

PROCESS FOR PREPARING SOLUBLE GUANYLATE CYCLASE STIMULATORS

RELATED APPLICATIONS

[0001] This application claims the benefit of the filing date, under 35 U.S.C. §119(e), of U.S. Provisional Application No. 62/639,642, filed on March 7, 2018, which is incorporated herein by reference by its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to novel methods for preparing soluble guanylate cyclase (sGC) stimulators.

BACKGROUND OF THE INVENTION

[0003] Compounds that stimulate soluble guanylate cyclase (sGC) can be used to treat many diseases and conditions in which an increase in the concentration of nitric oxide (NO) or cyclic guanosine 3',5'-monophosphate (cGMP) or both, or wherein an upregulation of the NO pathway is desirable. Such diseases and conditions include, but not limited to pulmonary hypertension, arterial hypertension, heart failure, atherosclerosis, inflammation, thrombosis, renal fibrosis and failure, liver cirrhosis, erectile dysfunction, female sexual disorders, disorders related to diabetes, ocular disorders and other related cardiovascular disorders. sGC stimulators offer considerable advantages over other current alternative therapies that either target the aberrant NO pathway or that are directed at diseases wherein upregulation of the NO pathway is beneficial.

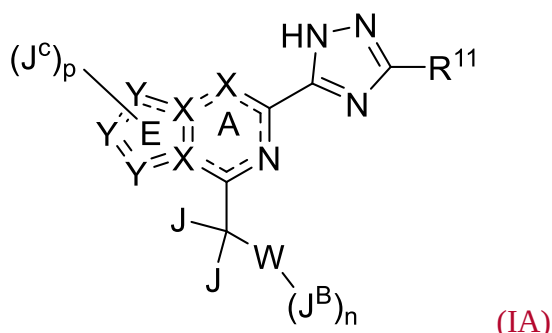
[0004] sGC stimulators are disclosed in U.S. Application Serial No. 15/693,758, the entire teachings of which are incorporated herein by reference. Successful commercialization of a new therapeutic agent requires an efficient process for preparing the agent in high yield and purity. Therefore, there still exists a need for improved processes for preparing the sGC stimulators that are more efficient and suitable for large scale manufacturing process.

SUMMARY OF THE INVENTION

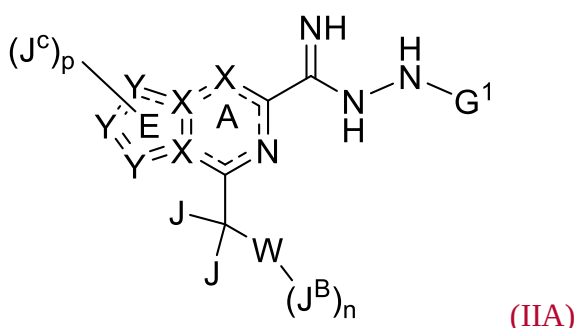
[0005] The present ~~invention-disclosure~~ provides various methods for preparing 3-substituted 1,2,4-triazole compounds as sGC stimulators and their synthetic precursors. Compared to the previously disclosed method, the processes of the present ~~invention-disclosure~~ can produce the sGC stimulators with higher yield and high purity. Specifically, the present methods can produce the sGC stimulators via a shortened, more practical and higher-yielding synthetic sequence

that delivers the final product in much higher purity while eliminating all chromatographic purifications and use of hazardous hydrazine as reagent (hence more suitable for large scale manufacturing). These processes are more suitable for large scale manufacturing process.

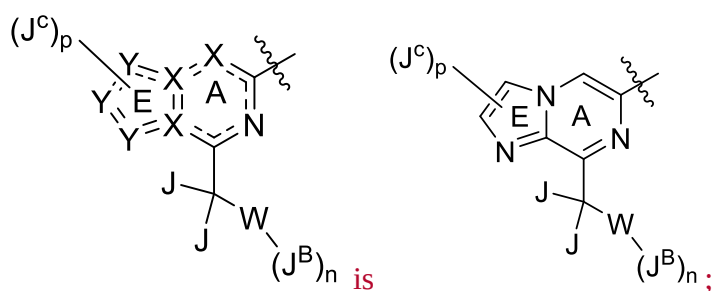
[0005a] In an aspect of the present disclosure, there is provided a process for preparing a 3-substituted 1,2,4-triazole compound represented by Formula IA:



wherein the process comprises reacting the amidrazone compound represented by Formula IIA:



or a salt thereof,
with $R^{11}C(O)OE'$ in the presence of a base, wherein:
the base is LiOH, NaOH, KOH, NaOCH₃, trialkylamine, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), guanidine, 1,1,3,3-tetramethylguanidine, 4-dimethylaminopyridine (DMAP), or 1,4-diazabicyclo[2.2.2]octane (DABCO);



W is a ring B that is a phenyl, a C₃₋₇ cycloalkyl ring or a 5 or 6-membered heteroaryl ring, containing 1 or 2 ring nitrogen atoms;

wherein when ring B is the phenyl or 5 or 6-membered heteroaryl ring; each J is independently hydrogen or methyl; n is an integer selected from 0 to 3; and each J^B is independently selected from halo, -CN, a C₁₋₆ aliphatic, -OR^B and a C₃₋₈ cycloaliphatic ring; and

5 wherein when ring B is the C₃₋₇ cycloalkyl ring; each J is hydrogen; n is an integer selected from 0 to 3 and each J^B is independently selected from halo, -CN, a C₁₋₆ aliphatic and -OR^{B1};

wherein each J^B that is a C₁₋₆ aliphatic and each J^B that is a C₃₋₈ cycloaliphatic ring are optionally and independently substituted with up to 3 instances of R³;

10 each R^B is independently a C₁₋₆ aliphatic or a C₃₋₈ cycloaliphatic ring; said R^B optionally and independently substituted with up to 3 instances of R^{3a};

each R^{B1} is independently selected from hydrogen, a C₁₋₆ aliphatic and a C₃₋₈ cycloaliphatic ring; wherein each of said C₁₋₆ aliphatic and each of said C₃₋₈ cycloaliphatic ring are optionally and independently substituted with up to 3 instances of R^{3b};

15 each R³, R^{3a} and R^{3b} is, in each instance, independently selected from halo, -CN, C₁₋₄ alkyl, C₁₋₄ haloalkyl, -O(C₁₋₄ alkyl) and -O(C₁₋₄ haloalkyl);

p is an integer selected from 1 or 2;

each J^C is independently selected from hydrogen, halo, C₁₋₄ aliphatic, C₁₋₄ alkoxy and -CN; wherein each said C₁₋₄ aliphatic and C₁₋₄ alkoxy is optionally and independently substituted by up to 3 instances of C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, -OH or halo;

20 R¹¹ is C₂₋₆ alkenyl optionally and independently substituted with 1 or 2 occurrences of R^{b2}, C₂₋₆ alkynyl optionally and independently substituted with 1 or 2 occurrences of R^{b2}; or C₁₋₆ alkyl optionally and independently substituted with 1, 2, or 3 occurrences of R¹⁵;

each R¹⁵ is independently halo, -OR^{b2}, -SR^{b2}, -NR^{a2}R^{b2}, -C(O)R^{b2}, -C(O)NR^{a2}R^{b2}, -NR^{b2}C(O)OR^{b2}, -OC(O)NR^{a2}R^{b2}, C₂₋₄ alkenoxy, C₃₋₄ cycloalkyl optionally and independently substituted with 1, 2, or 3 occurrences of R¹⁸, phenyl optionally and independently substituted with 1, 2, or 3 occurrences of R¹⁸, 5- or 6-membered heteroaryl optionally and independently substituted with 1, 2, or 3 occurrences of R¹⁸ or 3-10 membered heterocyclyl optionally and independently substituted with 1, 2, or 3 occurrences of R¹⁸; wherein each of said 5- or 6-

25 membered heteroaryl ring and each of said 3-10 membered heterocyclyl contain up to 3 ring heteroatoms independently selected from N, O and S;

30

each R¹⁸ is independently selected from halo, hydroxyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl and phenyl;

R^{a2} is hydrogen, $-C(O)R^{b2}$, C_{1-6} alkyl or C_{1-6} haloalkyl;

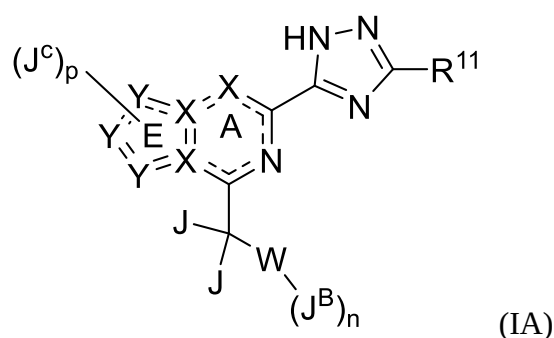
R^{b2} is hydrogen, C_{1-6} alkyl or C_{1-6} haloalkyl;

OE' is $-O-(C_{1-6}\text{alkyl})$, $-O-(C_{1-6}\text{haloalkyl})$, $-O-(\text{phenyl})$, $-O-(\text{heteroaryl})$, $-O-(\text{heterocyclyl})$, wherein the phenyl, heteroaryl, and heterocyclyl are optionally substituted with 1 to 6 groups independently selected from halo, cyano, nitro, oxo, SO_3H , and $SO_3C_{1-6}\text{alkyl}$;

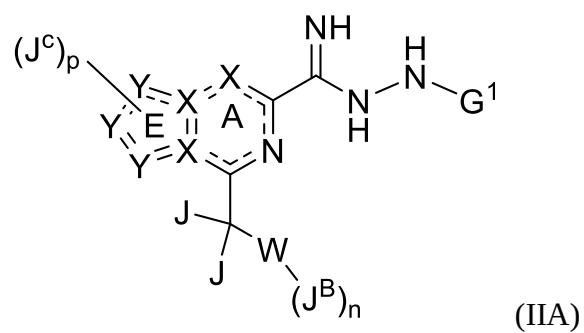
G^1 is tert-butoxycarbonyl (Boc), 2,2,2-trichloroethyloxycarbonyl (Troc), benzyloxycarbonyl (Cbz), 9-fluorenylmethoxycarbonyl (Fmoc), methylsulfonyl, p-toluenesulfonyl (Tos), 4-nitrobenzenesulfonyl (NOSyl), 2-nitrobenzenesulfonyl, p-bromobenzenesulfonyl (Brosyl), trifluoroacetyl, acetyl, benzoyl, 2-trimethylsilylethyl, (2-phenyl-2-trimethylsilyl)ethyl, triisopropylsiloxy, 2-(trimethylsilyl)ethoxymethyl, allyloxycarbonyl, or 2-(trimethylsilyl)ethoxycarbonyl.

[0006] In a first ~~aspect~~example, disclosed herein is a process for preparing a 3-substituted 1,2,4-triazole compound, comprising reacting an amidrazone compound with a carboxylic acid, an activated ester, a thioester, an acid halide, a thioacyl halide or an acid anhydride in the presence of a base. When the carboxylic acid is used, an activating agent is also present. The amidrazone compound comprises an amidrazone bonded to an optionally substituted aryl or heteroaryl; the substituent at the 3 position of the 3-substituted 1,2,4-triazole compound is the optionally substituted aryl or heteroaryl bonded to the amidrazone compound; and the 3-substituted 1,2,4-triazole compound may be optionally substituted at the 5-position.

[0007] The disclosed process can be advantageously used to prepare the 3-substituted 1,2,4-triazole compounds disclosed in U.S. Application Serial No. 15/693,758. Specifically, ~~a the first example embodiment of the first aspect~~ is a process of preparing a 3-substituted 1,2,4-triazole compound represented by Formula IA:



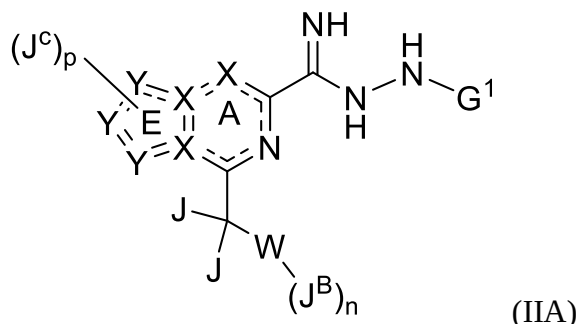
or a salt thereof. The process comprises reacting the amidrazone compound represented by Formula IIA:



or a salt thereof, in the presence of a base with $R^{11}C(O)OH$, $R^{11}C(O)X'$, $R^{11}C(S)X'$, $R^{11}C(O)OE'$, $R^{11}C(O)SR'$, or $R^{11}C(O)OR''$, wherein when $R^{11}C(O)OH$ is used, an activating

G¹ is an amidrazone protecting group.

[0008] In a second aspect example, the present invention disclosure provides synthetic intermediates for the processes of the present invention disclosure. A first embodiment of the further second aspect example is a compound represented by Formula IIA:



or a salt thereof, wherein:

rings E and A form the core of the molecule and are aromatic; each instance of X and Y is independently selected from N, NRⁿ and C; wherein a maximum of 4 instances of X and Y are simultaneously N and Rⁿ is H or C₁₋₆alkyl;

W is either

i) absent, with J^B connected directly to the carbon atom bearing two J groups, each J is independently hydrogen or methyl, n is 1 and J^B is a C₁₋₇ alkyl chain optionally substituted by up to 9 instances of fluorine; or

ii) a ring B that is a phenyl, a C₃₋₇ cycloalkyl ring or a 5 or 6-membered heteroaryl ring, containing 1 or 2 ring nitrogen atoms;

wherein when ring B is the phenyl or 5 or 6-membered heteroaryl ring; each J is independently hydrogen or methyl; n is an integer selected from 0 to 3; and each J^B is independently selected from halo, -CN, a C₁₋₆ aliphatic, -OR^B and a C₃₋₈ cycloaliphatic ring; and

wherein when ring B is the C₃₋₇ cycloalkyl ring; each J is hydrogen; n is an integer selected from 0 to 3 and each J^B is independently selected from halo, -CN, a C₁₋₆ aliphatic and -OR^{B1};

wherein each J^B that is a C₁₋₆ aliphatic and each J^B that is a C₃₋₈ cycloaliphatic ring are optionally and independently substituted with up to 3 instances of R³;

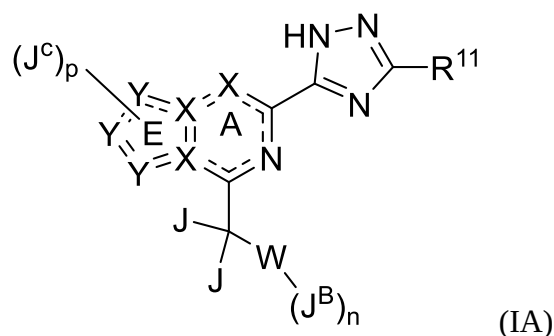
each R^B is independently a C₁₋₆ aliphatic or a C₃₋₈ cycloaliphatic ring; said R^B optionally and independently substituted with up to 3 instances of R^{3a};

each R^{B1} is independently selected from hydrogen, a C₁₋₆ aliphatic and a C₃₋₈ cycloaliphatic ring; wherein each of said C₁₋₆ aliphatic and each of said C₃₋₈ cycloaliphatic ring are optionally and independently substituted with up to 3 instances of R^{3b};

CLAIMS

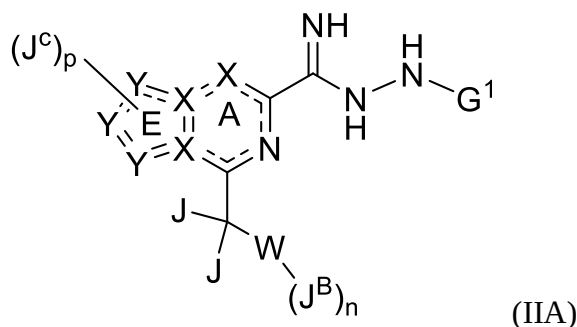
1. ~~A process for preparing a 3-substituted 1,2,4-triazole compound, comprising reacting an amidrazone compound with a carboxylic acid, an activated ester, a thioester, an acid halide, a thioacyl halide or an acid anhydride in the presence of a base; wherein when the carboxylic acid is used, an activating agent is also present, and wherein:~~
- (i) ~~the amidrazone compound comprises an amidrazone bonded to an optionally substituted aryl or heteroaryl;~~
- (ii) ~~the substituent at the 3-position of the 3-substituted 1,2,4-triazole compound is the optionally substituted aryl or heteroaryl bonded to the amidrazone;~~
- and
- (iii) ~~the 3-substituted 1,2,4-triazole compound may be optionally substituted at the 5-position.~~

21. ~~The A~~ process ~~of claim 1, wherein the~~ for preparing a 3-substituted 1,2,4-triazole compound ~~is~~ represented by Formula IA:



~~or a salt thereof, and~~

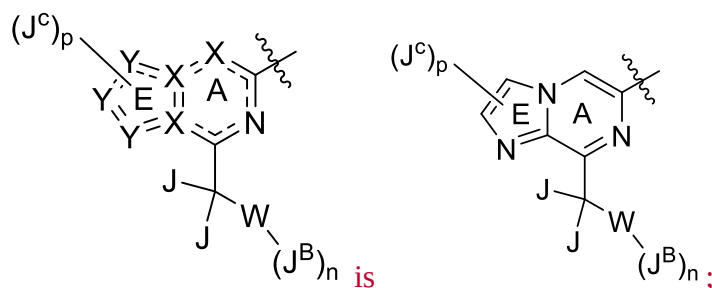
wherein the process comprises reacting the amidrazone compound represented by Formula IIA:



or a salt thereof,

with $R^{11}C(O)OH$, $R^{11}C(O)X'$, $R^{11}C(S)X'$, $R^{11}C(O)OE'$ in the presence of a base; $R^{11}C(O)SR'$, or $R^{11}C(O)OR''$, wherein ~~when $R^{11}C(O)OH$ is used, an activating agent is also present;~~

5 the base is LiOH, NaOH, KOH, NaOCH₃, trialkylamine, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), guanidine, 1,1,3,3-tetramethylguanidine, 4-dimethylaminopyridine (DMAP), or 1,4-diazabicyclo[2.2.2]-octane (DABCO);



wherein:

10 rings E and A form the core of the molecule and are aromatic; each instance of X and Y is independently selected from N, NRⁿ and C; wherein a maximum of 4 instances of X and Y are simultaneously N and Rⁿ is H or C₁₋₆alkyl;

W is either

15 i) absent, with J^B connected directly to the carbon atom bearing two J groups, each J is independently hydrogen or methyl, n is 1 and J^B is a C₁₋₇ alkyl chain optionally substituted by up to 9 instances of fluorine; or

ii) a ring B that is a phenyl, a C₃₋₇ cycloalkyl ring or a 5 or 6-membered heteroaryl ring, containing 1 or 2 ring nitrogen atoms;

20 wherein when ring B is the phenyl or 5 or 6-membered heteroaryl ring; each J is independently hydrogen or methyl; n is an integer selected from 0 to 3; and each J^B is independently selected from halo, -CN, a C₁₋₆ aliphatic, -OR^B and a C₃₋₈ cycloaliphatic ring; and

25 wherein when ring B is the C₃₋₇ cycloalkyl ring; each J is hydrogen; n is an integer selected from 0 to 3 and each J^B is independently selected from halo, -CN, a C₁₋₆ aliphatic and -OR^{B1};

wherein each J^B that is a C₁₋₆ aliphatic and each J^B that is a C₃₋₈ cycloaliphatic ring are optionally and independently substituted with up to 3 instances of R³;

each R^B is independently a C₁₋₆ aliphatic or a C₃₋₈ cycloaliphatic ring; said R^B optionally and independently substituted with up to 3 instances of R^{3a};

each R^{B1} is independently selected from hydrogen, a C₁₋₆ aliphatic and a C₃₋₈ cycloaliphatic ring; wherein each of said C₁₋₆ aliphatic and each of said C₃₋₈ cycloaliphatic ring are optionally and independently substituted with up to 3 instances of R^{3b};

5 each R³, R^{3a} and R^{3b} is, in each instance, independently selected from halo, -CN, C₁₋₄ alkyl, C₁₋₄ haloalkyl, -O(C₁₋₄ alkyl) and -O(C₁₋₄ haloalkyl);

p is an integer selected from 1, or 2 ~~or 3~~;

each J^C is independently selected from hydrogen, halo, C₁₋₄ aliphatic, C₁₋₄ alkoxy and -CN; wherein each said C₁₋₄ aliphatic and C₁₋₄ alkoxy is optionally and independently substituted by up to 3 instances of C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, -OH or halo;

10 R¹¹ is ~~H, -NR^{a2}R^{b2}, -C(O)NR^{a2}R^{b2}, -C(O)R^{15a}, -CN,~~ C₂₋₆ alkenyl optionally and independently substituted with 0-1 or 2 occurrences of R^{b2}, C₂₋₆ alkynyl optionally and independently substituted with 0-1 or 2 occurrences of R^{b2}; or C₁₋₆ alkyl optionally and independently substituted with 0-1, 2, or 3 occurrences of R¹⁵; ~~C₁₋₆-alkoxy optionally and independently substituted with 0-5 occurrences of R¹⁵; phenyl optionally and independently substituted with 0-3 occurrences of R¹⁵; 5- to 6-membered heteroaryl optionally and independently substituted with 0-3 occurrences of R¹⁵; C₃₋₈-cycloalkyl optionally and independently substituted with 0-3 occurrences of R¹⁵; or 3-8 membered heterocyclyl optionally and independently substituted with 0-3 occurrences of R¹⁵; wherein each of said 5- to 6-membered heteroaryl and each of said 3-8 membered heterocyclyl contain up to 3 ring heteroatoms independently selected from N, O and S;~~

20 each R¹⁵ is independently halo, -OR^{b2}, -SR^{b2}, -NR^{a2}R^{b2}, -C(O)R^{b2}, -C(O)NR^{a2}R^{b2}, -NR^{b2}C(O)OR^{b2}, -OC(O)NR^{a2}R^{b2}, C₂₋₄ alkenoxy, C₃₋₄ cycloalkyl optionally and independently substituted with 0-1, 2, or 3 occurrences of R¹⁸, phenyl optionally and independently substituted with 0-1, 2, or 3 occurrences of R¹⁸, 5- or 6-membered heteroaryl optionally and independently substituted with 0-1, 2, or 3 occurrences of R¹⁸ or 3-10 membered heterocyclyl optionally and independently substituted with 0-1, 2, or 3 occurrences of R¹⁸; wherein each of said 5- or 6-membered heteroaryl ring and each of said 3-10 membered heterocyclyl contain up to 3 ring heteroatoms independently selected from N, O and S;

30 ~~R^{15a} is C₃₋₈-cycloalkyl optionally and independently substituted with 0-3 occurrences of R¹⁸; phenyl optionally and independently substituted with 0-3~~

occurrences of R^{18} , 5- or 6-membered heteroaryl optionally and independently substituted with 0-3 occurrences of R^{18} or 3-10 membered heterocyclyl optionally and independently substituted with 0-3 occurrences of R^{18} ; wherein each of said 5- or 6-membered heteroaryl ring and each of said 3-10 membered heterocyclyl contain up to 3 ring heteroatoms independently selected from N, O and S;

each R^{18} is independently selected from halo, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl and phenyl;

R^{a2} is hydrogen, $-C(O)R^{b2}$, C_{1-6} alkyl or C_{1-6} haloalkyl;

R^{b2} is hydrogen, C_{1-6} alkyl or C_{1-6} haloalkyl;

~~X' is a halide;~~

~~OE' is $-O-(C_{1-6}\text{alkyl})$, $-O-(C_{1-6}\text{ haloalkyl})$, $-O-(\text{phenyl})$, $-O-(\text{heteroaryl})$, $-O-(\text{heterocyclyl})$, wherein the phenyl, heteroaryl, and heterocyclyl are optionally substituted with 1 to 6 groups independently selected from halo, cyano, nitro, oxo, SO_3H , and $SO_3C_{1-6}\text{alkyl}$ a leaving group of an activated ester;~~

~~SR' is a leaving group of a thioester;~~

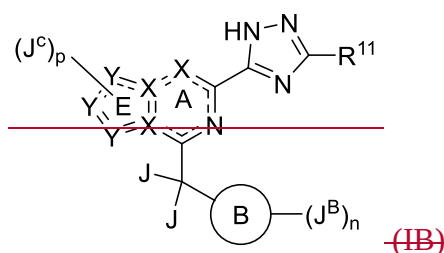
~~R'' is $C(O)R^{11}$, $C(O)R^{11a}$, $N=CR^{11b}R^{11c}$, $P(O)(OH)_2$, or $PH(O)OH$;~~

~~R^{11a} is a $C_{1-6}\text{alkyl}$;~~

~~R^{11b} and R^{11c} are each independently a $C_{1-6}\text{alkyl}$ or phenyl, or R^{11b} and R^{11c} together with the carbon atom from which they are attached form a $C_{4-6}\text{cycloalkyl}$; and~~

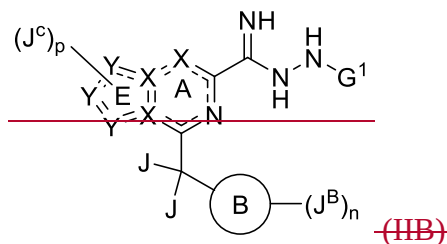
~~G^1 is tert-butoxycarbonyl (Boc), 2,2,2-trichloroethyloxycarbonyl (Troc), benzyloxycarbonyl (Cbz), 9-fluorenylmethoxycarbonyl (Fmoc), methylsulfonyl, p-toluenesulfonyl (Tos), 4-nitrobenzenesulfonyl (NOSyl), 2-nitrobenzenesulfonyl, p-bromobenzenesulfonyl (Brosyl), trifluoroacetyl, acetyl, benzoyl, 2-trimethylsilylethyl, (2-phenyl-2-trimethylsilyl)ethyl, triisopropylsiloxy, 2-(trimethylsilyl)ethoxymethyl, allyloxycarbonyl, or 2-(trimethylsilyl)ethoxycarbonyl an amidrazone protecting group.~~

3. The process of claim 2, wherein the 3-substituted 1,2,4 triazole compound of Formula IA or a salt thereof is of Formula IB



or a salt thereof, and

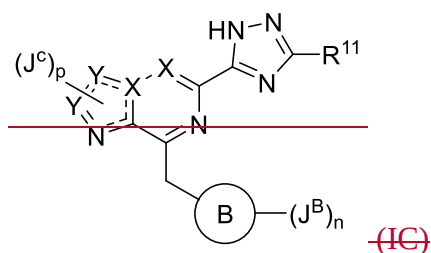
the amidrazone compound of Formula IIA is of Formula IIB



or a salt thereof.

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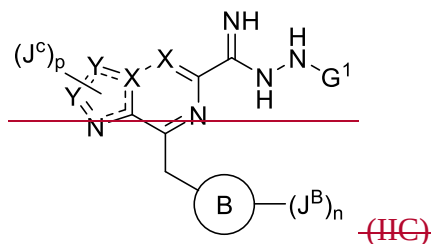
4. The process of claim 3, wherein the 3-substituted 1,2,4 triazole compound of Formula IB or a salt thereof is of Formula IC



or a salt thereof,

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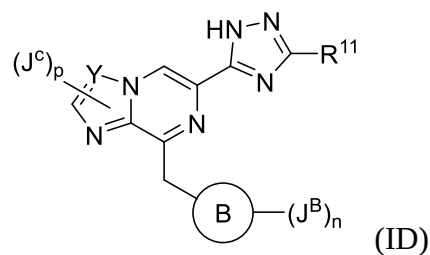
and the amidrazone compound of Formula IIB is of Formula IIC



or a salt thereof.

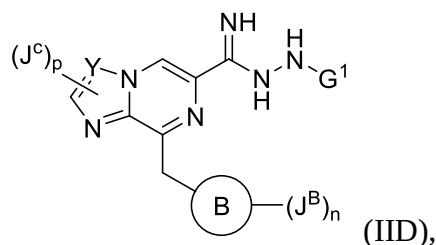
52. The process of claim 41, wherein the 3-substituted 1,2,4-triazole compound of Formula IC-IA or a salt thereof is of Formula ID

15



or a salt thereof, and

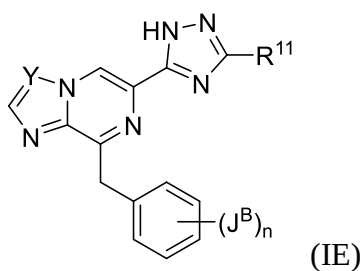
the amidrazone compound of Formula HC-IIA is of Formula IID



or a salt thereof,

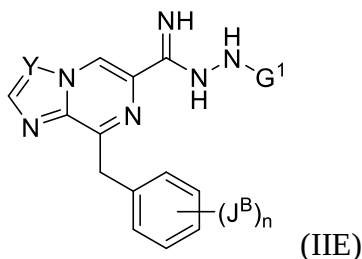
wherein Y is ~~N or C~~.

- 5 36. The process of claim 25, wherein the 3-substituted 1,2,4-triazole compound of Formula ID ~~or a salt thereof~~ is of Formula IE



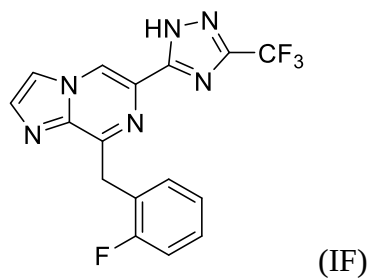
~~or a salt thereof~~, and

the amidrazone compound of Formula IID is of Formula IIE



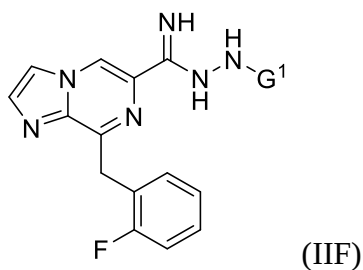
or a salt thereof.

47. The process of claim 36, wherein the 3-substituted 1,2,4-triazole compound of Formula IE or a salt thereof is of Formula IF:



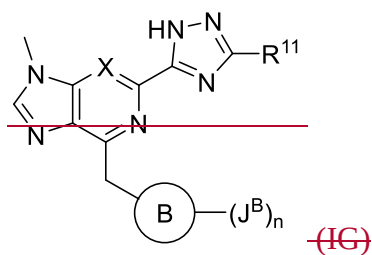
~~or a salt thereof~~, and

the amidrazone compound of Formula IIE is of Formula IIF



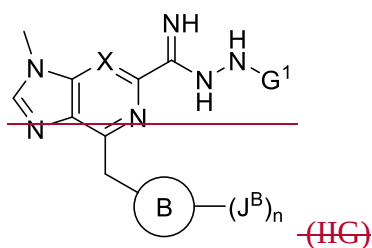
or a salt thereof.

8. ~~The process of claim 4, wherein the 3-substituted 1,2,4-triazole compound of Formula IG or a salt thereof is of Formula IG~~



or a salt thereof, and

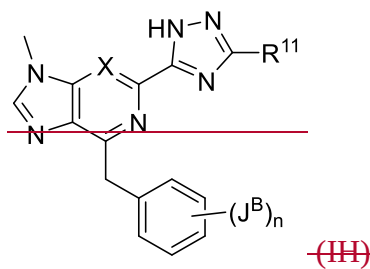
the amidrazone compound of Formula IIG is of Formula IIG



or a salt thereof,

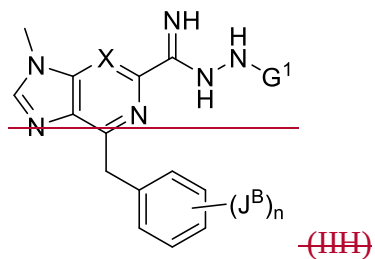
wherein X is C or N.

9. ~~The process of claim 8, wherein the 3-substituted 1,2,4-triazole compound of Formula IG or a salt thereof is of Formula IH~~



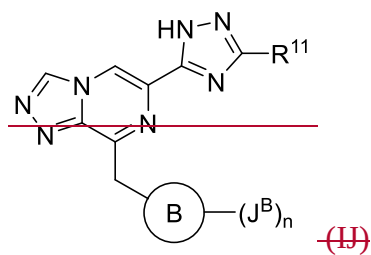
or a salt thereof, and

the amidrazone compound of Formula IIG is of Formula IHH



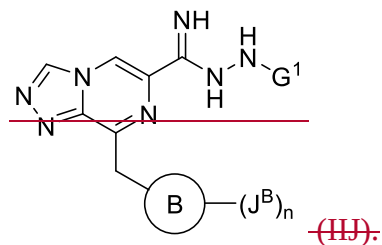
or a salt thereof.

10. ~~The process of claim 4, wherein the 3-substituted 1,2,4-triazole compound of Formula IC or a salt thereof is of Formula II~~

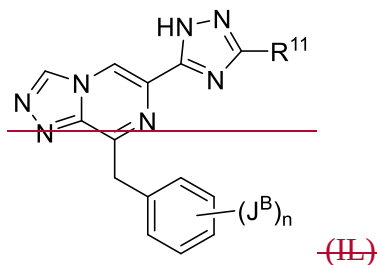


or a salt thereof, and

the amidrazone compound of Formula IIC is of Formula III

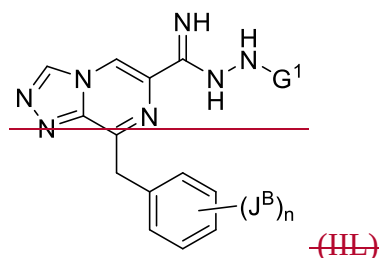


11. ~~The process of claim 10, wherein the 3-substituted 1,2,4-triazole compound of Formula II or a salt thereof is of Formula II~~



or a salt thereof, and

the amidrazone compound of Formula IIJ is of Formula III



~~or a salt thereof.~~

~~125.~~ The process of any one of claims ~~1-42-5, 8 and 10~~, wherein

5 Ring B is phenyl or a 5 or 6-membered heteroaryl ring, containing 1 or 2 ring nitrogen atoms.

~~613.~~ The process of any one of claims ~~1-52-12~~, wherein:

10 J^B is independently halo or a C₁₋₆ alkyl optionally substituted with up to 3 instances of halo;

 each J^C, when present, is independently selected from hydrogen, halo, -CN, and C₁₋₄ alkyl optionally and independently substituted by up to 3 instances of halo;

~~p, when present, is 1 or 2;~~

15 ~~R¹¹ is H, -NR^{a2}R^{b2}, -C(O)NR^{a2}R^{b2}, -C(O)R^{15a}, -CN, C₁₋₆ alkyl optionally and independently substituted with 0-3 occurrences of R¹⁵, C₂₋₆ alkenyl optionally and independently substituted with 0-2 occurrences of R^{b2}, C₂₋₆ alkynyl optionally and independently substituted with 0-2 occurrences of R^{b2}, C₁₋₆ alkoxy optionally and independently substituted with 0-5 occurrences of R¹⁵, phenyl optionally and independently substituted with 0-3 occurrences of R¹⁵, 5- to 6-membered heteroaryl optionally and independently substituted with 0-3 occurrences of R¹⁵, C₃₋₈ cycloalkyl optionally and independently substituted with 0-3 occurrences of R¹⁵ or 3-8 membered heterocyclyl optionally and independently substituted with 0-3 occurrences of R¹⁵; wherein each of said 5- to 6-membered heteroaryl and each of said 3-8 membered heterocyclyl contain up to 3 ring heteroatoms independently selected from N, O and S;~~

20

25

 R¹⁵ is halo, -OR^{b2}, -SR^{b2}, -NR^{a2}R^{b2}, -C(O)R^{b2}, -C(O)NR^{a2}R^{b2}, -NR^{b2}C(O)OR^{b2}, -OC(O)NR^{a2}R^{b2}, C₂₋₄ alkenoxy, C₃₋₄₈ cycloalkyl, phenyl, 5- or 6-membered heteroaryl, or 3-10 membered heterocyclyl; wherein each of said 5- or 6-membered heteroaryl ring and each of said 3-10 membered heterocyclyl contain up to 3 ring heteroatoms independently selected from N, O and S;

30

~~R^{15a} is C₃₋₈-cycloalkyl, phenyl, 5- or 6-membered or 3-10-membered heterocyclyl; wherein each of said 5- or 6-membered heteroaryl ring and each of said 3-10-membered heterocyclyl contain up to 3 ring heteroatoms independently selected from N, O and S; and~~

5 R^{a2} is hydrogen, C₁₋₆ alkyl or C₁₋₆ haloalkyl; and

 R^{b2} is hydrogen, C₁₋₆ alkyl or C₁₋₆ haloalkyl.

10 147. The process of claim ~~613~~, wherein R¹¹ is ~~NR^{a2}R^{b2}~~, C₁₋₆ alkyl optionally and independently substituted with ~~0-1, 2, or 3~~ occurrences of halo, ~~5- to 6-membered heteroaryl optionally and independently substituted with 0-3 occurrences of halo, or C₃₋₈-cycloalkyl optionally and independently substituted with 0-3 occurrences of halo.~~

15 ~~15. The process of claim 14, wherein R¹¹ is C₁₋₆-alkyl optionally and independently substituted with 0-3 occurrences of halo.~~

168. The process of claim ~~146~~, wherein R¹¹ is CF₃.

20 ~~17. The process of any one of claims 2-16, wherein G¹ is carbamate-amino-protecting group, amide-amino-protecting group, or sulfonyl-amino-protecting group.~~

25 189. The process of any one of claims ~~171-8~~, wherein G¹ is tert-butoxycarbonyl (Boc), 2,2,2-trichloroethyloxycarbonyl (Troc), benzyloxycarbonyl (Cbz), 9-Fluorenylmethoxycarbonyl (Fmoc), methylsulfonyl, p-toluenesulfonyl (Tos), 4-nitrobenzenesulfonyl (NOSyl), 2-nitrobenzenesulfonyl, p-bromobenzenesulfonyl (Brosyl), trifluoroacetyl, acetyl or benzoyl.

30 ~~19. The process of any one of claims 1-18, wherein the process comprises reacting the amidazone with R¹¹C(O)OE', wherein OE' is O-(C₁₋₆alkyl), O-(C₁₋₆ haloalkyl), O-(phenyl), O-(heteroaryl), O-(heterocyclyl), wherein the phenyl, heteroaryl, and heterocyclyl are optionally substituted with 1 to 6 groups independently selected from halo, cyano, nitro, oxo, SO₃H, and SO₃C₁₋₆alkyl.~~

2010. The process of any one of claims ~~1-9~~, wherein -OE' is -O-(C₁₋₆ haloalkyl).

~~1124.~~ The process of any one of claims 1-9, wherein -OE' is -O-(CH₂CF₃), -O-(nitrophenyl) (e.g, 2 or 4-nitrophenyl), -O-(dinitrophenyl) (e.g. 2,4-dinitrophenyl ester), -O-(trichlorophenyl) (e.g., 2,4,5-trichlorophenyl), -O-(pentafluorophenyl), -O-(sulfo-tetrafluorophenyl) (e.g., 4-sulfo-2,3,5,6-tetrafluorophenyl), -O-(succinimidyl), -O-(benzotriazole), -O-(7-azabenzotriazole), -O-(phthalimidyl), -O-(5-norbornene-endo-2,3-dicarboxyimide), or -O-(sulfo-succinimidyl).

~~22.~~ The process of any one of claims 1-18, wherein the process comprises reacting the amidazone with R¹¹C(O)OR'', wherein R'' is N=CR^{11b}R^{11c}, P(O)(OH)₂, or PH(O)OH.

~~23.~~ The process of any one of claims 1-18, wherein the process comprises reacting the amidazone with R¹¹C(O)OH in the presence of an activating agent.

~~24.~~ The process of claim 23, wherein the activating agent is a carbodiimide, a uronium, a phosphonium, 2-alkyl-1-alkylcarbonyl-1,2-dihydroquinoline, 2-alkoxy-1-alkoxycarbonyl-1,2-dihydroquinoline, ethyl cyanohydroxyiminoacetate (Oxyma®), or alkylchloroformate.

~~25.~~ The process of any one of claims 1-18, wherein the process comprises reacting the amidazone with R¹¹C(O)SR', wherein SR' is S-(aryl), S-(C₁₋₂₀alkyl), or S-(heteroaryl).

~~26.~~ The process of claim 25, wherein SR' is S-(ethyl), S-(dodecyl), S-(p-chlorophenyl), or S-(2-benzothiazolyl).

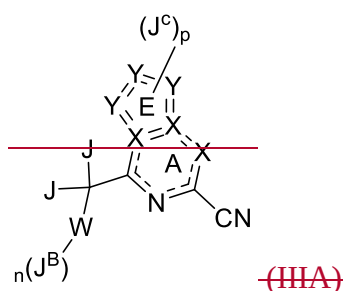
~~27.~~ The process of any one of claims 1-26, wherein the base is selected from the group consisting of trialkylamine, a phosphazene, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), guanidine, 1,1,3,3-tetramethylguanidine, optionally substituted pyridine or 1,4-diazabicyclo[2.2.2]octane (DABCO).

~~2812.~~ The process of any one of claims 1-1127, wherein the base is 4-dimethylaminopyridine (DMAP).

~~2913.~~ The process of any one of claims 271-11, wherein the base is DABCO.

~~30.~~ The process of any one of claims 1-29, wherein the process further comprises deprotecting the amidrazone protecting group if necessary after the reaction of the amidrazone compound with the carboxylic acid, the acid halide, the thioacyl halide, the activated ester, the thioester or the acid anhydride by reacting the reaction product with an amidrazone deprotecting agent.

~~31.~~ The process of claim 2, wherein the amidrazone compound of Formula IIA or a salt thereof is prepared by a process comprising reacting a compound of Formula IIIA:



~~or a salt thereof,~~

~~first with a second base and second with a compound of Formula H_2NNHC^+ in a reaction solvent.~~

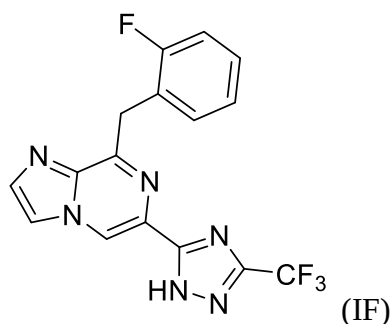
~~32.~~ The process of claim 31, wherein the reaction solvent is an alcohol.

~~33.~~ The process of claim 32, wherein the reaction solvent is MeOH.

~~34.~~ The process of any one of claims 31-33, wherein the second base is NaOMe.

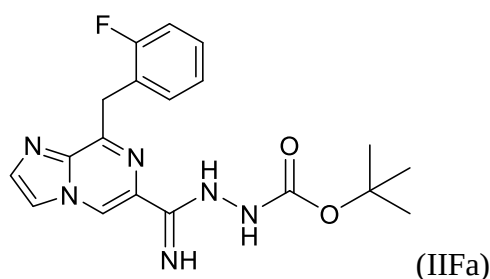
~~35.~~ The process of any one of claims 31-34, where the compound of Formula H_2NNHC^+ is $H_2NNHC(O)OC(CH_3)_3$, $H_2NNHC(O)OCH_2CCl_3$, $H_2NNHC(O)Obenzyl$, $H_2NNHC(O)OCH_2(9-fluorenyl)$, $NH_2NHSO_2CH_3$, $NH_2NHSO_2(p-toluene)$, $NH_2NHSO_2(4-nitrophenyl)$, $NH_2NHSO_2(2-nitrophenyl)$, $NH_2NHSO_2(4-bromophenyl)$, $NH_2NHC(O)CF_3$, $H_2NNHC(O)phenyl$ or $H_2NNHC(O)CH_3$.

~~3614.~~ The process of claim 1, wherein the 1,2,4-triazole compound is represented by Formula IF

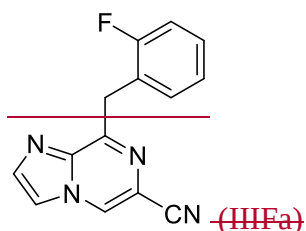


~~or a salt thereof;~~ and

wherein the process comprising reacting an amidrazone of Formula IIFa:



- 5 or a salt thereof, with $\text{CF}_3\text{C}(\text{O})\text{OCH}_2\text{CF}_3$ in the presence of the base, wherein the base is trialkylamine, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), guanidine, 1,1,3,3-tetramethylguanidine, 4-dimethylaminopyridine (DMAP), or 1,4-diazabicyclo[2.2.2]-octane (DABCO).
- 10 ~~37~~15. The process of claim ~~36~~14, wherein the base is DABCO.
- ~~38. The process of claim 36 or 37, wherein the process further comprises purifying the 1,2,4-triazole compound of Formula IF by crystallization.~~
- 15 ~~39. The process of claim 38, wherein the crystallization is carried out by adding n-heptane to the reaction mixture after the completion of the reaction between the amidrazone compound of Formula IIFa and $\text{CF}_3\text{C}(\text{O})\text{OCH}_2\text{CF}_3$.~~
- ~~40. The process of any one of claims 36-39, wherein the amidrazone compound of Formula IIFa or a salt thereof is prepared by a process comprising the step of reacting a compound of Formula IIIFa:~~
- 20



or a salt thereof,

first with a second base and second with $\text{H}_2\text{NNHC(O)OC(CH}_3)_3$ in a reaction solvent.

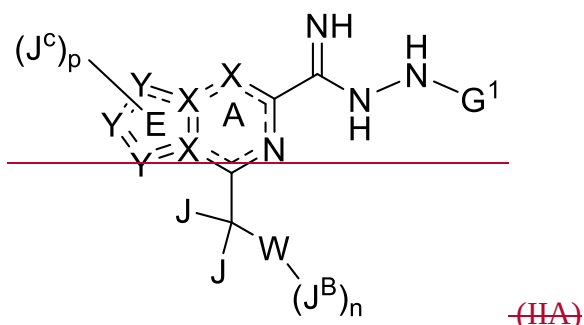
5 41. — The process of claim 40, wherein the reaction solvent is an alcohol.

42. — The process of claim 41, wherein the reaction solvent is MeOH.

43. — The process of any one of claims 40–42, wherein the second base is NaOMe.

10

44. — A compound represented by Formula IIA:



or a salt thereof, wherein:

rings E and A form the core of the molecule and are aromatic; each instance of X and Y is

15 independently selected from N, NR^{a} and C; wherein a maximum of 4 instances of X and Y are simultaneously N and R^{a} is H or C_{1-6} alkyl;

W is either

i) absent, with J^{B} connected directly to the carbon atom bearing two J groups, each J is independently hydrogen or methyl, n is 1 and J^{B} is a C_{1-7} alkyl chain optionally substituted by up to 9 instances of fluorine; or

20

ii) a ring B that is a phenyl, a C_{3-7} cycloalkyl ring or a 5- or 6-membered heteroaryl ring, containing 1 or 2 ring nitrogen atoms;

wherein when ring B is the phenyl or 5- or 6-membered heteroaryl ring; each J is

independently hydrogen or methyl; n is an integer selected from 0 to 3; and each J^{B} is

independently selected from halo, =CN , a C_{1-6} aliphatic, =OR^{B} and a C_{3-8} cycloaliphatic ring; and

wherein when ring B is the C_{3-7} cycloalkyl ring; each J is hydrogen; n is an integer selected from 0 to 3 and each J^{B} is independently selected from halo, =CN , a C_{1-6} aliphatic and =OR^{B1} ;

wherein each J^{B} that is a C_{1-6} aliphatic and each J^{B} that is a C_{3-8} cycloaliphatic ring are optionally and independently substituted with up to 3 instances of R^3 ; each R^{B} is independently a C_{1-6} aliphatic or a C_{3-8} cycloaliphatic ring; said R^{B} optionally and independently substituted with up to 3 instances of R^{3a} ;

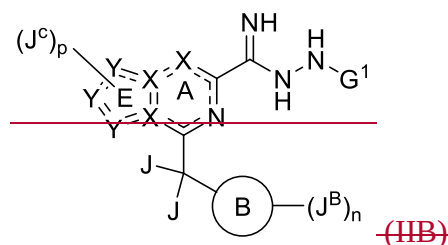
each R^{B1} is independently selected from hydrogen, a C_{1-6} aliphatic and a C_{3-8} cycloaliphatic ring; wherein each of said C_{1-6} aliphatic and each of said C_{3-8} cycloaliphatic ring are optionally and independently substituted with up to 3 instances of R^{3b} ;

each R^3 , R^{3a} and R^{3b} is, in each instance, independently selected from halo, =CN , C_{1-4} alkyl, C_{1-4} haloalkyl, $\text{=O}(\text{C}_{1-4}$ alkyl) and $\text{=O}(\text{C}_{1-4}$ haloalkyl);

p is an integer selected from 1, 2 or 3;

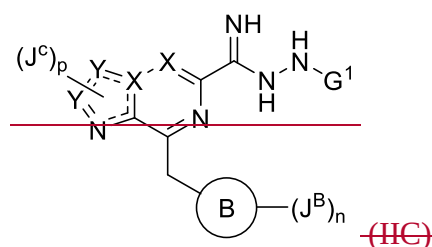
each J^{C} is independently selected from hydrogen, halo, C_{1-4} aliphatic, C_{1-4} alkoxy and =CN ; wherein each said C_{1-4} aliphatic and C_{1-4} alkoxy is optionally and independently substituted by up to 3 instances of C_{1-4} alkoxy, C_{1-4} haloalkoxy, =OH or halo; and G^1 is an amidrazone protecting group.

45. The compound of claim 43, wherein the compound of Formula IIA is of Formula IIB



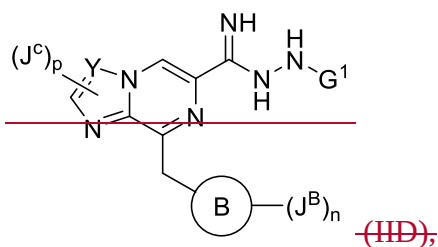
or a salt thereof.

46. The compound of claim 45, wherein the compound of Formula IIB is of Formula IIC



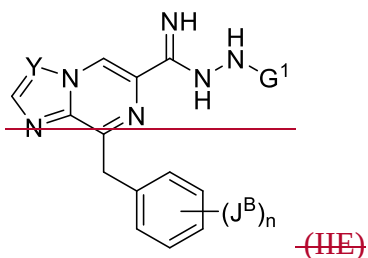
or a salt thereof.

~~47. The compound of claim 46, wherein the compound of Formula IIC is of Formula IID~~



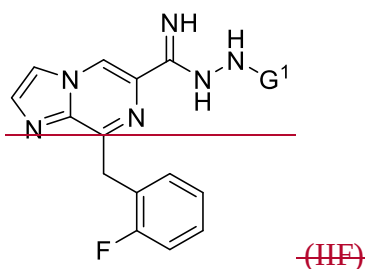
5 or a salt thereof; and
wherein Y is N or C.

~~48. The compound of claim 47, wherein the compound of Formula IID is of Formula IIE~~



10 or a salt thereof.

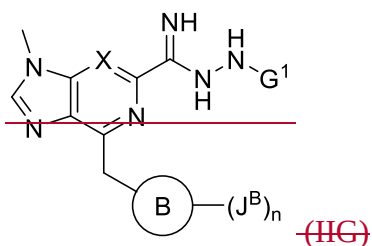
~~49. The compound of claim 48, wherein the compound of Formula IIE is of Formula IIF~~



or a salt thereof.

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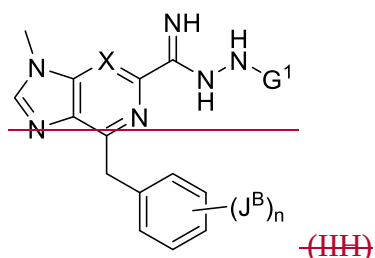
~~50. The compound of claim 46, wherein the compound of Formula IIC is of Formula IIG~~



or a salt thereof; and

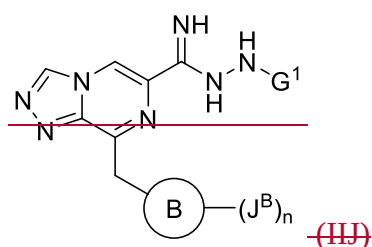
wherein X is C or N.

~~51. The compound of claim 50, wherein the compound of Formula IIG is of Formula IIIH~~



5 ~~or a salt thereof.~~

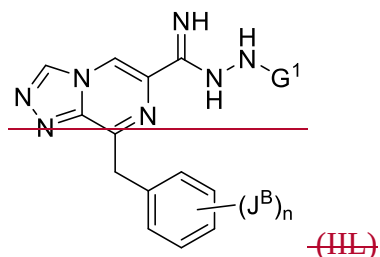
~~52. The compound of claim 46, wherein the compound of Formula IIC is of Formula IIJ~~



~~or a salt thereof.~~

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~~53. The compound of claim 52, wherein the compound of Formula IIJ is of Formula IIIL~~



~~or a salt thereof.~~

15 ~~54. The compound of any one of claims 44-47, 50 and 52, wherein
Ring B is phenyl or a 5- or 6-membered heteroaryl ring, containing 1 or 2 ring nitrogen atoms.~~

~~55. The compound of any one of claims 44-54, wherein:~~

~~Jᴮ is independently halo or a C₁-₆ alkyl optionally substituted with up to 3 instances of halo;~~

20 ~~each Jᶜ, when present, is independently selected from hydrogen, halo, -CN, and C₁-₄ alkyl~~

~~optionally and independently substituted by up to 3 instances of halo;~~

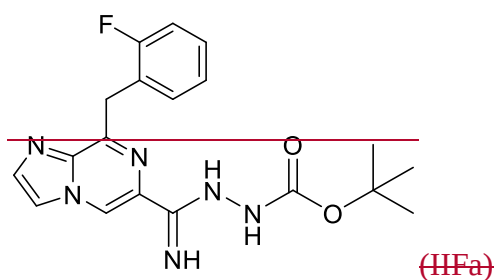
~~p, when present, is 1 or 2.~~

~~56. The compound of any one of claims 44-55, wherein G¹ is carbamate amino-protecting group, amide amino-protecting group, or sulfonyl amino-protecting group.~~

- 5 ~~57. The compound of claim 56, wherein G¹ is tert-butoxycarbonyl (Boc), 2,2,2-trichloroethyloxycarbonyl (Troc), benzyloxycarbonyl (Z), 9-Fluorenylmethoxycarbonyl (Fmoc), methylsulfonyl, p-toluenesulfonyl (Tos), 4-nitrobenzenesulfonyl (NOSyl), 2-nitrobenzenesulfonyl, p-bromobenzenesulfonyl (Brosyl), trifluoroacetyl, acetyl or benzoyl.~~

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~~58. The compound of claim 44, wherein the compound is represented by Formula IIFa:~~



~~or a salt thereof.~~