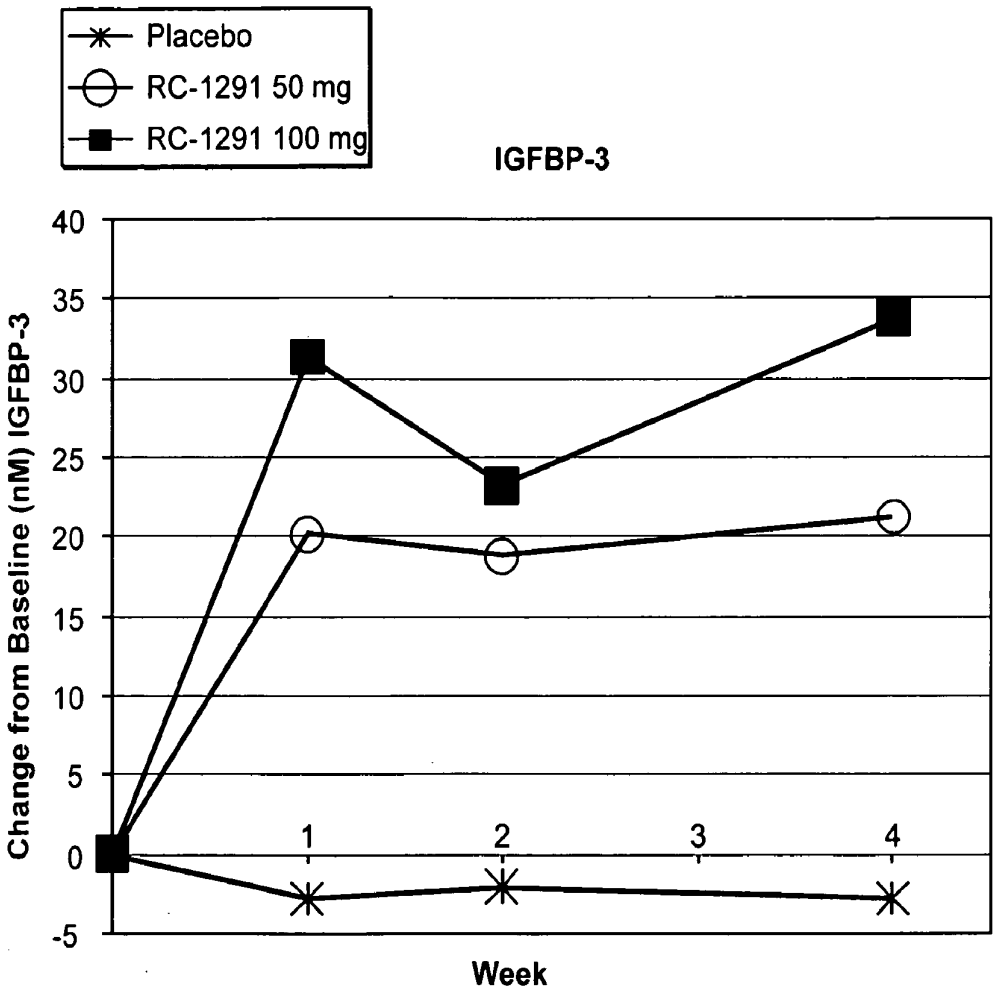

Placebo
RC-1291 50 mg
RC-1291 100 mg
IGFBP-3
Change from Baseline (nM) IGFBP-3
40
35
30
25
20
15
10
5
0
-5
1
2
3
4
Week

FIG. 3

Summary of IGF-1 (ng/ml)
Baseline Through Day 7

Timepoint / Statistic	RC-1291 HCl 50 mg Observed	RC-1291 HCl 50 mg Change	RC-1291 HCl 100 mg Observed	RC-1291 HCl 100 mg Change	Placebo Observed	Placebo Change
Baseline						
N	15		20		16	
Mean	95.87		78.85		112.19	
Std Dev	39.937		42.675		63.789	
Median	98.0		70.0		90.0	
Range	33.0 - 152.0		0.0 - 190.0		44.0 - 297.0	
p-value [1]						0.1437
Day 7						
N	13	13	20	20	14	14
Mean	135.23	40.69	159.10	80.25	112.00	-5.86
Std Dev	58.672	35.352	88.196	52.796	58.904	21.038
Median	132.0	28.0	139.5	64.0	100.5	-2.0
Range	61.0 - 221.0	4.0 - 139.0	42.0 - 386.0	7.0 - 196.0	46.0 - 271.0	-43.0 - 23.0
p-value [2]		0.0013		<0.0001		0.3165
p-value, (CI) [3]		0.0203 (7.5, 85.6)		<0.0001 (50.7, 121.5)		0.0001 (33.7, 98.9)
p-value, (CI) [4]				0.0325 (-75.7, -3.4)		

[1] p-value at baseline from a one-way ANOVA with a term for treatment.

[2] p-value for within-group change from baseline from a paired t-test.

[3] p-value and 95% CI for active treatment versus placebo from a repeated measures ANOVA with terms for treatment, time point, and their interaction.

The p-value under the Placebo column evaluates the combined RC-1291 treatments versus placebo.

[4] p-value and 95% CI for 50 mg vs 100 mg from the same repeated measures ANOVA as in [3].

FIG. 4

FIG. 5A

FIG. 5B

FIG. 5

Summary of IGF-1 (ng/ml) (Continued)
Day 14 Through Week 4

Timepoint	RC-1291 HCl 50 mg		RC-1291 HCl 100 mg		Placebo	
Statistic	Observed	Change	Observed	Change	Observed	Change
Day 14						
N	14	14	16	16	9	9
Mean	152.64	57.00	159.75	76.25	95.11	-22.33
Std Dev	102.366	75.034	88.483	55.241	50.528	36.821
Median	126.0	32.0	135.0	60.0	91.0	-12.0
Range	52.0 - 396.0	-31.0 - 247.0	60.0 - 358.0	11.0 - 184.0	37.0 - 184.0	-113.0 -16.0
p-value [2]		0.0139		<0.0001		0.1063
p-value, (CI) [3]		0.0005 (36.0, 122.7)		<0.0001 (56.3, 140.9)		<0.0001 (50.4, 127.6)
p-value, (CI) [4]				0.3049 (-56.4, 17.9)		

FIG. 5A

Week 4						
N	12	12	15	15	11	11
Mean	136.25	46.50	155.13	73.40	98.27	-16.82
Std Dev	72.870	45.688	97.991	64.626	47.936	35.905
Median	126.5	38.0	116.0	56.0	86.0	-3.0
Range	52.0 - 243.0	-21.0 - 151.0	47.0 - 376.0	5.0 - 204.0	32.0 - 210.0	-87.0 -16.0
p-value [2]		0.0048		0.0006		0.1513
p-value, (CI) [3]		0.0040 (20.9, 105.7)		<0.0001 (49.9, 130.5)		<0.0001 (40.4, 113.1)
p-value, (CI) [4]				0.1767 (-66.2, 12.4)		

[1] p-value at baseline from a one-way ANOVA with a term for treatment.

[2] p-value for within-group change from baseline from a paired t-test.

[3] p-value and 95% CI for active treatment versus placebo from a repeated measures ANOVA with terms for treatment, time point, and their interaction. The p-value under the Placebo column evaluates the combined RC-1291 treatments versus placebo.

[4] p-value and 95% CI for 50 mg vs 100 mg from the same repeated measures ANOVA as in [3].

Table 5

FIG. 5B

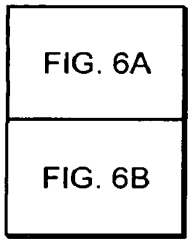


FIG. 6

Summary of IGF-1 (ng/ml)
Week 4 Through Week 12

Timepoint / Statistic	Randomized at Baseline to RC-1291 HCl 50 mg		Randomized at Baseline to RC-1291 HCl 100 mg		Switched at Week 4 from Placebo to RC-1291 HCl 100 mg	
	Observed	Change from W4	Observed	Change from W4	Observed	Change from W4
Week 4						
N	12		15		11	
Mean	136.25		155.13		98.27	
Std Dev	72.870		97.991		47.936	
Median	126.5		116.0		86.0	
Range	52.0 - 243.0		47.0 - 376.0		32.0 - 210.0	

FIG. 6A

Week 8						
N	10	9	11	11	10	10
Mean	113.30	-8.22	161.64	-13.45	178.50	78.80
Std Dev	62.718	21.064	69.856	69.100	123.298	75.482
Median	91.0	-8.0	130.0	-6.0	145.5	60.5
Range	47.0 - 215.0	-53.0 - 16.0	52.0 - 267.0	-143.0 - 92.0	18.0 - 426.0	-14.0 - 216.0
p-value [1]		0.2753		0.5330		0.0092
Week 12						
N	7	7	9	9	8	8
Mean	125.86	9.29	147.33	-12.33	136.88	41.88
Std Dev	62.542	22.647	54.923	78.347	120.668	69.118
Median	99.0	14.0	152.0	-11.0	118.5	29.0
Range	51.0 - 201.0	-32.0 - 38.0	73.0 - 233.0	-159.0 - 111.0	36.0 - 406.0	-19.0 - 196.0
p-value [1]		0.3197		0.6494		0.1303
Slope [2]	-6.88		-3.05		22.67	
p-value [3]	0.6627		0.8553		0.3492	

[1] p-value for within-group change from Week 4 from a paired t-test.

[2] Slope from a linear regression by treatment through the Week 4, Week 8, and Week 12 data.

[3] p-value testing whether the slope of the regression line in [2] is equal to 0.

Table 6

FIG. 6B

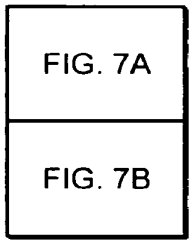


FIG. 7

Summary of IGFBP-3 (ug/ml)
Baseline Through Week 4

Timepoint	RC-1291 HCl 50 mg		RC-1291 HCl 100 mg		Placebo	
Statistic	Observed	Change	Observed	Change	Observed	Change
Baseline						
N	15		20		16	
Mean	3.22		2.69		3.34	
Std Dev	1.297		0.952		1.159	
Median	3.3		2.5		3.0	
Range	1.6 - 5.4		1.3 - 5.2		1.6 - 5.3	
p-value [1]						0.1939

FIG. 7A

Day 7						
N	13	13	20	20	14	14
Mean	3.97	0.58	3.59	0.90	3.43	-0.08
Std Dev	1.402	0.548	1.219	0.543	1.099	0.490
Median	4.7	0.4	3.8	0.9	3.4	-0.1
Range	1.7 - 5.7	-0.3 - 1.8	1.8 - 6.4	0.1 - 2.3	1.6 - 5.1	-1.0 - 1.0
p-value [2]		0.0026		<0.0001		0.5518
p-value, (CI) [3]		0.0141 (0.1, 1.2)		<0.0001 (0.5, 1.5)		0.0003 (0.4, 1.3)
p-value, (CI) [4]				0.1836 (-0.8, 0.2)		

[1] p-value at baseline from a one-way ANOVA with a term for treatment.

[2] p-value for within-group change from baseline from a paired t-test.

[3] p-value and 95% CI for active treatment versus placebo from a repeated measures ANOVA with terms for treatment, time point, and their interaction. The p-value under the Placebo column evaluates the combined RC-1291 treatments versus placebo.

[4] p-value and 95% CI for 50 mg vs 100 mg from the same repeated measures ANOVA as in [3].

FIG. 7B

FIG. 8A

FIG. 8B

FIG. 8

Summary of IGFBP-3 (ug/ml) (Continued)
Baseline Through Week 4

Timepoint / Statistic	RC-1291 HCl 50 mg Observed	RC-1291 HCl 50 mg Change	RC-1291 HCl 100 mg Observed	RC-1291 HCl 100 mg Change	Placebo Observed	Placebo Change
Day 14						
N	14	14	16	16	9	9
Mean	3.83	0.54	3.45	0.67	3.36	-0.06
Std Dev	1.832	0.798	1.443	0.848	0.985	0.602
Median	3.9	0.4	3.3	0.7	3.2	-0.2
Range	0.8 - 6.9	-0.8 - 2.4	0.9 - 6.1	-1.4 - 2.5	2.0 - 5.0	-0.9 - 0.7
p-value [2]		0.0260		0.0064		0.7685
p-value, (CI) [3]		0.0427 (0.0, 1.2)		0.0115 (0.2, 1.3)		0.0120 (0.2, 1.2)
p-value, (CI) [4]				0.5877 (-0.6, 0.4)		

FIG. 8A

Week 4						
N	12	12	15	15	11	11
Mean	3.89	0.61	3.67	0.97	3.29	-0.08
Std Dev	1.451	0.595	1.352	0.706	0.977	0.867
Median	4.3	0.5	3.3	0.9	3.1	0.4
Range	2.0 - 5.8	-0.5 - 2.0	1.7 - 6.8	-0.2 - 2.4	1.9 - 5.2	-1.7 - 1.0
p-value [2]		0.0046		0.0001		0.7581
p-value, (CI) [3]		0.0168 (0.1, 1.3)		0.0002 (0.5, 1.6)		0.0006 (0.4, 1.4)
p-value, (CI) [4]				0.1700 (-0.9, 0.2)		

[1] p-value at baseline from a one-way ANOVA with a term for treatment.

[2] p-value for within-group change from baseline from a paired t-test.

[3] p-value and 95% CI for active treatment versus placebo from a repeated measures ANOVA with terms for treatment, time point, and their interaction. The p-value under the Placebo column evaluates the combined RC-1291 treatments versus placebo.

[4] p-value and 95% CI for 50 mg vs 100 mg from the same repeated measures ANOVA as in [3].

Table 8

FIG. 8B

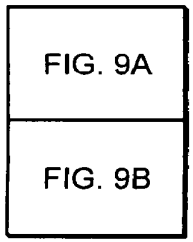


FIG. 9

Summary of IGFBP-3 (ug/ml)
Week 4 Through Week 12

Timepoint Statistic	Randomized at Baseline to RC-1291 HCl 50 mg Observed	Change from W4	Randomized at Baseline to RC-1291 HCl 100 mg Observed	Change from W4	Switched at Week 4 from Placebo to RC-1291 HCl 100 mg Observed	Change from W4
Week 4						
N	12		15		11	
Mean	3.89		3.67		3.29	
Std Dev	1.451		1.352		0.977	
Median	4.3		3.3		3.1	
Range	2.0 - 5.8		1.7 - 6.8		1.9 - 5.2	

FIG. 9A

Week 8						
N	11	10	11	11	10	10
Mean	3.74	-0.16	3.79	-0.26	4.26	0.97
Std Dev	1.643	0.448	1.106	0.838	1.518	0.729
Median	3.7	-0.1	3.8	0.1	4.0	0.8
Range	1.9 - 5.9	-1.0 - 0.4	1.3 - 5.2	-1.6 - 0.8	1.8 - 7.2	-0.1 - 2.1
p-value [1]		0.2964		0.3228		0.0023
Week 12						
N	7	7	9	9	8	8
Mean	4.05	0.12	3.76	-0.12	3.58	0.49
Std Dev	1.946	0.841	0.904	0.873	1.501	0.710
Median	4.0	0.1	4.1	0.0	3.7	0.3
Range	2.1 - 6.4	-1.5 - 1.3	1.9 - 4.6	-1.6 - 1.1	1.5 - 6.2	-0.8 - 1.8
p-value [1]		0.7157		0.6881		0.0933
Slope [2]	0.05		0.05		0.19	
p-value [3]	0.8870		0.8369		0.5516	

[1] p-value for within-group change from Week 4 from a paired t-test.

[2] Slope from a linear regression by treatment through the Week 4, Week 8, and Week 12 data.

[3] p-value testing whether the slope of the regression line in [2] is equal to 0.

Table 9

FIG. 9B

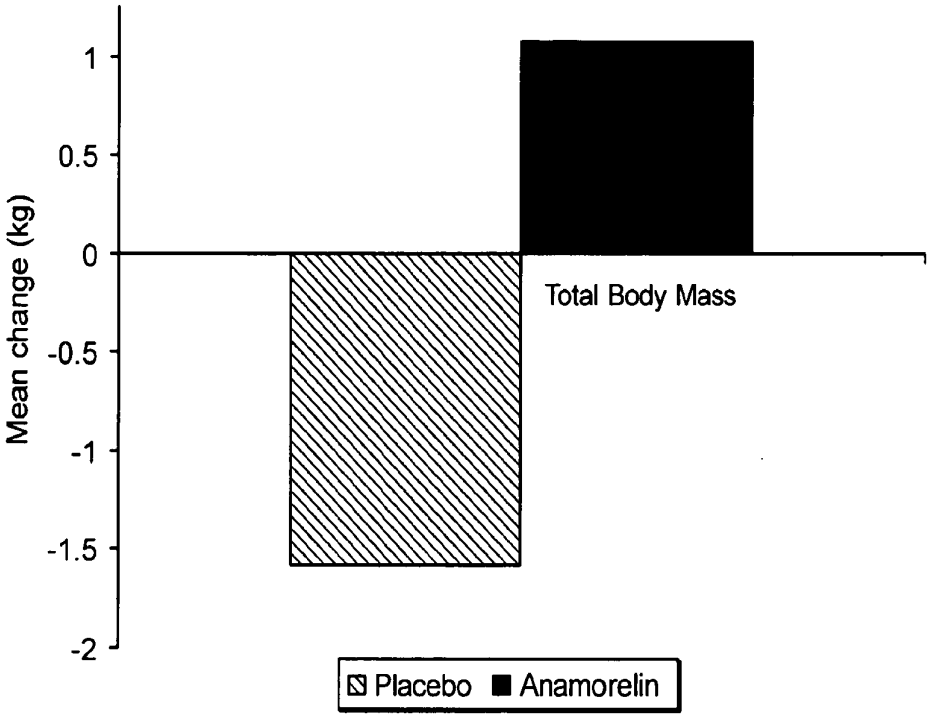

1
0.5
0
-0.5
-1
-1.5
-2
Mean change (kg)
Total Body Mass
Placebo
Anamorelin

FIG. 10

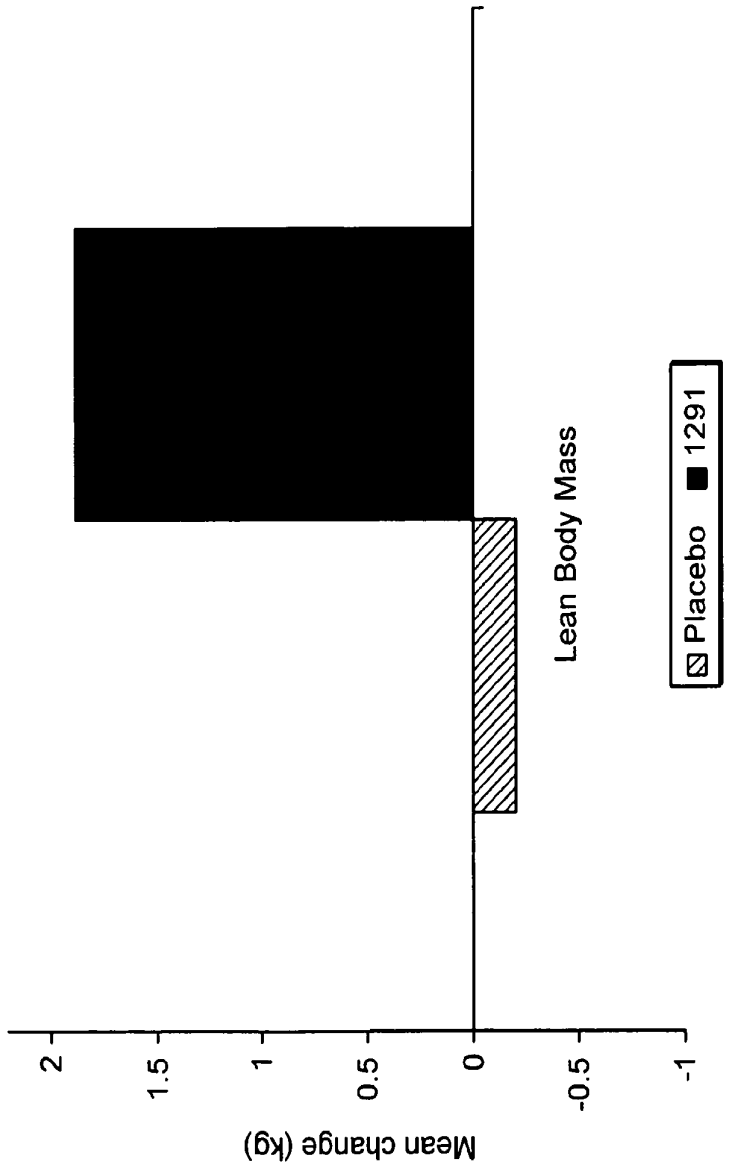


FIG. 11

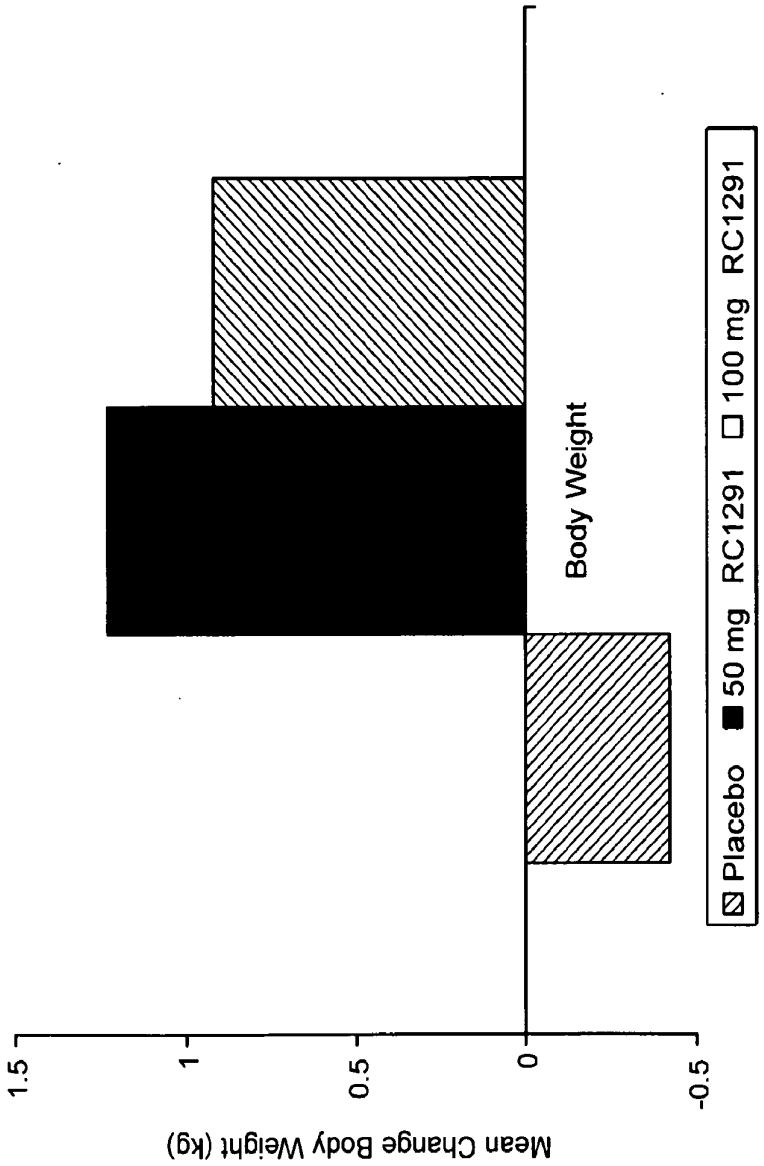

Mean Change Body Weight (kg)
1.5
1
0.5
0
-0.5
Body Weight
Placebo
50 mg RC1291
100 mg RC1291

FIG. 12