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(54) Title: SELECTIVE ANTAGONISTS OF A_{2A} ADENOSINE RECEPTORS

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Selective antagonists of A_{2A} adenosine receptors are provided. The novel A_{2A} blockers are useful for the treatment of Parkinson's disease and other diseases.

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(54) Title: SELECTIVE ANTAGONISTS OF A_{2A} ADENOSINE RECEPTORS

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SELECTIVE ANTAGONISTS OF A_{2A} ADENOSINE RECEPTORS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/559,159, filed April 2, 2004, entitled "Selective Antagonists of A_{2A} Adenosine Receptors" the disclosure of which is incorporated herein in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to compounds and pharmaceutical compositions that are selective antagonists of the A_{2A} adenosine receptor (AR). These compounds are useful as pharmaceutical agents.

[0003] Selective antagonists of A_{2A} adenosine receptors have proven to be effective for the treatment of Parkinson's disease (PD) both in animal models and in a human trial.[1] However, the initial clinical trial was stopped in phase 3 due to detection of animal toxicity of the investigational drug, KW6002. Other investigational compounds lack sufficient potency, selectivity or bioavaility to be considered clinical candidates.

BACKGROUND OF THE INVENTION

[0004] Parkinson's disease is the second most common neurodegenerative disorder and affects over 1 million people in North America.[2] The pathological process, degeneration of the dopaminergic neurons in the substantial nigra, causes profound depletion of striatal dopamine and motor impairment. This insight led to the introduction of L-dopa as a dopamine-replacement treatment for PD.[3] Today, L-dopa continues to be the "Gold Standard" treatment for the motor symptoms of PD.[4,5] Despite the considerable symptomatic relief it affords, long-term treatment with L-dopa has major limitations.[6] After five to ten years of treatment with L-dopa, up to 60% of patients experience loss of L-dopa effectiveness and some debilitating complications,[7,8] notably, an "on" and "off" motor fluctuation and involuntary choreic or dystonic movements, dyskinesia. This has become the limiting factor in management of patients in the later stages of PD.[9] The development of dyskinesia might reflect desensitization of dopamine receptors.[10] Most importantly, there is no clear evidence that L-dopa slows or halts the degeneration of dopaminergic neurons. In fact, *in vitro* cell culture studies suggested that dopamine and its oxidative metabolites are toxic to dopaminergic neurons, and raised the concern that L-dopa may actually accelerate the

degeneration of dopaminergic neurons. Because of this concern, many clinicians avoid prescribing L-dopa early in the course of PD.[11]

[0005] These major limitations of L-dopa therapy are linked to the activation of dopamine receptors. This has prompted a search for alternative treatment for PD not targeting the dopaminergic system.[12] Striatal neuromodulators and transmitters other than dopamine are increasingly appreciated as critical regulators of motor function and offer new therapeutic opportunities to complement dopamine-replacement.

[0006] Over the last 10 years, the A_{2A} adenosine receptor (A_{2A}AR) has received increasing attention as a treatment for PD.[13,14] This contention is based on our understanding of the role of the A_{2A}AR in the basal ganglia and on the recent development of new, more selective A_{2A}AR antagonists. Anatomical, neurochemical and behavioral evidence of adenosine-dopamine interactions underlie this new therapeutic approach.[15-17] Anatomically, A_{2A}AR density is high in the striatum, where receptor mRNA is co-expressed with D_2 receptor mRNA in the striatopallidal neurons.[18-20] This unique cellular distribution of A_{2A} receptors suggests that A_{2A} receptor antagonists can selectively modulate the "indirect" striatopallidal pathway to affect motor activity. At the neurochemical level, activation of the A_{2A}AR reduces the binding affinity of D_2 receptors in the striatum,[21] and antagonizes many neurochemical and cellular changes brought about by the activation of striatal D_2 receptors, including release of acetylcholine and GABA and expression of c-Fos. Furthermore, behavioral studies have demonstrated that the unselective adenosine antagonists caffeine and theophylline stimulate locomotor activity[22,23] whereas the unselective agonist NECA[24] inhibits spontaneous locomotor activity as well as motor activity induced by dopamine agonists. Thus, A_{2A}AR agonists and antagonists function as dopamine antagonists and agonists, respectively, in modulating motor activity. The three possible mechanisms have been proposed to explain for motor enhancement by the A_{2A} antagonists: (1) a direct receptor-receptor (A_{2A}-D_2) antagonistic interaction,[25,26] (2) an opposing but independent of A_{2A} and D_2 receptor signaling[27-29] or (3) A_{2A}AR modulation of GABA release in the basal ganglia.[30-32] These receptors also form A_{2A}AR-D2 heterodimers,[33] but how dimerization affects receptor function is unclear.

A_{2A} receptor antagonists may offer multiple therapeutic benefits for PD patients

[0007] First, A_{2A} antagonists stimulate motor activity in normal as well as dopamine-depleted animals. In rodent models of PD, unselective adenosine antagonists (caffeine and theophylline)[22,34] and the A_{2A}AR-selective antagonists SCH58261, KW6002 and CSC can reverse motor deficits induced by MPTP, 6-hydroxydopamine, haloperidol or reserpine[35-41] as well as by genetic deletion of D_2 receptors.[42] More recently, the A_{2A} antagonists KW6002 reversed motor deficit in MPTP-treated non-human primates.[43,44] Furthermore, A_{2A} antagonists can stimulate motor activity when combined with sub-threshold doses of dopaminergic agents such as L-dopa or D_1 and D_2 agonists such as

aporphormine or quinpirole.[45] For example, combining KW6002 with L-dopa reduces the dose of L-dopa, thereby reducing the complications associated with L-dopa. In contrast to some non-specific adenosine antagonists or some dopamine agonists, motor stimulation was observed after acute treatment and persisted following treatment continued for 15 days.[44,46,47] Thus, tolerance to the motor stimulant effect of A_{2A} antagonists did not develop.

[0008] Second, studies of the MPTP-treated monkey model of PD revealed a novel feature of A_{2A} antagonists, namely, stimulation of motor activity without dyskinesia.[43,44,48] In contrast to L-dopa, repeated treatment with KW6002 reversed the motor deficit but did not induce dyskinesia, even in monkeys primed with L-dopa. Further, our recent findings in A_{2A}AR knockout mice suggest that development of behavioral sensitization by chronic treatment of L-dopa requires activation of the A_{2A}AR. Genetic inactivation of the A_{2A} receptor attenuated L-dopa-induced rotational behavior.[49] This is consistent with a recent study showing that co-administration of KW6002 with apomorphine to MPTP-treated monkeys completely abolished the development of apomorphine-induced dyskinesia.[50] Further studies are warranted to explore the molecular mechanism underlying this novel aspect of A_{2A}AR function.

[0009] Third, accumulating evidence suggests that the specific inactivation of A_{2A}ARs consistently attenuates brain damage induced by ischemia[51-53] and excitoxicity,[54,55] as well as in animal models of Huntington's disease[56] and Alzheimer's disease.[57] The neuroprotection by A_{2A}AR antagonists has been recently extended to a rodent model of PD. Co-administration of A_{2A}AR antagonists, such as CSC, DMPX, SCH58261 and KW6002 (but not the A_1AR antagonist DPCPX) attenuated dopaminergic neurotoxicity in several neurotoxin models of PD.[58] A_{2A}AR antagonists provided not only functional protection (such as reduced dopamine content and expression of molecular markers for the dopaminergic terminals), but also reduced the loss of dopaminergic neurons in substantia nigra in both MPTP- and 6-OHDA models of PD.[59,60] Likewise, knockout of A_{2A}ARs attenuated MPTP-induced dopaminergic neurotoxicity in mice.[59] Together with the demonstration of neuroprotection by A_{2A}AR antagonists against a wide range of neuronal injury models. These results raise the possibility that A_{2A} antagonists may offer a neuroprotection, slowing or even halting degeneration of dopaminergic neurons.

[0010] Finally, in contrast to the widespread distribution of other neurotransmitter receptors, for example, glutamate receptors, the expression of the A_{2A}AR is almost exclusively in striatum, which might allow selective modulation of dopamine-mediated motor pathways without serious side effects due to drug actions outside the basal ganglia (a serious problem for drugs such as glutamate antagonists). It is important to emphasize that ambient adenosine levels and A_{2A}AR density are normal in PD patients,[61] indicating that A_{2A} antagonists might remain effective, even in the later stages of PD.

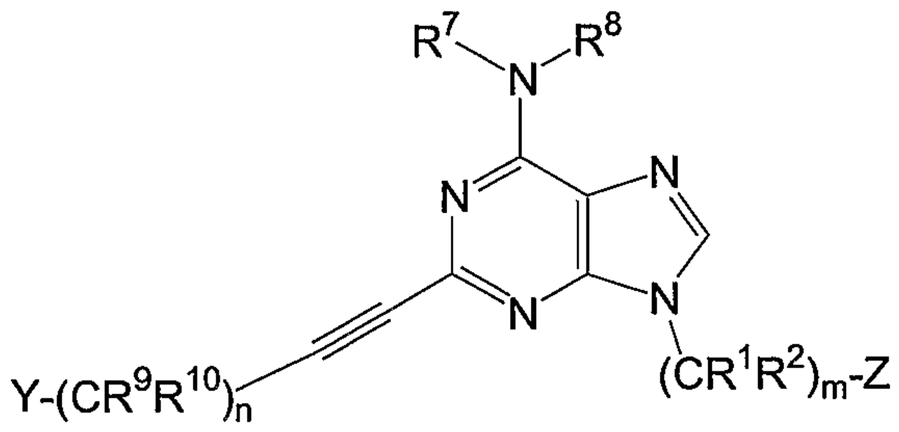
[0011] The prospective use of A_{2A}R antagonists as potential neuroprotective agents against dopaminergic neuron degeneration was markedly enhanced by a May 2000 report of an epidemiological study of the relationship between caffeine and PD. Ross et al described a large prospective study with a 30-year follow-up of 8004 Japanese-American men that showed that in this population there is an inverse relationship between caffeine consumption and the risk of developing PD.[62] Two other ongoing, large-cohort studies (Heath Professional Follow-up Studies and Nurse's Heath Study) involving 47,351 men and 88,565 women also showed that moderate caffeine consumption (3-5 cups/day) reduced their risk of developing PD.[63] Thus, the inverse relationship of caffeine consumption and the risk of developing PD seem firmly established by these two large, prospective epidemiological studies. These results are consistent with the animal studies showing neuroprotection by A_{2A}AR antagonists and strongly argue that A_{2A} antagonists including caffeine may offer an opportunity to slow down or halt the degeneration of dopaminergic neurons.

[0012] Initial clinical trial results of KW6002 indicated that (20-80 mg/day) enhanced motor activity in one study and potentiated a motor stimulant effect by low (but not high) doses of L-dopa in another study.[64,65] KW6002 was well tolerated and had few side effects. Unfortunately, trials with KW6002 have been stopped because this compound was found to produce a long-term toxicity in rats. Hence, there is a pressing need to develop alternative molecules that lack toxicity.

[0013] The first relatively selective A_{2A}AR antagonists, the 8-styrylxanthines, appeared about ten years ago. This class includes KW-6002, which has low nanomolar affinity for the A_{2A}AR and >100-fold selectivity for the A_{2A}AR over the A_1AR. KW-6002, entered clinical trials in 2002 as an agent for the treatment of PD.[1,66] SCH58261, a pyrazolo[4,3-*e*]-1,2,4 triazolo[1,5-*c*]pyrimidine was a prototype for a series of second-generation derivatives that appeared over the next several years. These, too, had low nanomolar affinity and good selectivity for the A_{2A}AR *in vitro*.[67] The third class of antagonists to appear, the 1,2,4-triazolo[4,5-e]-1,3,5-triazines, was typified by ZM241385, which was active at the A_{2A}AR in the sub-nanomolar range but less selective, interacting with A_{2B}AR as well.[68] These potent A_{2A} antagonists have been important research tools, greatly facilitating pharmacological investigations of A_{2A}AR function *in vitro* as well as *in vivo* significantly enhancing our understanding of the neurobiology of the A_{2A}AR. However, each of these antagonists has important drawbacks. KW-6002 is light-sensitive, undergoing photoisomerization from the active *E*-isomer to the 800-fold less active *Z*-isomer.[69] SCH58261 is very poorly soluble and even its second-generation derivatives have marginal bioavailability.[70] As mentioned above, ZM241385 is unselective and, additionally, has poor bioavailability. Other nitrogen heterocycles such as the 1,2,4-triazolo[4,3-*a*]quinoxalin-1-ones[71] and the oxazolo[4,5-*d*]pyrimidines from ICI are also unselective, and their bioavailability is unknown. Therefore a continuing need exists for compounds that are selective A_{2A} AR antagonists.

SUMMARY OF THE INVENTION

[0014] In one aspect, there is provided a compound of the formula I:



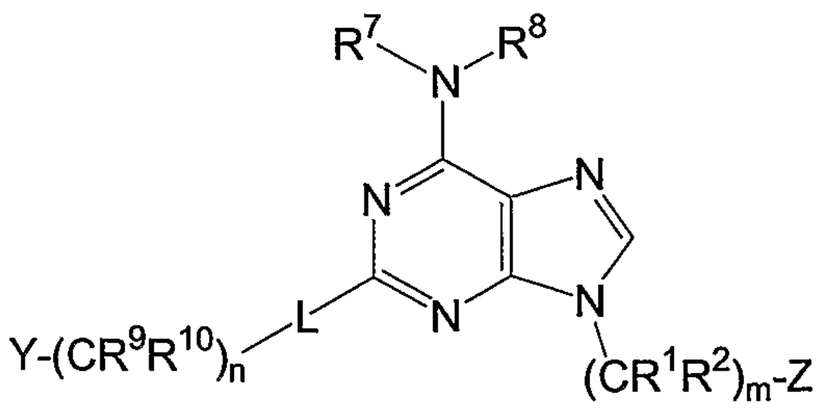
I

wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, -NH_2, -OH, -SH, -$NHCH_3$, –$N(CH_3)_2$, -OMe, –SMe, (C_1-C_8)alkyl, aryl and aryl(C_1-C_8)alkyl, wherein R^1 and R^2 are optionally substituted with 1 to 4 substituents of R^a, wherein the alkyl is optionally interrupted by 1-4 heteroatoms selected from –O–, -S–, –SO–

, -$S(O)_2$– or amino (–NR^a–), or where R^1 and R^2 are independently absent, with the proviso that R^a is not thio or halogen in the case where R^1 and R^2 to which R^a is bound is halogen, -NH_2, -OH, -SH, -$NHCH_3$, -$N(CH_3)_2$, -OMe and –SMe; R^3 is selected from the group consisting of hydrogen, halo, -OR^a, -SR^a, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_3-C_8)cycloalkyl, heterocycle, hetrocycle(C_1-C_8)alkyl, aryl, aryl(C_1-C_8)alkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl, -CO_2R^a, $R^aC(=O)O$-, $R^aC(=O)$-, -OCO_2R^a, $R^aR^bNC(=O)O$-, $R^bOC(=O)N(R^a)$-, R^aR^bN-, $R^aR^bNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^aR^bNC(=O)N(R^b)$-, $R^aR^bNC(=S)N(R^b)$-, -OPO_3R^a, $R^aOC(=S)$-, $R^aC(=S)$-, -SSR^a, $R^aS(=O)$-, $R^aS(=O)_2$-, -NNR^a and -OPO_2R^a; or if the ring formed from the group $CR^3R^4R^5$ is aryl or heteroaryl or partially unsaturated, then R^3 can be absent; R^4 and R^5 together with the atoms to which they are attached form a saturated or partially unsaturated, mono-, bi- or tricyclic- or aromatic ring having 3, 4, 5, 6, 7, 8, 9,10, 11 or 12 ring atoms, wherein the ring atoms are optionally interrupted by 1, 2, 3 or 4 heteroatoms selected from the group consisting of -O-, -S-, -SO-, -$S(O)_2$- or amine (-NR^a-) in the ring, wherein any ring comprising R^4 and R^5 is optionally further substituted with from 1 to 14 R^6 groups; wherein each R^6 is independently selected from the group consisting of halo, -OR^a, -SR^a, substituted or unsubstituted (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_1-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, heterocycle, hetrocyclyl(C_1-C_8)alkyl, aryl, aryl(C_1-C_8)alkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl, -CO_2R^a, $R^aC(=O)O$-, $R^aC(=O)$-, -OCO_2R^a, $R^aR^bNC(=O)O$-, $R^bOC(=O)N(R^a)$-, R^aR^bN-, $R^aR^bNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^aR^bNC(=O)N(R^b)$-, $R^aR^bNC(=S)N(R^b)$-, -OPO_3R^a, $R^aOC(=S)$-, $R^aC(=S)$-, -SSR^a, $R^aS(=O)$-, -NNR^a and -OPO_2R^a or two R^6 groups and the atom to which they are attached combined to form C=O or C=S, or wherein two R^6 groups together with the atom or atoms to which they are attached can form a carbocyclic or heterocyclic ring; R^7 and R^8 are each independently hydrogen, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, aryl or aryl(C_1-C_8)alkylene, heteroaryl, heteroaryl(C_1-C_8)alkylene-; or wherein R^7 and R^8 together with the nitrogen atom to which they attach form a heterocycle or heteroaromatic ring; R^9 and R^{10} are each independently selected from the group consisting of hydrogen, halogen, -NH_2, -OH, -SH, -$NHCH_3$, –$N(CH_3)_2$, -OMe, –SMe, (C_1-C_8)alkyl, aryl and aryl(C_1-C_8)alkyl, wherein R^9 and R^{10} are optionally substituted with 1 to 4 substituents of R^a, wherein the alkyl is optionally interrupted by 1 to 4 heteroatoms selected from –O–, -S–, –SO–, -$S(O)_2$– or amino (–NR^a–), or where R^9 and R^{10} are independently absent, with the

proviso that R^a is not thio or halogen in the case where R^9 and R^{10} to which R^a is bound is halogen, $-NH_2$, -OH, -SH, $-NHCH_3$, $-N(CH_3)_2$, -OMe and –SMe; Y is $-CR^3R^4R^5$ or NR^4R^5; Z is selected from the group consisting of hydrogen, halogen, (C_1-C_8)alkyl, (C_1-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, (C_6-C_{20})polycyclyl, heterocyclyl, cycloalkyl(C_1-C_8)alkyl, bicycloalkyl(C_6-C_{12})alkyl, heterocyclyl(C_1-C_8)alkyl, aryl, aryl(C_5-C_{14}), aryl(C_1-C_8)alkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl, $-NR^aR^b$, $-OR^a$, $-SR^a$, cyano, nitro, trifluoromethyl, trifluoromethoxy, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)NR^a-$, $R^aR^bNC(=O)-$, $R^aC(=O)NR^b-$, $R^aR^bNC(=O)NR^b-$, $R^aR^bNC(=S)NR^b-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $-NNR^a$, $-OPO_2R^a$, $-OS(O_2)R^a$, $-OS(=O)OR^a$, $-OS(O_2)OR^a$ and $-O(SO_2)NR^aR^b$; R^a and R^b are each independently selected from the group consisting of hydrogen,
halogen, $-NH_2$, -OH, -SH, $-NHCH_3$, $-N(CH_3)_2$, -OMe, -SMe, propargyl,
cyano, -NNH, $-NNCH_3$, $-OPO_2H$, $-OPO_2CH_3$, $-OS(O_2)H$, $-OS(O_2)OH$, $-OS(O_2)CH_3$, $-OS(O_2)OCH_3$, (C_1-C_8)alkyl, aryl, aryl(C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, cycloalkyl(C_1-C_8)alkyl, bicycloalkyl(C_6-C_{12})alkyl, heteroaryl and heteroaryl(C_1-C_8)alkyl, wherein the alkyl and cycloalkyl are optionally interrupted with 1-4 heteroatoms selected from the group consisting of –O–, –S–, -SO–, $-S(O)_2-$ and amino ($-NR^c-$); and wherein the alkyl, cycloalkyl, aryl and heteroaryl are optionally substituted with 1, 2, 3 or 4 substituents selected from the group consisting of $-OR^c$,
$-NR^cR^c$, $-SR^c$, cyano, -NNH, $-NNCH_3$, $-OPO_2H$, $-OPO_2CH_3$, $-OS(O_2)H$, $-OS(O_2)OH$, $-OS(O_2)CH_3$ and $-OS(O_2)OCH_3$, provided that R^a is not a heteroatom when it is attached to another heteroatom; R^c is selected from the group consisting of hydrogen and (C_1-C_8)alkyl; and m is 0 to 8; n is 0, 1, 2 or 3, provided that when m is 0, Z is not halogen, cyano, nitro or a heteroatom, and when n is 0, Y is not $-NR^4R^5$; or a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof.

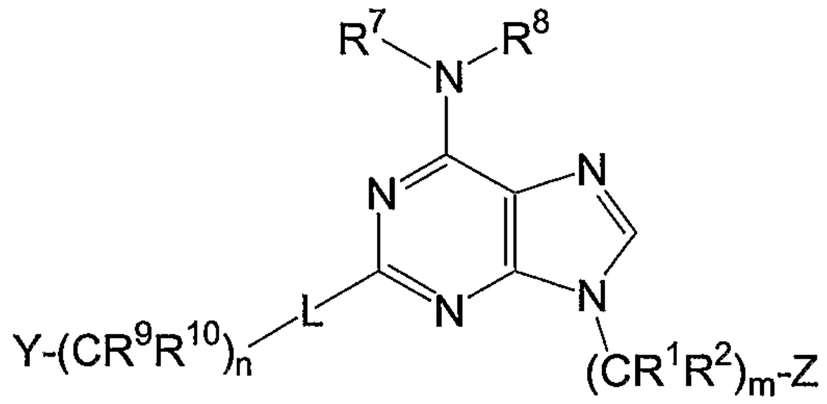
In another aspect, there is provided a compound of the formula II:



II

wherein R^1, R^2, R^7, R^8, R^9, R^{10}, m, n, Y and Z are as defined above; and L is a linker selected from the group consisting of -(C_1-C_3)alkyl-C≡C-, -C≡C-(C_1-C_3)alkyl-, -$(CH_2)_{1-3}$-CH=CH-, -CH=CH-$CH_2)_{1-3}$-, -$(CH_2)_{1-2}$-CH=CH-CH_2- and -CH_2-CH=CH-$(CH_2)_{1-2}$-; or a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof.

In another aspect, there is provided a compound of the formula III:



III

wherein R^1, R^2, R^7, R^8, R^9, R^{10}, m, n, Y and Z are as defined above; and L is a linker selected from the group consisting of -NH–, –N=N–, –NH–N=, –O–, –S–, -SO_2– and pyrazolyl; a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof.

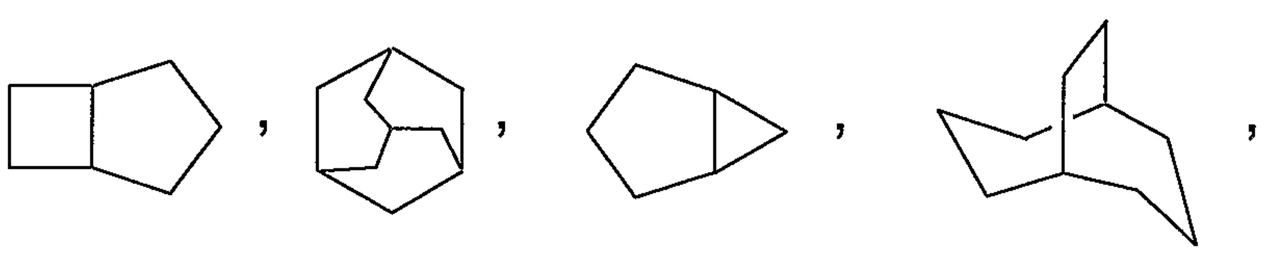
[0015] In one variation of each of the above compound of formulae I, II and III, the group $(CR^1R^2)_m$ together is selected from the group consisting of methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene, octylene, *iso*-propylene, *iso*-butylene, *sec*-butylene and *tert*-butylene. In another variation, $(CR^1R^2)_m$ together is selected from the group consisting of methylene, ethylene, propylene and *iso*-propylene. In anotehr variation, $(CR^1R^2)_m$-Z together is selected from the group consisting of –CH_2CH=CH_2-, –CH_2C≡CH, –CH_2C≡CCH_3 or -CH_2CH_2C≡CH. In yet another variation, $(CR^1R^2)_m$-Z together is –CH_2C≡CH.

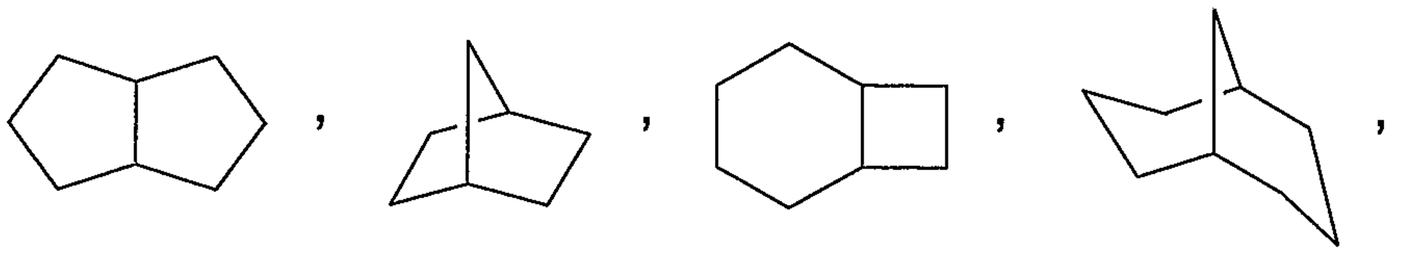
[0016] In another variation of the above formulae, R_1 and R_2 are hydrogen or are absent, m is 2 to 8 and the group $(CR^1R^2)_m$ optionally comprises 1 to 4 alkenyl or alkynyl conjugated or unconjugated groups. In another variation, m is 1 to 8 and Z is selected from the group consisting of -NH_2, -OH, -SH, -NR^aR^b, –OR^a ,-SR^a and cyano. In another particular variation, $(CR^1R^2)_m$-Z together is selected from the group consisting of methanol, ethanol, propanol, butanol, pentanol, hexanol, *iso*-propanol, *iso*-butanol, *sec*-butanol and *tert*-butanol. In yet another variation, $(CR^1R^2)_m$-Z together is selected from the group consisting of methanol, ethanol, propanol and -CH_2CN.

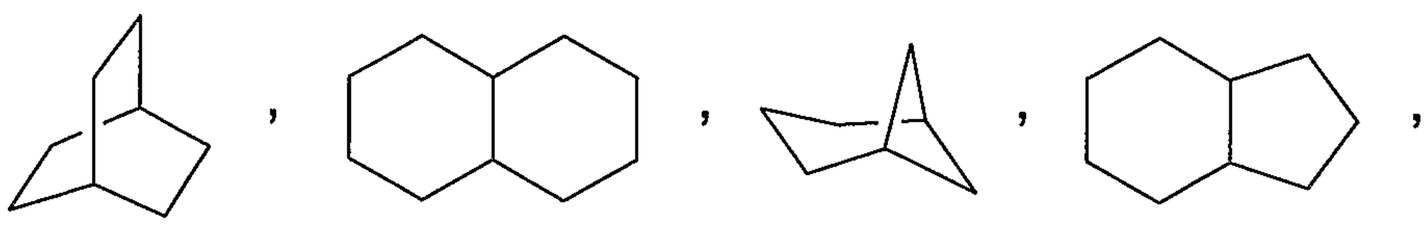
[0017] In one variation of each of the above, R^1 and R^2 are hydrogen, and the group $(CR^1R^2)_m$ is linear or branched, m is 1 to 6, and Z is selected from the group consisting of

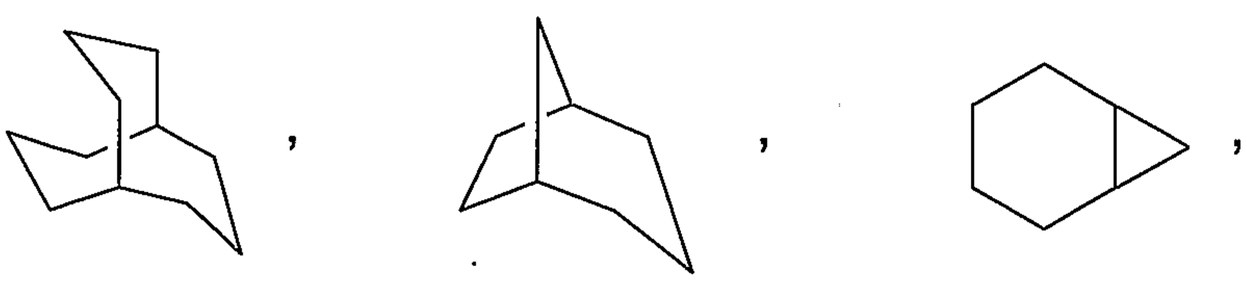
methoxy, ethoxy, propoxy, butoxy, pentoxy and hexyloxy. In another variation, Z is selected from the group consisting of methoxy, ethoxy and propoxy. In another variation, Z is a mono-, bicyclic-, tricyclic- or aromatic or non-aromatic (C_3-C_{20})cycloalkyl ring, wherein the ring atoms are optionally interrupted by 1 to 8 heteroatoms selected from the group consisting of –O–, –S–, –SO–, –$S(O)_2$– and amino (–NR^a–). In yet another variation, Z is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl ring optionally substituted with 1 to 4 substituents of R^a. In yet another variation, Z is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, where m is 0 or 1. In another variation, Z is cyclopentyl and where m is 0. In a particular variation, Z is cyclobutyl, m is 1 and R^1 and R^2 are hydrogen.

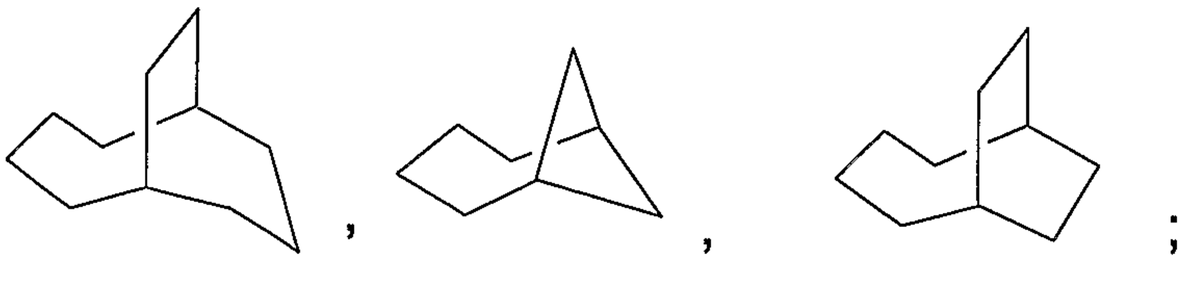
[0018] In one particular variation of each of the above; Y and Z are each independently selected from the group consisting of hydrogen, or



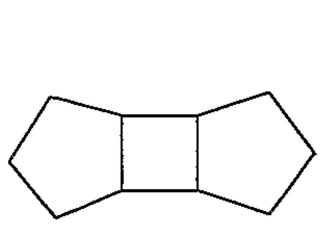
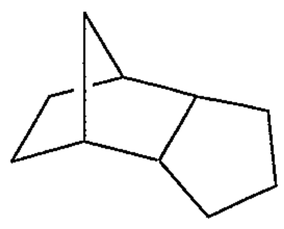
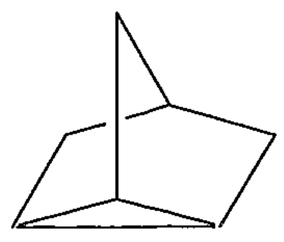








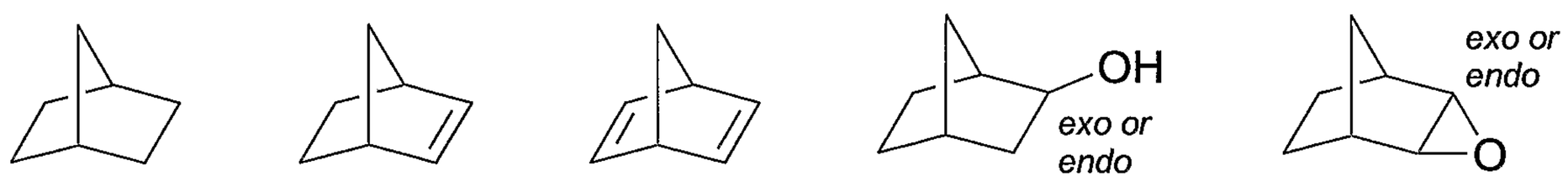
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wherein each Y or Z group is optionally comprises 1, 2 or 3 double bonds; each carbon in the ring is optionally replaced by or interrupted by 1 to 6 heteroatoms selected from –O–, –S–, –SO–, -$S(O)_2$–, or amino (–NR^a–), and is optionally further substituted with from 1 to 10 R^6 groups, provided that the Y or Z ring is not attached at a bridgehead carbon atom or at a trisubstituted carbon atom. In another variation, each Y or Z is independently hydrogen or a bicyclic ring selected from the group consisting of



wherein any two adjacent carbon ring atom is optionally interrupted with 1 to 6 heteroatoms selected from –O–, –S–, -SO–, –$S(O)_2$– or amino (–NR^a–), and the ring is optionally substituted with from 1 to 7 R^a groups selected from the group consisting of -NH_2, -OH, -SH, -$NHCH_3$, -$N(CH_3)_2$, -OMe, -SMe, propargyl, cyano, -NNH, -$NNCH_3$, -OPO_2H, –OPO_2CH_3, –$OS(O_2)H$, –$OS(O_2)OH$, -$OS(O_2)CH_3$ and –$OS(O_2)OCH_3$, and m and n are each independently 0 or 1. In another variation, each Y or Z is independently selected from the group consisting of hydrogen, or



wherein m and n are each independently 0 or 1, and R^1, R^2, R^9 and R^{10} are each independently absent or selected from the group consisting of hydrogen, -NH_2, -OH, -SH, -$NHCH_3$, –$N(CH_3)_2$ -OMe and -SMe, and each Z group is optionally substituted with from 1 to 7 R^a groups selected from the group consisting of halo, –NH_2, –OH, -SH, –$NHCH_3$, –$N(CH_3)_2$, -OMe, -SMe, propargyl, cyano, -NNH, -$NNCH_3$, -OPO_2H, -OPO_2CH_3, -$S(SO_2)H$, –$S(SO_2)OH$, -$S(SO_2)CH_3$ and -$S(SO_2)OCH_3$.

[0019] In another variation of the above, R^1 and R^2 are hydrogen, m is 0, 1, 2 or 3 and Z is selected from the group consisting of furan, dihydro-furan, tetrahydrofuran, thiophene, pyrrole, 2*H*-pyrrole, 2-pyrroline, 3-pyrroline, pyrrolidine, 1,3-dioxolane, oxazole, thiazole, imidazole, dihydro-imidazole, 2-imidazoline, imidazolidine, pyrazole, 2-pyrazoline,

pyrazolidine, isoxazole, isothiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,3,4-thiadiazole, 2*H*-pyran, 1*H*-tetrazole, 4*H*-pyran, pyridine, dihydro-pyridine, tetrahydro-pyridine, piperidine, 1,4-dioxane, morpholine, 1,4-dithiane, thiomorpholine, pyridazine, pyrimidine, dihydro-pyrimidine, tetrahydro-pyrimidine, hexahydro-pyrimidine, pyrazine, dihydro-pyrazine, tetrahydro-pyrazine, piperazine, 1,3,5-triazine and 1,3,5-trithiane, wherein each Z group is optionally substituted with from 1 to 10 R^a groups.

[0020] In yet another variation, R^1 and R^2 are hydrogen, m is 0 or 1, and Z is selected from the group consisting of furan, thiophene, pyrrole, 2H-pyrrole, oxazole, thiazole, imidazole, pyrazole, isoxazole, isothiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,3,4-thiadiazole and 1H-tetrazole, wherein each Z group is optionally substituted with from 1 to 3 Ra groups selected from the group consisting of methyl, ethyl, propyl, iso-propyl, $-NH_2$, -OH, -SH, $-NHCH_3$, $-N(CH_3)_2$, $-OCH_3$ and $-SCH_3$. In another variation, Z is selected from the group consisting of $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)NR^a-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)NR^b-$, $R^aR^bNC(=O)NR^b-$, $R^aR^bNC(=S)NR^b-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $R^aS(O_2)-$, $-N=NR^a$, $-OPO_2R^a$, $-OS(O_2)R^a$, $-OS(=O)OR^a$, $-OS(O_2)OR^a$ and $-OS(O_2)NR^aR^b$, wherein m is 1 to 8, and the group $(CR^1R^2)_m$ is optionally saturated or partially unsaturated. In yet another variation, Z is selected from the group consisting of $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)NR^a-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)NR^b-$, $R^aR^bNC(=O)NR^b-$, $R^aR^bNC(=S)NR^b-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $R^aS(=O)_2-$, $-N=NR^a$, $-OPO_2R^a$, $-OS(O_2)R^a$, $-OS(=O)OR^a$, $-OS(O_2)OR^a$ and $-O(SO_2)NR^aR^b$, and wherein $(R^1R^2)_m$ together is selected from the group consisitng of $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$, $-CH=CHCH_2-$, $-CH_2CH=CH-$, $-CH=CHCH_2CH_2-$, $-CH_2CH=CHCH_2-$, $-CH_2CH_2CH=CH-$, $-C\equiv CCH_2-$, $-CH_2C\equiv C-$, $-C\equiv CCH_2CH_2-$, $-CH_2C\equiv CCH_2-$ and $-CH_2CH_2C\equiv C-$. In still another variation of the above, Z is independently $-CO_2R^a$, $R^aC(=O)-$, R^aR^bN-, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $R^aS(=O)-$, $R^aS(=O)_2-$, $-OPO_2R^a$, $-OS(O_2)R^a$, $-OS(=O)OR^a$, $-OS(O_2)OR^a$ or $-OS(O_2)NR^aR^b$, and wherein $(CR^1R^2)_m$ together is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$, $-CH=CHCH_2-$, $-CH_2CH=CH-$, $-CH=CHCH_2CH_2-$, $-CH_2CH=CHCH_2-$, $-CH_2CH_2CH=CH-$, $-C\equiv CCH_2-$, $-CH_2C\equiv C-$, $-C\equiv CCH_2CH_2-$, $-CH_2C\equiv CCH_2-$ and $-CH_2CH_2C\equiv C-$.

[0021] In one particular variation of each of the above; each R^9 is independently slected from the group consisting of hydrogen, halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_3-C_8)cycloalkyl, heterocyclyl, hetrocyclyl(C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $R^aS(=O)_2-$, $-N=NR^a$ and $-OPO_2R^a$. In another variation, R^1 and R^2 together with the carbon atom to which they are attached is C=O, C=S or $C=NR^c$. In yet another variation, R^3 is selected from the group consisting of hydrogen, halo, $-OR^a$, $-SR^a$, cyano, nitro, trifluoromethyl, trifluoromethoxy, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $R^aS(=O)_2-$, $-NNR^a$ and $-OPO_2R^a$; or if the ring formed from the group $CR^3R^4R^5$ is aryl or heteroaryl or partially unsaturated then R^3 can be absent. In another variation of the above, R^3 is selected from the group consisting of hydrogen, OH, OMe, OAc, NH_2, NHMe, NMe_2 and NHAc. In a particular variation, R^3 is hydrogen or OH.

[0022] In one particular variation of each of the above; R^4 and R^5 together with the atom to which they are attached form a saturated or partially unsaturated, mono-, bi- or tricyclic ring, or aromatic ring having 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 ring atoms, wherein the ring atoms are optionally interrupted by 1, 2, 3 or 4 heteroatoms selected from the group consisting of -O-, -S-, -SO-, $-S(O)_2-$ or amine $(-NR^a-)$ in the ring, wherein any ring comprising R^4 and R^5 is optionally further substituted with from 1 to 14 R^6 groups; wherein each R^6 is independently selected from the group consisting of halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_1-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, heterocycle, hetrocyclyl(C_1-C_8)alkyl, aryl, aryl(C_1-C_8)alkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $-NNR^a$,$-OPO_2R^a$, or two R^6 groups and the atom to which they are attached combined to form C=O or C=S, or wherein two R^6 groups together with the atom or atoms to which they are attached can form a carbocyclic or heterocyclic ring. In another variation, the ring comprising R^4 and R^5 and the

atom to which they are attached is selected from the group consisting of cyclopentane, cyclohexane, piperidine, dihydro-pyridine, tetrahydro-pyridine, pyridine, piperazine, decaline, tetrahydro-pyrazine, dihydro-pyrazine, pyrazine, dihydro-pyrimidine, tetrahydro-pyrimidine, hexahydro-pyrimidine, pyrazine, imidazole, dihydro-imidazole, imidazolidine, pyrazole, dihydro-pyrazole, pyrazolidine, norbornane and adamantane, each unsubstituted or substituted.

[0023] In one particular variation of each of the above, R^6 is selected from the group consisting of substituted or unsubstituted $(C_1\text{-}C_8)$alkyl, $-OR^a$, $-CO_2R^a$, $R^aC(=O)$-, $R^aC(=O)O$-, R^aR^bN-, $R^aR^bNC(=O)$- and aryl, provided that when the ring comprising R^4 and R^5 contains a heteroatom that is O or S, the heteroatom is not substituted with R^6. In another variation, R^6 is selected from the group consisting of OH, OMe, methyl, ethyl, t-butyl, $-CO_2Ra$, $-CONR^aR^b$, OAc, NH_2, NHMe, NMe_2, NHEt and $N(Et)_2$, provided that when the ring comprising R^4 and R^5 contains a heteroatom that is O or S, the heteroatom is not substituted with R^6. In yet another variation, R^6 is selected from the group consisting of methyl, ethyl, $-CO_2R^a$, $-CONR^aR^b$ and OAc, provided that when the ring comprising R^4 and R^5 contains a heteroatom, the heteroatom is not substituted with OAc. In yet another variation, R^6 is selected from the group consisting of $-(CH_2)_{1\text{-}2}OR^a$, $-(CH_2)_{1\text{-}2}C(=O)OR^a$, $-(CH_2)_{1\text{-}2}OC(=O)R^a$, $-(CH_2)_{1\text{-}2}C(=O)R^a$, $-(CH2)_{1\text{-}2}OCO_2R^a$, $-(CH_2)_{1\text{-}2}NHR^a$, $-(CH_2)_{1\text{-}2}NR^aR^b$, $-(CH_2)_{1\text{-}2}OC(=O)NHR^a$ and $-(CH_2)_{1\text{-}2}OC(=O)NR^aR^b$. In yet another variation, R^6 is $-CH_2C(=O)OR^a$, $-CH_2OC(=O)ORa$, $-CH_2OH$, $-CH_2OAc$, $-CH_2NH(CH_3)$ and $-(CH_2)_{1\text{-}2}N(CH_3)_2$. In another variation, the number of R_6 groups substituted on the R_4R_5 ring is from 1 to 4.

[0024] In another variation, R^7 and R^8 is selected from the group consisting of hydrogen, $(C_1\text{-}C_8)$alkyl–, aryl, aryl$(C_1\text{-}C_8)$alkylene–, mono-, bicyclic- or aromatic or nonaromatic ring having 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms, wherein the ring atoms are optionally interrupted by 1, 2, 3 or 4 heteroatoms selected from the group consisting of -O-, -S-, -SO-, $-S(O)_2$- or amine $(-NR^a-)$ in the ring, and each is optionally substituted with from 1, 2, 3 or 4 R^a groups. In yet another variation, R^7 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl,3-pentyl, *iso*-propyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, phenyl and benzyl, or wherein R^7 is hydrogen, methyl or *sec*-butyl. In another variation, R^7 and R^8 are each independently selected from the group consisting of hydrogen, $(C_1\text{-}C_8)$alkyl,

(C_3-C_8)cycloalkyl, aryl, aryl(C_1-C_8)alkylene, heteroaryl and heteroaryl(C_1-C_8)alkylene-; or wherein R^7 and R^8 together with the nitrogen atom to which they attach form a heterocycle or heteroaromatic ring.

[0025] In one particular variation of each of the above, -NR^7R^8 is selected from the group consisting of amino, methylamino, dimethylamino, ethylamino, pentylamino, diphenylethylamino, pyridylmethylamino, diethylamino and benzylamino. In another variation, -NR^7R^8 is selected from the group consisting of amino, methylamino, dimethylamino, ethylamino, diethylamino and benzylamino, or wherein -NR^7R^8 is amino.

[0026] In one particular variation of each of the above; R^a and R^b are each independently selected from the group consisting of hydrogen, (C_1-C_8)alkyl and (C_1-C_8)alkyl substituted with 1 to 3 (C_1-C_8)alkoxy, (C_3-C_8)cycloalkyl, (C_1-C_8)alkylthio, aryl, aryl(C_1-C_8)alkylene, heteroaryl, or heteroaryl(C_1-C_8)alkylene; or R^a and R^b together with the nitrogen to which they are attached, form a pyrrolidino, piperidino, morpholino, or thiomorpholino ring; R^c is hydrogen or (C_1-C_6)alkyl; m is 0 to about 8 and p is 0 to 2; and Y is -$CR^3R^4R^5$ or NR^4R^5.

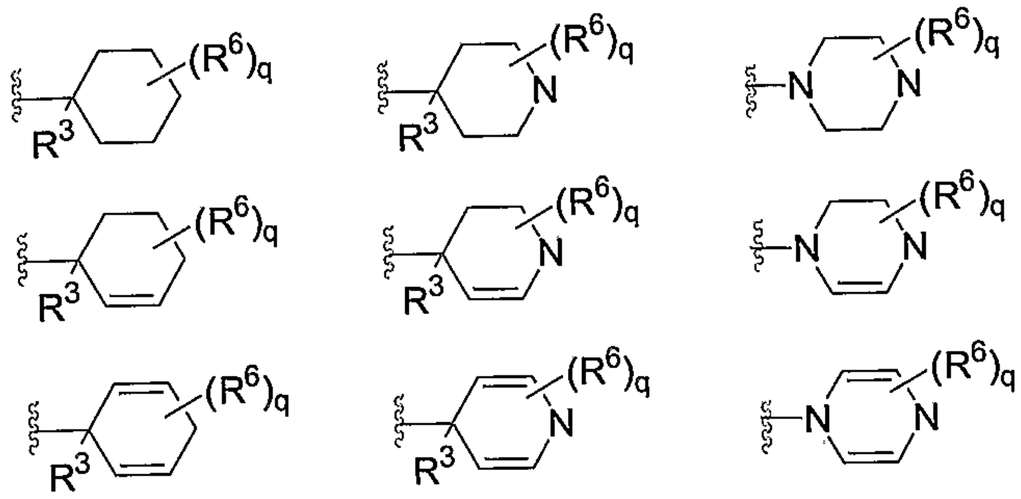
[0027] In another variation, R^7 is selected from the group consisting of benzyl, phenethyl, phenylpropyl and each is optionally substituted with from 1, 2 or 3 substituents of R^a. In a particular variation, R^7 is selected from the group consisting of benzyl, phenethyl, phenylpropyl and each is optionally substituted with from 1, 2 or 3 substituents of R^a selected from the group consisting of methyl, ethyl, propyl, methoxy, ethoxy and propoxy; or wherein R^7 is benzyl and R^a is methoxy.

[0028] In another aspect of the above, R^9 is selected from the group consisting of hydrogen, fluoro, -OH, -CH_2OH, -OMe, -OAc, -NH_2, -NHMe, -NMe_2 and –NHAc; or wherein R^9 is hydrogen or OH. In one variation, each R^{10} is independently selected from the group consisting of hydrogen, fluoro, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, heterocyclyl, heterocycle(C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene-, heteroaryl and heteroaryl(C_1-C_8)alkylene-. In another variation, R^{10} is selected from the group consisting of hydrogen, (C_1-C_8)alkyl, cyclopropyl, cyclohexyl and benzyl; or wherein R^{10} is hydrogen. In yet another variation of the above, R^9 and R^{10} and the carbon atom to which they are attached is a C=O group.

[0029] In a variation of the above compound, R^a and R^b are each independently selected from the group consisting of hydrogen, (C_1-C_4)alkyl, aryl and aryl(C_1-C_8)alkylene.

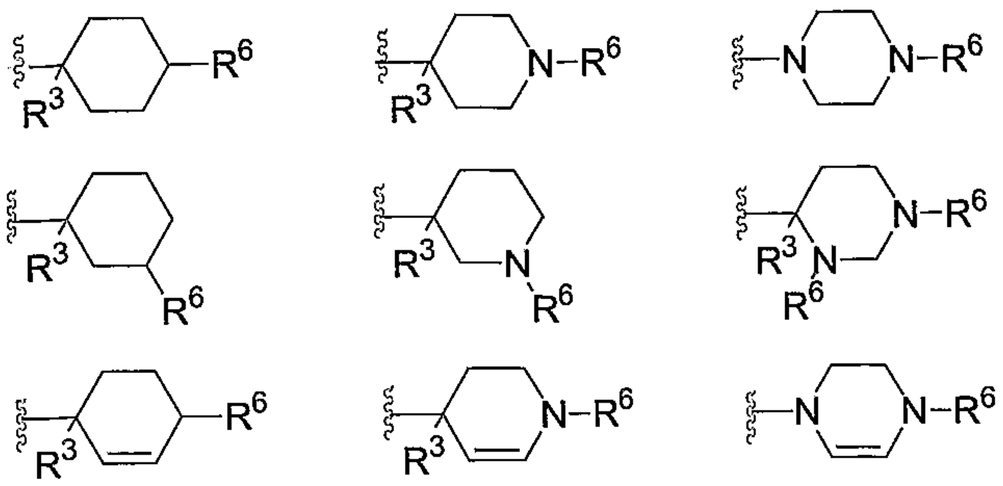
In a particular variation, R^a and R^b are each independently selected from the group consisting of hydrogen, methyl, ethyl, phenyl and benzyl. In another variation, R^a is $(C_1\text{-}C_8)$alkyl. In yet another variation, R^a is selected from the group consisting of methyl, ethyl, propyl and butyl. In yet another variation, R^a is selected from the group consisting of methyl, ethyl, i-propyl, i-butyl and tert-butyl. In still another variation, R^a and R^b is a ring.

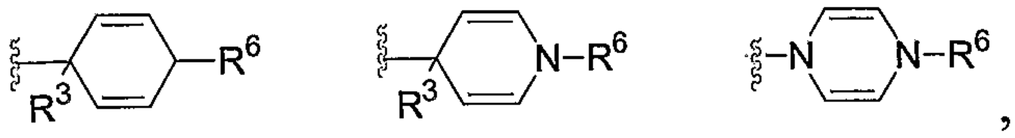
[0030] In one variation of each of the above, Y is $-CR_3R_4R_5$ or NR_4R_5, and is selected from the group consisting of:



wherein q is 0, 1, 2, 3 or 4; R^3 is selected from the group consisting of hydrogen, halo, $-OR^a$, $-SR^a$, $(C_1\text{-}C_8)$alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, $(C_3\text{-}C_8)$cycloalkyl, heterocycle, hetrocycle$(C_1\text{-}C_8)$alkyl, aryl, aryl$(C_1\text{-}C_8)$alkyl, heteroaryl, heteroaryl$(C_1\text{-}C_8)$alkyl, $-CO_2R^a$, $R^aC(=O)O$-, $R^aC(=O)$-, $-OCO_2R^a$, $R^aR^bNC(=O)O$-, $R^bOC(=O)N(R^a)$-, R^aR^bN-, $R^aR^bNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^aR^bNC(=O)N(R^b)$-, $R^aR^bNC(=S)N(R^b)$-, $-OPO_3R^a$, $R^aOC(=S)$-, $R^aC(=S)$-, $-SSR^a$, $R^aS(=O)$-, $R^aS(=O)_2$-, $-NNR^a$ and $-OPO_2R^a$; and each R^6 is independently selected from the group consisting of halo, $-OR^a$, $-SR^a$, substituted or unsubstituted $(C_1\text{-}C_8)$alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, $(C_1\text{-}C_8)$cycloalkyl, $(C_6\text{-}C_{12})$bicycloalkyl, heterocycle, hetrocyclyl$(C_1\text{-}C_8)$alkyl, aryl, aryl$(C_1\text{-}C_8)$alkyl, heteroaryl, heteroaryl$(C_1\text{-}C_8)$alkyl, $-CO_2R^a$, $R^aC(=O)O$-, $R^aC(=O)$-, $-OCO_2R^a$, $R^aR^bNC(=O)O$-, $R^bOC(=O)N(R^a)$-, R^aR^bN-, $R^aR^bNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^aR^bNC(=O)N(R^b)$-, $R^aR^bNC(=S)N(R^b)$-, $-OPO_3R^a$, $R^aOC(=S)$-, $R^aC(=S)$-, $-SSR^a$, $R^aS(=O)$-, $-NNR^a$ and $-OPO_2R^a$, provided that R^6 is not halogen or a heteroatom when R^6 is attached to a heteroatom.

[0031] In another variation, Y is $-CR^3R^4R^5$ or NR^4R^5 and is selected from the group consisting of:





,

wherein R^3 is selected from the group consisting of hydrogen, halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_3-C_8)cycloalkyl, heterocycle, hetrocycle(C_1-C_8)alkyl, aryl, aryl(C_1-C_8)alkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $R^aS(=O)_2-$, $-NNR^a$ and $-OPO_2R^a$; and each R^6 is independently selected from the group consisting of halo, $-OR^a$, $-SR^a$, substituted or unsubstituted (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_1-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, heterocycle, hetrocyclyl(C_1-C_8)alkyl, aryl, aryl(C_1-C_8)alkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $-NNR^a$ and $-OPO_2R^a$.

[0032] In another variation, the ring comprising $-C(R^3)R^4R^5$ is 2-methylcyclohexan-1-yl, 2,2-dimethylcyclohexan-1-yl, 2-ethylcyclohexan-1-yl, 2,2-diethylcyclohexan-1-yl, 2-tert-butylcyclohexan-1-yl, 2-phenylcyclohexan-1-yl, 3-methylcyclohexan-1-yl, 3-ethylcyclohexan-1-yl, 3,3-dimethylcyclohexan-1-yl, 4-methylcyclohexan-1-yl, 4-ethylcyclohexan-1-yl, 4,4-dimethylcyclohexan-1-yl, 4-tert-butylcyclohexan-1-yl, 4-phenylcyclohexan-1-yl, 3,3,5,5-tetramethylcyclohexan-1-yl, 2,4-dimethylcyclopentan-1-yl, 4-(carboxyl)cyclohexan-1-yl, 4-(carboxymethyl)cyclohexan-1-yl and 4-(carboxyethyl)cyclohexan-1-yl. In yet another variation, the ring comprises $-C(R^3)R^4R^5$ is piperidin-4-yl, 1-carboxypiperiden-4-yl, 1-(methoxycarbonyl)piperidin-4-yl, 1-(ethoxycarbonyl)piperidin-4-yl, 1-(n-propoxycarbonyl)piperidin-4-yl, 1-(2,2-dimethylpropoxycarbonyl)piperidin-4-yl, piperidin-1-yl, 4-carboxypiperiden-1-yl, 4-(methoxycarbonyl)piperidine-1-yl, 4-(ethoxycarbonyl)piperidine-1-yl, 4-(n-

propoxy)piperidine-1-yl, 4-(2,2-dimethylpropoxycarbonyl)piperidine-1-yl, piperidin-3-yl, 1-carboxypiperidene-3-yl, 1-(methoxycarbonyl)piperidine-3-yl, 1-(ethoxycarbonyl)piperidine-3-yl, 1-(n-propoxycarbonyl)piperidine-3-yl, 1-(2,2-dimethylpropoxycarbonyl)piperidine-3-yl, 3-carboxypiperidene-1-yl, 3-(methoxycarbonyl)piperidine-1-yl, 3-(ethoxycarbonyl)piperidine-1-yl, 3-(n-propoxycarbonyl)piperidine-1-yl, 3-(2,2-dimethylpropoxycarbonyl)piperidine-1-yl, piperazin-1-yl, 1-caboxypiperazin-4-yl, 1-(methoxycarbonyl)piperazin-4-yl, 1-(ethoxycarbonyl)piperazin-4-yl and 1-(n-propoxycarbonyl)piperazin-4-yl.

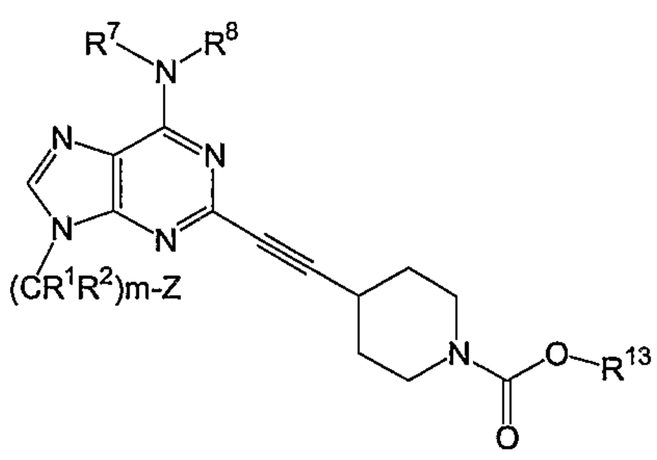
[0033] In another variation, the ring comprising $-C(R^3)R^4R^5$ is selected from the group consisting of 2-methylcyclohexan-1-yl, 2,2-dimethylcyclohexan-1-yl, 2-ethylcyclohexan-1-yl, 2,2-diethylcyclohexan-1-yl, 2-tert-butylcyclohexan-1-yl, 2-phenylcyclohexan-1-yl, 3-methylcyclohexan-1-yl, 3-ethylcyclohexan-1-yl, 3,3-dimethylcyclohexan-1-yl, 4-methylcyclohexan-1-yl, 4-ethylcyclohexan-1-yl, 4,4-dimethylcyclohexan-1-yl, 4-tert-butylcyclohexan-1-yl, 4-phenylcyclohexan-1-yl, 3,3,5,5-tetramethylcyclohexan-1-yl, 2,4-dimethylcyclopentan-1-yl, 4-(carboxyl)cyclohexan-1-yl, 4-(carboxymethyl)cyclohexan-1-yl, 4-(carboxyethyl)cyclohexan-1-yl, piperidin-4-yl, 1-(methoxycarbonyl)piperidin-4-yl, 1-(2,2-dimethylpropoxycarbonyl)piperidin-4-yl, piperidin-1-yl, 4-(methoxycarbonyl)piperidine-1-yl, 4-(2,2-dimethylpropoxycarbonyl)piperidine-1-yl, piperidin-3-yl, 1-(methoxycarbonyl)piperidine-3-yl, 1-(2,2-dimethylpropoxycarbonyl)piperidine-3-yl, 3-(methoxycarbonyl)piperidine-1-yl and 3-(2,2-dimethylpropoxycarbonyl)piperidine-1-yl.

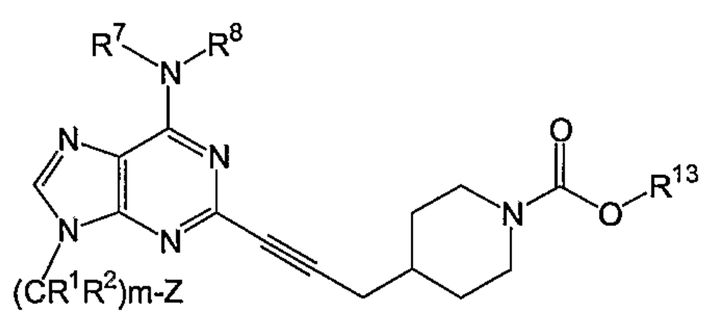
[0034] In a particular variation, Z is a mono-, bicyclic-, tricyclic- or aromatic or non-aromatic (C_3-C_{20})cycloalkyl ring, wherein the ring atoms are optionally interrupted by 1-8 heteroatoms selected from the group consisting of –O–, –S–, –SO–, $–S(O)_2–$ and amino ($–NR^a–$). In one variation of the above, R^1 and R^2 are hydrogen, m is 0, 1, 2 or 3 and Z is selected from the group consisting of furan, dihydro-furan, tetrahydrofuran, thiophene, pyrrole, 2H-pyrrole, 2-pyrroline, 3-pyrroline, pyrrolidine, 1,3-dioxolane, oxazole, thiazole, imidazole, dihydro-imidazole, 2-imidazoline, imidazolidine, pyrazole, 2-pyrazoline, pyrazolidine, isoxazole, isothiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,3,4-thiadiazole, 2H-pyran, 1H-tetrazole, 4H-pyran, pyridine, dihydro-pyridine, tetrahydro-pyridine, piperidine, 1,4-dioxane, morpholine, 1,4-dithiane, thiomorpholine, pyridazine, pyrimidine, dihydro-pyrimidine, tetrahydro-pyrimidine, hexahydro-pyrimidine,

pyrazine, dihydro-pyrazine, tetrahydro-pyrazine, piperazine, 1,3,5-triazine and 1,3,5-trithiane, wherein each Z group is optionally substituted with from 1 to 10 R^a groups. In another variation, Z is a mono-, bicyclic-, tricyclic- or aromatic or non-aromatic (C_3-C_{20})cycloalkyl ring, wherein the ring atoms are optionally interrupted by 1-8 heteroatoms selected from the group consisting of –O–, –S–, –SO–, –S(O)2– and amino (–NR^a–).

[0035] In a particular variation, R^1 and R^2 are hydrogen, m is 0, 1, 2 or 3 and Z is selected from the group consisting of furan, dihydro-furan, tetrahydrofuran, thiophene, pyrrole, 2*H*-pyrrole, 2-pyrroline, 3-pyrroline, pyrrolidine, 1,3-dioxolane, oxazole, thiazole, imidazole, dihydro-imidazole, 2-imidazoline, imidazolidine, pyrazole, 2-pyrazoline, pyrazolidine, isoxazole, isothiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,3,4-thiadiazole, 2*H*-pyran, 1*H*-tetrazole, 4*H*-pyran, pyridine, dihydro-pyridine, tetrahydro-pyridine, piperidine, 1,4-dioxane, morpholine, 1,4-dithiane, thiomorpholine, pyridazine, pyrimidine, dihydro-pyrimidine, tetrahydro-pyrimidine, hexahydro-pyrimidine, pyrazine, dihydro-pyrazine, tetrahydro-pyrazine, piperazine, 1,3,5-triazine and 1,3,5-trithiane, wherein each Z group is optionally substituted with from 1 to 10 R^a groups.

[0036] In another aspect, there is provided a compound of the formula:





wherein R^7 and R^8 are each independently selected from the group consisting of hydrogen, (C_2-C_4)alkyl, 3-pentyl, aryl(C_2-C_4)alkyl, heteroaryl(C_2-C_4)alkyl, each unsubstituted or substituted, R^8 is selected from the group consisting of hydrogen or (C_1-C_4)alkyl; and R^{11} is selected from the group consisting of (C_1-C_4)alkyl, propargyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_4)alkyl, aryl(C_1-C_4)alkyl, heteroaryl(C_1-C_4)alkyl, heterocyclyl(C_1-C_4)alkyl, HO(C_1-C_4)alkyl, halo(C_1-C_4)alkyl, -COO(C_1-C_4)alkyl, (C_1-C_4)alkylCOO(C_1-C_4)alkyl, each unsubstituted or substituted; R^{13} is methyl, *iso*-propyl, *iso*-butyl, or *tert*-butyl; and R^1, R^2 and m are as defined herein; or a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof.

[0037] In another aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of each of the above, and a

pharmaceutically acceptable excipient. Some of the compounds of formulae I, II, and III may further form pharmaceutically acceptable salts and esters. All of these forms are included within the scope of the present invention. Pharmaceutically acceptable base addition salts of the compounds of formulae I, II, and III include salts which may be formed when acidic protons present in the parent compound are capable of reacting with inorganic or organic bases as known in the art. Acceptable inorganic bases, include for example, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium-hydroxide. Salts may also be prepared using organic bases, such as choline, dicyclohexylamine, ethylenediamine, ethanolamine, diethanolamine, triethanolamine, procaine, N-methylglucamine, and the like [see, for example, Berge et al., "Pharmaceutical Salts," *J. Pharma. Sci.* 66:1 (1977)]. Pharmaceutically acceptable acid addition salts of the compounds of formulae I, II, and III include salts which may be formed when the parent compound contains a basic group. Acid addition salts of the compounds may be prepared in a suitable solvent from the parent compound and an excess of a non-toxic inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid (giving the sulfate and bisulfate salts), nitric acid, phosphoric acid and the like, or a non-toxic organic acid such as aceticacid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, camphorsulfonic acid, tert-butylacetic acid, laurylsulfuric acid, glucuronic acid, glutamic acid, and the like. The free base form may be regenerated by contacting the acid addition salt with a base and isolating the free base in the conventional manner. The free base forms can differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents.

[0038] Also included in the above embodiments, aspects and variations are salts of amino acids such as arginate and the like, gluconate, and galacturonate. Some of the compounds of the invention may form inner salts or Zwitterions. Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms, and are intended to be within the scope of the present invention. Certain of the above compounds may also exist in one or more solid or crystalline phases or polymorphs, the variable biological activities of such polymorphs or mixtures of such polymorphs are also included in the scope of this invention. Also provided are

pharmaceutical compositions comprising pharmaceutically acceptable excipients and a therapeutically effective amount of at least one compound of this invention.

[0039] Pharmaceutical compositions of the compounds of this invention, or derivatives thereof, may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation is generally a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulations are especially suitable for parenteral administration but may also be used for oral administration. Excipients, such as polyvinylpyrrolidinone, gelatin, hydroxycellulose, acacia, polyethylene glycol, mannitol, sodium chloride, or sodium citrate, may also be added. Alternatively, these compounds may be encapsulated, tableted, or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin, saline, alcohols, or water. Solid carriers include starch, lactose, calcium sulfate, dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar, or gelatin. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulation, and compressing, when necessary, for tablet forms; or milling, mixing, and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule. Suitable formulations for each of these methods of administration may be found in, for example, *Remington: The Science and Practice of Pharmacy*, A. Gennaro, ed., 20th edition, Lippincott, Williams & Wilkins, Philadelphia, Pa.

[0040] In one variation, there is provided the above compound, or a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof. In one aspect, there is provided a method for stimulating motor activity without dyskinesia in a mammal, comprising administering a therapeutically

effective amount of an A_{2A} anatagonist compound of the above to the mammal in need of such treatment. In one variation of the above method, the therapeutically effective amount is effective to treat ischemia, brain damage induced by ischemia and excitoxicity, Huntington disease, catalepsy, cancer, drug addiction and withdrawal, Parkinson's disease (drug induced, post-encephalitic, poison induced or post-traumatic induced), acute or chronic pain, narcolepsy and Alzheimer's disease. In another variation of the above, the therapeutically effective amount is effective to stimulate motor activity for treating a movement disorder, where the disorder is progressive supernuclear palsy, Huntington's disease, multiple system atrophy, corticobasal degeneration, Wilsons disease, Hallerrorden-Spatz disease, progressive pallidal atrophy, Dopa-responsive dystonia-Parkinsonism, spasticity or other disoders of the basal ganglia which result in dyskinesias. In another variation of the above, the compound is used in combination with one or more additional drugs in the treatment of movement disorders (i.e. L-DOPA or dopamine agonist), addiction, or cancer with the components being in the same formulation or in a separate formulation for administration simultaneously or sequentially. In yet another variation of the method, the therapeutically effective amount is effective to provide neuroprotection and slow or halt the degeneration of dopaminergic neurons. In yet anotehr variation, the therapeutically effective amount is effective to enhance the immune response by increasing the activity of an immune cell in a mammal. In one variation, the activity is pro-inflammatory cytokine production. In another variation, the activity of the immune cell results in an increase in inflammation. In yet another variation of the above method, the mammal is human.

[0041] In another embodiment of the invention, there is provided a method for stimulating motor activity without dyskinesia in a mammal, comprising administering a therapeutically effective amount of an A_{2A} antagonist compound of the above to the mammal in need of such treatment. In one variation of the above embodiment, there is provided a method as described above wherein the A_{2A} antagonist is selected from a compound of each of the above embodiments, aspects and variations.

[0042] In another embodiment, there is provided a method to evaluate novel A_{2A} antagonists in four mouse models of PD. These include: A) motor function in normal and dopamine-depleted mice; B) synergistic activity with L-dopa to stimulate motor activity in dopamine-depleted mice; C) attenuation MPTP-induced neurotoxicity by inhibiting MPTP

metabolism; and D) delayed L-dopa-induced locomotor sensitization in unilateral 6-OHDA-lesioned mice.

[0043] In another embodiment, there is provided a method comprising contacting a compound of each of the above formula with an isotope such as those from hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, or iodine (e.g. ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, ^{125}I) optionally being a radioactive isotope (radionuclide), such as, for example, tritium, radioactive iodine (for example, ^{125}I for binding assays or ^{123}I for Spect Imaging) or other non-radioactive isotope (such as deuterium) and the like. Isotopically labeled compounds may be useful for drug/tissue distribution assays and/or manipulating oxidative metabolism via the primary kinetic isotope effect. They are also valuable in identifying potential therapeutic agents for the treatment of diseases or conditions associated with target-receptor mediation, by contacting said agents with said radioligands and receptors, and measuring the extent of displacement of the radioligand and/or binding of the agent. Representative references for Deuterium-for hydrogen substitution include Hanzlik et al., *J. Org. Chem.* 55, 3992-3997, 1990; Reider et aL, *J. Org. Chem.* 52, 3326-3334, 1987; Foster, *Adv. Drug Res.* 14 1-40, 1985; Gillette et al., *Biochemistry* 33(10) 2927-2937, 1994; and Jarman et al. *Carcinogenesis* 16(4) 683-688, 1993, the references of which are incorporated herein in their entirety. The use of radiolabelled compounds that may be detected using imaging techniques, such as, for instance, Single Photon Emission Computerized Tomography (SPECT) or Positron Emission Tomography (PET) and the like, are known in the art. See for example, U.S. Patent Nos. 6,395,742; 6,472,667 and references cited therein.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS:

[0044] Unless specifically noted otherwise herein, the definition of the terms used are standard definitions used in the art of organic synthesis and pharmaceutical sciences.

[0045] Where a carbonyl group or a carbonyl derivative such as a thio carbonyl or an imine and the like, is represented by a group such as –C(=O)O– or –C(=O)NR^{a}–, for example, it is intended that the corresponding isomeric group that is –OC(=O)– or –NR^{a}C(=O)– is also included.

[0046] An "alkyl" group is a straight, branched, saturated or unsaturated, aliphatic group having a chain of carbon atoms, optionally with oxygen, nitrogen or sulfur atoms

inserted between the carbon atoms in the chain or as indicated. A (C_1-C_{20})alkyl, for example, includes alkyl groups that have a chain of between 1 and 20 carbon atoms, and include, for example, the groups methyl, ethyl, propyl, isopropyl, vinyl, allyl, 1-propenyl, isopropenyl, ethynyl, 1-propynyl, 2-propynyl, 1,3-butadienyl, penta-1,3-dienyl, penta-1,4-dienyl, hexa-1,3-dienyl, hexa-1,3,5-trienyl, and the like. An alkyl group may also be represented, for example, as a -$(CR^1R^2)_m$- group where R^1 and R^2 are independently hydrogen or are independently absent, and for example, m is 1 to 8, and such representation is also intended to cover both saturated and unsaturated alkyl groups. An alkyl as noted with another group such as an aryl group, represented as "arylalkyl" for example, is intended to be a straight, branched, saturated or unsaturated aliphatic divalent group with the number of atoms indicated in the alkyl group (as in (C_1-C_{20})alkyl, for example) and/or aryl group (as in (C_5-C_{14})aryl, for example) or when no atoms are indicated means a bond between the aryl and the alkyl group. Nonexclusive examples of such group include benzyl, phenethyl and the like.

[0047] An "alkylene" group is a straight, branched, saturated or unsaturated aliphatic divalent group with the number of atoms indicated in the alkyl group (as in -(C_1-C_{20})alkylene- or -(C_1-C_{20})alkylenyl-, for example), optionally with one or more oxygen, nitrogen or sulfur atoms inserted (or "interrupted") between the carbon atoms in the chain or as indicated.

[0048] A "cyclyl" such as a monocyclyl or polycyclyl group includes monocyclic, or linearly fused, angularly fused or bridged polycycloalkyl, or combinations thereof. Such cyclyl group is intended to include the heterocyclyl analogs. A cyclyl group may be saturated, partically saturated or aromatic.

[0049] "Halogen" or "halo" means fluorine, chlorine, bromine or iodine.

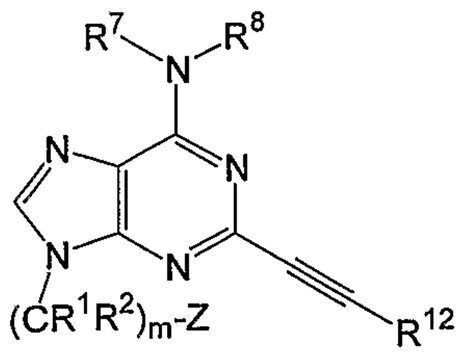
[0050] A "heterocyclyl" or "heterocycle" is a cycloalkyl wherein one or more of the atoms forming the ring is a heteroatom that is a N, O, or S. Non-exclusive examples of heterocyclyl include piperidyl, 4-morpholyl, 4-piperazinyl, pyrrolidinyl, 1,4-diazaperhydroepinyl, 1,3-dioxanyl, and the like.

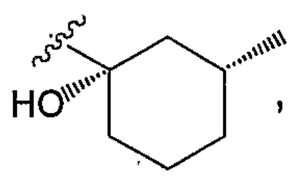
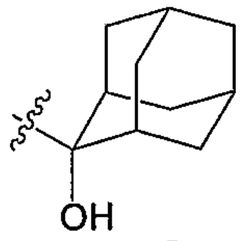
[0051] "Pharmaceutically acceptable salts" means salt compositions that is generally considered to have the desired pharmacological activity, is considered to be safe, non-toxic and is acceptable for veterinary and human pharmaceutical applications. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid,

sulfuric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, malonic acid, succinic acid, malic acid, citric acid, gluconic acid, salicylic acid and the like.

[0052] "Substituted or unsubstituted" means that a group such as, for example, alkyl, aryl, heterocyclyl, (C_1-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, hetrocyclyl(C_1-C_8)alkyl, aryl(C_1-C_8)alkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl, the mono-, bi- or polycyclic rings that define the Z group, and the like, unless specifically noted otherwise, may be unsubstituted or, may substituted by 1, 2, 3, 4 or 5 substitutents selected from the group such as halo, nitro, trifluoromethyl, trifluoromethoxy, methoxy,
carboxy, $-NH_2$, -OH, -SH, $-NHCH_3$, $-N(CH_3)_2$, -SMe, propargyl,
cyano, -NNH, $-NNCH_3$, $-OPO_2H$, $-OPO_2CH_3$, $-S(SO_2)H$, $-S(SO_2)OH$, $-S(SO_2)CH_3$
and $-S(SO_2)OCH_3$, and the like.

REPRESENTATIVE A_{2A}AR ANTAGONISTS:



R^{12} =  , 

A B

Table 1. Binding Affinity and Selectivity of A_{2A}AR Ligands[a]

				Ki, nM			
ATL #	R^{12}	R^7	$(CR^1R^2)_m$-Z	A_1AR	A_{2A}AR	A_{2B}AR	A_3AR
Antagonists							
11	**A**	3-P	Me	172 (1.3)	137	20 %	30 %
17	**A**	3-P	Proparg	11 (2)	5	147 (29)	188 (38)
2	**A**	NH_2	Proparg	4.6 (5)	0.95	50 (11)	599 (630)
3	**A**	NH_2	*c*Pent	368 (37)	10	357 (36)	633 (63)
51	**B**	NH_2	Proparg	25 (16)	1.6	155 (97)	>650(>400)
50	**B**	NH_2	*c*Pent	> 325 (> 27)	12	40 %	40 %

[a]Abbreviations: 3-P, 3-pentyl; Me, methyl; Proparg, prop-2-ynyl; *c*Pent, cyclopentyl. Numbers in parentheses are selectivity ratios vs. the A_{2A}AR. Activities expressed as percentage are displacement of radioligand by 1 μM candidate ligand.

Motor enhancement by the lipophilic A_{2A} receptor antagonist ATL-2 in normal mice

[0053] The ability of compounds to stimulate motor activity in normal mice was measured using a simple, computer-assisted locomotor activity cage system. C57BL/6 mice (n=6-8 purchased from the Jackson's lab) were habituated for the testing environment for 120 minute prior to drug treatment. The test compounds were dissolved in vehicle (10% DMSO, 10% castrol oil EL-620 and 80% saline). The drug was administrated intraperitoneally at a dose of 15 mg/kg, and locomotor activity was recorded for 2 hours before and after drug administration.

[0054] **Figure 2** shows that ATL-2 produced strong motor stimulation, reaching peak within 20 minutes and lasting for about 60 minutes (arrow marks the injection). From our previous experience with other A_{2A}R antagonists, the motor stimulant effect of ATL2 is comparable or stronger than other A_{2A}R antagonists such as SCH58261 and KW6002.

Absence of motor stimulant effect of ATL-2 in mice lacking the A_{2A} receptor

[0055] We validated that ATL-2 acts on the A_{2A} receptor to stimulate motor activity by using A_{2A}R KO mice (in both mixed (129sv X C57BL/6) as well as congenic (C57BL/6 genetic background) developed over the last several years. We evaluated the motor stimulant effect of ATL-2 in A_{2A} receptor KO and their WT littermates. WT and A_{2A} KO mice (n=4) were habituated for 60 minutes and treated with ATL-2 (15 mg/kg) and recorded for motor activity for 120 minutes.

[0056] **Figure 3** shows that ATL-2 produced motor activity in WT mice (relatively high basal locomotion is likely due to short habituation time (60 minute instead of 120 minutes) and to tendency of relatively higher basal locomotion in WT compared to KO mice as we noted previously,[35] but this motor stimulation was absent in A_{2A} receptor KO mice.

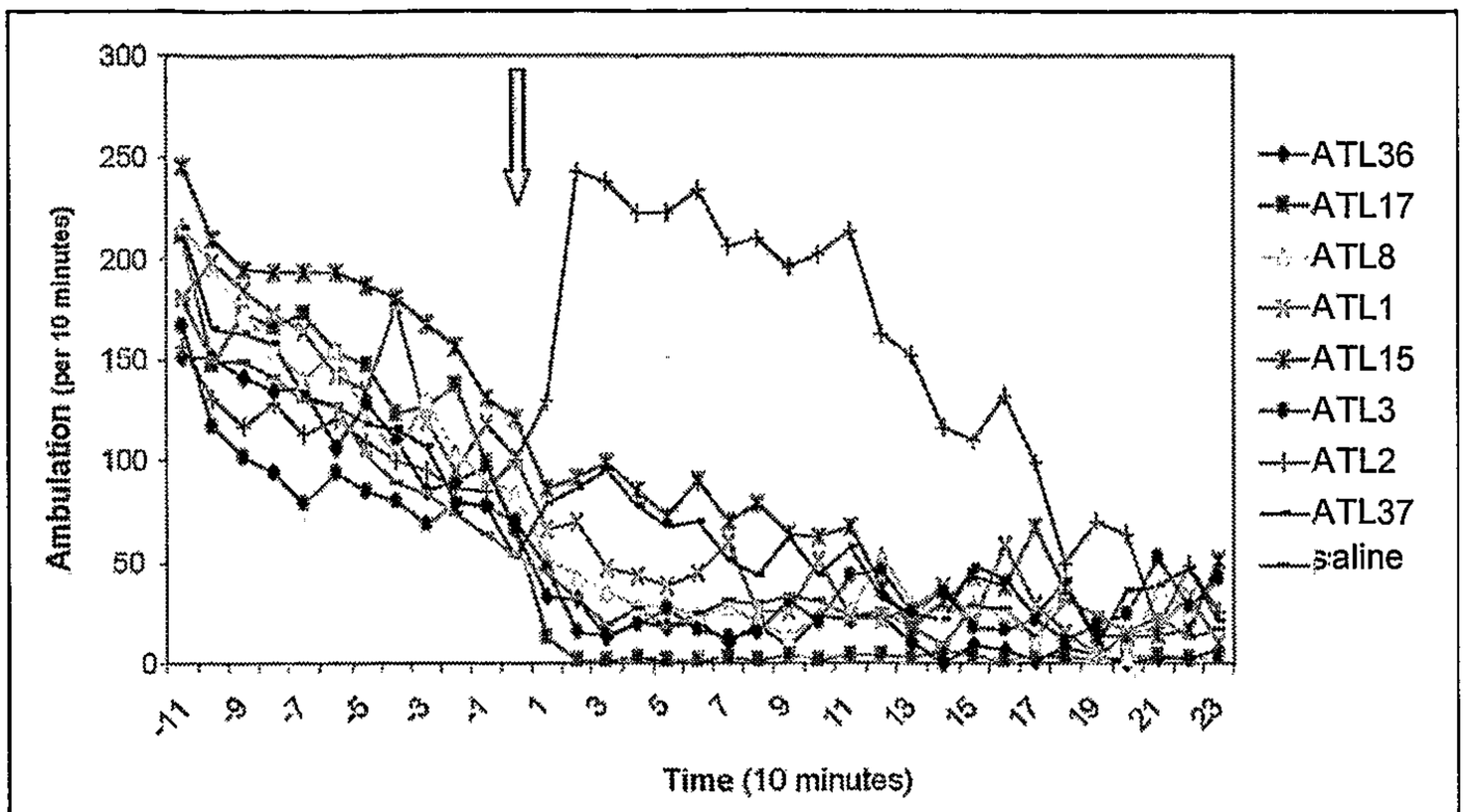


Figure 2. Locomotor stimulant activity of $A_{2A}AR$ antagonists injected into mice. Locomotion declined over time after a cage changes was increase following injection of compounds of the invention.

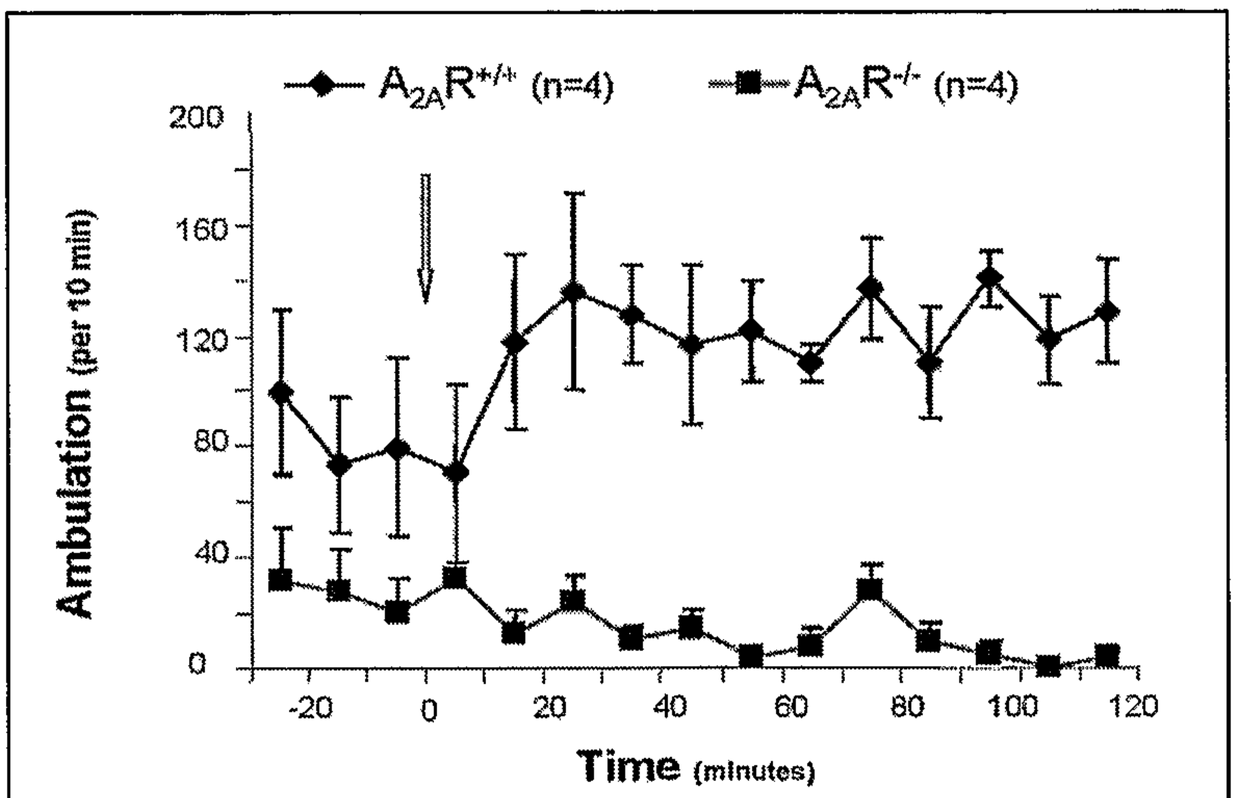


Figure 3. Effect of $A_{2A}AR$ gene deletion on locomotor effect of ATL-2.

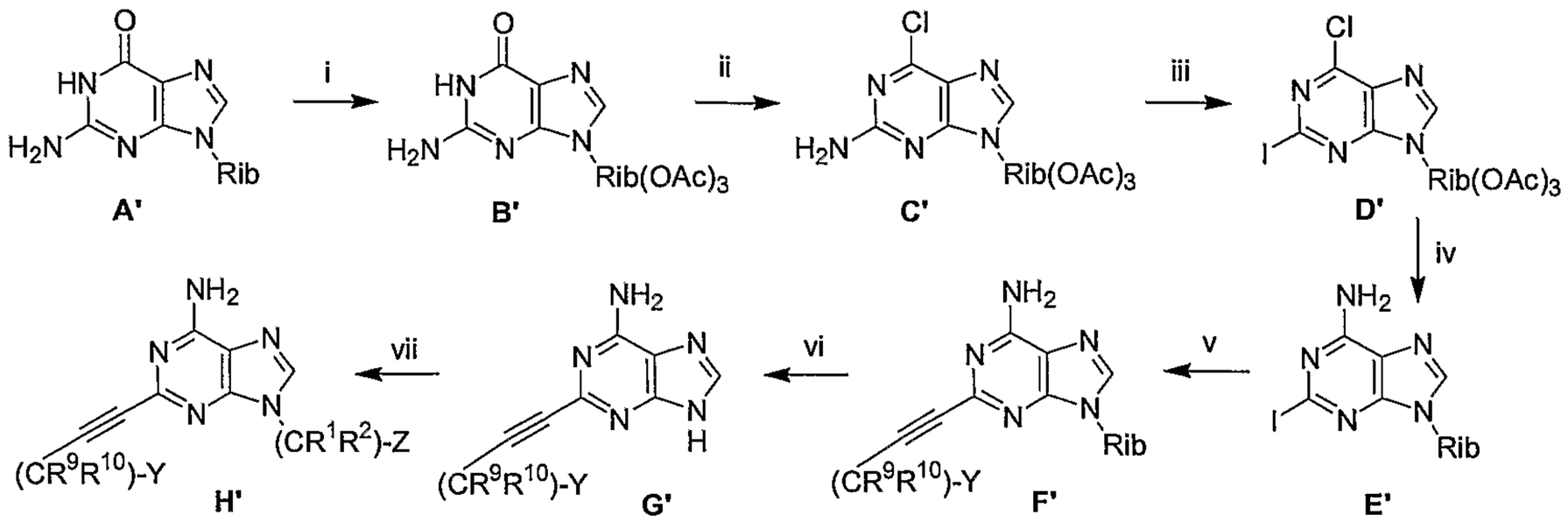
Experimental

Synthesis of A_{2A}AR antagonists

[0057] The following procedures may be employed for the preparation of the compounds of the present invention. The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as the Aldrich Chemical Company (Milwaukee, Wis.), Bachem (Torrance, Calif.), Sigma (St. Louis, Mo.), or are prepared by methods well known to a person of ordinary skill in the art, following procedures described in such references as *Fieser and Fieser's Reagents for Organic Synthesis*, vols. 1-17, John Wiley and Sons, New York, N.Y., 1991; *Rodd's Chemistry of Carbon Compounds*, vols. 1-5 and supps., Elsevier Science Publishers, 1989; *Organic Reactions*, vols. 1-40, John Wiley and Sons, New York, N.Y., 1991; March J.: *Advanced Organic Chemistry*, 4th ed., John Wiley and Sons, New York, N.Y.; and Larock: *Comprehensive Organic Transformations*, VCH Publishers, New York, 1989. In some cases, protective groups may be introduced and finally removed. Suitable protective groups for amino, hydroxy, and carboxy groups are described in Greene et al., *Protective Groups in Organic Synthesis*, Second Edition, John Wiley and Sons, New York, 1991. Standard organic chemical reactions can be achieved by using a number of different reagents, for examples, as described in Larock: *Comprehensive Organic Transformations*, VCH Publishers, New York, 1989.

[0058] In one variation, the compounds of this invention can be synthesized by the steps outlined in Scheme 1. Guanosine, **A'**, is acetylated to protect the ribose during reductive chlorination by $POCl_3$/diethylaniline to form 6-chloroguanosine, **C'**. Non-aqueous diazotization in the presence of elemental iodine in diiodomethane is a standard route to the protected 6-chloro-2-iodonebularine, **D'**. Heating in methanolic ammonia deprotects the sugar and displaces the 6-chloro substituent to form 2-iodoadenosine, **E'**. Palladium-catalyzed coupling of **E'** with a terminal alkyne generates 2-alkynyladenosine **F'**, which undergoes acid hydrolysis to form 9*H*-adenine **G'**. Alkylation with an appropriate halide (alkyl, cycloalkyl or heterocyclic) completes the synthesis of target 2,9-disubstituted adenine **H'**.

Scheme 1.

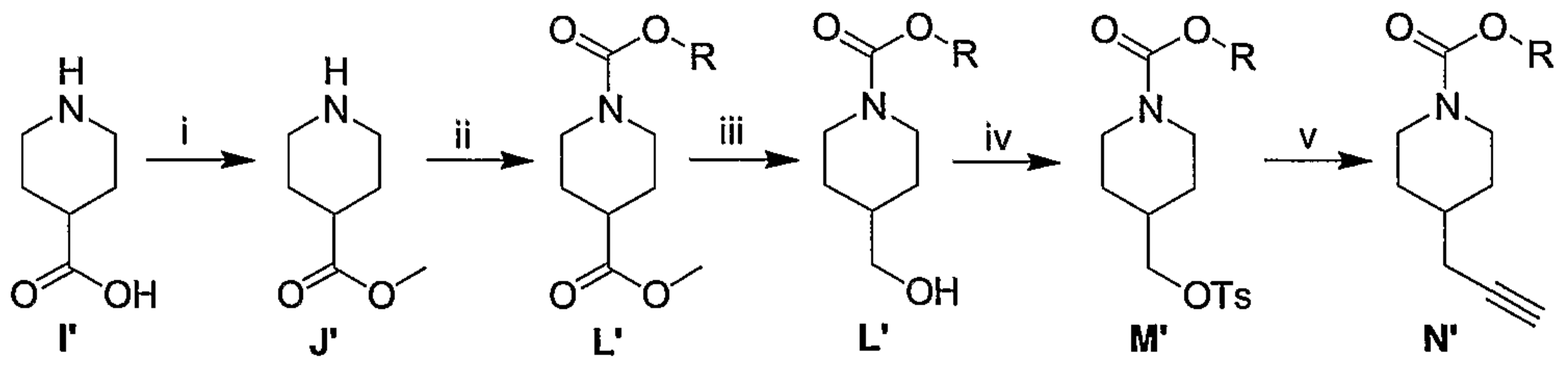


i, Ac_2O/Pyd; ii, $POCl_3$/$PhNMe_2$; iii, I_2/CH_2I_2/CuI/RONO; iv, NH_3; v, (CR^9R^{10})-YCCH/$Pd(PPh_3)_4$/CuI; vi, H^+; vii, (CR^1R^2)-ZX/K_2CO_3.

[0059] Preparation of the terminal alkynes (S)-1-ethynyl-1-hydroxy-(R)-3-methylcyclohexane and 2-ethynyladamantan-2-ol is achieved by treatment of the corresponding ketone with ethynylmagnesium bromide.

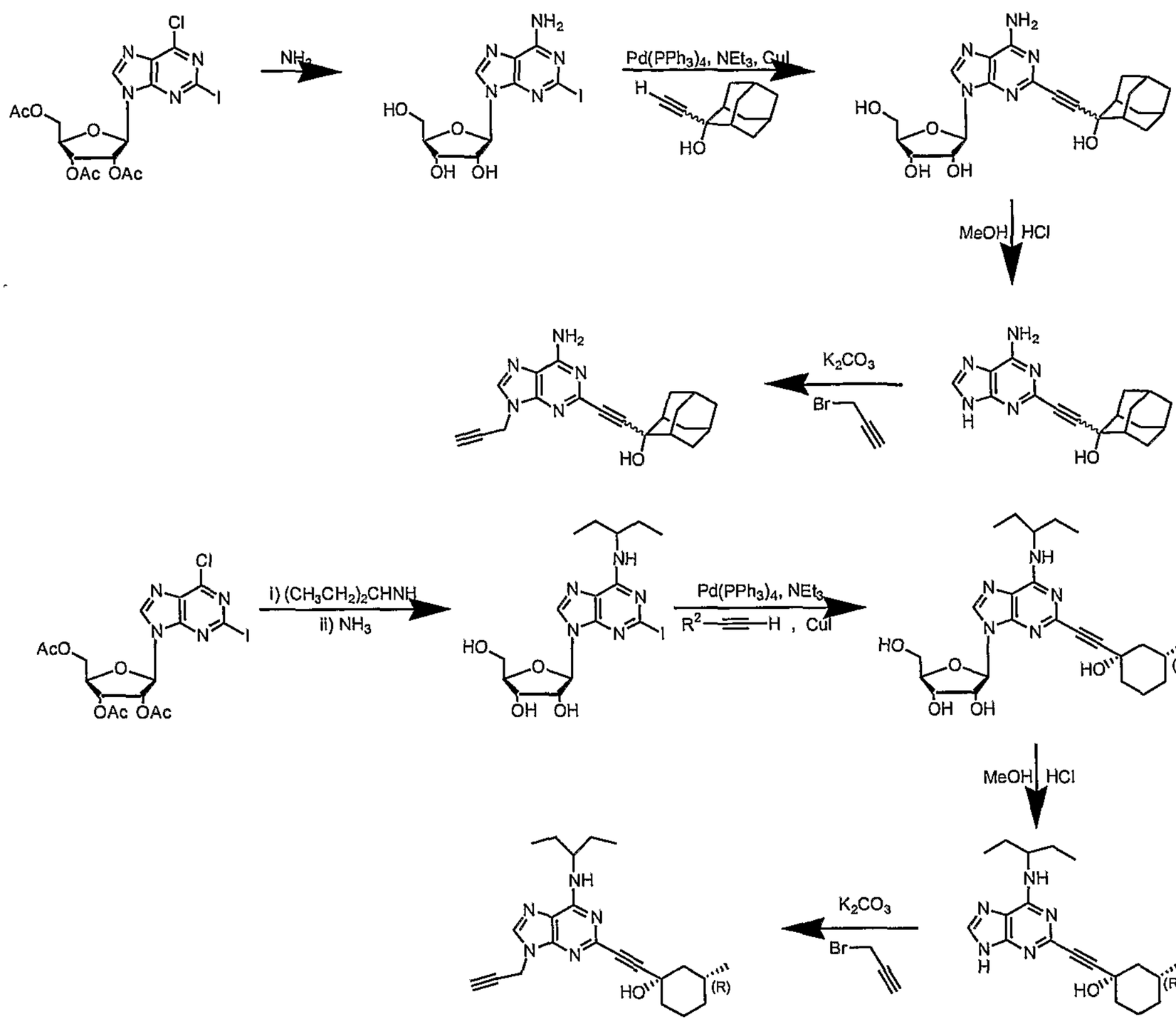
[0060] Preparation of the substituted piperidine-carboxylate terminal alkynes (Scheme 2) starts with 4-carboxypiperidine (isonipecotic acid) **I'** in anticipation of acylating the methyl ester, **J'**, with the appropriate alkyl chloroformate to form the N-carbamoyl ester **K'**. Borohydride reduction of the ester generates the 4-hydroxymethylpiperidine, **L'**, which undergoes tosylation to **M'** in preparation for condensation with lithium acetylide to form terminal alkyne **N'**.

Scheme 2. Synthesis of terminal alkynes

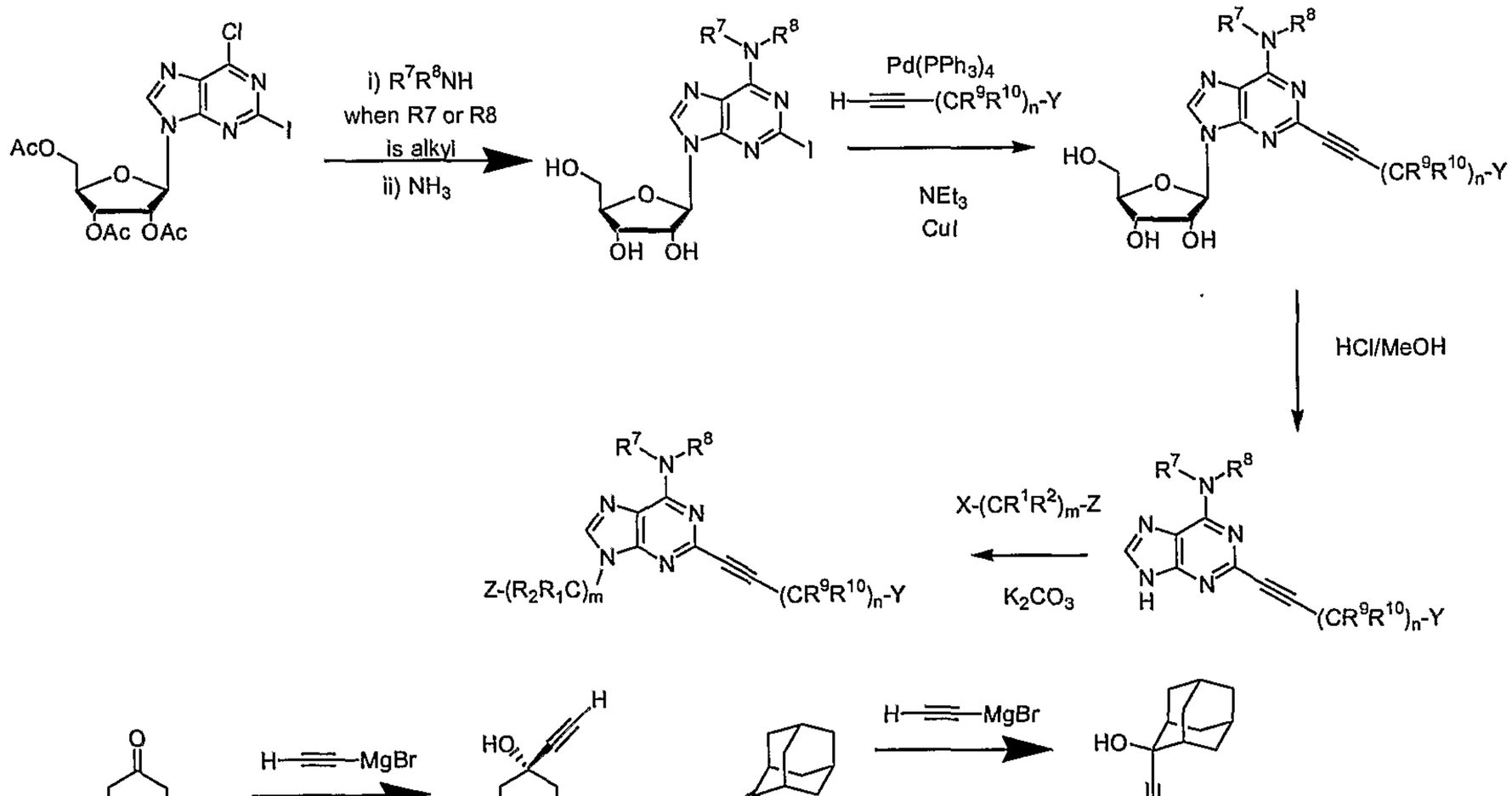


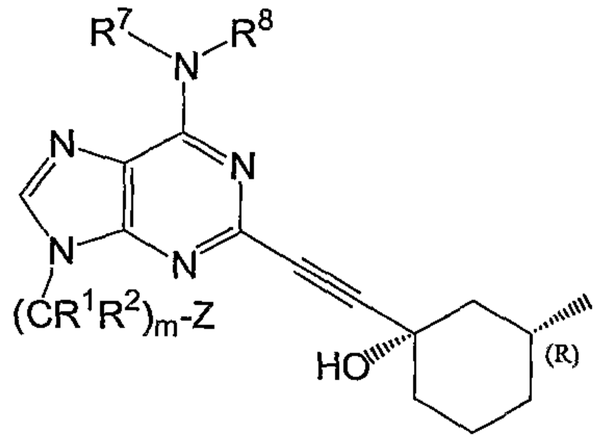
i, MeOH, H^+; ii, ClCOOR/base; iii, $NaBH_4$;iv, TsOCl/base; v, $LiCCR_2$.

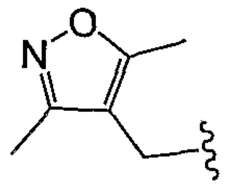
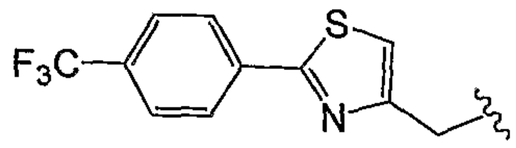
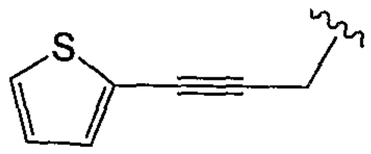
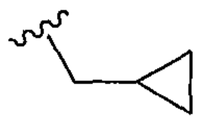
Scheme 3: Representative Processes for the Preparation of A2a Antagonists and Examples of A2a Antagonists:

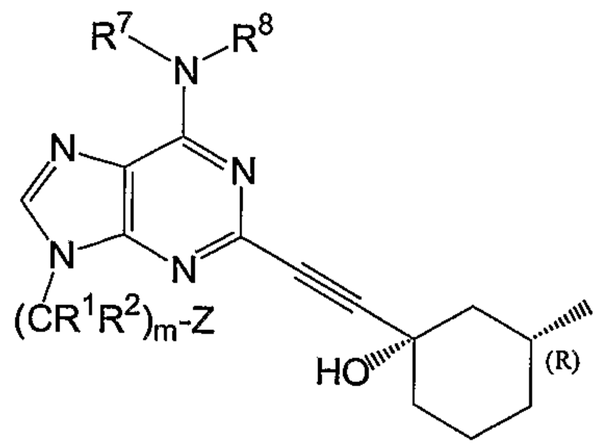


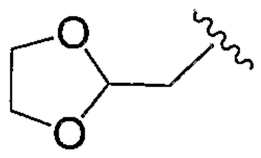
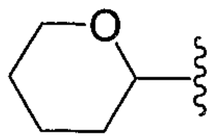
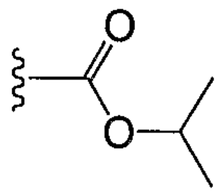
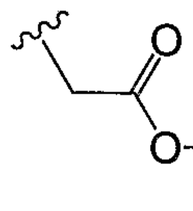
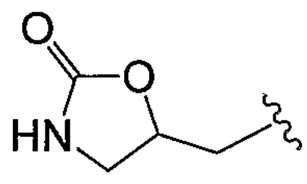
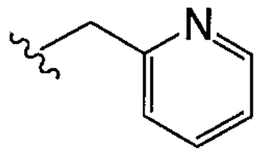
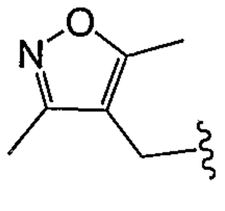
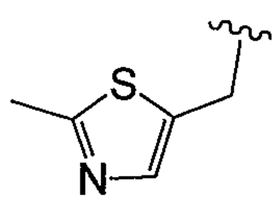
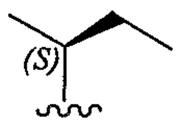
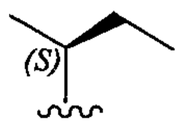
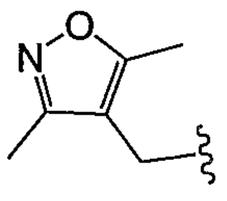
Scheme 4: Representative Processes for the Preparation of A2a Antagonists

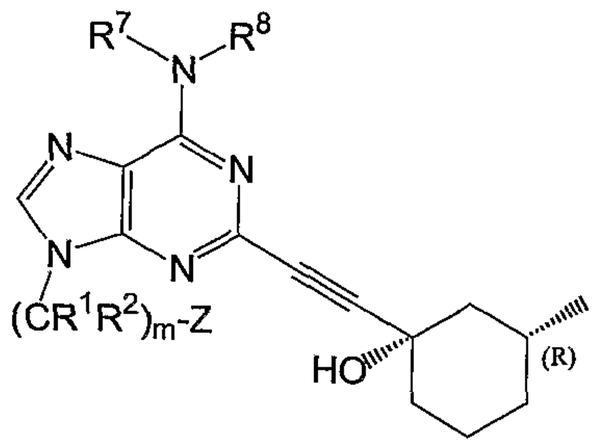


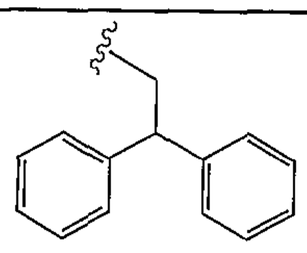
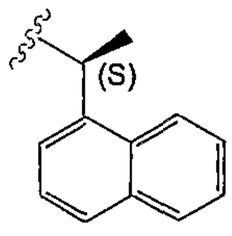
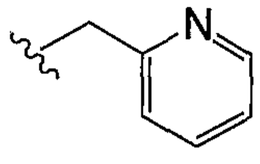
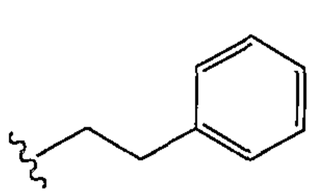


Compound No.	R^7	R^8	$(CR^1R^2)_m$-Z	Human K_i (nM)
1	H	H		++++
2	H	H	Propargyl	++++
3	H	H	Cyclopentyl	++++
4	H	H	$-CH_2CN$	++++
5	H	H	4-Methoxybenzyl	
6	H	H	3,4-Dichlorobenzyl	
7	H	H	4-(Trifluoromethyl)benzyl	
8	H	H		++++
9	H	H		
10	H	H		+++
11	Pent-3-yl	H	$-CH_3$	+++
12	Pent-3-yl	H	$-CH_2CH_2CH_3$	++++
13	Pent-3-yl	H	*Iso*-propyl	+++
14	Pent-3-yl	H		++++
15	Pent-3-yl	H	Cyclopentyl	++++
16	Pent-3-yl	H	Allyl	++++
17	Pent-3-yl	H	Propargyl	++++
18	Pent-3-yl	H	$-(CH_2)_3C\equiv CH$	++++
19	Pent-3-yl	H	$-CH_2CH_2OH$	++++
20	Pent-3-yl	H	$-CH_2CH_2CH_2OH$	+++

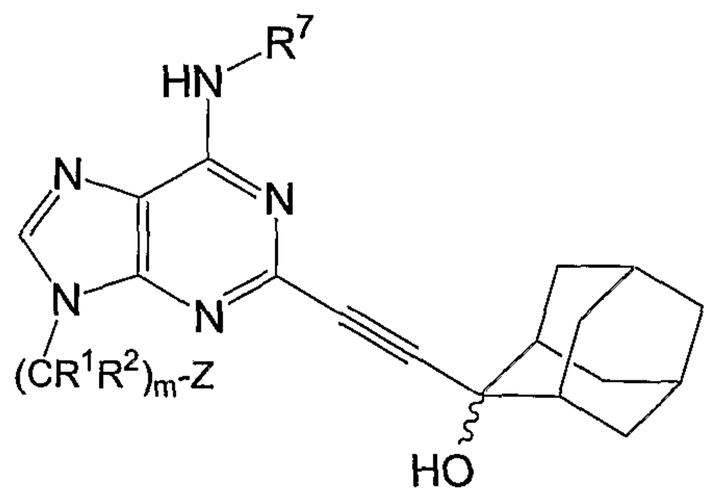


Compound No.	R^7	R^8	$(CR^1R^2)_m$-Z	Human K_i (nM)
21	Pent-3-yl	H	$-CH_2CH_2Cl$	
22	Pent-3-yl	H		+++
23	Pent-3-yl	H		
24	Pent-3-yl	H		
25	Pent-3-yl	H		+++
26	Pent-3-yl	H		
27	Pent-3-yl	H	Benzyl	++++
28	Pent-3-yl	H		++++
29	Pent-3-yl	H	4-Nitrobenzyl	
30	Pent-3-yl	H		++++
31	Pent-3-yl	H		
32		H	Propargyl	++++
33		H		++++

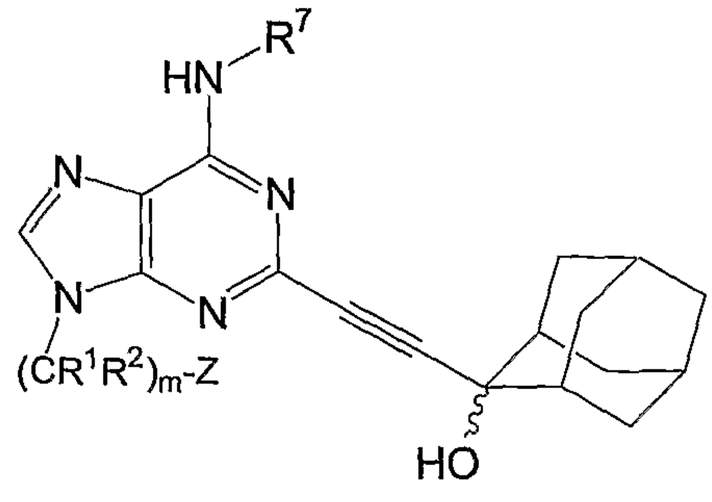


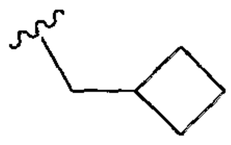
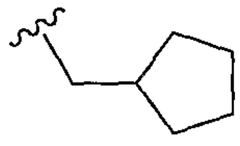
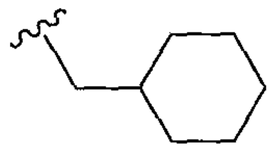
Compound No.	R^7	R^8	$(CR^1R^2)_m$-Z	Human K_i (nM)
34		H	$-CH_3$	+++
35		H	Propargyl	+++
36	3-Methoxybenzyl	H	Propargyl	++++
37		H	Propargyl	++++
38		$-CH_3$	Propargyl	

+ K_i < 10,000 nM; ++ K_i < 1,000 nM; +++ K_i < 500 nM; ++++ K_i < 100 nM.

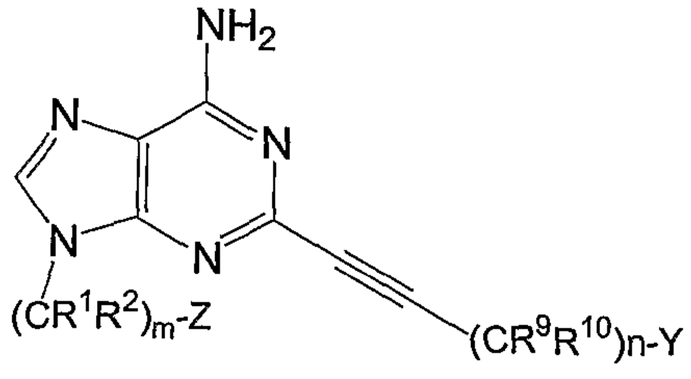


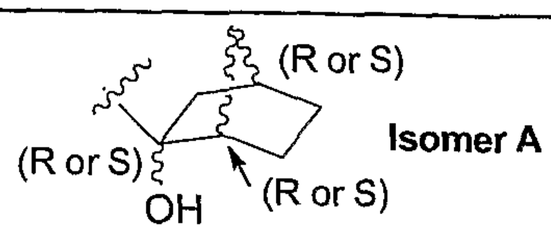
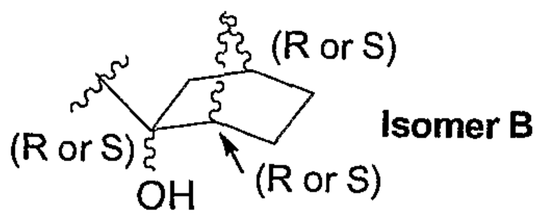
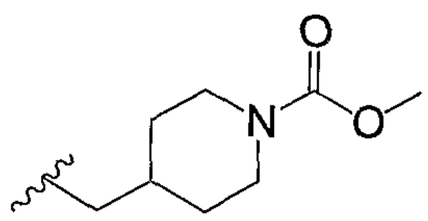
Compound No.	R^7	$(CR^1R^2)_m$-Z	Human K_i (nM)
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40	H	$-CH_2CH_3$	++++
41	H	$-CH_2CH_2CH_3$	++++
42	H	$-(CH_2)_5CH_3$	++
43	H	$-(CH_2)_8CH_3$	
44	H	*Iso*-propyl	+++



Compound No.	R^7	$(CR^1R^2)_m$-Z	Human K_i (nM)
45	H		++++
46	H		++++
47	H		+++
48	H		
49	H	Cyclobutyl	++++
50	H	Cyclopentyl	++++
51	H	Propargyl	++++
52	H	$-CH_2CH_2OH$	+++
53	H	$-CH_2CH_2CH_2OH$	+++
62	H	But-3-ynyl	++++

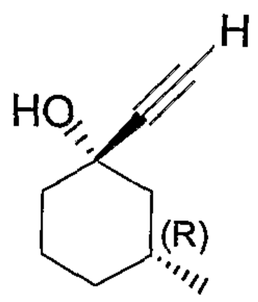
+ K_i < 10,000 nM; ++ K_i < 1,000 nM; +++ K_i < 500 nM; ++++ K_i < 100 nM.



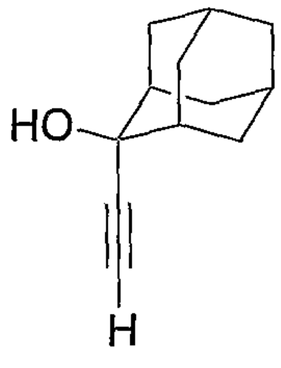
Compound No.	$(CR^9R^{10})_n$-Y	$(CR^1R^2)_m$-Z	Human K_i (nM)
60	 **Isomer A**	Propargyl	++++
61	 **Isomer B**	Propargyl	++++
63		Propargyl	++++

+ K_i < 10,000 nM; ++ K_i < 1,000 nM; +++ K_i < 500 nM; ++++ K_i < 100 nM.

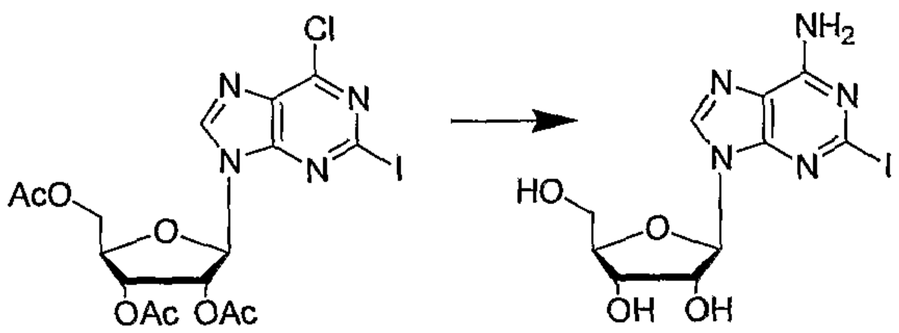
Synthesis:

[0061] 

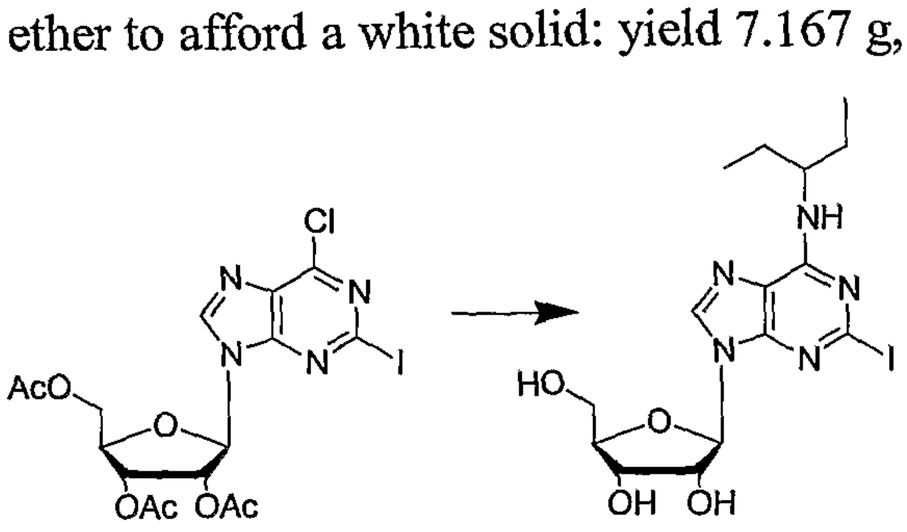
[0062] **(S)-1,1-Ethynyl-hydroxy-(R)-3-methylcyclohexane.** A solution of 0.5 M ethynylmagnesium bromide in THF (150.0 mL, 0.0750 mol) was added to an ice cold solution of (R)-(+)-3-methylcyclohexanone (2.77 g, 0.02469 mol) in anhydrous THF (100 mL). The ice bath was removed and the mixture stirred at room temperature 24 h. The mixture was cooled over ice and quenched with water (15.0 mL). The volume of THF was reduced to approximately 50 mL and the mixture filtered through a bed of celite/sand, washing with ether. The solution is then evaporated to dryness and the crude purified by column chromatography, eluting with a gradient of hexanes to hexanes/ethyl acetate (10%) to afford the pure product as a white crystalline solid: yield 1.412 g, 41%. ^{1}H NMR ($CDCl_3$) δ 0.73-0.95, 1.10-1.19, 1.35-1.45, 1.51-1.84, 1.93-2.03 (5 x m, 9H, cyclohexyl), 0.93 (d, 3H, –CH_3), 2.48 (s, 1H, alkyne).

[0063] 

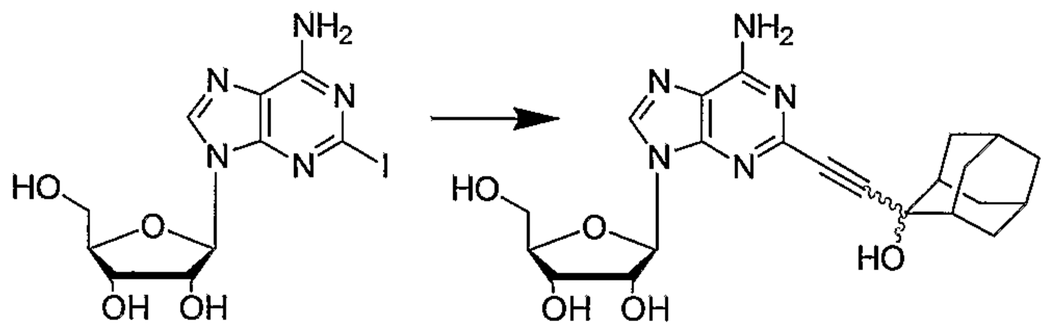
[0064] **2-Ethynyl-adamantan-2-ol.** A solution of 0.5 M ethynylmagnesium bromide in THF (400.0 mL, 0.2000 mol) was added to an ice cold solution of 2-adamantone (7.706 g, 0.05130 mol) in anhydrous THF (250 mL). The mixture was stirred over ice 0.5 h and then at room temperature 21 h. The volume was reduced to half and the solution cooled over ice. The reaction was quenched with water (5.0 mL), filtered through a bed of celite/sand and evaporated to dryness. The crude was taken up in ether (400 mL) and washed with water (2 x 40 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and evaporated to dryness to afford the pure product as a crystalline white solid: yield 8.961 g, 99%. ^1H NMR ($CDCl_3$) δ 1.54-1.61, 1.68-1.72, 1.76-1.99, 2.11-2.21 (4 x m, 14H, adamantly), 2.53 (s, 1H, alkyne).

[0065] 

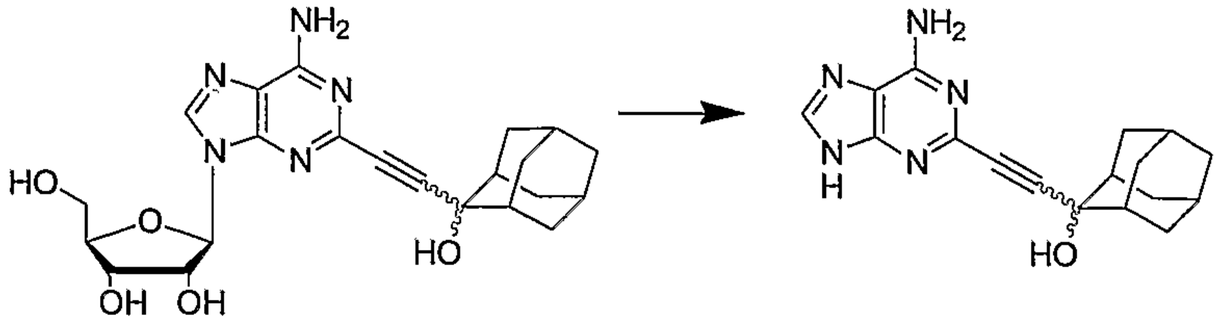
[0066] **Representative procedure for N6-amino substitution: 2-Iodoadenosine.** A suspension of 6-chloro-2-iodo-9-(2',3',5'-*O*-triacetylfuranosyl)-9*H*-purine (14.70 g, 0.02729 mol) in MeOH (300 mL) was cooled over an ice bath. Ammonia gas was then bubbled through the mixture until it was saturated. The reaction vessel was sealed and heated at 40 °C for 18 h and at 60 °C for 5 days. The mixture was cooled over ice and nitrogen gas bubbled through the solution, the mixture being allowed to warm to room temperature. The solvent was then removed under reduced pressure and the crude recrystallized from water containing 3-4 drops of glacial acetic acid. The resulting precipitate was filtered and washed with water and ether to afford a white solid: yield 7.167 g, 67%.

[0067] 

[0068] **Representative procedure for N6-alkylamino substitution: 2-Iodo-6-(3-pentyl)adenosine.** 6-chloro-2-iodo-9-(2',3',5'-*O*-triacetylfuranosyl)-9*H*-purine (6.723 g, 0.01248 mol), 3-aminopentane (1.673 mL, 0.01436 mol) and diisopropylethylamine (2.725 mL, 0.01560 mol) were stirred in denatured ethanol (150 mL) at 90 °C in a pressure apparatus for 21 h. The reaction was then cooled over ice and ammonia gas bubbled through the mixture until it was saturated. The reaction vessel was closed and the mixture stirred at room temperature 21 h. The mixture was cooled over ice and nitrogen gas bubbled through the solution, the mixture being allowed to warm to room temperature. The solvent was removed under reduced pressure and the crude purified by column chromatography, eluting with a gradient of DCM/MeOH (0-4%) to afford the pure product as an off white solid: yield 4.838 g, 84%.

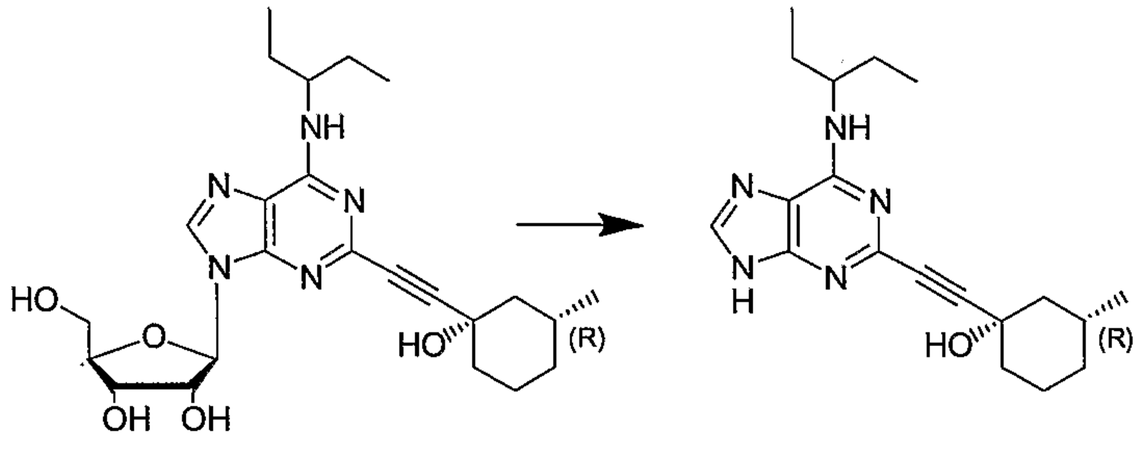
[0069] 

[0070] **Representative procedure for C2 coupling: 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenosine.** To a solution of 2-iodoadenosine (3.105 g, 7.898 mmol) in freshly degassed acetonitrile/DMF (100 mL, 1:1) was added degassed triethylamine (11.0 mL, 78.9 mmol), $Pd(PPh_3)_4$ (113 mg, 0.09779 mmol), CuI (catalytic), and 2,2-ethynyl-hydroxy-adamantanyl (1.516 g, 8.601 mmol). The mixture was stirred at room temperature under and inert atmosphere for 71 h. Silica bound Pd(II) scavenger Si-thiol (561 mg) and Pd(0) scavenger Si-TAAcOH (541 mg) were added and stirring continued a further 4.5 h. The suspension was filtered through celite and the resulting solution evaporated to dryness. The crude was purified by column chromatography, eluting with a gradient of DCM/MeOH (0-15%) to afford the pure product as a white solid: yield 3.476 g, 100%.

[0071] 

[0072] **Representative procedure for ribose cleavage: 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine.** A solution of 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenosine (3.486 g, 7.896 mmol) in methanol (100 mL) and 1.0 M HCl (10.0 mL) was

stirred at 90 °C in a pressure apparatus for 18-50 h. The pH was adjusted to 4.2 with 5.0 M NaOH and the volume was reduced to half under reduced pressure. After cooling the resulting precipitate was filtered and washed with methanol to afford the pure product as a white solid: yield 2.153 g, 88%. ^{1}H NMR (DMSO-d_6) δ 8.13 (s, 1H), 7.25 (br s, 2H), 5.56 (s, 1H), 2.18-2.09, 1.94-1.89, 1.82-1.64, 1.52-1.45 (4 x m, 12H). LRMS ESI (M+H$^+$) 310.1.

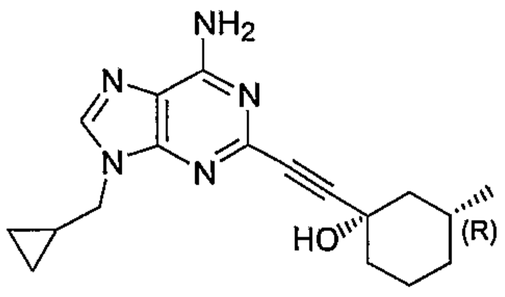
[0073] 

[0074] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine.** Using the representative procedure for ribose cleavage above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenosine (1.03 g) gave the product as a white solid: yield 0.725 g, 98%. LRMS ESI (M+H$^+$) 342.2.

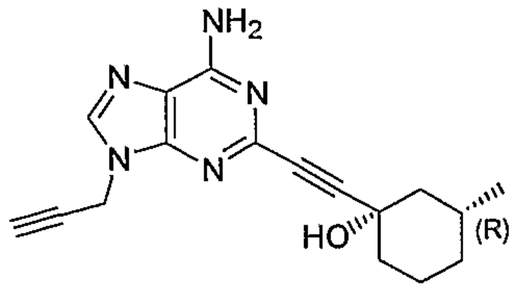
Synthesis of C2, N9-Adenines:

[0075] **Representative procedure for N9-alklation using an appropriate alkyl halide:**

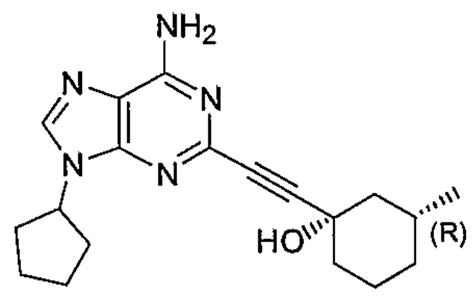
An appropriate 9-unsubstituted adenine (1.649 mmol) was dissolved in DMF (80 mL). Anhydrous potassium carbonate (358 mg, 2.590 mmol) and an appropriate alkyl halide (3.295 mmol) were added and the mix stirred at between 25-100 °C for 5 – 100 h. The reaction mixture was adhered to silica and purified by column chromatography, eluting with a gradient of DCM/MeOH (0-10%) to afford the pure product.

[0076] 

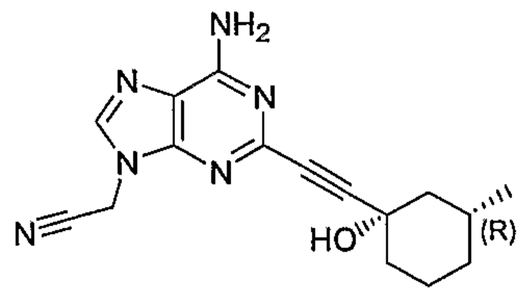
[0077] **9-Cyclopropylmethyl-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (1).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (29 mg) gave **1** as a white solid: yield 19 mg, 55%. ^{1}H NMR (CD_3OD) δ 8.21 (s, 1H), 4.06 (d, 2H, J = 7.3 Hz), 2.13-2.05, 1.94-1.66, 1.49-1.28, 0.92-0.80, 0.66-0.59, 0.49-0.44 (6 x m; 14H), 1.17 (t, 1H, J = 12.3 Hz), 0.96 (d, 2H, J = 6.6 Hz). LRMS ESI (M+H$^+$) 326.1.

[0078] 

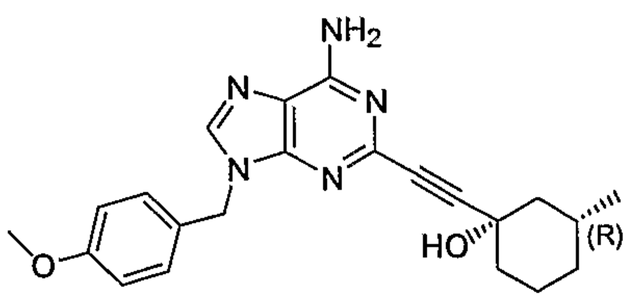
[0079] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-propargyladenine (2).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (112 mg) gave **2** as an off white solid: yield 88 mg, 69%. ^{1}H NMR (CD_3OD) δ 8.23 (s, 1H), 5.04 (s, 2H), 2.98 (t, 1H, J = 2.6 Hz), 2.13-2.05, 1.94-1.65, 1.49-1.38, 0.91-0.80, (4 x m, 7H), 1.17 (t, 1H, J = 12.3 Hz), 0.95 (d, 2H, J = 6.6 Hz). LRMS ESI ($M+H^+$) 310.1.

[0080] 

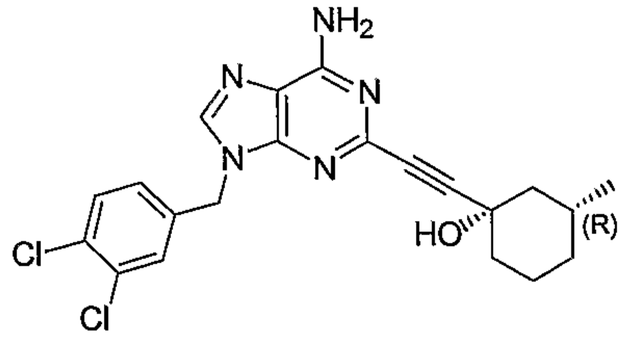
[0081] **9-Cyclopentyl-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (3).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (34 mg) gave **3** as a white solid: yield 21 mg, 50%. ^{1}H NMR (CD_3OD) δ 8.21 (s, 1H), 4.91 (tt, 1H, J = 7.0 Hz), 2.31-2.19, 2.13-1.65, 1.49-1.38, 0.92-0.79 (4 x m, 17H), 1.15 (t, 1H, J = 12.3 Hz), 0.96 (d, 2H, J = 6.6 Hz). LRMS ESI ($M+H^+$) 340.2.

[0082] 

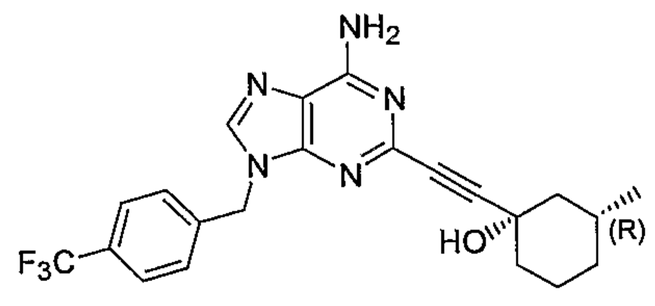
[0083] **9-Acetonitrile-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (4).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (43 mg) gave **4** as a white solid: yield 25 mg, 51%. ^{1}H NMR (CD_3OD) δ 8.20 (s, 1H), 5.35 (s, 1H), 2.33-2.05, 1.93-1.66, 1.49-1.38, 0.92-0.80 (4 x m, 9H), 1.18 (t, 1H, J = 12.3 Hz), 0.96 (d, 2H, J = 6.6 Hz). LRMS ESI ($M+H^+$) 311.1.

[0084] 

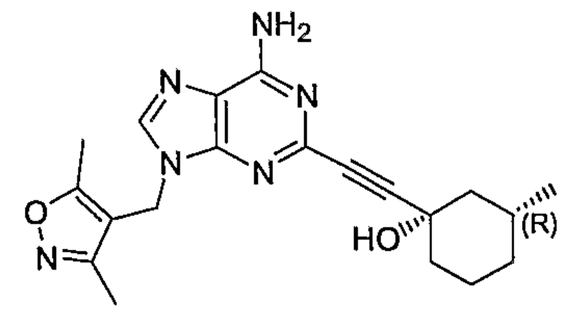
[0085] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-(4-methoxybenzyl)adenine (5).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (24 mg) gave **5** as a white solid: yield 29 mg, 84%. ^{1}H NMR (CD_3OD) δ 8.10 (s, 1H), 7.26 (d, 2H, J = 8.8 Hz), 6.88 (d, 2H, J = 8.8 Hz), 5.32 (s, 2H), 3.75 (s, 3H), 2.33-2.05, 1.92-1.66, 1.49-1.38, 0.92-0.80 (4 x m, 9H), 1.17 (t, 1H, J = 12.3 Hz), 0.95 (d, 2H, J = 6.6 Hz). LRMS ESI ($M+H^+$) 392.2.

[0086] 

[0087] **9-(3,4-Dichlorobenzyl)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (6).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (26 mg) gave **6** as a white solid: yield 28 mg, 68%. ^{1}H NMR (CD_3OD) δ 8.20 (s, 1H), 7.52 (d, 1H, J = 2.1 Hz), 7.48 (d, 1H, J = 8.3 Hz), 7.19 (dd, 1H, J = 2.1 Hz, J = 8.3 Hz), 5.40 (s, 2H), 2.11-2.04, 1.92-1.64, 1.48-1.37, 0.92-0.79 (4 x m, 9H), 1.16 (t, 1H, J = 12.3 Hz), 0.94 (d, 2H, J = 6.6 Hz). LRMS ESI ($M+H^+$) 430.2.

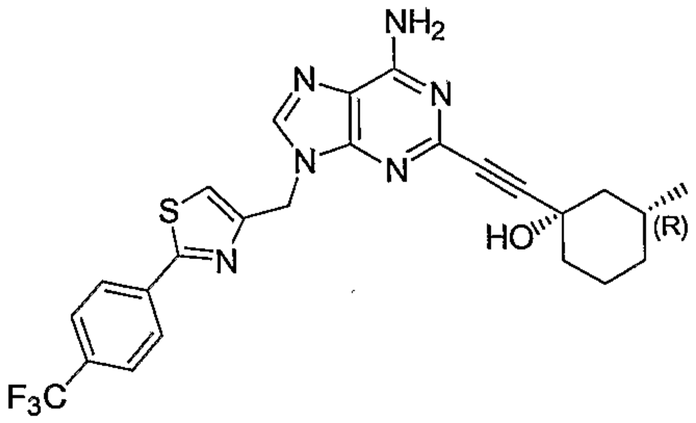
[0088] 

[0089] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-(4-trifluoromethylbenzyl)adenine (7).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (30 mg) gave **7** as a white solid: yield 33 mg, 70%. ^{1}H NMR (CD_3OD) δ 8.20 (s, 1H), 7.64 (d, 2H, J = 8.2 Hz), 7.44 (d, 2H, J = 8.1 Hz), 5.52 (s, 2H), 2.10-2.03, 1.90-1.63, 1.47-1.36, 0.90-0.78 (4 x m, 9H), 1.15 (t, 1H, J = 12.3 Hz), 0.93 (d, 2H, J = 6.6 Hz). LRMS ESI ($M+H^+$) 430.1.

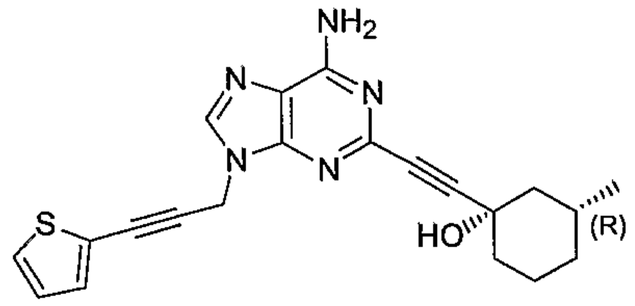
[0090] 

[0091] **9-(3,5-Dimethyl-isoxazol-4-ylmethyl)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (8).** Using the representative procedure for N9-alkylation

above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (32 mg) gave **8** as a white solid: yield 36 mg, 80%. ^{1}H NMR (CD_3OD) δ 8.15 (s, 1H), 5.20 (s, 2H), 2.50 (s, 3H), 2.22 (s, 3H), 2.11-2.03, 1.92-1.65, 1.49-1.38, 0.92-0.81 (4 x m, 9H), 1.18 (t, 1H, J = 12.2 Hz), 0.96 (d, 2H, J = 6.6 Hz). LRMS ESI ($M+H^+$) 381.1.

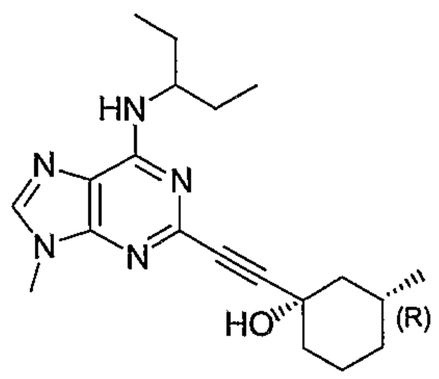
[0092] 

[0093] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-[2-(trifluoromethylphenyl)thiazol-4-ylmethyl]adenine (9).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (26 mg) gave **9** as a white solid: yield 30 mg, 61%. ^{1}H NMR (CD_3OD) δ 8.31 (s, 1H), 8.09 (d, 2H, J = 8.8 Hz), 7.74 (d, 2H, J = 8.3 Hz), 7.55 (s, 1H), 5.58 (s, 2H), 2.12-2.04, 1.91-1.64, 1.48-1.37, 0.91-0.78 (4 x m, 9H), 1.16 (t, 1H, J = 12.4 Hz), 0.94 (d, 2H, J = 6.6 Hz). LRMS ESI ($M+H^+$) 513.1.

[0094] 

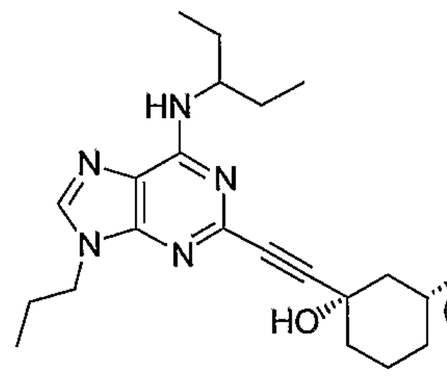
[0095] **2-{2-[Hydroxy-adamantan-2-yl]ethyn-1-yl}-9-(3-(thiophen-2-yl)prop-2-ynyl)adenine (10).** To a solution of 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-propargyladenine (30 mg, 0.09697 mmol) in freshly degassed acetonitrile/DMF (15 mL, 2:1) was added degassed triethylamine (1.0 mL, 7.0175 mmol), $Pd(PPh_3)_4$ (30 mg, 0.02596 mmol), CuI (catalytic), and 98+% 2-bromothiophene (13.7 μL, 0.1161 mmol). The mixture was stirred at room temperature under and inert atmosphere for 28 h. Silica bound Pd(II) scavenger Si-thiol (240 mg) and Pd(0) scavenger Si-TAAcOH (155 mg) were added and stirring continued a further 72 h. The suspension was filtered through celite and the resulting solution evaporated to dryness. The crude was purified by column chromatography, eluting with a gradient of DCM/MeOH (0-6%) to afford the impure product (27 mg). The product was further purified by reverse phase column chromatography, eluting with a gradient of H_2O/MeOH (50-75%) to afford the pure product **10** as a white solid: yield 8.5 mg, 22%. ^{1}H NMR (CD_3OD) δ 8.27 (s, 1H), 7.41(dd, 1H, J = 1.1 Hz, J = 5.3 Hz), 7.25 (dd,

2H, J = 1.1 Hz, J = 3.5 Hz), 6.99 (dd, 1H, J = 3.7 Hz, J = 5.0 Hz), 5.29 (s, 2H), 2.14-2.05, 1.94-1.65, 1.49-1.37, 0.99-0.79 (4 x m, 12H), 1.17 (t, 1H, J = 12.2 Hz). LRMS ESI ($M+H^+$) 392.1.



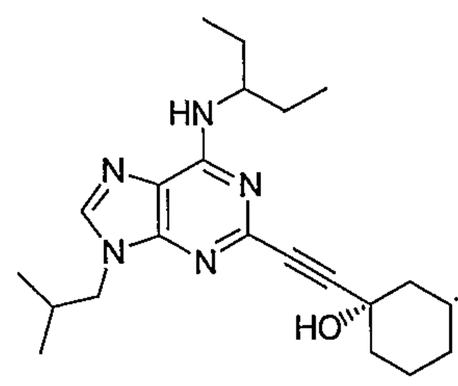
[0096]

[0097] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-methyl-N6-(3-pentyl)adenine (11).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (20 mg) gave **11** as a white solid: yield 9 mg, 43%. ^{1}H NMR (CD_3OD) δ 8.02 (s, 1H), 4.23 (m, 1H), 3.79 (s, 3H), 2.14-2.06, 1.96-1.38, 0.99-0.80 (3 x m, 20H), 1.17 (t, 1H, J = 12.3 Hz). LRMS ESI ($M+H^+$) 356.3.



[0098]

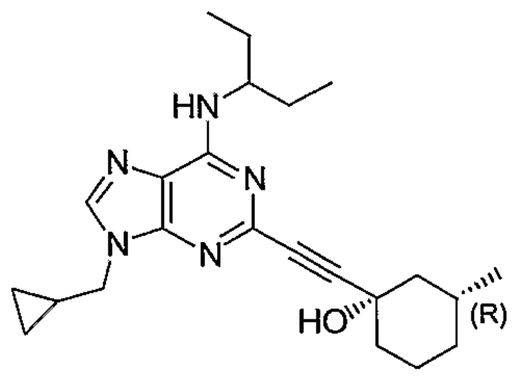
[0099] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)-9-propyladenine (12).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (29 mg) gave **12** as a white solid: yield 26 mg, 80%. ^{1}H NMR (CD_3OD) δ 8.08 (s, 1H), 4.28-4.13 (m, 3H), 2.15-2.06, 1.95-1.38, 0.99-0.80 (3 x m, 26H), 1.17 (t, 1H, J = 12.3 Hz). LRMS ESI ($M+H^+$) 384.3.



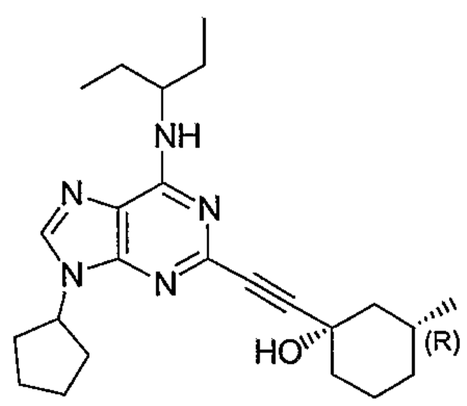
[00100]

[00101] **9-Isobutyl-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (13).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (27 mg) gave **13** as a white solid: yield 23 mg, 73%. ^{1}H NMR (CD_3OD) δ 8.06 (s, 1H), 4.21 (m, 1H), 4.01 (d,

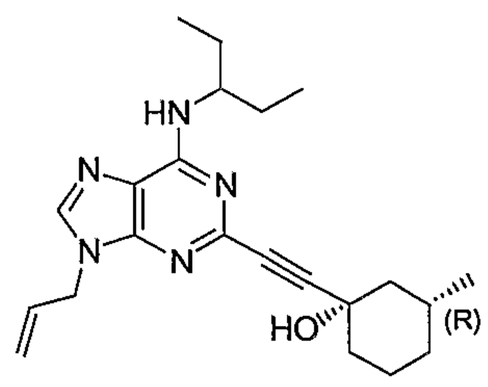
2H, J = 7.4 Hz), 2.21 (septet, 1H, J = 6.8 Hz), 2.12-2.05, 1.96-1.38, 0.98-0.81 (3 x m, 27H), 1.17 (t, 1H, J = 12.2 Hz). LRMS ESI ($M+H^+$) 398.2.

[00102] 

[00103] **9-Cyclopropylmethyl-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (14).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (30 mg) gave **14** as a white solid: yield 17 mg, 57%. ^{1}H NMR (CD_3OD) δ 8.15 (s, 1H), 4.22 (m, 1H), 4.05 (d, 2H, J = 7.3 Hz), 2.14-2.05, 1.96-1.28, 0.98-0.79 (3 x m, 22H), 1.17 (t, 1H, J = 12.2 Hz), 0.65-0.58 (m, 2H), 0.48-0.44 (m, 2H). LRMS ESI ($M+H^+$) 396.3.

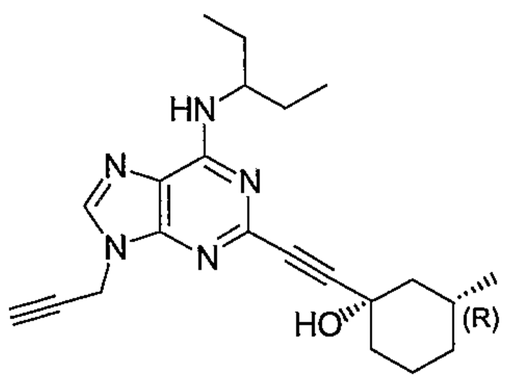
[00104] 

[00105] **9-Cyclopentyl-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (15).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (37 mg) gave **15** as a white solid: yield 29 mg, 65%. ^{1}H NMR (CD_3OD) δ 8.15 (s, 1H), 4.91 (tt, 1H, J = 7.0 Hz), 4.21 (m, 1H), 2.31-2.17, 2.14-1.35, 0.98-0.79 (3 x m, 29H), 1.17 (t, 1H, J = 12.2 Hz). LRMS ESI ($M+H^+$) 410.3.

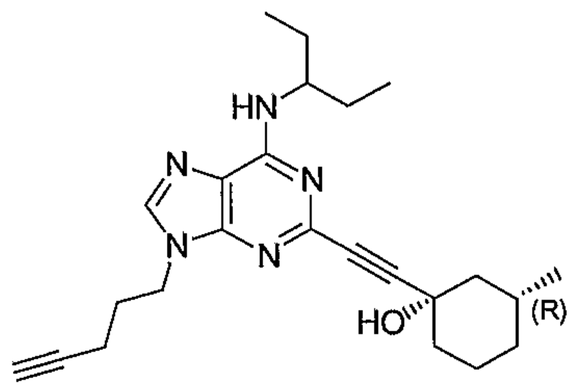
[00106] 

[00107] **9-Allyl-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (16).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (33 mg) gave **16** as a white solid: yield 26 mg, 71%. ^{1}H NMR ($CDCl_3$) δ 7.77 (br s, 1H), 6.09-5.95 (m, 1H), 5.34-

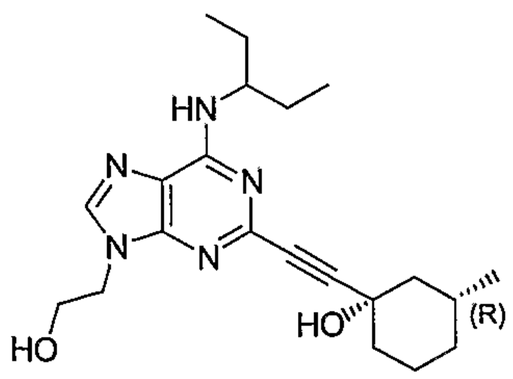
5.20 (m, 2H), 4.79 (dt, 2H, J = 5.8 Hz, J = 1.5 Hz), 4.28 (m, 1H), 2.21-2.11, 1.96-1.42, 0.96-0.78 (3 x m, 21H), 1.23 (t, 1H, J = 12.2 Hz). LRMS ESI ($M+H^+$) 382.3.

[00108] 

[00109] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)-9-(propargyl)adenine (17).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (134 mg) gave **17** as a white solid: yield 79 mg, 53%. ^{1}H NMR (CD_3OD) δ 8.17 (s, 1H), 5.03 (d, 2H, J = 2.6 Hz), 4.22 (m, 1H), 2.97 (t, 1H, J = 2.6), 2.14-2.06, 1.95-1.38, 0.98-0.80 (3 x m, 21H), 1.17 (t, 1H, J = 12.4 Hz). LRMS ESI ($M+H^+$) 380.2.

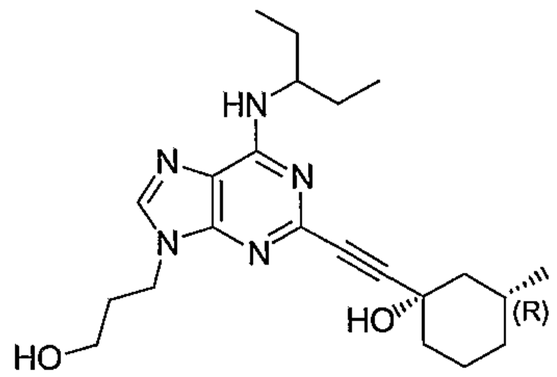
[00110] 

[00111] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)-9-(pent-4-yne)adenine (18).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (35 mg) gave **18** as a white solid: yield 31 mg, 74%. ^{1}H NMR (CD_3OD) δ 8.07 (s, 1H), 4.32 (t, 2H, J = 6.9 Hz), 4.21 (m, 1H), 2.31-2.19, 2.14-2.00, 1.95-1.38, 1.00-0.79 (4 x m, 21H), 1.17 (t, 1H, J = 12.3 Hz). LRMS ESI ($M+H^+$) 408.1.

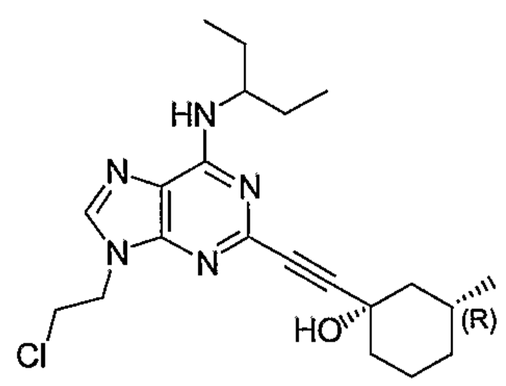
[00112] 

[00113] **9-(2-Hydroxyethyl)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (19).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (103 mg) gave **19** as a white solid: yield 60 mg, 52%. ^{1}H NMR (CD_3OD) δ 8.06 (s, 1H), 4.30 (t, 2H, J

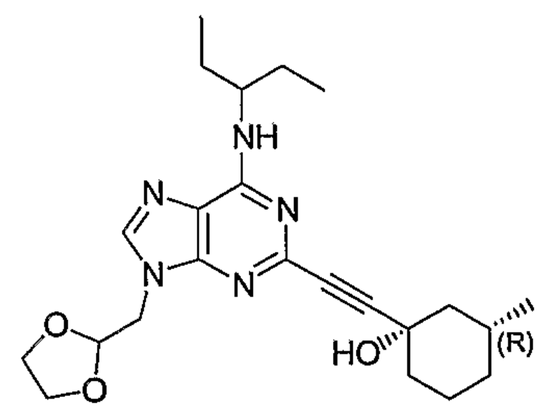
= 5.1 Hz), 4.22 (m, 1H), 3.86 (t, 2H, *J* = 5.1 Hz), 2.14-2.05, 1.95-1.38, 0.99-0.80 (3 x m, 21H), 1.17 (t, 1H, *J* = 12.2 Hz). LRMS ESI ($M+H^+$) 386.2.

[00114] 

[00115] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-(3-hydroxypropyl)-N6-(3-pentyl)adenine (20).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (59 mg) gave **20** as a white solid: yield 35 mg, 51%. ^1H NMR (CD_3OD) δ 8.11 (s, 1H), 4.32 (t, 2H, *J* = 7.0 Hz), 4.20 (m, 1H), 3.56 (t, 2H, *J* = 5.9 Hz), 2.14-2.00, 1.93-1.38, 0.99-0.80 (3 x m, 23H), 1.17 (t, 1H, *J* = 12.2 Hz). LRMS ESI ($M+H^+$) 400.3.

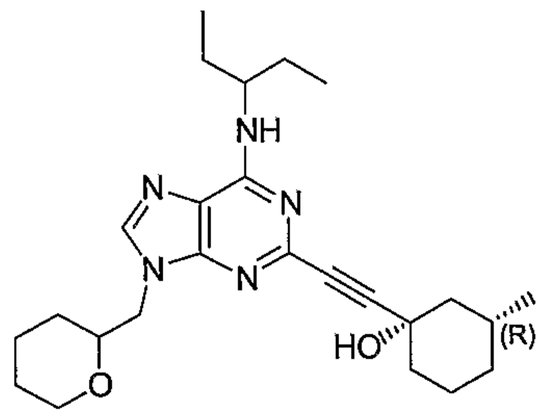
[00116] 

[00117] **9-(2-Chloroethyl)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (21).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (38 mg) gave **21** as a white solid: yield 28 mg, 62%. ^1H NMR (CD_3OD) δ 8.11 (s, 1H), 4.55 (t, 2H, *J* = 5.7 Hz), 4.22 (m, 1H), 3.96 (t, 2H, *J* = 5.7 Hz), 2.14-2.05, 1.94-1.38, 0.99-0.79 (3 x m, 21H), 1.17 (t, 1H, *J* = 12.1 Hz). LRMS ESI ($M+H^+$) 404.2.

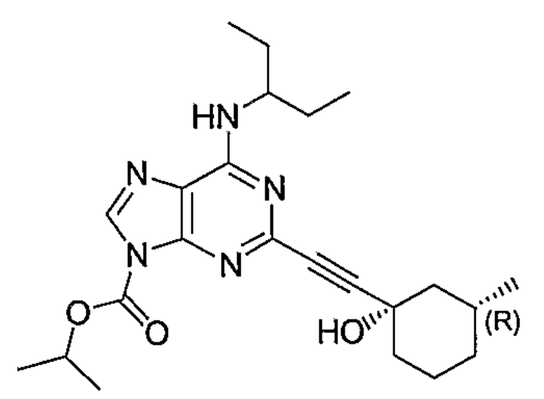
[00118] 

[00119] **9-([1,3]-Dioxolan-2-ylmethyl)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (22).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (37 mg) gave **22** as a white solid: yield 32 mg, 69%. ^1H NMR (CD_3OD) δ

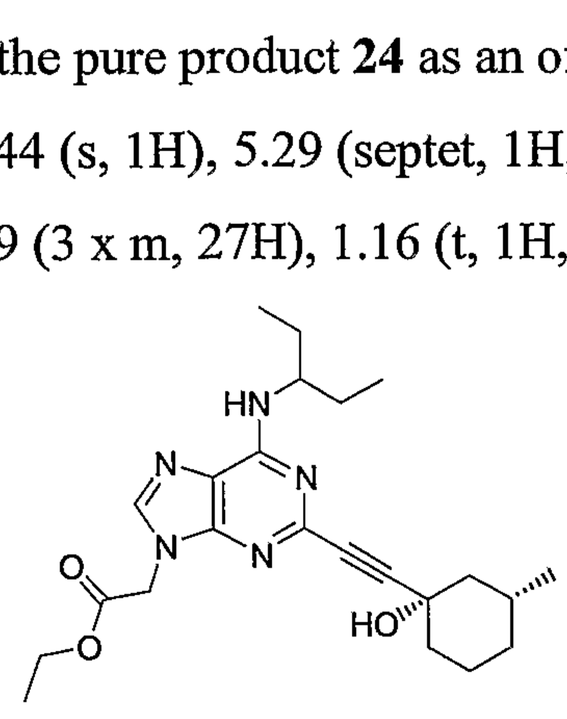
8.04 (s, 1H), 5.20 (t, 1H, J = 3.3 Hz), 4.40 (d, 2H, J = 3.3 Hz), 4.21 (m, 1H), 3.88-3.76 (m, 4H), 2.14-2.06, 1.92-1.38, 0.98-0.79 (3 x m, 21H), 1.17 (t, 1H, J = 12.2 Hz). LRMS ESI ($M+H^+$) 428.3.

[00120] 

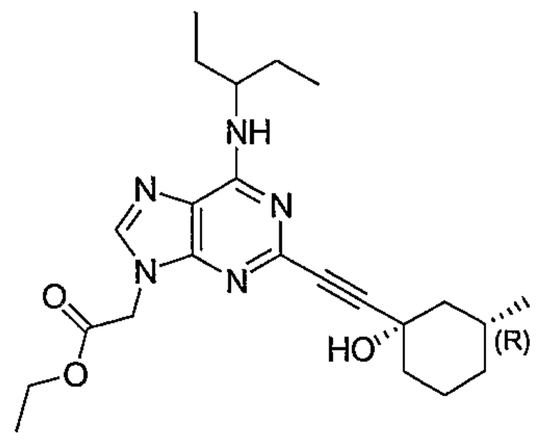
[00121] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)-9-(tetrahydro-pyran-2-ylmethyl)adenine (23).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (32 mg) gave **23** as a white solid: yield 27 mg, 66%. ^{1}H NMR (CD_3OD) δ 8.01 (s, 1H), 4.31-4.07 (m, 3H), 3.96-3.87 (m, 1H), 3.67-3.58 (m, 1H), 3.93-3.32 (m, 1H), 2.14-2.06, 1.95-1.38, 1.31-1.12, 0.99-0.80 (4 x m, 28H). LRMS ESI ($M+H^+$) 440.4.

[00122] 

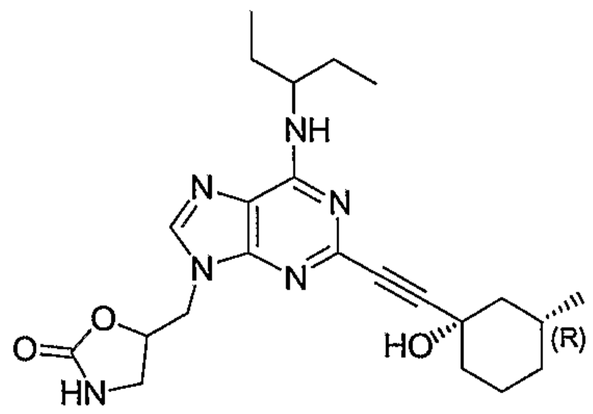
[00123] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)-9-(isopropylcarboxylate)adenine (24).** A 1.0 M solution of isopropyl chloroformate in toluene (150 μL, 0.1500 mmol) was added to an ice cold solution of 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (34 mg) in anhydrous pyridine (2.0 mL). After stirring over ice 1.5 h the solvent was removed under reduced pressure and the crude purified by column chromatography, eluting with a gradient of DCM/MeOH (0-5%) to afford the pure product **24** as an off white solid: yield 18 mg, 42%. ^{1}H NMR (CD_3OD) δ 8.44 (s, 1H), 5.29 (septet, 1H, J = 6.4, J = 6.2 Hz), 4.21 (m, 1H), 2.14-2.05, 1.97-1.37, 1.00-0.79 (3 x m, 27H), 1.16 (t, 1H, J = 12.2 Hz). LRMS ESI ($M+H^+$) 427.9.

[00124] 

[00125] **9-(Acetic acid ethyl ester)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (25).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (38 mg) gave **25** as a white solid: yield 9 mg, 19%. ^{1}H NMR (CD_3OD) δ 8.06 (s, 1H), 5.06 (s, 2H), 4.24 (br q, 3H, J = 7.0, 7.3 Hz), 2.15-2.05, 1.95-1.37, 1.05-0.79 (3 x m, 22H), 1.29 (t, 3H, J = 7.0, 7.3 Hz), 1.17 (t, 1H, J = 12.2 Hz). LRMS ESI ($M+H^+$) 428.2.

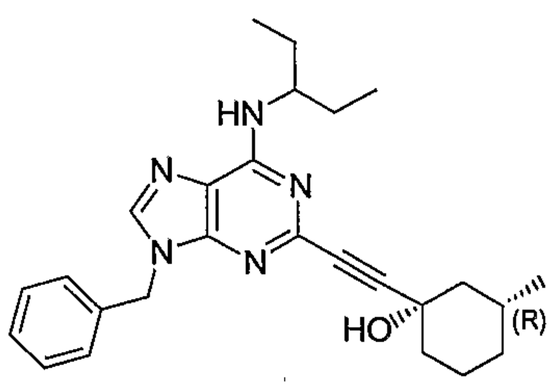


[00126]

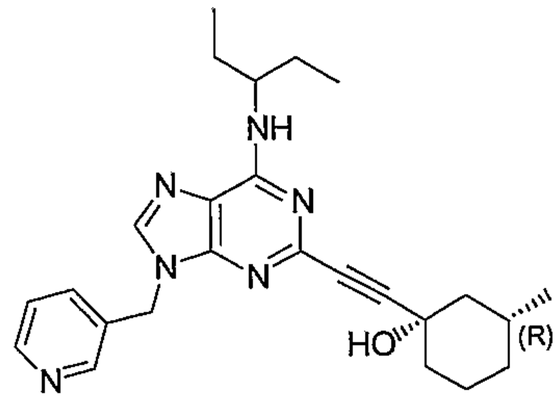


[00127] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-(2-oxo-oxazolidin-5-ylmethyl)-N6-(3-pentyl)adenine (26).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (56 mg) gave **26** as a white solid: yield 43 mg, 60%. ^{1}H NMR (CD_3OD) δ 8.09 (s, 1H), 5.04 (m, 1H), 4.52 (d, 2H, J = 4.8 Hz), 4.21 (m, 1H), 3.79-3.70 (m, 1H), 3.47-3.39 (m, 1H), 2.13-2.04, 1.95-1.38, 0.99-0.79 (3 x m, 21H), 1.17 (t, 1H, J = 12.2 Hz). LRMS ESI ($M+H^+$) 441.3.

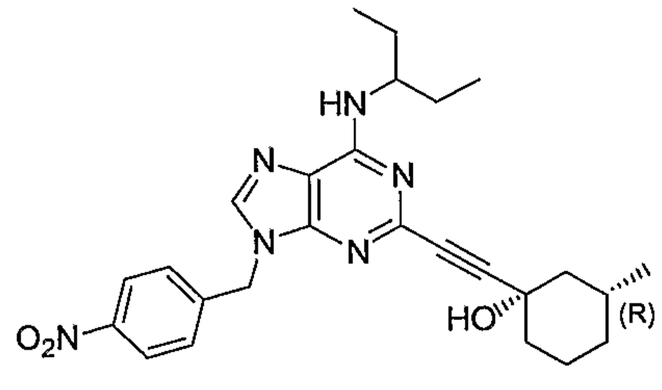
[00128]



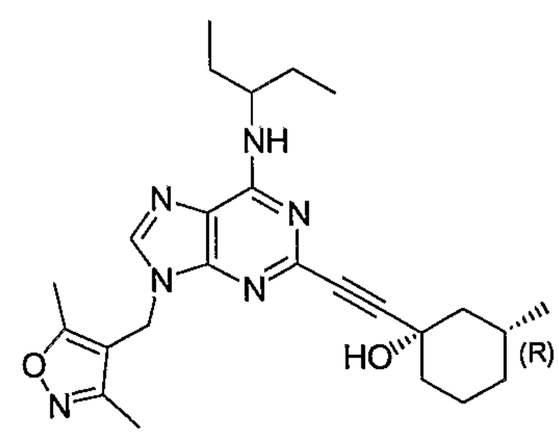
[00129] **9-Benzyl-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (27).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (37 mg) gave **27** as a white solid: yield 31 mg, 66%. ^{1}H NMR (CD_3OD) δ 8.06 (s, 1H), 7.37-7.25 (m, 5H), 5.40 (s, 2H), 4.22 (m, 1H), 2.14-2.05, 1.95-1.37, 0.99-0.79 (3 x m, 21H), 1.16 (t, 1H, J = 12.3 Hz). LRMS ESI ($M+H^+$) 432.3.

[00130] 

[00131] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)-9-(pyridin-3-ylmethyl)adenine (28).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (34 mg) gave **28** as a white solid: yield 8 mg, 19%. ^{1}H NMR (CD_3OD) δ 8.57 (m, 1H), 8.48 (m, 1H), 8.17 (s, 1H), 7.77 (m, 1H), 7.41 (m, 1H), 5.49 (s, 2H), 4.22 (m, 1H), 2.13-2.04, 1.93-1.37, 0.99-0.79 (3 x m, 21H), 1.16 (t, 1H, J = 12.3 Hz). LRMS ESI ($M+H^+$) 433.3.

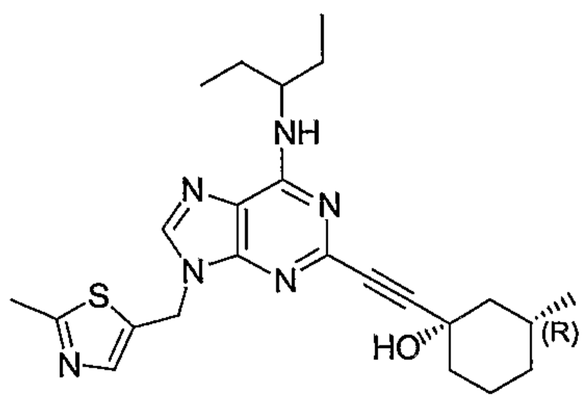
[00132] 

[00133] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-(4-nitrobenzyl)-N6-(3-pentyl)adenine (29).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (33 mg) gave **29** as a white solid: yield 36 mg, 78%. ^{1}H NMR (CD_3OD) δ 8.19 (d, 2H, J = 8.8 Hz), 8.16 (s, 1H), 7.46 (d, 2H, J = 8.8 Hz), 5.55 (s, 2H), 4.22 (m, 1H), 2.12-2.02, 1.92-1.36, 1.00-0.78 (3 x m, 21H), 1.15 (t, 1H, J = 12.2 Hz). LRMS ESI ($M+H^+$) 477.3.

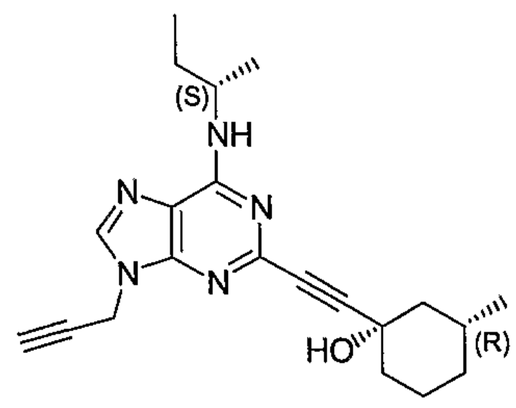
[00134] 

[00135] **9-(3,5-Dimethyl-isoxazol-4-ylmethyl)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (30).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (50 mg) gave **30** as a white crystalline solid: yield 50 mg, 76%. ^{1}H NMR

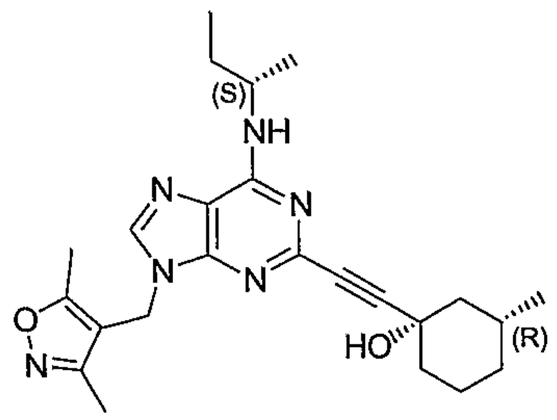
(CD_3OD) δ 8.08 (s, 1H), 5.18 (s, 2H), 4.19 (m, 1H), 2.50 (s, 3H), 2.23 (s, 3H), 2.13-2.04, 1.94-1.38, 0.99-0.80 (3 x m, 21H), 1.18 (t, 1H, J = 12.1 Hz). LRMS ESI ($M+H^+$) 451.3.

[00136] 

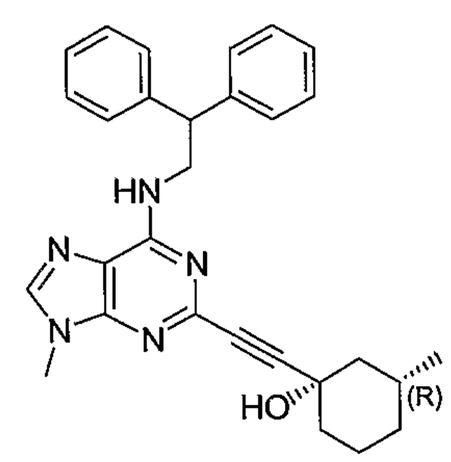
[00137] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-(2-methyl-thiazol-5-ylmethyl)-N6-(3-pentyl)adenine (31).** 2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (56 mg, 0.1640 mmol) and 4-chloromethyl-2-methylthiazole hydrochloride (127 mg, 0.6899 mmol) were stirred in DMF (8 mL) at 150 °C for 22 h. The reaction mixture was adhered to silica and purified by column chromatography, eluting with a gradient of DCM/MeOH (0-6%) to afford pure **31** as an off white solid: yield 2 mg, 3%. ^1H NMR (CD_3OD) δ 8.12 (s, 1H), 7.29 (s, 1H), 5.44 (s, 2H), 4.22 (m, 1H), 2.65 (s, 3H), 2.14-2.05, 1.94-1.37, 0.99-0.80 (3 x m, 21H), 1.18 (t, 1H, J = 12.2 Hz). LRMS ESI ($M+H^+$) 453.2.

[0100] 

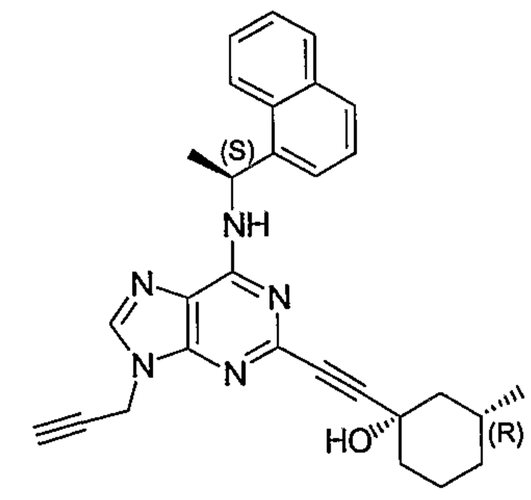
[0101] **N6-[(S)-(+)-sec-Butyl]-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-propargyl-adenine (32).** Using the representative procedure for N9-alkylation above N6-[(S)-(+)-sec-butyl]-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (29 mg) gave **32** as a white solid: yield 20 mg, 62%. ^1H NMR (CD_3OD) δ 8.17 (s, 1H), 5.03 (d, 2H, J = 2.6 Hz), 4.32 (m, 1H), 2.97 (t, 1H, J = 2.6 Hz), 2.14-2.06, 1.95-1.58, 1.49-1.38, 1.00-0.79 (4 x m, 16H), 1.25 (d, 3H, J = 6.4 Hz), 1.17 (t, 1H, J = 12.2 Hz). LRMS ESI ($M+H^+$) 366.1.

[0102] 

[0103] **N6-[(s)-(+)-sec-Butyl]-9-(3,5-dimethyl-isoxazol-4-ylmethyl)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (33).** Using the representative procedure for N9-alkylation above N6-[(S)-(+)-sec-butyl]-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (42 mg) gave **33** as a white solid: yield 31 mg, 55%. ^{1}H NMR (CD_3OD) δ 8.08 (s, 1H), 5.19 (s, 2H), 4.29 (m, 1H), 2.50 (s, 3H), 2.22 (s, 3H), 2.14-2.04, 1.95-1.57, 1.49-1.38, 0.99-0.82 (4 x m, 16H), 1.24 (d, 3H, J = 6.4 Hz), 1.18 (t, 1H, J = 12.2 Hz). LRMS ESI ($M+H^+$) 437.2.

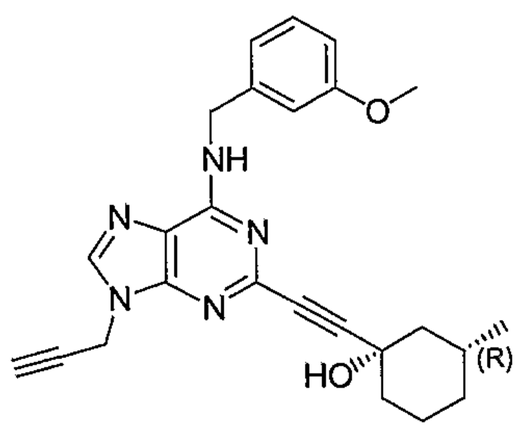
[0104] 

[0105] **N6-(2-Diphenylethyl)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-methyladenine (34).** Using the representative procedure for N9-alkylation above N6-(2-diphenylethyl)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (14 mg) gave **34** as a white solid: yield 5 mg, 35%. LRMS ESI ($M+H^+$) 466.3.

[0106] 

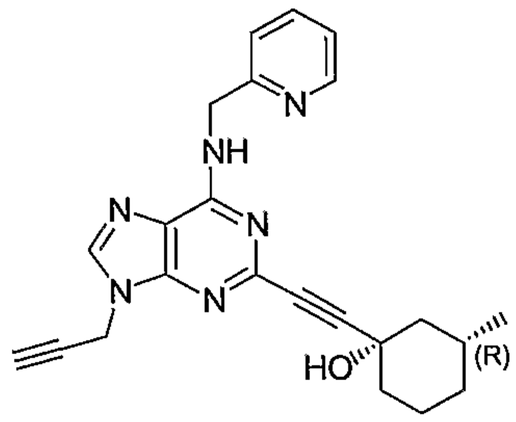
[0107] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-[(s)-(-)-alpha-napthalen-1-yl-ethyl]-9-(propargyl)adenine (35).** Using the representative procedure for N9-alkylation above 2-{2- [1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-[(S)-(-)-alpha-napthalen-1-yl-ethyl]adenine (29 mg) gave **35** as a white solid: yield 22

mg, 70%. ^{1}H NMR (CD_3OD) δ 8.23 (m, 1H), 8.15 (s, 1H), 7.88-7.84 (m, 1H), 7.76 (d, 1H, *J* = 8.4 Hz), 7.64 (d, 1H, *J* = 7.0 Hz), 7.53-7.40 (m, 3H), 6.33 (br s, 1H), 5.00 (d, 2H, *J* = 2.6 Hz), 2.96 (t, 1H, *J* = 2.6 Hz), 2.08-1.99, 1.87-1.59, 1.45-1.33, 1.18-1.08, 0.95-0.70 (5 x m, 12H). LRMS ESI ($M+H^+$) 464.1.



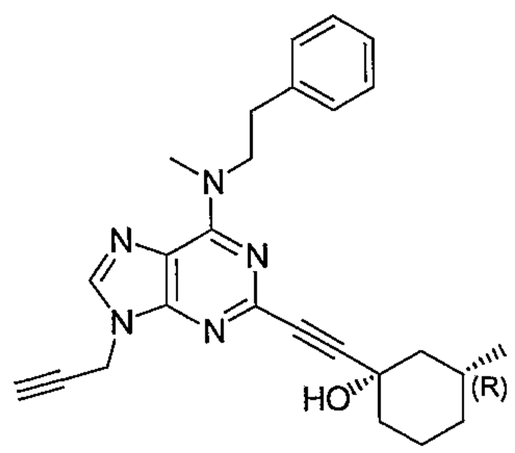
[0108]

[0109] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-methoxybenzyl)-9-(propargyl)adenine (36).** Using the representative procedure for N9-alkylation above 2-{2- [1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-methoxybenzyl)adenine (48 mg) gave **36** as a white solid: yield 40 mg, 76%. ^{1}H NMR (CD_3OD) δ 8.14 (s, 1H), 7.18 (t, 1H, *J* = 7.9 Hz), 6.96-6.90 (m, 2H), 6.77 (m, 1H), 5.01 (d, 2H, *J* = 2.6 Hz), 4.75 (br s, 2H), 3.74 (s, 3H), 2.97 (t, 1H, *J* = 2.6 Hz), 2.13-2.04, 1.94-1.64, 1.48-1.37, 1.21-1.11, 0.96-0.77 (5 x m, 12H). LRMS ESI ($M+H^+$) 430.2.



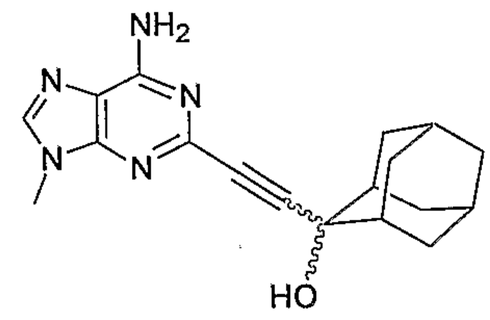
[0110]

[0111] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-(propargyl)-N6-(pyridin-2-ylmethyl)adenine (37).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(pyridin-2-ylmethyl)adenine (29 mg) gave **37** as a white solid: yield 27 mg, 84%. ^{1}H NMR (CD_3OD) δ 8.49 (d, 1H, *J* = 4.4 Hz), 8.20 (s, 1H), 7.76 (dt, 1H, *J* = 1.8 Hz, *J* = 7.7 Hz), 7.43 (d, 1H, *J* = 7.9 Hz), 7.29 (m, 1H), 5.04 (d, 2H, *J* = 2.6 Hz), 4.91 (br s, 2H), 2.98 (t, 1H, *J* = 2.6 Hz), 2.10-2.03, 1.90-1.63, 1.47-1.36, 1.20-1.10, 0.96-0.73 (5 x m, 12H). LRMS ESI ($M+H^+$) 401.2.



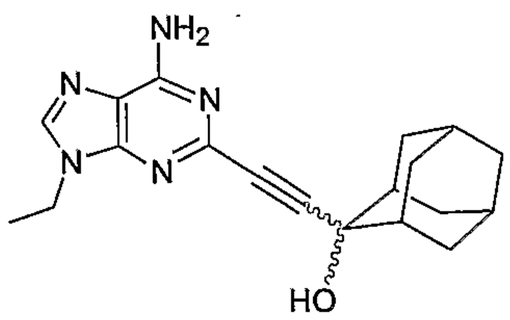
[0112]

[0113] **2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-[(methyl)(2-phenethyl)]-9- (propargyl)adenine (38).** Using the representative procedure for N9-alkylation above 2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-[(methyl)(2-phenethyl)]adenine (54 mg) gave **38** as a white solid: yield 47 mg, 79%. ^{1}H NMR (CD_3OD) δ 8.09 (s, 1H), 7.30-7.11 (m, 5H), 5.00 (d, 2H, J = 2.6 Hz), 4.19 (br s, 2H), 3.35 (br s, 3H), 2.98-2.91 (m, 3H), 2.14-2.06, 1.96-1.66, 1.50-1.39, 1.27-1.13, 0.98-0.80 (5 x m, 12H). LRMS ESI ($M+H^+$) 428.3.



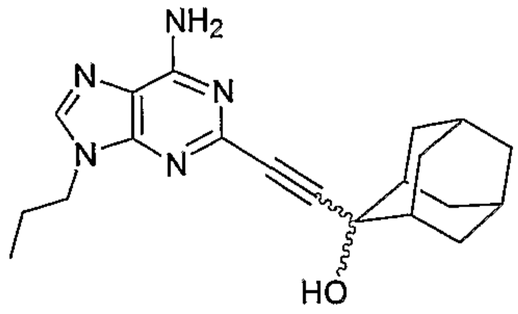
[0114]

[0115] **2-{2-[Hydroxy-adamantan-2-yl]ethyn-1-yl}-9-methyladenine (39).** Using the representative procedure for N9-alkylation above 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (58 mg) gave **39** as a white solid: yield 39 mg, 64%. ^{1}H NMR (CD_3OD) δ 8.08 (s, 1H), 3.80 (s, 3H), 2.37-2.22, 2.08-2.03, 1.89-1.74, 1.64-1.57 (4 x m, 14H). LRMS ESI ($M+H^+$) 324.2.



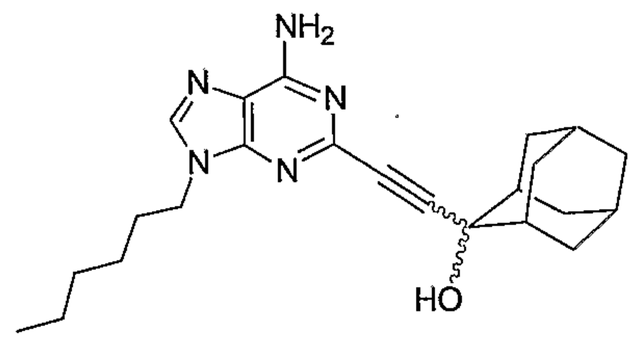
[0116]

[0117] **9-Ethyl-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (40).** Using the representative procedure for N9-alkylation above 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (59 mg) gave **40** as a white solid: yield 42 mg, 65%. ^{1}H NMR (CD_3OD) δ 8.15 (s, 1H), 4.25 (t, 2H, J = 7.4 Hz), 2.36-2.22, 2.08-2.03, 1.89-1.74, 1.64-1.57 (4 x m, 14H), 1.47 (t, 3H, J = 7.3 Hz). LRMS ESI ($M+H^+$) 338.2.



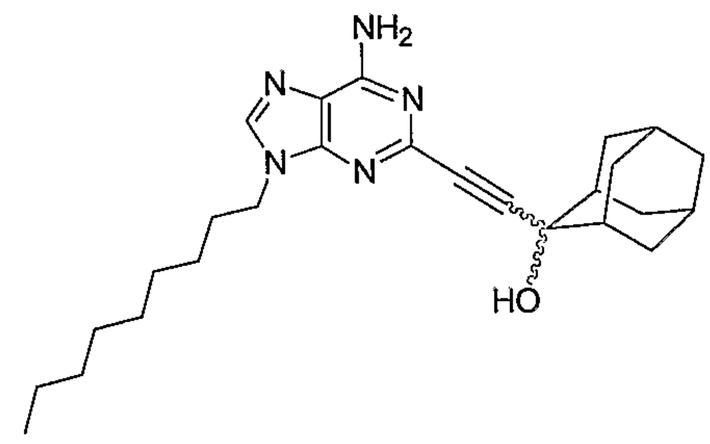
[0118]

[0119] **2-{2-[Hydroxy-adamantan-2-yl]ethyn-1-yl}-9-propyladenine (41).** Using the representative procedure for N9-alkylation above 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (56 mg) gave **41** as a white solid: yield 46 mg, 72%. ^{1}H NMR (CD_3OD) δ 8.13 (s, 1H), 4.17 (t, 2H, J = 7.2 Hz), 2.36-2.22, 2.08-2.03, 1.92-1.74, 1.64-1.57 (4 x m, 16H), 0.93 (t, 3H, J = 7.5 Hz). LRMS ESI ($M+H^+$) 352.2.



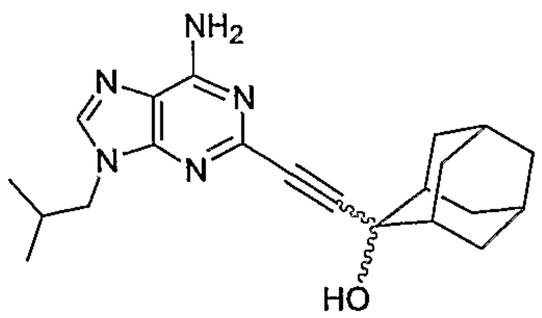
[0120]

[0121] **9-Hexyl-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (42).** Using the representative procedure for N9-alkylation above 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (50 mg) gave **42** as a white solid: yield 43 mg, 68%. ^{1}H NMR (CD_3OD) δ 8.13 (s, 1H), 4.21 (t, 2H, J = 7.0, 7.5 Hz), 2.37-2.22, 2.08-2.03, 1.91-1.74, 1.65-1.57, 1.37-1.27 (5 x m, 22H), 0.88 (t, 3H). LRMS ESI ($M+H^+$) 394.1.



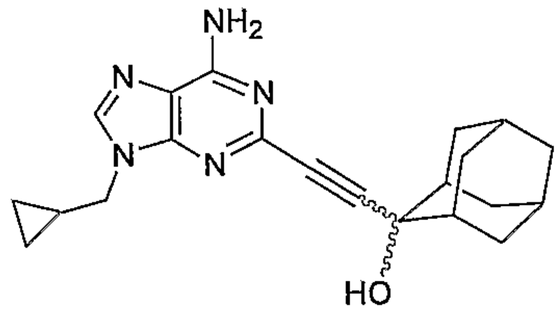
[0122]

[0123] **2-{2-[Hydroxy-adamantan-2-yl]ethyn-1-yl}-9-nonyladenine (43).** Using the representative procedure for N9-alkylation above 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (43 mg) gave **43** as a white solid: yield 47 mg, 78%. ^{1}H NMR (CD_3OD) δ 8.13 (s, 1H), 4.20 (t, 2H, J = 7.3 Hz), 2.36-2.22, 2.08-2.03, 1.90-1.74, 1.64-1.56, 1.35-1.23 (5 x m, 28H), 0.87 (t, 3H, J = 7.0 Hz). LRMS ESI ($M+H^+$) 436.1.

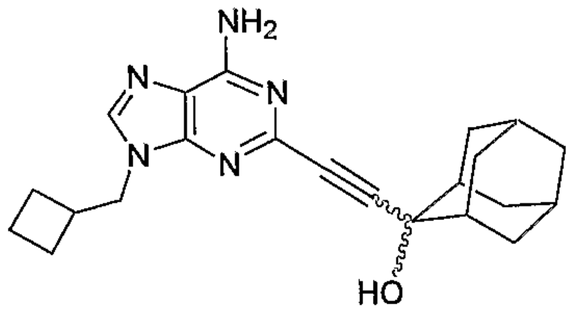


[0124]

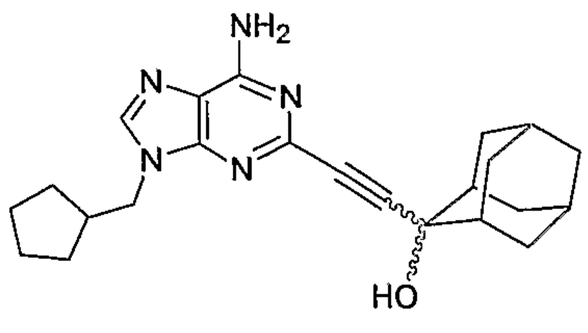
[0125] **2-{2-[Hydroxy-adamantan-2-yl]ethyn-1-yl}-9-isobutyl-adenine (44).** Using the representative procedure for N9-alkylation above 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (52 mg) gave **44** as a white solid: yield 46 mg, 75%. ^{1}H NMR (CD_3OD) δ 8.11 (s, 1H), 4.02 (d, 2H, J = 7.5 Hz), 2.36-2.16, 2.08-2.03, 1.88-1.73, 1.64-1.56, (4 x m, 15H), 0.91 (d, 6H, J = 6.6 Hz). LRMS ESI ($M+H^+$) 366.2.

[0126] 

[0127] **9-Cyclopropylmethyl-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (45).** Using the representative procedure for N9-alkylation above 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (33 mg) gave **45** as a white solid: yield 11 mg, 28%. ^{1}H NMR (CD_3OD) δ 8.21 (s, 1H), 4.06 (d, 2H, J = 7.3 Hz), 2.36-2.22, 2.08-2.03, 1.89-1.74, 1.65-1.57, (4 x m, 14H), 1.42-1.27 (m, 1H), 0.65-0.58, 0.49-0.43 (2 x m, 4H). LRMS ESI ($M+H^+$) 364.2.

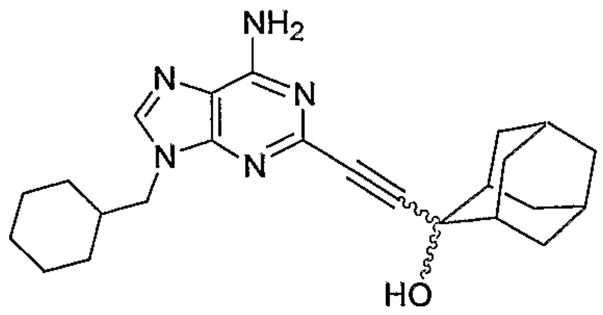
[0128] 

[0129] **9-Cyclobutylmethyl-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (46).** Using the representative procedure for N9-alkylation above 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (54 mg) gave **46** as a white crystalline solid: yield 21 mg, 32%. ^{1}H NMR (CD_3OD) δ 8.12 (s, 1H), 4.22 (d, 2H, J = 7.5 Hz), 2.87 (quintet, 1H, J = 7.7 Hz), 2.37-2.22, 2.09-1.74, 1.65-1.57, (3 x m, 20H). LRMS ESI ($M+H^+$) 378.2.

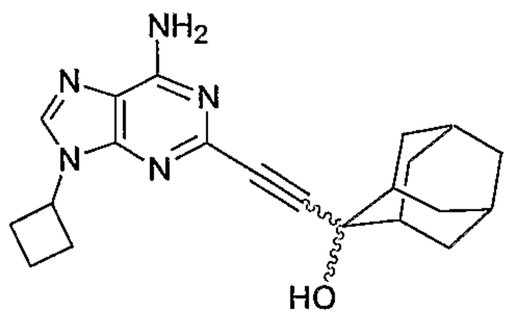
[0130] 

[0131] **9-Cyclopentylmethyl-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (47).** 2-{2-[Hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (44 mg, 0.1422 mmol) was dissolved in DMF (20 mL) with heating. Anhydrous potassium carbonate (51 mg, 0.3690 mmol) and cyclopentylmethyl 4-methylbenzenesulfonate (54 mg, 0.2123 mmol) were added and the mixture stirred at 70 °C for 72 h. Extra cyclopentylmethyl 4-methylbenzenesulfonate

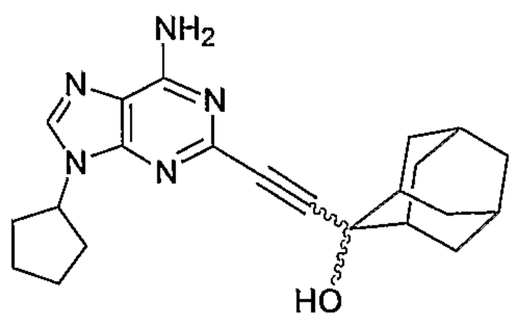
(82 mg, 0.3224 mmol) was added and stirring continued at 100 °C a further 4.5 h. The reaction mixture was adhered to silica and purified by column chromatography, eluting with a gradient of DCM/MeOH (0-6%) to afford the pure **47** as a white solid: yield 38 mg, 68%. ^{1}H NMR (CD_3OD) δ 8.15 (s, 1H), 4.14 (d, 2H, J = 7.7 Hz), 2.48 (quintet, 1H, J = 7.5 Hz), 2.37-2.22, 2.08-2.02, 1.89-1.58, 1.37-1.24 (4 x m, 22H). LRMS ESI ($M+H^+$) 392.0.

[0132] 

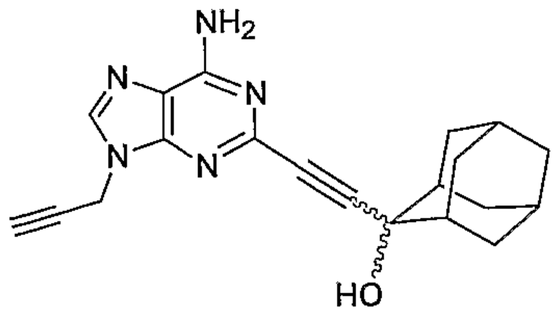
[0133] **9-Cyclohexylmethyl-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (48).** Using the representative procedure for N9-alkylation above 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (49 mg) gave **48** as a white solid: yield 45 mg, 70%. ^{1}H NMR (CD_3OD) δ 8.10 (s, 1H), 4.04 (d, 2H, J = 7.3 Hz), 2.37-2.22, 2.09-2.03, 1.92-1.54, 1.31-0.96, (4 x m, 25H). LRMS ESI ($M+H^+$) 406.3.

[0134] 

[0135] **9-Cyclobutyl-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (49).** Using the representative procedure for N9-alkylation above 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (34 mg) gave **49** as a white solid: yield 18 mg, 45%. ^{1}H NMR (CD_3OD) δ 8.32 (s, 1H), 5.03 (m, 1H), 2.72-2.49, 2.38-2.22, 2.04-1.74, 1.64-1.57 (4 x m, 20H). LRMS ESI ($M+H^+$) 364.2.

[0136] 

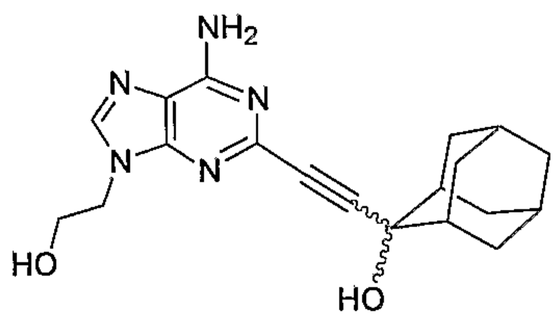
[0137] **9-Cyclopentyl-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (50).** Using the representative procedure for N9-alkylation above 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (473 mg) gave **50** as a white solid: yield 371 mg, 64%. ^{1}H NMR (CD_3OD) δ 8.21 (s, 1H), 4.90 (m, 1H), 2.37-2.20, 2.08-1.73, 1.64-1.57 (4 x m, 22H). LRMS ESI ($M+H^+$) 378.2.



[0138]

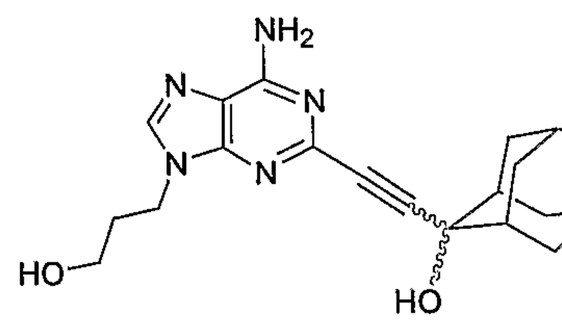
[0139] **2-{2-[Hydroxy-adamantan-2-yl]ethyn-1-yl}-9-propargyl-adenine (51).**

Using the representative procedure for N9-alkylation above 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (510 mg) gave **51** as a white solid: yield 416 mg, 73%. ^{1}H NMR (CD_3OD) δ 8.22 (s, 1H), 5.04 (d, 2H, J = 2.6 Hz), 2.98 (t, 1H, J = 2.5 Hz), 2.36-2.22, 2.08-2.03, 1.89-1.75, 1.65-1.57 (4 x m, 14H). LRMS ESI ($M+H^+$) 348.2.



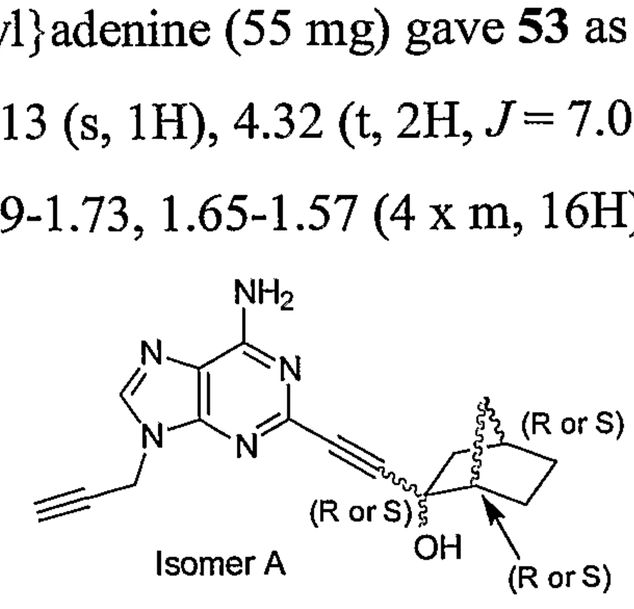
[0140]

[0141] **2-{2-[Hydroxy-adamantan-2-yl]ethyn-1-yl}-9-(2-hydroxyethyl)adenine (52).** Using the representative procedure for N9-alkylation above 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (49 mg) gave **52** as a white solid: yield 21 mg, 38%. ^{1}H NMR (CD_3OD) δ 8.12 (s, 1H), 4.31 (t, 2H, J = 5.2 Hz), 3.87 (t, 2H, J = 4.7 Hz), 2.36-2.21, 2.08-2.01, 1.89-1.73, 1.65-1.57 (4 x m, 14H). LRMS ESI ($M+H^+$) 354.2.



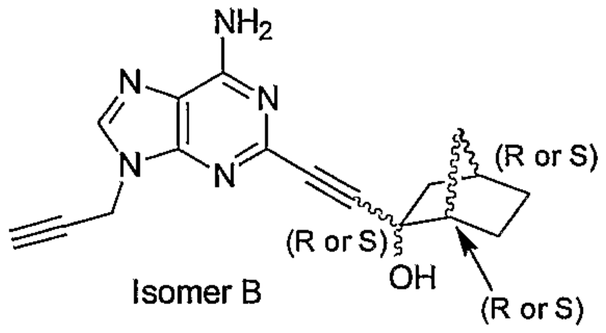
[0121]

[0122] **2-{2-[Hydroxy-adamantan-2-yl]ethyn-1-yl}-9-(2-hydroxypropyl)adenine (53).** Using the representative procedure for N9-alkylation above 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (55 mg) gave **53** as a white solid: yield 37 mg, 57%. ^{1}H NMR (CD_3OD) δ 8.13 (s, 1H), 4.32 (t, 2H, J = 7.0 Hz), 3.55 (t, 2H, J = 5.9, 6.2 Hz), 2.36-2.21, 2.11-2.00, 1.89-1.73, 1.65-1.57 (4 x m, 16H). LRMS ESI ($M+H^+$) 368.2.



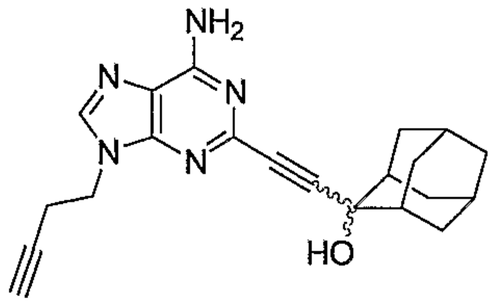
[0123]

[0124] **2-{2-[Hydroxy-norbornan-2-yl]ethyn-1-yl}-9-propargyladenine: Isomer A (60).** Using the representative procedure for N9-alkylation above 2-{2-[hydroxy-norbornan-2-yl]ethyn-1-yl}adenine (42 mg) gave **60** as a white solid: yield 18 mg, 38%. ^{1}H NMR (CD_3OD) δ 8.22 (s, 1H), 5.03 (s, 2H), 2.47-2.51 (m, 1H), 2.19-2.30 (m, 2H), 1.90-2.08 (m, 2H), 1.53-1.66 (m, 1H), 1.27-1.47 (m, 4H). LRMS ESI ($M+H^+$) 308.1.

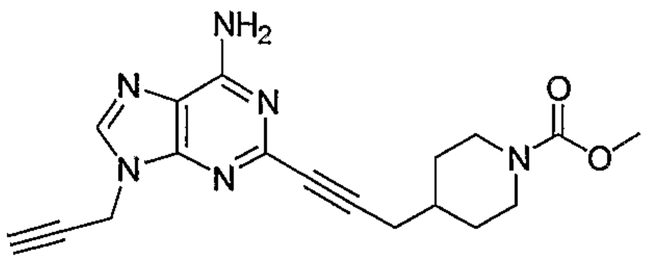
[0125] 

Isomer B

[0126] **2-{2-[Hydroxy-norbornan-2-yl]ethyn-1-yl}-9-propargyladenine: Isomer B (61).** Using the representative procedure for N9-alkylation above 2-{2-[hydroxy-norbornan-2-yl]ethyn-1-yl}adenine (31 mg) gave **61** as a white solid: yield 10 mg, 29%. ^{1}H NMR (CD_3OD) δ 8.22 (s, 1H), 5.03 (s, 2H), 2.47-2.51 (m, 1H), 2.19-2.30 (m, 2H), 1.90-2.08 (m, 2H), 1.53-1.66 (m, 1H), 1.27-1.47 (m, 4H). LRMS ESI ($M+H^+$) 308.1.

[0127] 

[0128] **9-(But-3-ynyl)-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (62).** Using the representative procedure for N9-alkylation above 2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (52 mg) gave **62** as a white solid: yield 14 mg, 24%. ^{1}H NMR (CD_3OD) δ 8.18 (s, 1H), 4.36 (t, 2H, J = 6.6 Hz), 2.77 (dt, 2H, J = 2.6, 6.6 Hz), 2.36 (t, 1H, J = 2.6 Hz), 2.36-2.22, 2.08-2.03, 1.89-1.74, 1.64-1.57 (4 x m, 16H). LRMS ESI ($M+H^+$) 362.0.

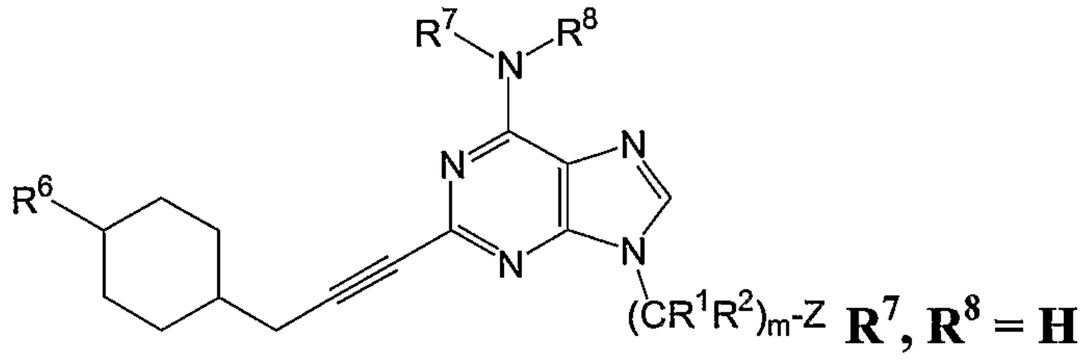
[0129] 

[0130] **2-{3-[1-(Methoxycarbanoyl)piperidin-4-yl]propyn-1-yl}-9-propargyladenine (63).** Using the representative procedure for N9-alkylation above 2-{3-[1-(methoxycarbanoyl)piperidin-4-yl]propyn-1-yl}adenine (53 mg) gave **63** as a white solid: yield 18 mg, 30%. ^{1}H NMR (CD_3OD) δ 8.21 (s, 1H), 5.02 (s, 2H), 4.21-4.09 (m, 2H), 3.66

(s, 3H), 2.94-2.74 (m, 2H), 2.47-2.40 (m, 3H), 1.95-1.74 (m, 3H), 1.38-1.20 (m, 2H). LRMS ESI ($M+H^+$) 353.1.

[0131] The compounds in tables 1 to 7, or their pharmaceutically acceptable salts either as single stereoisomers or mixtures are representative examples of the invention.

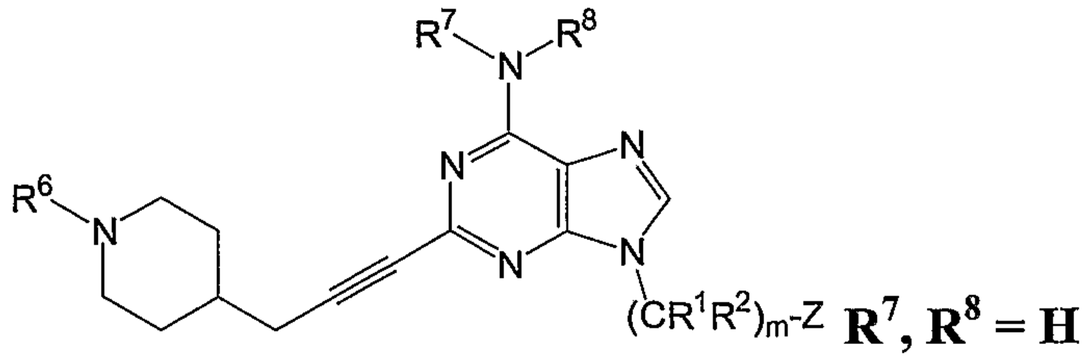
Table 1



R^7, R^8 = H

Compound	**$(CR^1R^2)_m$-Z**	**R^6**
NC100	Propargyl	CH_2OH
NC101	*c*-Pentyl	CH_2OH
NC102	Propargyl	CO_2H
NC103	*c*-Pentyl	CO_2H
NC104	Propargyl	CO_2Me
NC105	*c*-Pentyl	CO_2Me
NC106	Propargyl	CH_2OAc
NC107	*c*-Pentyl	CH_2OAc
NC108	Propargyl	$CH_2N(CH_3)_2$
NC109	*c*-Pentyl	$CH_2N(CH_3)_2$
NC110	Propargyl	$COOCH_2CH_2NHBoc$
NC111	*c*-Pentyl	$COOCH_2CH_2NHBoc$
NC112	Propargyl	$COOCH_2CH_2NH_2$
NC113	*c*-Pentyl	$COOCH_2CH_2NH_2$
NC114	Propargyl	$CONHCH_2CH_3$
NC115	*c*-Pentyl	$CONHCH_2CH_3$
NC116	Propargyl	$CONH_2$
NC117	*c*-Pentyl	$CONH_2$
NC118	Propargyl	CONHMe
NC119	*c*-Pentyl	CONHMe
NC120	Propargyl	Me, cis CO_2Me
NC121	*c*-Pentyl	Me, cis CO_2Me
NC122	Propargyl	Me, trans CO_2Me
NC123	*c*-Pentyl	Me, trans CO_2Me
NC124	Propargyl	CH_2CH_3
NC125	*c*-Pentyl	CH_2CH_3
NC126	Propargyl	H
NC127	*c*-Pentyl	H
NC128	Propargyl	$COCH_3$
NC129	*c*-Pentyl	$COCH_3$
NC130	Propargyl	$CHCH_3(OH)$
NC131	*c*-Pentyl	$CHCH_3(OH)$

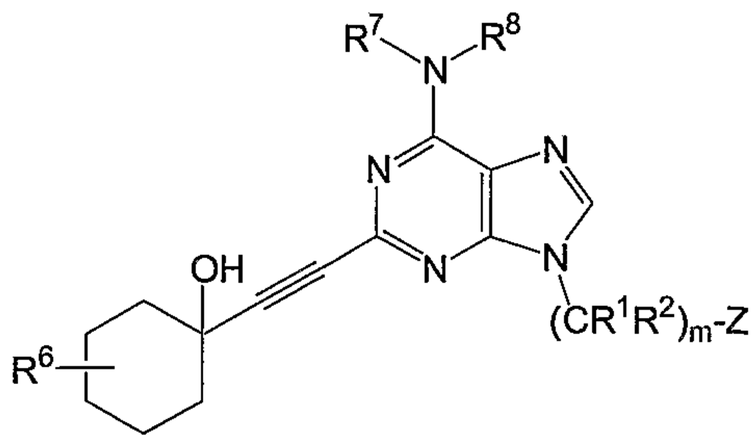
Table 2



R^7, R^8 = H

Compound	$(CR^1R^2)_m$-Z	R^6
NC132	Propargyl	H
NC133	*c*-Pentyl	H
NC134	Propargyl	CO_2tBu
NC135	*c*-Pentyl	CO_2tBu
NC136	Propargyl	CO_2Et
NC137	*c*-Pentyl	CO_2Et
NC138	Propargyl	CO_2iBu
NC139	*c*-Pentyl	CO_2iBu
NC140	Propargyl	CO_2iPr
NC141	*c*-Pentyl	CO_2iPr
63	Propargyl	COMe
NC142	*c*-Pentyl	COMe
NC143	Propargyl	$COC(CH_3)_3$
NC144	*c*-Pentyl	$COC(CH_3)_3$
NC145	Propargyl	$COCH_2(CH_3)_3$
NC146	*c*-Pentyl	$COCH_2(CH_3)_3$
NC147	Propargyl	$C(O)N(CH_3)_2$
NC148	*c*-Pentyl	$C(O)N(CH_3)_2$
NC149	Propargyl	$C(O)N(CH_3)Et$
NC150	*c*-Pentyl	$C(O)N(CH_3)Et$
NC142	Propargyl	$C(O)N(CH_3)iPr$
NC143	*c*-Pentyl	$C(O)N(CH_3)iPr$
NC144	Propargyl	$C(O)N(CH_3)iBu$
NC145	*c*-Pentyl	$C(O)N(CH_3)iBu$
NC146	Propargyl	$C(O)NH(CH_3)$
NC147	*c*-Pentyl	$C(O)NH(CH_3)$
NC148	Propargyl	C(O)NH(Et)
NC149	*c*-Pentyl	C(O)NH(Et)
NC150	Propargyl	C(O)NH(iPr)
NC142	*c*-Pentyl	C(O)NH(iPr)
NC143	Propargyl	C(O)NH(iBu)
NC144	*c*-Pentyl	C(O)NH(iBu)

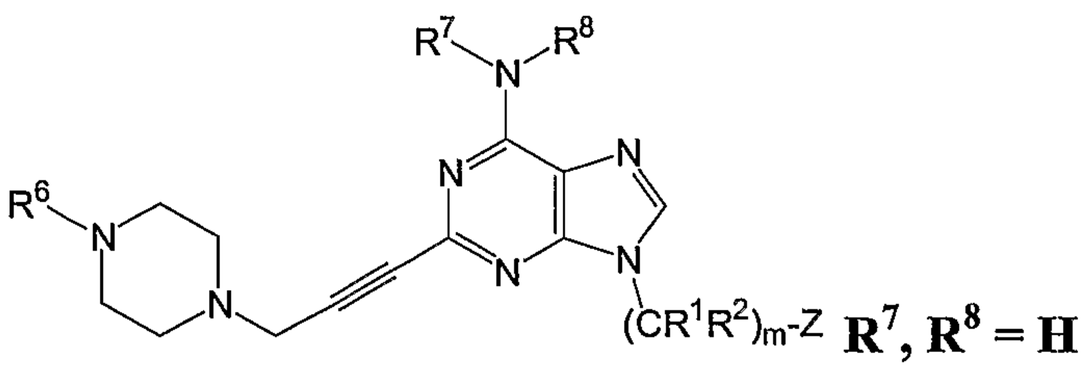
Table 3



R^7, R^8 = H

Compound	**$(CR^1R^2)_m$-Z**	**R^6**
NC151	Propargyl	H
NC152	*c*-Pentyl	H
NC153	Propargyl	2-CH_3
NC154	*c*-Pentyl	2-CH_3
NC155	Propargyl	2-$C(CH_3)_3$
NC156	*c*-Pentyl	2-$C(CH_3)_3$
NC157	Propargyl	2-C_6H_5
NC158	*c*-Pentyl	2-C_6H_5
2	Propargyl	3-CH_3
3	*c*-Pentyl	3-CH_3
NC159	Propargyl	3-$(CH_3)_2$
NC160	*c*-Pentyl	3-$(CH_3)_2$
NC161	Propargyl	3-CH_2CH_3
NC162	*c*-Pentyl	3-CH_2CH_3
NC163	Propargyl	3-$(CH_3)_2$, 5-$(CH_3)_2$
NC164	*c*-Pentyl	3-$(CH_3)_2$, 5-$(CH_3)_2$
NC165	Propargyl	4-CH_3
NC166	*c*-Pentyl	4-CH_3
NC167	Propargyl	4-C_2H_5
NC168	*c*-Pentyl	4-C_2H_5
NC169	Propargyl	4-$C(CH_3)_3$
NC170	*c*-Pentyl	4-$C(CH_3)_3$
NC171	Propargyl	4-C_6H_5
NC172	*c*-Pentyl	4-C_6H_5

Table 4

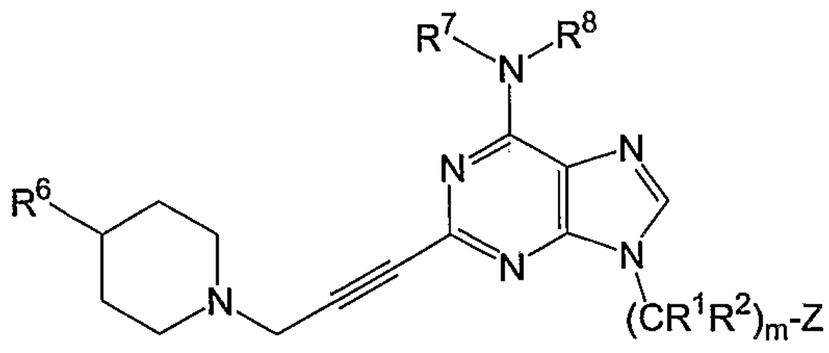


R^7, R^8 = H

Compound	**$(CR^1R^2)_m$-Z**	**R^6**
NC173	Propargyl	H
NC174	*c*-Pentyl	H
NC175	Propargyl	cyclohexyl
NC176	*c*-Pentyl	cyclohexyl

NC177	Propargyl	CO_2Et
NC178	*c*-Pentyl	CO_2Et
NC179	Propargyl	CO_2tBu
NC180	*c*-Pentyl	CO_2tBu
NC181	Propargyl	COMe
NC182	*c*-Pentyl	COMe
NC183	Propargyl	CO_2iBu
NC184	*c*-Pentyl	CO_2iBu
NC185	Propargyl	2-Pyrimidinyl
NC186	*c*-Pentyl	2-Pyrimidinyl
NC187	Propargyl	$COC(CH_3)_3$
NC188	*c*-Pentyl	$COC(CH_3)_3$
NC189	Propargyl	COMe
NC190	*c*-Pentyl	COMe
NC191	Propargyl	$COCH_2(CH_3)_3$
NC192	*c*-Pentyl	$COCH_2(CH_3)_3$
NC193	Propargyl	$COCH_3$
NC194	*c*-Pentyl	$COCH_3$
NC195	Propargyl	$C(O)N(CH_3)_2$
NC196	*c*-Pentyl	$C(O)N(CH_3)_2$
NC197	Propargyl	$C(O)N(CH_3)Et$
NC198	*c*-Pentyl	$C(O)N(CH_3)Et$
NC199	Propargyl	$C(O)N(CH_3)iPr$
NC200	*c*-Pentyl	$C(O)N(CH_3)iPr$
NC201	Propargyl	$C(O)N(CH_3)iBu$
NC202	*c*-Pentyl	$C(O)N(CH_3)iBu$
NC203	Propargyl	$C(O)NH(CH_3)$
NC204	*c*-Pentyl	$C(O)NH(CH_3)$
NC205	Propargyl	C(O)NH(Et)
NC206	*c*-Pentyl	C(O)NH(Et)
NC207	Propargyl	C(O)NH(iPr)
NC208	*c*-Pentyl	C(O)NH(iPr)
NC209	Propargyl	C(O)NH(iBu)
NC210	*c*-Pentyl	C(O)NH(iBu)

Table 5

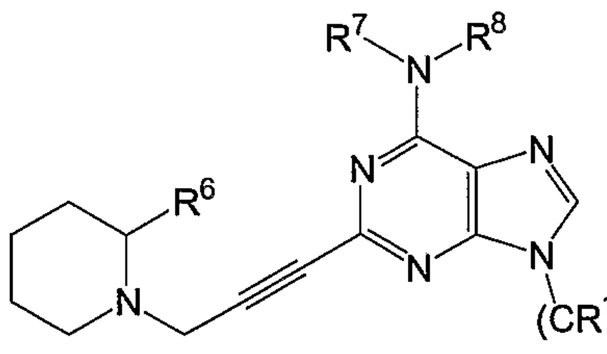


R^7, R^8 = H

Compound	**$(CR^1R^2)_m$-Z**	**R^6**
NC211	Propargyl	CH_2OH
NC212	*c*-Pentyl	CH_2OH
NC213	Propargyl	CO_2H
NC214	*c*-Pentyl	CO_2H
NC215	Propargyl	CO_2Me

NC216	*c*-Pentyl	CO_2Me
NC217	Propargyl	CO_2Et
NC218	*c*-Pentyl	CO_2Et
NC219	Propargyl	CH_2OAc
NC220	*c*-Pentyl	CH_2OAc
NC221	Propargyl	$CH_2N(CH_3)_2$
NC222	*c*-Pentyl	$CH_2N(CH_3)_2$
NC223	Propargyl	$COOCH_2CH_2NHBoc$
NC224	*c*-Pentyl	$COOCH_2CH_2NHBoc$
NC225	Propargyl	$COOCH_2CH_2NH_2$
NC226	*c*-Pentyl	$COOCH_2CH_2NH_2$
NC227	Propargyl	$CONHCH_2CH_3$
NC228	*c*-Pentyl	$CONHCH_2CH_3$
NC229	Propargyl	$CONH_2$
NC230	*c*-Pentyl	$CONH_2$
NC231	Propargyl	CONHMe
NC232	*c*-Pentyl	CONHMe
NC233	Propargyl	CH_2CH_3
NC234	*c*-Pentyl	CH_2CH_3
NC235	Propargyl	$COCH_3$
NC236	*c*-Pentyl	$COCH_3$
NC237	Propargyl	$CHCH_3(OH)$
NC238	*c*-Pentyl	$CHCH_3(OH)$

Table 6

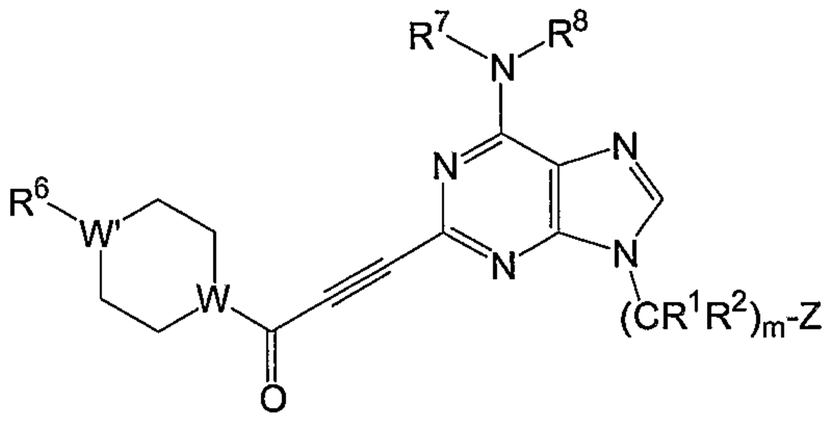


R^7, R^8 = H

Compound	**$(CR^1R^2)_m$-Z**	**R^6**
NC239	Propargyl	CH_2OH
NC240	*c*-Pentyl	CH_2OH
NC241	Propargyl	CO_2H
NC242	*c*-Pentyl	CO_2H
NC243	Propargyl	CO_2Me
NC244	*c*-Pentyl	CO_2Me
NC245	Propargyl	CH_2OAc
NC246	*c*-Pentyl	CH_2OAc
NC247	Propargyl	$CH_2N(CH_3)_2$
NC248	*c*-Pentyl	$CH_2N(CH_3)_2$
NC249	Propargyl	$COOCH_2CH_2NHBoc$
NC250	*c*-Pentyl	$COOCH_2CH_2NHBoc$
NC251	Propargyl	$COOCH_2CH_2NH_2$
NC252	*c*-Pentyl	$COOCH_2CH_2NH_2$
NC253	Propargyl	$CONHCH_2CH_3$
NC254	*c*-Pentyl	$CONHCH_2CH_3$

NC255	Propargyl	$CONH_2$
NC256	*c*-Pentyl	$CONH_2$
NC257	Propargyl	CONHMe
NC258	*c*-Pentyl	CONHMe
NC259	Propargyl	CH_2CH_3
NC260	*c*-Pentyl	CH_2CH_3
NC261	Propargyl	$COCH_3$
NC262	*c*-Pentyl	$COCH_3$
NC263	Propargyl	$CHCH_3(OH)$
NC264	*c*-Pentyl	$CHCH_3(OH)$

Table 7



R^7, R^8 = H

Compound	**$(CR^1R^2)_m$-Z**	**W**	**W'**	**R^6**
NC265	Propargyl	CH	CH	CO_2Me
NC266	*c*-Pentyl	CH	N	CO_2Me
NC267	Propargyl	N	CH	CO_2Me
NC268	*c*-Pentyl	N	N	CO_2Me
NC269	Propargyl	CH	CH	CO_2Me
NC270	*c*-Pentyl	CH	N	CO_2Me
NC271	Propargyl	N	CH	CO_2Me
NC272	*c*-Pentyl	N	N	CO_2Me
NC273	Propargyl	CH	CH	CH_2OH
NC274	*c*-Pentyl	CH	N	CH_2OH
NC275	Propargyl	N	CH	CH_2OH
NC276	*c*-Pentyl	N	N	CH_2OH
NC277	Propargyl	CH	CH	CH_2OH
NC278	*c*-Pentyl	CH	N	CH_2OH
NC279	Propargyl	N	CH	CH_2OH
NC280	*c*-Pentyl	N	N	CH_2OH
NC281	Propargyl	CH	CH	CO_2H
NC282	*c*-Pentyl	CH	N	CO_2H
NC283	Propargyl	N	CH	CO_2H
NC284	*c*-Pentyl	N	N	CO_2H
NC285	Propargyl	CH	CH	CO_2H
NC286	*c*-Pentyl	CH	N	CO_2H
NC287	Propargyl	N	CH	CO_2H
NC288	*c*-Pentyl	N	N	CO_2H
NC289	Propargyl	CH	CH	CH_2OAc
NC290	*c*-Pentyl	CH	N	CH_2OAc
NC291	Propargyl	N	CH	CH_2OAc
NC292	*c*-Pentyl	N	N	CH_2OAc

NC293	Propargyl	CH	CH	CH_2OAc
NC294	*c*-Pentyl	CH	N	CH_2OAc
NC295	Propargyl	N	CH	CH_2OAc
NC296	*c*-Pentyl	N	N	CH_2OAc
NC297	Propargyl	CH	CH	$CONH_2$
NC298	*c*-Pentyl	CH	N	$CONH_2$
NC299	Propargyl	N	CH	$CONH_2$
NC300	*c*-Pentyl	N	N	$CONH_2$
NC301	Propargyl	CH	CH	$CONH_2$
NC302	*c*-Pentyl	CH	N	$CONH_2$
NC303	Propargyl	N	CH	$CONH_2$
NC304	*c*-Pentyl	N	N	$CONH_2$
NC305	Propargyl	CH	CH	CONHMe
NC306	*c*-Pentyl	CH	N	CONHMe
NC307	Propargyl	N	CH	CONHMe
NC308	*c*-Pentyl	N	N	CONHMe
NC309	Propargyl	CH	CH	CONHMe
NC310	*c*-Pentyl	CH	N	CONHMe
NC311	Propargyl	N	CH	CONHMe
NC312	*c*-Pentyl	N	N	CONHMe
NC313	Propargyl	CH	CH	CO_2tBu
NC314	*c*-Pentyl	CH	N	CO_2tBu
NC315	Propargyl	N	CH	CO_2tBu
NC316	*c*-Pentyl	N	N	CO_2tBu
NC317	Propargyl	CH	CH	CO_2tBu
NC318	*c*-Pentyl	CH	N	CO_2tBu
NC319	Propargyl	N	CH	CO_2tBu
NC320	*c*-Pentyl	N	N	CO_2tBu
NC321	Propargyl	CH	CH	CO_2Et
NC322	*c*-Pentyl	CH	N	CO_2Et
NC323	Propargyl	N	CH	CO_2Et
NC324	*c*-Pentyl	N	N	CO_2Et
NC325	Propargyl	CH	CH	CO_2Et
NC326	*c*-Pentyl	CH	N	CO_2Et
NC327	Propargyl	N	CH	CO_2Et
NC328	*c*-Pentyl	N	N	CO_2Et
NC329	Propargyl	CH	CH	CO_2iBu
NC330	*c*-Pentyl	CH	N	CO_2iBu
NC331	Propargyl	N	CH	CO_2iBu
NC332	*c*-Pentyl	N	N	CO_2iBu
NC333	Propargyl	CH	CH	CO_2iBu
NC334	*c*-Pentyl	CH	N	CO_2iBu
NC335	Propargyl	N	CH	CO_2iBu
NC336	*c*-Pentyl	N	N	CO_2iBu
NC337	Propargyl	CH	CH	CO_2iPr
NC338	*c*-Pentyl	CH	N	CO_2iPr
NC339	Propargyl	N	CH	CO_2iPr
NC340	*c*-Pentyl	N	N	CO_2iPr

NC341	Propargyl	CH	CH	CO_2iPr
NC342	*c*-Pentyl	CH	N	CO_2iPr
NC343	Propargyl	N	CH	CO_2iPr
NC344	*c*-Pentyl	N	N	CO_2iPr
NC345	Propargyl	CH	CH	COMe
NC346	*c*-Pentyl	CH	N	COMe
NC347	Propargyl	N	CH	COMe
NC348	*c*-Pentyl	N	N	COMe
NC349	Propargyl	CH	CH	COMe
NC350	*c*-Pentyl	CH	N	COMe
NC351	Propargyl	N	CH	COMe
NC352	*c*-Pentyl	N	N	COMe
NC353	Propargyl	CH	CH	$COC(CH_3)_3$
NC354	*c*-Pentyl	CH	N	$COC(CH_3)_3$
NC355	Propargyl	N	CH	$COC(CH_3)_3$
NC356	*c*-Pentyl	N	N	$COC(CH_3)_3$
NC357	Propargyl	CH	CH	$COC(CH_3)_3$
NC358	*c*-Pentyl	CH	N	$COC(CH_3)_3$
NC359	Propargyl	N	CH	$COC(CH_3)_3$
NC360	*c*-Pentyl	N	N	$COC(CH_3)_3$
NC361	Propargyl	CH	CH	$COCH_2(CH_3)_3$
NC362	*c*-Pentyl	CH	N	$COCH_2(CH_3)_3$
NC363	Propargyl	N	CH	$COCH_2(CH_3)_3$
NC364	*c*-Pentyl	N	N	$COCH_2(CH_3)_3$
NC365	Propargyl	CH	CH	$COCH_2(CH_3)_3$
NC366	*c*-Pentyl	CH	N	$COCH_2(CH_3)_3$
NC367	Propargyl	N	CH	$COCH_2(CH_3)_3$
NC368	*c*-Pentyl	N	N	$COCH_2(CH_3)_3$
NC369	Propargyl	CH	CH	$C(O)N(CH_3)_2$
NC370	*c*-Pentyl	CH	N	$C(O)N(CH_3)_2$
NC371	Propargyl	N	CH	$C(O)N(CH_3)_2$
NC372	*c*-Pentyl	N	N	$C(O)N(CH_3)_2$
NC373	Propargyl	CH	CH	$C(O)N(CH_3)_2$
NC374	*c*-Pentyl	CH	N	$C(O)N(CH_3)_2$
NC375	Propargyl	N	CH	$C(O)N(CH_3)_2$
NC376	*c*-Pentyl	N	N	$C(O)N(CH_3)_2$
NC377	Propargyl	CH	CH	$C(O)N(CH_3)Et$
NC378	*c*-Pentyl	CH	N	$C(O)N(CH_3)Et$
NC379	Propargyl	N	CH	$C(O)N(CH_3)Et$
NC380	*c*-Pentyl	N	N	$C(O)N(CH_3)Et$
NC381	Propargyl	CH	CH	$C(O)N(CH_3)Et$
NC382	*c*-Pentyl	CH	N	$C(O)N(CH_3)Et$
NC383	Propargyl	N	CH	$C(O)N(CH_3)Et$
NC384	*c*-Pentyl	N	N	$C(O)N(CH_3)Et$
NC385	Propargyl	CH	CH	$C(O)N(CH_3)iPr$
NC386	*c*-Pentyl	CH	N	$C(O)N(CH_3)iPr$
NC387	Propargyl	N	CH	$C(O)N(CH_3)iPr$
NC388	*c*-Pentyl	N	N	$C(O)N(CH_3)iPr$

NC389	Propargyl	CH	CH	$C(O)N(CH_3)iPr$
NC390	*c*-Pentyl	CH	N	$C(O)N(CH_3)iPr$
NC391	Propargyl	N	CH	$C(O)N(CH_3)iPr$
NC392	*c*-Pentyl	N	N	$C(O)N(CH_3)iPr$
NC393	Propargyl	CH	CH	$C(O)N(CH_3)iBu$
NC394	*c*-Pentyl	CH	N	$C(O)N(CH_3)iBu$
NC395	Propargyl	N	CH	$C(O)N(CH_3)iBu$
NC396	*c*-Pentyl	N	N	$C(O)N(CH_3)iBu$
NC397	Propargyl	CH	CH	$C(O)N(CH_3)iBu$
NC398	*c*-Pentyl	CH	N	$C(O)N(CH_3)iBu$
NC399	Propargyl	N	CH	$C(O)N(CH_3)iBu$
NC400	*c*-Pentyl	N	N	$C(O)N(CH_3)iBu$
NC401	Propargyl	CH	CH	C(O)NH(Et)
NC402	*c*-Pentyl	CH	N	C(O)NH(Et)
NC403	Propargyl	N	CH	C(O)NH(Et)
NC404	*c*-Pentyl	N	N	C(O)NH(Et)
NC405	Propargyl	CH	CH	C(O)NH(Et)
NC406	*c*-Pentyl	CH	N	C(O)NH(Et)
NC407	Propargyl	N	CH	C(O)NH(Et)
NC408	*c*-Pentyl	N	N	C(O)NH(Et)
NC409	Propargyl	CH	CH	C(O)NH(iPr)
NC410	*c*-Pentyl	CH	N	C(O)NH(iPr)
NC411	Propargyl	N	CH	C(O)NH(iPr)
NC412	*c*-Pentyl	N	N	C(O)NH(iPr)
NC413	Propargyl	CH	CH	C(O)NH(iPr)
NC414	*c*-Pentyl	CH	N	C(O)NH(iPr)
NC415	Propargyl	N	CH	C(O)NH(iPr)
NC416	*c*-Pentyl	N	N	C(O)NH(iPr)
NC417	Propargyl	CH	CH	C(O)NH(iBu)
NC418	*c*-Pentyl	CH	N	C(O)NH(iBu)
NC419	Propargyl	N	CH	C(O)NH(iBu)
NC420	*c*-Pentyl	N	N	C(O)NH(iBu)
NC421	Propargyl	CH	CH	C(O)NH(iBu)
NC422	*c*-Pentyl	CH	N	C(O)NH(iBu)
NC423	Propargyl	N	CH	C(O)NH(iBu)
NC424	*c*-Pentyl	N	N	C(O)NH(iBu)
NC425	Propargyl	CH	CH	CH_2OCOCH_3
NC426	*c*-Pentyl	CH	N	CH_2OCOCH_3
NC427	Propargyl	N	CH	CH_2OCOCH_3
NC428	*c*-Pentyl	N	N	CH_2OCOCH_3
NC429	Propargyl	CH	CH	CH_2OCOCH_3
NC430	*c*-Pentyl	CH	N	CH_2OCOCH_3
NC431	Propargyl	N	CH	CH_2OCOCH_3
NC432	*c*-Pentyl	N	N	CH_2OCOCH_3
NC433	Propargyl	CH	CH	CH_2OCOEt
NC434	*c*-Pentyl	CH	N	CH_2OCOEt
NC435	Propargyl	N	CH	CH_2OCOEt
NC436	*c*-Pentyl	N	N	CH_2OCOEt

NC437	Propargyl	CH	CH	CH_2OCOEt
NC438	*c*-Pentyl	CH	N	CH_2OCOEt
NC439	Propargyl	N	CH	CH_2OCOEt
NC440	*c*-Pentyl	N	N	CH_2OCOEt
NC441	Propargyl	CH	CH	$CH_2OCOiPr$
NC442	*c*-Pentyl	CH	N	$CH_2OCOiPr$
NC443	Propargyl	N	CH	$CH_2OCOiPr$
NC444	*c*-Pentyl	N	N	$CH_2OCOiPr$
NC445	Propargyl	CH	CH	$CH_2OCOiPr$
NC446	*c*-Pentyl	CH	N	$CH_2OCOiPr$
NC447	Propargyl	N	CH	$CH_2OCOiPr$
NC448	*c*-Pentyl	N	N	$CH_2OCOiPr$
NC449	Propargyl	CH	CH	$CH_2OCOiBu$
NC450	*c*-Pentyl	CH	N	$CH_2OCOiBu$
NC451	Propargyl	N	CH	$CH_2OCOiBu$
NC452	*c*-Pentyl	N	N	$CH_2OCOiBu$
NC453	Propargyl	CH	CH	$CH_2OCOiBu$
NC454	*c*-Pentyl	CH	N	$CH_2OCOiBu$
NC455	Propargyl	N	CH	$CH_2OCOiBu$
NC456	*c*-Pentyl	N	N	$CH_2OCOiBu$

Evaluation of novel A_{2A} antagonists in four mouse models of PD: The A_{2A} receptor antagonist ATL-2 enhances motor function in a dose-dependent manner in normal and dopamine-depleted mice.

[0132] In the set of experiments, we perform a dose response study of ATL-2 in stimulating motor activity in normal mice, and then we further extend this to dopamine-depleted mice. Adult male mice are habituated for 120 minutes and treated (i.p.) with saline or varying doses of compound, and their locomotor activity recorded for 120 minutes.

[0133] In a second set of experiments, we utilize the MPTP treatment paradigm to create animal model of PD by severely depleting dopamine in mice. We use a single MPTP treatment paradigm (40 mg/kg) which has been reproducibly reducing dopamine to 30-40% of normal dopamine contents in striatum in our previous studies.[35,74] Adult male mice (~25 mg/kg) are treated with single dose of MPTP (40 mg/kg). Thirty minutes after the MPTP treatment, mice are injected (i.p.) with vehicle or compounds of the invention at the same doses discussed above. Their motor activity is recorded for 180 minutes.

[0134] **Results:** Based on our previous experiments with other $A_{2A}R$ antagonists and our pilot study, we observe the maximal stimulant dose as well as sub-threshold doses of ATL compounds in normal and MPTP-treated mice. Without being bound by any theory, it is proposed that motor stimulant effect may manifest best in dopamine-depleted animals than

normal animals, indicating that $A_{2A}R$ antagonists preferentially act at the $A_{2A}R$ in a PD condition to stimulate motor activity.

[0135] A_{2A} receptor antagonists synergize with L-dopa to stimulate motor activity in dopamine-depleted mice.

[0136] We further tested the ability of these compounds to synergistically enhance motor function in conjunction with L-dopa, the standard therapy. Mice are injected (i.p.) with MPTP at a dose (1-2.5 mg/kg) that markedly decreases striatal dopamine levels. Thirty minutes later (when the mice exhibit an immobility), the mice are then randomly assigned to the following different treatment groups (n=10): (1) L-dopa (25 mg/kg); (2) ATL-2 (0.3, 1, 3, and 10 mg/kg), and (3) L-dopa (25 mg/kg) + ATL-2 (0.3, 1, 3, and 10 mg/kg). Locomotor behavior is monitored for 120 min before and after the treatment.

[0137] **Results:** Based on the Preliminary Results and on the known feature of other $A_{2A}R$ antagonists, a synergistic effect of ATL-2 with L-dopa in stimulating locomotor activity in dopamine-depleted mice is observed. This synergistic effect of ATL-2 and L-dopa is exhibited in a left-shift of the dose-response curve.

A_{2A} antagonists potently and specifically attenuate MPTP-induced neurotoxicity by inhibiting MPTP metabolism.

[0138] C57Bl/6 mice (n=10-12 mice per group) are pretreated with the A_{2A} antagonist ATL-2 (0.3, 1.0, 3.0 and 10.0 mg/kg, i.p) 5 min prior to each of four MPTP (40 mg/kg) injections at 2 hr intervals. These doses are selected based on our preliminary results (with CSC) and on motor and neuroprotective effects (against ischemia) by SCH58261 and DPCPX. The specificities for the $A_{2A}R$ in these dose ranges of ATL-2 have been confirmed using A_{2A} KO mice. Seven days after the MPTP (± CSC, SCH58261 or CPA) treatment, the striatum from one side are dissected out and processed for HPLC analysis of dopamine and DOPAC levels. The other half brain is quickly frozen for sectioning coronally through the striatum and substantial nigra. DAT binding density in striatum may be determined by receptor autoradiography using ^{3}H-mazindol as a specific ligand. Quantitation of DAT (^{3}H-mazindol) binding autoradiography may be performed by densitometry analysis. The numbers of dopaminergic neurons may be determined by TH immunohistochemistry in the substantial nigra. Stereological methods may be used to estimate the absolute reduction in TH^+ nigral neurons in MPTP-treated WT mice and any attenuation in those pretreated with

ATL-2. In the same sections, cell counts may also be performed for TH^+ neurons in the more medial VTA, which is less affected in MPTP treated mice as well as in PD.

[0139] **Results:** Guided by our preliminary results, neuroprotection in a dose-dependent manner (at least from 0.5 to 5 mg/kg range) may be observed. The potency of A_{2A} antagonists for neuroprotection may be observed with their potency for motor stimulation and for possible attenuation of behavioral sensitization (see above). Similarly, the potency of CSC or SCH58261 for neuroprotection against MPTP may be compared to that for neuroprotection against ischemic injury and excitoxicity. A significant difference in an A_{2A} antagonist's potency in neuroprotection against MPTP and against ischemia or excitoxicity may suggest different mechanisms and sites of action (e.g. glial versus neuronal compartments which may have different G-protein coupling mechanisms). On the other hand, the same potency of A_{2A} antagonists for motor stimulation, neuroprotection and possibly delayed sensitization to L-dopa would suggest that the same type of $A_{2A}R$ is responsible for all these potential benefits of A_{2A} antagonists in different animal models of PD.

A_{2A} antagonists delay and A_{2A} agonists accelerate L-dopa-induced locomotor sensitization in unilateral 6-OHDA-lesioned mice.

[0140] The ability of ATL-2 to modify the development of L-dopa-induced locomotor sensitization in hemiparkinsonian mice are tested. C57BL/6 mice (from the Jackson's lab, Bar Harbor, MI) are lesioned with 6-OHDA by unilateral intrastriatal using a standard lesioning protocol. Seven days after the 6-OHDA (or MPP^+) treatment, mice are injected with L-dopa (2.0 mg/kg, daily) for 14 days. Five min prior to each L-dopa treatment, the mice receive intraperitoneal pretreatment with: (1) vehicle, (2) ATL-2 (3 mg/kg) or (3) ATL-2 (10 mg/kg). In these dose ranges, the selective A_{2A} antagonists have been shown to produce motor stimulant effects (see *Preliminary Results*). Rotational responses to L-dopa are recorded on the days 1, 3, 5, 7, 10 and 15. Following the behavioral measurement, mice may be sacrificed and their brains sectioned through striatum and substantia nigra. Striatal enkephalin mRNA levels are determined by *in situ* hybridization histochemistry. Similarly, DAT (^{3}H-mazindol) binding is measured by receptor autoradiography to ensure successful and equivalent lesions among different experimental groups.

[0141] **Results:** Based on our previous study with SCH58261 in this repeated L-dopa-induced sensitization model, ATL-2 delays or prevent the development of locomotor

sensitization. The prevention or delayed appearance with L-dopa locomotor sensitization by co-injection of an A_{2A} antagonist indicates an important role of the $A_{2A}R$ in the development of L-dopa-induced behavioral sensitization. Furthermore, this helps exclude the possibility that an attenuated behavioral sensitization to chronic L-dopa observed in A_{2A} KO mice results from a developmental effect of $A_{2A}R$ deficiency. Thus combined genetic and pharmacological approaches provide the clearest assessment of the $A_{2A}R$'s role in the development of behavioral sensitization to L-dopa, and provides insights into its role in L-dopa-induced dyskinesia.

Methods

Animal Treatments and Catalepsy Behavioral Assessments:

[0142] WT and A_{2A} KO mice (generated as above) as well as commercially procured C57Bl/6 mice (Taconic, NY) may be used for this study. Since our pilot study and other reports [40, 88] indicate that animal age is a critical factor in determining the extent of an MPTP lesion, animal body weight around 25-30 grams (corresponding to approximately 10 weeks of age) is tightly controlled. The mice are housed in temperature and humidity-controlled rooms with a 24-hour 1:1 light:dark cycle. Adenosinergic and dopaminergic agents are injected at the volume of 0.1 ml/10 gram body weight of mice. Other adenosinergic and dopaminergic drugs are purchased from RBI (Natick, MA). From our previous work, we have adapted a special solvent (15% DMSO, 15% Alkamuls-EL 620 and 70% saline) for dissolving A_{2A} antagonists, including CSC and SCH58261.

[0143] Catalepsy behavior may be induced by haloperidol (1 mg/kg, i.p.) or reserpine (5 mg/kg, i.p. see below). Catalepsy score may be determined by the bar and grid tests. For the bar test, both mouse forepaws are placed on a 6 cm-high horizontal bar (diameter 0.7 cm). In the grid test, mice are allowed to cling to a metal-framed vertical grid (1.3 cm squares). The latency from paw placement until the first complete removal of one paw from the support is measured (maximal test duration 180 sec). Upon the completion of behavioral assessment, mice are sacrificed and the brains are processed for neurochemical and histochemical analyses.

Dopamine Depletion by the Treatment with MPTP or 6-OHDA:

[0144] a) Intraperitoneal Injection of MPTP: The MPTP administration regimen (20 mg/kg x 4 at 2 hr interval) has been shown to produce severe dopamine depletion

(consistently greater than ~80% in our Preliminary Results Figs. 6 and 7). Naive C57Bl/6 mice are pretreated with adenosine antagonists 5 min prior to MPTP treatment.

[0145] b) Intrastriatal Injection of 6-OHDA: Wild-type C57Bl/6 or A2AR mutant mice are anesthetized with Avertin and positioned in a stereotaxic frame. Three microliters of 6-OHDA (3 μg/μl) are injected into the left striatum (coordinates from bregma: AP+0.0, L+2.5.0, DV -4.4) via a infusion minipump over a 4 min period. Due to its photolability, 6-OHDA is dissolved in 0.01% ascorbic acid and injected under a light-protected environment.

[0146] c) Post-treatment Care: Dopamine-depleted mice may be continually monitored, and special care may be taken to maintain mouse body temperature with a heating blanket or warming lights. During the first 48 hours post-operation, mashed food pellets and water are provided to the mice inside the cage at floor-level for easy access.

Neurochemical Analysis:

[0147] (a) Measurements of Catecholamines and Indoleamines in Striatum by HPLC: To measure tissue catecholamine and indoleamine levels, mice are decapitated, their brains are removed rapidly, and striata are dissected out and frozen on dry ice. Striata are weighed frozen and then homogenized in 200 μl of 150 mM trichloroacetic acid containing 0.1 mM EDTA and 1 μM epinephrine (as an internal standard). Homogenates are centrifuged for 5 min at 15,000 g. The catecholamines in the supernatant are separated over a reverse-phase hydrophobic interaction C-18 HPLC column (Beckman, 5μ ODS) and measured using an electrochemical detector (ESA Coulochem 5100A) with electrodes set in series at oxidizing (+0.22 V) and then reducing (-0.35 V) potentials. Both the retention time and the ratio of oxidation to reduction currents for given sample peaks are compared against those for external standards to ensure proper identification of analytes.

[0148] (b) Stereologic quantitation of neuronal loss in substantia nigra: One week after lesioning, mice may be perfusion-fixed and their brains may be microtome-cut into 40 μm coronal free-floating sections. Every sixth section may be processed for TH immunohistochemistry using a 1:1,000 dilution of a polyclonal rabbit antiserum against rat TH (Eugene Tech. Intl., NJ). Immunostaining is completed using standard avidin-biotin procedures described previously [18,130]. A non-biased stereological technique is employed to quantify the effect of treatment on total TH+ nigra (pars compacta) cell counts as described previously [81]. All counts are performed by a single observer who is unaware of the

treatment group at the time of neuronal estimates. Based on our pilot studies in WT mice MPP+ at this dose (3 μg/striatum) produced a ~40% loss of ipsilateral TH+ nigral neurons.

[0149] (c) A2A receptor binding autoradiography: Twenty micron striatal sections are preincubated for 5 minutes with ice-cold buffer (509 mM Tris-HCl, 5 mM KCl and 300 mM NaCl, pH 7.9) and then incubated for 60 minutes in the same buffer containing 6 nM 3H-SCH58261 (provided generously by Dr. E. Ongini) [131]. The slides are washed twice and then air-dried before exposure to Hyperfilm (Amersham, IL) for 2-4 weeks. The films are analyzed with a video-based image analysis system (MultiAnalyst; Biorad), and total striatal 3H-SCH58261 binding (fmol/mg tissue) is calculated using a tritium-labeled calibration standard [17,131].

Statistical analysis

[0150] Single statistical comparisons of an A2AR KO group to its WT control are generally performed using a Student's t test, two-tailed. Comparison of more than two factors (e.g. genotype, drug treatment and time course) and their interactions are made using 2-way ANOVA followed by Newman-Keuls post hoc analysis. If data are not normally distributed, non-parametric tests (Kruskal-Wallis or Mann-Whitney U test) are used.

[0151] Vertebrate Animals. Mice are the only animals that are be used in experiments. The mice are monitored daily (co-investigators or technician) under the supervision of a staff veterinarian. In the majority of the experiments the mice are kept under SPF conditions with no more than 5 mice/cage of females and 4 mice/cage of males. All husbandry and veterinary care meets NIH and AAALAC standards for humane care for use of laboratory animals. In addition, because of daily observation of all animals, any moribund animal is humanely euthanized by CO_2.

[0152] Models of PD are used to investigate pre-clinical efficacy and pharmacokinetics of A2AAR antagonist. Because we have used these model in our laboratory, the model is now well characterized and the experimental manipulation of mice for these studies are well established.

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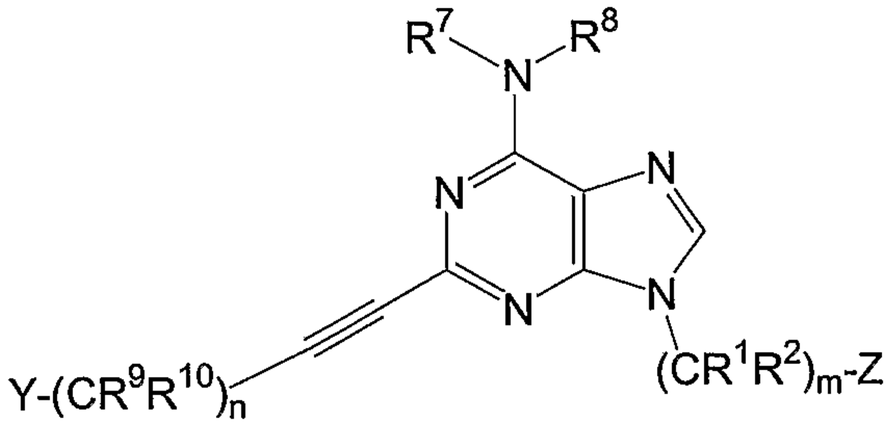
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The entire disclosure of all documents cited throughout this application are incorporated herein by reference.

CLAIMS

What is claimed is:

1. A compound of the formula I:



I

wherein:

R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, $-NH_2$, -OH, -SH, $-NHCH_3$, $-N(CH_3)_2$, -OMe, –SMe, $(C_1\text{-}C_8)$alkyl, aryl and aryl$(C_1\text{-}C_8)$alkyl, wherein R^1 and R^2 are optionally substituted with 1 to 4 substituents of R^a, wherein the alkyl is optionally interrupted by 1-4 heteroatoms selected from –O–, -S–, –SO–, $-S(O)_2-$ or amino ($-NR^a-$), or where R^1 and R^2 are independently absent, with the proviso that R^a is not thio or halogen when the R^1 or R^2 to which R^a is bound is halogen, $-NH_2$, -OH, -SH,

$-NHCH_3$, $-N(CH_3)_2$, -OMe or -SMe;

R^3 is selected from the group consisting of hydrogen, halo, $-OR^a$, $-SR^a$, $(C_1\text{-}C_8)$alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, $(C_3\text{-}C_8)$cycloalkyl, heterocycle, hetrocycle$(C_1\text{-}C_8)$alkyl, aryl, aryl$(C_1\text{-}C_8)$alkyl, heteroaryl, heteroaryl$(C_1\text{-}C_8)$alkyl, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $R^aS(=O)_2-$, $-NNR^a$ and $-OPO_2R^a$; or if the ring formed from the group $CR^3R^4R^5$ is aryl or heteroaryl or partially unsaturated, then R^3 can be absent;

R^4 and R^5 together with the atoms to which they are attached form a saturated or partially unsaturated, mono-, bi- or tricyclic or aromatic ring having 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 ring atoms, wherein the ring atoms are optionally interrupted by 1, 2, 3 or 4 heteroatoms selected from the group consisting of -O-, -S-, -SO-, $-S(O)_2-$ or amine ($-NR^a-$) in the ring, wherein any ring comprising R^4 and R^5 is optionally further substituted with from 1 to 14 R^6 groups; wherein each R^6 is independently selected from the group consisting of halo, $-OR^a$, $-SR^a$, substituted or unsubstituted $(C_1\text{-}C_8)$alkyl, cyano, nitro, trifluoromethyl,

trifluoromethoxy, (C_1-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, heterocycle, hetrocyclyl(C_1-C_8)alkyl, aryl, aryl(C_1-C_8)alkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl, -CO_2R^a, $R^aC(=O)O$-, $R^aC(=O)$-, -OCO_2R^a, $R^aR^bNC(=O)O$-, $R^bOC(=O)N(R^a)$-, R^aR^bN-, $R^aR^bNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^aR^bNC(=O)N(R^b)$-, $R^aR^bNC(=S)N(R^b)$-, -OPO_3R^a, $R^aOC(=S)$-, $R^aC(=S)$-, -SSR^a, $R^aS(=O)$-, -NNR^a and -OPO_2R^a or two R^6 groups and the atom to which they are attached combined to form C=O or C=S, or wherein two R^6 groups together with the atom or atoms to which they are attached can form a carbocyclic or heterocyclic ring;

R^7 and R^8 are each independently hydrogen, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, aryl or aryl(C_1-C_8)alkylene, heteroaryl, heteroaryl(C_1-C_8)alkylene-; or wherein R^7 and R^8 together with the nitrogen atom to which they attach form a heterocycle or heteroaromatic ring;

R^9 and R^{10} are each independently selected from the group consisting of hydrogen, halogen, -NH_2, -OH, -SH, -$NHCH_3$, –$N(CH_3)_2$, -OMe, –SMe, (C_1-C_8)alkyl, aryl and aryl(C_1-C_8)alkyl, wherein R^9 and R^{10} are optionally substituted with 1 to 4 substituents of R^a, wherein the alkyl is optionally interrupted by 1 to 4 heteroatoms selected from –O–, -S–, –SO–, -$S(O)_2$– or amino (–NR^a–), or where R^9 and R^{10} are independently absent, with the proviso that R^a is not thio or halogen in the case where the R^9 or R^{10} to which R^a is bound is halogen, -NH_2,

-OH, -SH, -$NHCH_3$, -$N(CH_3)_2$, -OMe or -SMe;

Y is -$CR^3R^4R^5$ or NR^4R^5;

Z is selected from the group consisting of hydrogen, halogen, (C_1-C_8)alkyl, (C_1-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, (C_6-C_{20})polycyclyl, heterocyclyl, cycloalkyl(C_1-C_8)alkyl, bicycloalkyl(C_6-C_{12})alkyl, heterocyclyl(C_1-C_8)alkyl, aryl, aryl(C_5-C_{14}), aryl(C_1-C_8)alkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl, –NR^aR^b, -OR^a, -SR^a, cyano, nitro, trifluoromethyl, trifluoromethoxy, -CO_2R^a, $R^aC(=O)O$-, $R^aC(=O)$-, -OCO_2R^a, $R^aR^bNC(=O)O$-, $R^bOC(=O)NR^a$-, $R^aR^bNC(=O)$-, $R^aC(=O)NR^b$-, $R^aR^bNC(=O)NR^b$-, $R^aR^bNC(=S)NR^b$-, -OPO_3R^a, $R^aOC(=S)$-, $R^aC(=S)$-, -SSR^a, $R^aS(=O)$-, -NNR^a, -OPO_2R^a, -$OS(O_2)R^a$, -$OS(=O)OR^a$,

-$OS(O_2)OR^a$ and -$O(SO_2)NR^aR^b$;

R^a and R^b are each independently selected from the group consisting of hydrogen, halogen, -NH_2, -OH, -SH, -$NHCH_3$, -$N(CH_3)_2$, -OMe, -SMe, propargyl, cyano, -NNH, -$NNCH_3$, -OPO_2H, –OPO_2CH_3, -$OS(O_2)H$, -$OS(O_2)OH$, -$OS(O_2)CH_3$, -$OS(O_2)OCH_3$, (C_1-C_8)alkyl, aryl, aryl(C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl,

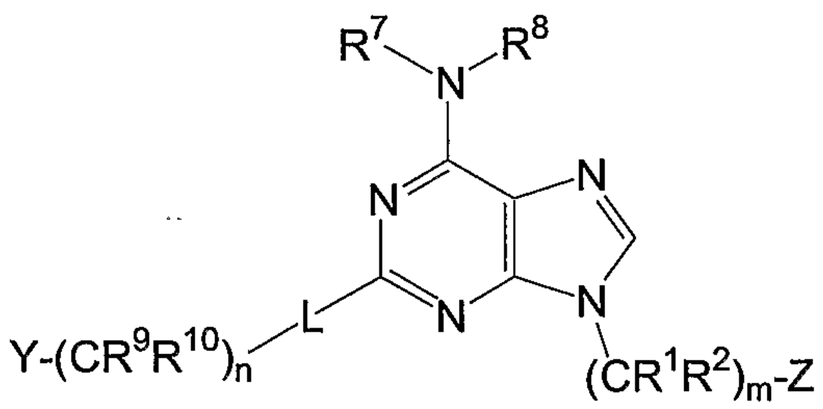
cycloalkyl(C_1-C_8)alkyl, bicycloalkyl(C_6-C_{12})alkyl, heteroaryl and heteroaryl(C_1-C_8)alkyl, wherein the alkyl and cycloalkyl are optionally interrupted with 1-4 heteroatoms selected from the group consisting of –O–, –S–, -SO–, -$S(O)_2$– and amino (–NR^c–); and wherein the alkyl, cycloalkyl, aryl and heteroaryl are optionally substituted with 1, 2, 3 or 4 substituents selected from the group consisting of -OR^c, -NR^cR^c, SR^c, cyano, -NNH, -$NNCH_3$, OPO_2H, OPO_2CH_3,
-$OS(O_2)H$, -$OS(O_2)OH$, -$OS(O_2)CH_3$ and -$OS(O_2)OCH_3$, provided that the point of attachment of R^a or R^b is not a heteroatom when it is attached to another heteroatom;

R^c is selected from the group consisting of hydrogen and (C_1-C_8)alkyl; and

m is 0 to 8; n is 0, 1, 2 or 3, provided that when m is 0, Z is not halogen, cyano, nitro or a heteroatom, and when n is 0, Y is not -NR^4R^5; or

a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof.

2. A compound of the formula II:



II

wherein:

R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, -NH_2, -OH, -SH, -$NHCH_3$, –$N(CH_3)_2$, -OMe, –SMe, (C_1-C_8)alkyl, aryl and aryl(C_1-C_8)alkyl, wherein R^1 and R^2 are optionally substituted with 1 to 4 substituents of R^a, wherein the alkyl is optionally interrupted by 1 to 4 heteroatoms selected from –O–, -S–, –SO–, -$S(O)_2$– or amino (–NR^a–), or where R^1 and R^2 are independently absent, with the proviso that R^a is not thio or halogen when the R^1 or R^2 to which R^a is bound is halogen, -NH_2, -OH, -SH,
–$NHCH_3$, –$N(CH_3)_2$, -OMe or -SMe;

R^3 is selected from the group consisting of hydrogen, halo, -OR^a, -SR^a, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_3-C_8)cycloalkyl, heterocycle, hetrocycle(C_1-C_8)alkyl, aryl, aryl(C_1-C_8)alkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl, -CO_2R^a, $R^aC(=O)O$-, $R^aC(=O)$-, -OCO_2R^a, $R^aR^bNC(=O)O$-, $R^bOC(=O)N(R^a)$-, R^aR^bN-,

$R^aR^bNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^aR^bNC(=O)N(R^b)$-, $R^aR^bNC(=S)N(R^b)$-, -OPO_3R^a, $R^aOC(=S)$-, $R^aC(=S)$-, -SSR^a, $R^aS(=O)$-, $R^aS(=O)_2$-, -NNR^a and -OPO_2R^a; or if the ring formed from the group $CR^3R^4R^5$ is aryl or heteroaryl or partially unsaturated, then R^3 can be absent;

R^4 and R^5 together with the atoms to which they are attached form a saturated or partially unsaturated, mono-, bi- or tricyclic, or aromatic ring having 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 ring atoms, wherein the ring atoms are optionally interrupted by 1, 2, 3 or 4 heteroatoms selected from the group consisting of -O-, -S-, -SO-, $-S(O)_2$- or amine (-NR^c-) in the ring, wherein any ring comprising R^4 and R^5 is optionally further substituted with from 1 to 14 R^6 groups; wherein each R^6 is independently selected from the group consisting of hydrogen, halo, -OR^a, -SR^a, substituted or unsubstituted $(C_1$-$C_8)$alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, $(C_1$-$C_8)$cycloalkyl, $(C_6$-$C_{12})$bicycloalkyl, heterocycle, hetrocyclyl$(C_1$-$C_8)$alkyl, aryl, aryl$(C_1$-$C_8)$alkyl, heteroaryl, heteroaryl$(C_1$-$C_8)$alkyl, -CO_2R^a, $R^aC(=O)O$-, $R^aC(=O)$-, -OCO_2R^a, $R^aR^bNC(=O)O$-, $R^bOC(=O)N(R^a)$-, R^aR^bN-, $R^aR^bNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^aR^bNC(=O)N(R^b)$-, $R^aR^bNC(=S)N(R^b)$-, -OPO_3R^a, $R^aOC(=S)$-, $R^aC(=S)$-, -SSR^a, $R^aS(=O)$-, -NNR^a and -OPO_2R^a, or two R^6 groups and the atom to which they are attached combined to form C=O or C=S, or wherein two R^6 groups together with the atom or atoms to which they are attached can form a carbocyclic or heterocyclic ring;

R^7 and R^8 are each independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_3$-$C_8)$cycloalkyl, aryl or aryl$(C_1$-$C_8)$alkylene, heteroaryl, heteroaryl$(C_1$-$C_8)$alkylene-; or wherein R^7 and R^8 together with the nitrogen atom to which they attach form a heterocycle or heteroaromatic ring;

R^9 and R^{10} are each independently selected from the group consisting of hydrogen, halogen, -NH_2, -OH, -SH, -$NHCH_3$, –$N(CH_3)_2$, -OMe, –SMe, $(C_1$-$C_8)$alkyl, aryl and aryl$(C_1$-$C_8)$alkyl, wherein R^9 and R^{10} are optionally substituted with 1 to 4 substituents of R^a, wherein the alkyl is optionally interrupted by 1 to 4 heteroatoms selected from –O–, -S–, –SO–, $-S(O)_2$– or amino (–NR^a–), or where R^9 and R^{10} are independently absent, with the proviso that R^a is not thio or halogen in the case where R^9 and R^{10} to which R^a is bound is halogen, -NH_2, -OH, -SH, -$NHCH_3$, -$N(CH_3)_2$, -OMe and –SMe;

L is a linker selected from the group consisting of -$(C_1$-$C_3)$alkyl–C≡C-, -C≡C-$(C_1$-$C_3)$alkyl-, -$(CH_2)_{1\text{-}3}$-CH=CH-, -CH=CH-$(CH_2)_{1\text{-}3}$-, -$(CH_2)_{1\text{-}2}$-CH=CH-CH_2- and -CH_2-CH=CH-$(CH_2)_{1\text{-}2}$-;

Y is -$CR^3R^4R^5$ or NR^4R^5;

Z is selected from the group consisting of hydrogen, halogen, (C_1-C_8)alkyl, (C_1-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, (C_6-C_{20})polycyclyl, heterocyclyl, cycloalkyl(C_1-C_8)alkyl, bicycloalkyl(C_6-C_{12})alkyl, heterocyclyl(C_1-C_8)alkyl, aryl, aryl(C_5-C_{14}), aryl(C_1-C_8)alkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl, –NR^aR^b, -OR^a, -SR^a, cyano, nitro, trifluoromethyl, trifluoromethoxy, -CO_2R^a, $R^aC(=O)O$-, $R^aC(=O)$-, -OCO_2R^a, $R^aR^bNC(=O)O$-, $R^bOC(=O)NR^a$-, $R^aR^bNC(=O)$-, $R^aC(=O)NR^b$-, $R^aR^bNC(=O)NR^b$-, $R^aR^bNC(=S)NR^b$-, -OPO_3R^a, $R^aOC(=S)$-, $R^aC(=S)$-, -SSR^a, $R^aS(=O)$-, -NNR^a, -OPO_2R^a, –$OS(O_2)R^a$, -$OS(=O)OR^a$,
-$OS(O_2)OR^a$ and -$O(SO_2)NR^aR^b$;

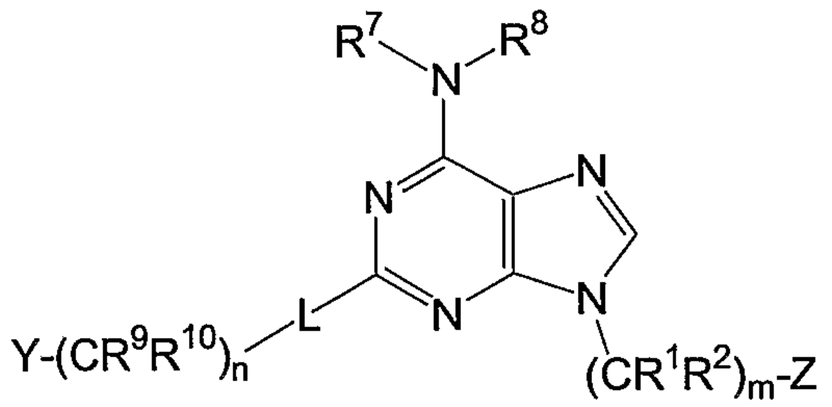
R^a and R^b are each independently selected from the group consisting of hydrogen, halogen, -NH_2, -OH, -SH, -$NHCH_3$, -$N(CH_3)_2$, -OMe, -SMe, propargyl,
cyano, -NNH, -$NNCH_3$, -OPO_2H, –OPO_2CH_3, -$OS(O_2)H$, -$OS(O_2)OH$, -$OS(O_2)CH_3$,
-$OS(O_2)OCH_3$, (C_1-C_8)alkyl, aryl, aryl(C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, cycloalkyl(C_1-C_8)alkyl, bicycloalkyl(C_6-C_{12})alkyl, heteroaryl and heteroaryl(C_1-C_8)alkyl, wherein the alkyl and cycloalkyl are optionally interrupted with 1 to 4 heteroatoms selected from the group consisting of –O–, –S–, -SO–, -$S(O)_2$– and amino (–NR^c–); and wherein the alkyl, cycloalkyl, aryl and heteroaryl are optionally substituted with 1, 2, 3 or 4 substituents selected from the group consisting of -OR^c, -NR^cR^c, SR^c, cyano, -NNH, -$NNCH_3$, -OPO_2H, -OPO_2CH_3,
-$OS(O_2)H$, -$OS(O_2)OH$, -$OS(O_2)CH_3$ and -$OS(O_2)OCH_3$, provided that the point of attachment of R^a or R^b is not a heteroatom when it is attached to another heteroatom;

R^c is selected from the group consisting of hydrogen and (C_1-C_8)alkyl; and

m is 0 to 8; n is 0, 1, 2 or 3 provided that when m is 0, Z is not halogen, cyano, nitro or a heteroatom; or

a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof.

3. A compound of the formula III:



III

wherein:

R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, $-NH_2$, -OH, -SH, $-NHCH_3$, $-N(CH_3)_2$, -OMe, –SMe, $(C_1\text{-}C_8)$alkyl, aryl and aryl$(C_1\text{-}C_8)$alkyl, wherein R^1 and R^2 are optionally substituted with 1 to 4 substituents of R^a, wherein the alkyl is optionally interrupted by 1 to 4 heteroatoms selected from –O–, -S–, –SO–, $-S(O)_2-$ or amino ($-NR^a-$), or where R^1 and R^2 are independently absent, with the proviso that R^a is not thio or halogen when the R^1 or R^2 to which R^a is bound is halogen, $-NH_2$, -OH, -SH,

$-NHCH_3$, $-N(CH_3)_2$, -OMe or -SMe;

R^3 is selected from the group consisting of hydrogen, halo, $-OR^a$, $-SR^a$, $(C_1\text{-}C_8)$alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, $(C_3\text{-}C_8)$cycloalkyl, heterocycle, hetrocycle$(C_1\text{-}C_8)$alkyl, aryl, aryl$(C_1\text{-}C_8)$alkyl, heteroaryl, heteroaryl$(C_1\text{-}C_8)$alkyl, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $R^aS(=O)_2-$, $-NNR^a$ and $-OPO_2R^a$; or if the ring formed from the group $CR^3R^4R^5$ is aryl or heteroaryl or partially unsaturated, then R^3 can be absent;

R^4 and R^5 together with the atoms to which they are attached form a saturated or partially unsaturated, mono-, bi- or tricyclic, or aromatic ring having 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 ring atoms, wherein the ring atoms are optionally interrupted by 1, 2, 3 or 4 heteroatoms selected from the group consisting of -O-, -S-, -SO-, $-S(O)_2-$ or amine ($-NR^c-$) in the ring, wherein any ring comprising R^4 and R^5 is optionally further substituted with from 1 to 14 R^6 groups; wherein each R^6 is independently selected from the group consisting of hydrogen, halo, $-OR^a$, $-SR^a$, substituted or unsubstituted $(C_1\text{-}C_8)$alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, $(C_1\text{-}C_8)$cycloalkyl, $(C_6\text{-}C_{12})$bicycloalkyl, heterocycle, hetrocyclyl$(C_1\text{-}C_8)$alkyl, aryl, aryl$(C_1\text{-}C_8)$alkyl, heteroaryl, heteroaryl$(C_1\text{-}C_8)$alkyl, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $-NNR^a$ and $-OPO_2R^a$, or two R^6 groups and the atom to which they are attached combined to form C=O or C=S, or wherein two R^6 groups together with the atom or atoms to which they are attached can form a carbocyclic or heterocyclic ring;

R^7 and R^8 are each independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_3$-$C_8)$cycloalkyl, aryl or aryl$(C_1$-$C_8)$alkylene, heteroaryl, heteroaryl$(C_1$-$C_8)$alkylene-; or wherein R^7 and R^8 together with the nitrogen atom to which they attach form a heterocycle or heteroaromatic ring;

R^9 and R^{10} are each independently selected from the group consisting of hydrogen, halogen, $-NH_2$, -OH, -SH, $-NHCH_3$, $–N(CH_3)_2$, -OMe, –SMe, $(C_1$-$C_8)$alkyl, aryl and aryl$(C_1$-$C_8)$alkyl, wherein R^9 and R^{10} are optionally substituted with 1 to 4 substituents of R^a, wherein the alkyl is optionally interrupted by 1 to 4 heteroatoms selected from –O–, -S–, –SO–, $-S(O)_2–$ or amino $(–NR^a–)$, or where R^9 and R^{10} are independently absent, with the proviso that R^a is not thio or halogen in the case where R^9 and R^{10} to which R^a is bound is halogen, $-NH_2$, -OH, -SH, $-NHCH_3$, $-N(CH_3)_2$, -OMe and –SMe;

L is a linker selected from the group consisting of -NH–, –N=N–, –NH–N=, –O–, –S–, $-SO_2–$ and pyrazolyl;

Y is $-CR^3R^4R^5$ or NR^4R^5;

Z is selected from the group consisting of hydrogen, halogen, $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$cycloalkyl, $(C_6$-$C_{12})$bicycloalkyl, $(C_6$-$C_{20})$polycyclyl, heterocyclyl, cycloalkyl$(C_1$-$C_8)$alkyl, bicycloalkyl$(C_6$-$C_{12})$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, aryl, aryl$(C_5$-$C_{14})$, aryl$(C_1$-$C_8)$alkyl, heteroaryl, heteroaryl$(C_1$-$C_8)$alkyl, $–NR^aR^b$, $-OR^a$, $-SR^a$, cyano, nitro, trifluoromethyl, trifluoromethoxy, $-CO_2R^a$, $R^aC(=O)O$-, $R^aC(=O)$-, $-OCO_2R^a$, $R^aR^bNC(=O)O$-, $R^bOC(=O)NR^a$-, $R^aR^bNC(=O)$-, $R^aC(=O)NR^b$-, $R^aR^bNC(=O)NR^b$-, $R^aR^bNC(=S)NR^b$-, $-OPO_3R^a$, $R^aOC(=S)$-, $R^aC(=S)$-, $-SSR^a$, $R^aS(=O)$-, $-NNR^a$, $-OPO_2R^a$, $–OS(O_2)R^a$, $-OS(=O)OR^a$, $-OS(O_2)OR^a$ and $-O(SO_2)NR^aR^b$;

R^a and R^b are each independently selected from the group consisting of hydrogen, halogen, $-NH_2$, -OH, -SH, $-NHCH_3$, $-N(CH_3)_2$, -OMe, -SMe, propargyl, cyano, -NNH, $-NNCH_3$, $-OPO_2H$, $-OPO_2CH_3$, $–OS(O_2)H$, $-OS(O_2)OH$, $-OS(O_2)CH_3$, $-OS(O_2)OCH_3$, $(C_1$-$C_8)$alkyl, aryl, aryl$(C_1$-$C_8)$alkyl, $(C_3$-$C_8)$cycloalkyl, $(C_6$-$C_{12})$bicycloalkyl, cycloalkyl$(C_1$-$C_8)$alkyl, bicycloalkyl$(C_6$-$C_{12})$alkyl, heteroaryl and heteroaryl$(C_1$-$C_8)$alkyl, wherein the alkyl and cycloalkyl are optionally interrupted with 1 to 4 heteroatoms selected from the group consisting of –O–, –S–, -SO–, $-S(O)_2–$ and amino $(–NR^c–)$; and wherein the alkyl, cycloalkyl, aryl and heteroaryl are optionally substituted with 1, 2, 3 or 4 substituents selected from the group consisting of $-OR^c$, $-NR^cR^c$, SR^c, cyano, -NNH, $-NNCH_3$, $-OPO_2H$, $-OPO_2CH_3$, $-OS(O_2)H$,

-$OS(O_2)OH$, -$OS(O_2)CH_3$ and -$OS(O_2)OCH_3$, provided that R^a is not a heteroatom when it is attached to another heteroatom;

R^c is selected from the group consisting of hydrogen and (C_1-C_8)alkyl; and

m is 0 to 8; n is 0, 1, 2 or 3, provided that when m is 0, Z is not halogen, cyano, nitro or a heteroatom; or

a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof.

4. The compound of Claim 1, wherein $(CR^1R^2)_m$ together is selected from the group consisting of methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene, octylene, *iso*-propylene, *iso*-butylene, *sec*-butylene and *tert*-butylene.

5. The compound of Claim 1, wherein $(CR^1R^2)_m$ together is selected from the group consisting of methylene, ethylene, propylene and *iso*-propylene.

6. The compound of Claim 1, wherein $(CR^1R^2)_m$-Z together is selected from the group consisting of $–CH_2CH=CH_2$-, $–CH_2C\equiv CH$, $–CH_2C\equiv CCH_3$ or $–CH_2CH_2C\equiv CH$.

7. The compound of Claim 1, wherein $(CR^1R^2)_m$-Z together is $–CH_2C\equiv CH$.

8. The compound of Claim 1, wherein R_1 and R_2 are hydrogen or are absent, m is 2 to 8 and the group $(CR^1R^2)_m$ optionally comprises 1 to 4 alkenyl or alkynyl conjugated or unconjugated groups.

9. The compound of Claim 1, wherein m is 1 to 8 and Z is selected from the group consisting of -NH_2, –OH, –SH, -NR^aR^b, $–OR^a$,-SR^a and cyano.

10. The compound of Claim 1, wherein $(CR^1R^2)_m$-Z together is selected from the group consisting of methanol, ethanol, propanol, butanol, pentanol, hexanol, *iso*-propanol, *iso*-butanol, *sec*-butanol and *tert*-butanol.

11. The compound of Claim 1, wherein $(CR^1R^2)_m$-Z together is selected from the group consisting of methanol, ethanol, propanol and $-CH_2CN$.

12. The compound of Claim 1, wherein R^1 and R^2 are hydrogen, and the group $(CR^1R^2)_m$ is linear or branched, m is 1 to 6, and Z is selected from the group consisting of methoxy, ethoxy, propoxy, butoxy, pentoxy and hexyloxy.

13. The compound of Claim 12, wherein Z is selected from the group consisting of methoxy, ethoxy and propoxy.

14. The compound of Claim 1, wherein Z is a mono-, bicyclic-, tricyclic- or aromatic or non-aromatic $(C_3$-$C_{20})$cycloalkyl ring, wherein the ring atoms are optionally interrupted by 1 to 8 heteroatoms selected from the group consisting of –O–, –S–, –SO–, $–S(O)_2–$ and amino $(–NR^a–)$.

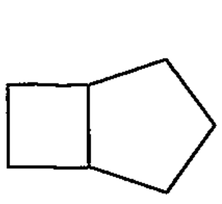
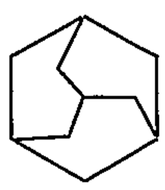
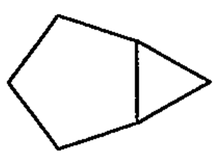
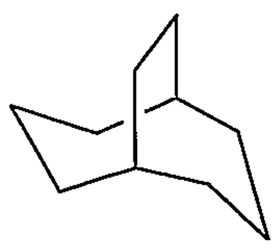
15. The compound of Claim 1, wherein Z is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl ring optionally substituted with 1 to 4 substituents of R^a.

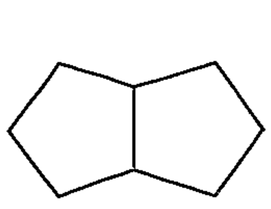
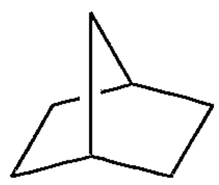
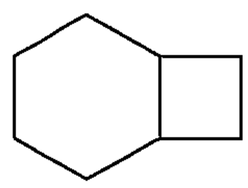
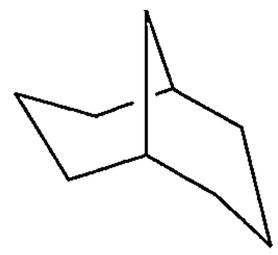
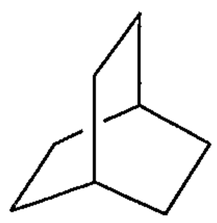
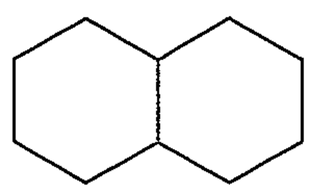
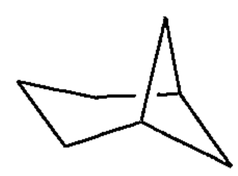
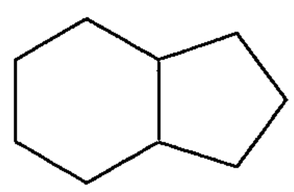
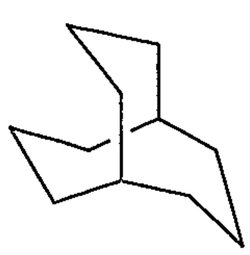
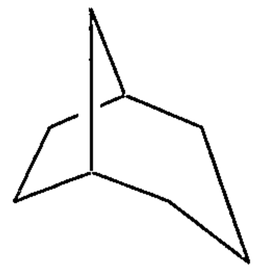
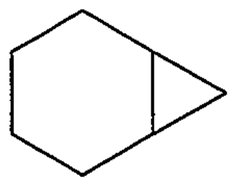
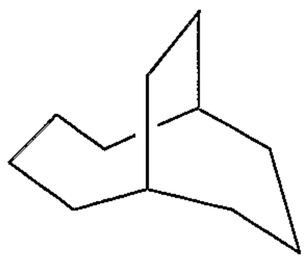
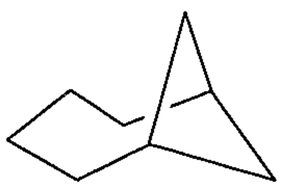
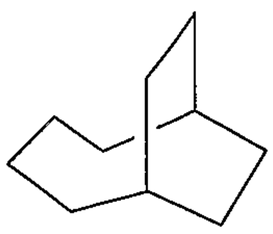
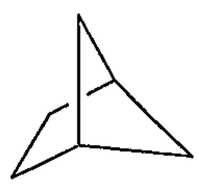
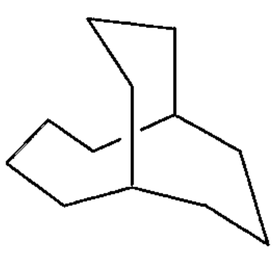
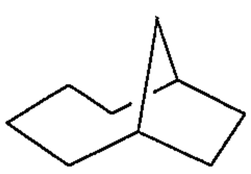
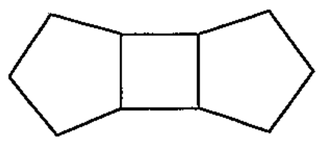
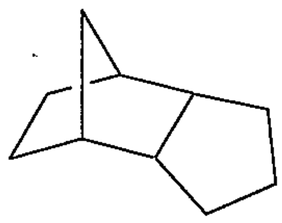
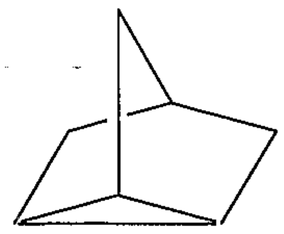
16. The compound of Claim 1, wherein Z is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, where m is 0 or 1.

17. The compound of Claim 1, wherein Z is cyclopentyl and where m is 0.

18. The compound of Claim 1, wherein Z is cyclobutyl, m is 1 and R^1 and R^2 are hydrogen.

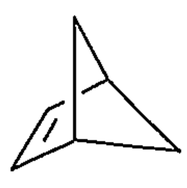
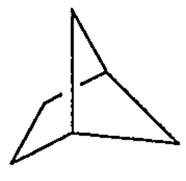
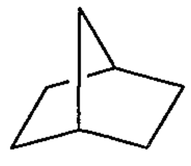
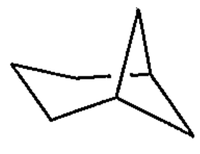
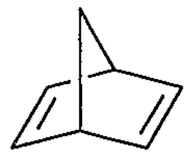
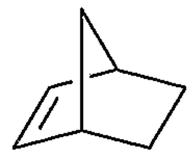
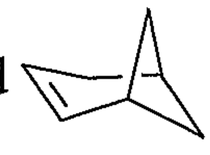
19. The compound of Claim 1, wherein Y and Z are each independently selected from the group consisting of hydrogen,


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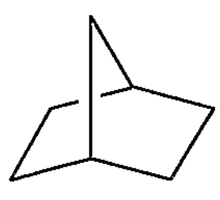
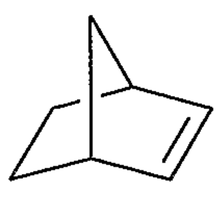
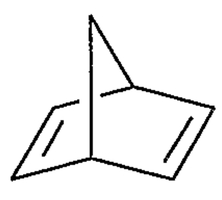
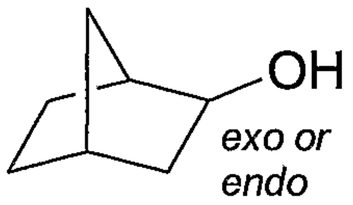
wherein each Y or Z group is optionally comprises 1, 2 or 3 double bonds; each carbon in the ring is optionally replaced by or interrupted by 1 to 6 heteroatoms selected from –O–, –S–, –SO–, -$S(O)_2$–, or amino (–NR^a–), and is optionally further substituted with from 1 to 10 R^6 groups, provided that the Y or Z ring is not attached at a bridgehead carbon atom or at a trisubstituted carbon atom.

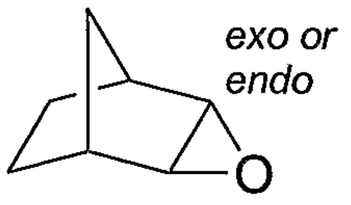
20. The compound of Claim 1, wherein each Y or Z is independently hydrogen or a bicyclic ring selected from the group consisting of







and


wherein any two adjacent carbon ring atom is optionally interrupted with 1 to 6 heteroatoms selected from –O–, –S–, -SO–, –$S(O)_2$– or amino (–NR^a–), and the ring is optionally substituted with from 1 to 7 R^a groups selected from the group consisting of methyl, ethyl, propyl, *iso*-propyl, -NH_2, -OH, -SH, -$NHCH_3$, -$N(CH_3)_2$, -OMe, -SMe, propargyl, cyano, -NNH, -$NNCH_3$, -OPO_2H, –OPO_2CH_3, –$OS(O_2)H$, –$OS(O_2)OH$, -$OS(O_2)CH_3$ and –$OS(O_2)OCH_3$, and m and n are each independently 0 or 1.

21. The compound of Claim 1, wherein each Y or Z is independently selected from the group consisting of hydrogen,

and


wherein m and n are each independently 0 or 1, and R^1, R^2, R^9 and R^{10} are each independently absent or selected from the group consisting of hydrogen, -NH_2, -OH, -SH, -$NHCH_3$, –$N(CH_3)_2$ -OMe and –SMe, and each Z group is optionally substituted with from 1 to 7 R^a groups selected from the group consisting of methyl, ethyl, propyl, *iso*-propyl, halo, –NH_2, –OH, -SH, –$NHCH_3$, –$N(CH_3)_2$, -OMe, -SMe, propargyl, cyano, -NNH, -$NNCH_3$, -OPO_2H, -OPO_2CH_3, -$S(SO_2)H$, –$S(SO_2)OH$, -$S(SO_2)CH_3$ and -$S(SO_2)OCH_3$.

22. The compound of Claim 1, wherein R^1 and R^2 are hydrogen, m is 0, 1, 2 or 3 and Z is selected from the group consisting of furan, dihydro-furan, tetrahydrofuran, thiophene, pyrrole, 2*H*-pyrrole, 2-pyrroline, 3-pyrroline, pyrrolidine, 1,3-dioxolane, oxazole, thiazole, imidazole, dihydro-imidazole, 2-imidazoline, imidazolidine, pyrazole, 2-pyrazoline, pyrazolidine, isoxazole, isothiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,3,4-thiadiazole, 2*H*-pyran, 1*H*-tetrazole, 4*H*-pyran, pyridine, dihydro-pyridine, tetrahydro-pyridine, piperidine, 1,4-dioxane, morpholine, 1,4-dithiane, thiomorpholine, pyridazine, pyrimidine, dihydro-pyrimidine, tetrahydro-pyrimidine, hexahydro-pyrimidine, pyrazine, dihydro-pyrazine, tetrahydro-pyrazine, piperazine, 1,3,5-triazine and 1,3,5-trithiane, wherein each Z group is optionally substituted with from 1 to 10 R^a groups.

23. The compound of Claim 1, wherein R^1 and R^2 are hydrogen, m is 0 or 1, and Z is selected from the group consisting of furan, thiophene, pyrrole, 2*H*-pyrrole, oxazole, thiazole,

imidazole, pyrazole, isoxazole, isothiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,3,4-thiadiazole and 1*H*-tetrazole, wherein each Z group is optionally substituted with from 1 to 3 R^a groups selected from the group consisting of methyl, ethyl, propyl, *iso*-propyl, $-NH_2$, –OH, –SH, $-NHCH_3$, $-N(CH_3)_2$, $-OCH_3$ and $-SCH_3$.

24. The compound of Claim 1, wherein Z is selected from the group consisting of $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)NR^a-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)NR^b-$, $R^aR^bNC(=O)NR^b-$, $R^aR^bNC(=S)NR^b-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $R^aS(O_2)-$, $-N=NR^a$, $-OPO_2R^a$, $–OS(O_2)R^a$, $–OS(=O)OR^a$, $–OS(O_2)OR^a$ and $-OS(O_2)NR^aR^b$, wherein m is 1 to 8, and the group $(CR^1R^2)_m$ is optionally saturated or partially unsaturated.

25. The compound of Claim 1, wherein Z is selected from the group consisting of $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)NR^a-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)NR^b-$, $R^aR^bNC(=O)NR^b-$, $R^aR^bNC(=S)NR^b-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $R^aS(=O)_2-$, $-N=NR^a$, $-OPO_2R^a$, $-OS(O_2)R^a$, $–OS(=O)OR^a$, $–OS(O_2)OR^a$ and $–O(SO_2)NR^aR^b$, and wherein $(R^1R^2)_m$ together is selected from the group consisitng of $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$, $-CH=CHCH_2-$, $-CH_2CH=CH-$, $-CH=CHCH_2CH_2-$, $-CH_2CH=CHCH_2-$, $-CH_2CH_2CH=CH-$, $-C\equiv CCH_2-$, $-CH_2C\equiv C-$, $-C\equiv CCH_2CH_2-$, $-CH_2C\equiv CCH_2-$ and $-CH_2CH_2C\equiv C-$.

26. The compound of Claim 1, wherein Z is independently $-CO_2R^a$, $R^aC(=O)-$, R^aR^bN-, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $R^aS(=O)-$, $R^aS(=O)_2-$, $-OPO_2R^a$, $–OS(O_2)R^a$, $-OS(=O)OR^a$, $–OS(O_2)OR^a$, or $-OS(O_2)NR^aR^b$, and wherein $(CR^1R^2)_m$ together is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$, $-CH=CHCH_2-$, $-CH_2CH=CH-$, $-CH=CHCH_2CH_2-$, $-CH_2CH=CHCH_2-$, $-CH_2CH_2CH=CH-$, $-C\equiv CCH_2-$, $-CH_2C\equiv C-$, $-C\equiv CCH_2CH_2-$, $-CH_2C\equiv CCH_2-$ and $-CH_2CH_2C\equiv C-$.

27. The compound of Claim 1, wherein each R^9 is independently selected from the group consisting of hydrogen, halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl,

trifluoromethoxy, (C_3-C_8)cycloalkyl, heterocyclyl, hetrocyclyl(C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, $-CO_2R^a$, $R^aC(=O)O$-, $R^aC(=O)$-, $-OCO_2R^a$, $R^aR^bNC(=O)O$-, $R^bOC(=O)N(R^a)$-, R^aR^bN-, $R^aR^bNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^aR^bNC(=O)N(R^b)$-, $R^aR^bNC(=S)N(R^b)$-, $-OPO_3R^a$, $R^aOC(=S)$-, $R^aC(=S)$-, $-SSR^a$, $R^aS(=O)$-, $R^aS(=O)_2$-, $-N=NR^a$ and $-OPO_2R^a$.

28. The compound of Claim 1, wherein R^1 and R^2 or R^9 and R^{10} together with the carbon atom to which they are attached is C=O, C=S or $C=NR^c$.

29. The compound of Claim 1, wherein R^3 is selected from the group consisting of hydrogen, halo, $-OR^a$, $-SR^a$, cyano, nitro, trifluoromethyl, trifluoromethoxy, $-CO_2R^a$, $R^aC(=O)O$-, $R^aC(=O)$-, $-OCO_2R^a$, $R^aR^bNC(=O)O$-, $R^bOC(=O)N(R^a)$-, R^aR^bN-, $R^aR^bNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^aR^bNC(=O)N(R^b)$-, $R^aR^bNC(=S)N(R^b)$-, $-OPO_3R^a$, $R^aOC(=S)$-, $R^aC(=S)$-, $-SSR^a$, $R^aS(=O)$-, $R^aS(=O)_2$-, $-NNR^a$ and $-OPO_2R^a$; or if the ring formed from the group $CR^3R^4R^5$ is aryl or heteroaryl or partially unsaturated then R^3 can be absent.

30. The compound of Claim 1, wherein R^3 is selected from the group consisting of hydrogen, OH, OMe, OAc, NH_2, NHMe, NMe_2 and NHAc.

31. The compound of Claim 30, wherein R^3 is hydrogen or OH.

32. The compound of Claim 1, wherein R^4 and R^5 together with the atom to which they are attached form a saturated or partially unsaturated, mono-, bi- or tricyclic ring, or aromatic ring having 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 ring atoms, wherein the ring atoms are optionally interrupted by 1, 2, 3 or 4 heteroatoms selected from the group consisting of -O-, -S-, -SO-, $-S(O)_2$- or amine ($-NR^a$-) in the ring, wherein any ring comprising R^4 and R^5 is optionally further substituted with from 1 to 14 R^6 groups; wherein each R^6 is independently selected from the group consisting of halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_1-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, heterocycle, hetrocyclyl(C_1-C_8)alkyl, aryl, aryl(C_1-C_8)alkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl, $-CO_2R^a$, $R^aC(=O)O$-, $R^aC(=O)$-, $-OCO_2R^a$, $R^aR^bNC(=O)O$-,

$R^bOC(=O)N(R^a)$-, R^aR^bN-, $R^aR^bNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^aR^bNC(=O)N(R^b)$-, $R^aR^bNC(=S)N(R^b)$-, $-OPO_3R^a$, $R^aOC(=S)$-, $R^aC(=S)$-, $-SSR^a$, $R^aS(=O)$-, $-NNR^a$,$-OPO_2R^a$, or two R^6 groups and the atom to which they are attached combined to form C=O or C=S, or wherein two R^6 groups together with the atom or atoms to which they are attached can form a carbocyclic or heterocyclic ring.

33. The compound of Claim 32, wherein the ring comprising R^4 and R^5 and the atom to which they are attached is selected from the group consisting of cyclopentane, cyclohexane, piperidine, dihydro-pyridine, tetrahydro-pyridine, pyridine, piperazine, decaline, tetrahydro-pyrazine, dihydro-pyrazine, pyrazine, dihydro-pyrimidine, tetrahydro-pyrimidine, hexahydro-pyrimidine, pyrazine, imidazole, dihydro-imidazole, imidazolidine, pyrazole, dihydro-pyrazole, pyrazolidine, norbornane and adamantane, each unsubstituted or substituted.

34. The compound of Claim 33, wherein the ring comprising R^4 and R^5 and the atom to which they are attached is selected from the group consisting of cyclohexane, piperidine, piperazine, norbornane, adamantane, each unsubstituted or substituted.

35. The compound of Claim 1, wherein R^6 is selected from the group consisting of substituted or unsubstituted $(C_1$-$C_8)$alkyl, $-OR^a$, $-CO_2R^a$, $R^aC(=O)$-, $R^aC(=O)O$-, R^aR^bN-, $R^aR^bNC(=O)$- and aryl, provided that when the ring comprising R^4 and R^5 contains a ring heteroatom that is O or S, the ring heteroatom that is O or S is not substituted with R^6.

36. The compound of Claim 1, wherein R^6 is selected from the group consisting of OH, OMe, methyl, ethyl, t-butyl, $-CO_2R^a$, $-CONR^aR^b$, OAc, NH_2, NHMe, NMe_2, NHEt and $N(Et)_2$, provided that when the ring comprising R^4 and R^5 contains a ring heteroatom that is O or S, the ring heteroatom that is O or S is not substituted with R^6.

37. The compound of Claim 36, wherein R^6 is selected from the group consisting of methyl, ethyl, $-CO_2R^a$, $-CONR^aR^b$ and OAc, provided that when the ring comprising R^4 and R^5 contains a heteroatom, the heteroatom is not substituted with OAc.

38. The compound of Claim 36, wherein R^6 is selected from the group consisting of $-(CH_2)_{1-2}OR^a$, $-(CH_2)_{1-2}C(=O)OR^a$, $-(CH_2)_{1-2}OC(=O)R^a$, $-(CH_2)_{1-2}C(=O)R^a$, $-(CH_2)_{1-2}OCO_2R^a$, $-(CH_2)_{1-2}NHR^a$, $-(CH_2)_{1-2}NR^aR^b$, $-(CH_2)_{1-2}OC(=O)NHR^a$ and $-(CH_2)_{1-2}OC(=O)NR^aR^b$.

39. The compound of Claim 38, wherein R^6 is $-CH_2C(=O)OR^a$, $-CH_2OC(=O)OR^a$, $-CH_2OH$, $-CH_2OAc$, $-CH_2NH(CH_3)$ and $-(CH_2)_{1-2}N(CH_3)_2$.

40. The compound of Claim 1, wherein number of R^6 groups substituted on the R^4R^5 ring is from 1 to 4.

41. The compound of Claim 1, wherein R^7 and R^8 is selected from the group consisting of hydrogen, (C_1-C_8)alkyl–, aryl, aryl(C_1-C_8)alkylene–, mono-, bicyclic- or aromatic or nonaromatic ring having 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms, wherein the ring atoms are optionally interrupted by 1, 2, 3 or 4 heteroatoms selected from the group consisting of -O-, -S-, -SO-, $-S(O)_2-$ or amine ($-NR^a-$) in the ring, and each is optionally substituted with from 1, 2, 3 or 4 R^a groups.

42. The compound of Claim 41, wherein R^7 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, 3-pentyl, *iso*-propyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, phenyl and benzyl.

43. The compound of Claim 42, wherein R^7 is hydrogen, methyl, 3-pentyl or *sec*-butyl.

44. The compound of Claim 1, wherein R^7 and R^8 are each independently selected from the group consisting of hydrogen, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, aryl, aryl(C_1-C_8)alkylene, heteroaryl and heteroaryl(C_1-C_8)alkylene-; or wherein R^7 and R^8 together with the nitrogen atom to which they attach form a heterocycle or heteroaromatic ring.

45. The compound of Claim 44, wherein $-NR^7R^8$ is selected from the group consisting of amino, methylamino, dimethylamino, ethylamino, 3-pentylamino, n-(diphenylethyl)-amino, n-(pyridylmethyl)-amino, diethylamino and benzylamino.

46. The compound of Claim 45, wherein -NR^7R^8 is selected from the group consisting of amino, methylamino, dimethylamino, ethylamino, diethylamino, 3-pentylamino and benzylamino.

47. The compound of Claim 46, wherein -NR^7R^8 is amino.

48. The compound of Claim 1, wherein R^7 is selected from the group consisting of benzyl, phenethyl, phenylpropyl and each is optionally substituted with from 1, 2 or 3 substituents of R^a.

49. The compound of Claim 1, wherein R^7 is selected from the group consisting of benzyl, phenethyl, phenylpropyl and each is optionally substituted with from 1, 2 or 3 substituents of R^a selected from the group consisting of methyl, ethyl, propyl, methoxy, ethoxy and propoxy.

50. The compound of Claim 1, wherein R^7 is benzyl and R^a is methoxy.

51. The compound of Claim 1, wherein R^9 is selected from the group consisting of hydrogen, fluoro, -OH, -CH_2OH, -OMe, -OAc, -NH_2, -NHMe, -NMe_2 and –NHAc.

52. The compound of Claim 52, wherein R^9 is hydrogen or OH.

53. The compound of Claim 1, wherein each R^{10} is independently selected from the group consisting of hydrogen, fluoro, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, heterocyclyl, heterocycle$(C_1\text{-}C_8)$alkylene-, aryl, aryl$(C_1\text{-}C_8)$alkylene-, heteroaryl and heteroaryl$(C_1\text{-}C_8)$alkylene-.

54. The compound of Claim 54, wherein R^{10} is selected from the group consisting of hydrogen, $(C_1\text{-}C_8)$alkyl, cyclopropyl, cyclohexyl and benzyl.

55. The compound of Claim 55, wherein R^{10} is hydrogen.

56. The compound of Claim 1, wherein R^9 and R^{10} and the carbon atom to which they are attached is a C=O group.

57. The compound of Claim 1, wherein:

R^a and R^b are each independently selected from the group consisting of hydrogen, $(C_1\text{-}C_8)$alkyl and $(C_1\text{-}C_8)$alkyl substituted with 1 to 3 $(C_1\text{-}C_8)$alkoxy, $(C_3\text{-}C_8)$cycloalkyl, $(C_1\text{-}C_8)$alkylthio, aryl, aryl$(C_1\text{-}C_8)$alkylene, heteroaryl, or heteroaryl$(C_1\text{-}C_8)$alkylene; or R^a and R^b together with the nitrogen to which they are attached, form a pyrrolidino, piperidino, morpholino, or thiomorpholino ring; R^c is hydrogen or $(C_1\text{-}C_6)$alkyl; m is 0 to about 8 and p is 0 to 2; and Y is $-CR^3R^4R^5$ or NR^4R^5.

58. The compound of Claim 1, wherein R^a and R^b are each independently selected from the group consisting of hydrogen, $(C_1\text{-}C_4)$alkyl, aryl and aryl$(C_1\text{-}C_8)$alkylene.

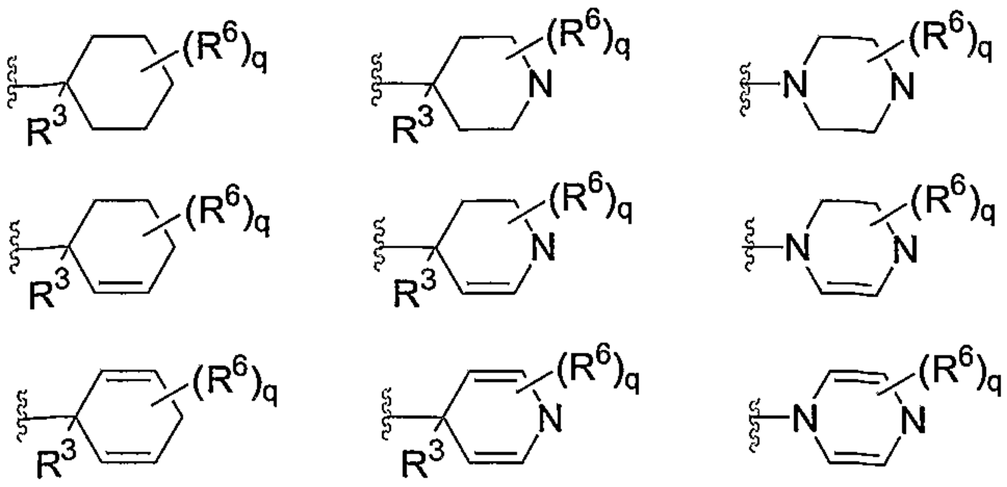
59. The compound of Claim 58, wherein R^a and R^b are each independently selected from the group consisting of hydrogen, methyl, ethyl, phenyl and benzyl.

60. The compound of Claim 58, wherein R^a is $(C_1\text{-}C_8)$alkyl.

61. The compound of Claim 60, wherein R^a is selected from the group consisting of methyl, ethyl, propyl and butyl.

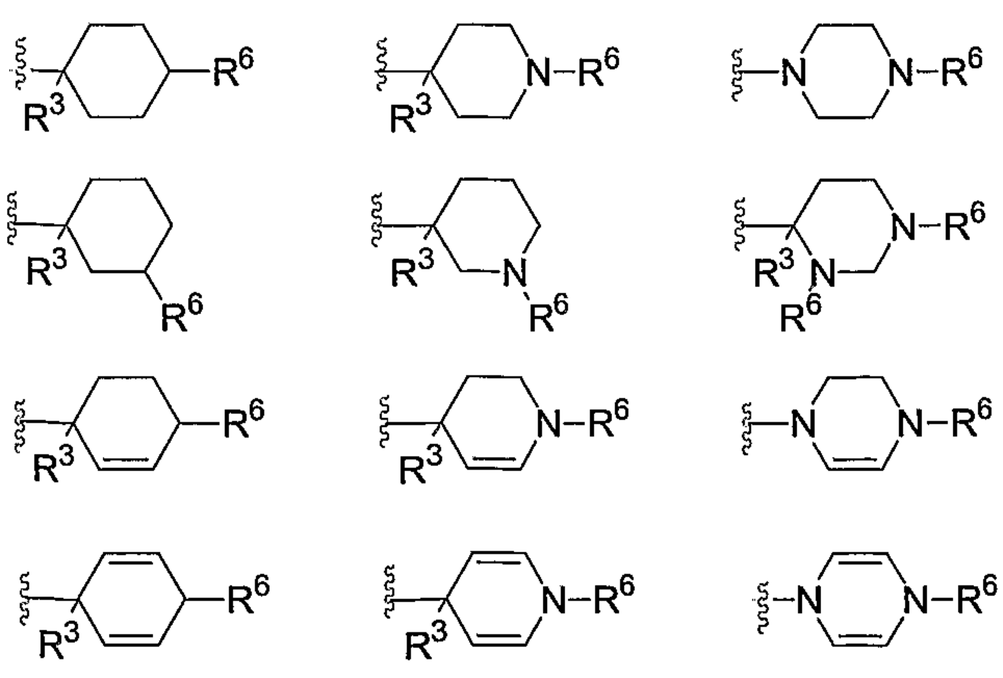
62. The compound of Claim 61, wherein R^a and R^b is a ring.

63. The compound of Claim 1, wherein Y is $-CR^3R^4R^5$ or NR^4R^5, and is selected from the group consisting of:



wherein q is 0, 1, 2, 3 or 4; R^3 is selected from the group consisting of hydrogen, halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_3-C_8)cycloalkyl, heterocycle, hetrocycle(C_1-C_8)alkyl, aryl, aryl(C_1-C_8)alkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $R^aS(=O)_2-$, $-NNR^a$ and $-OPO_2R^a$; and each R^6 is independently selected from the group consisting of halo, $-OR^a$, $-SR^a$, substituted or unsubstituted (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_1-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, heterocycle, hetrocyclyl(C_1-C_8)alkyl, aryl, aryl(C_1-C_8)alkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $-NNR^a$ and $-OPO_2R^a$, provided that R^6 is not halogen or a heteroatom when R^6 is attached to a heteroatom.

64. The compound of Claim 1, wherein Y is $-CR^3R^4R^5$ or NR^4R^5 and is selected from the group consisting of:



wherein R^3 is selected from the group consisting of hydrogen, halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_3-C_8)cycloalkyl, heterocycle,

hetrocycle(C_1-C_8)alkyl, aryl, aryl(C_1-C_8)alkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl, -CO_2R^a, $R^aC(=O)O$-, $R^aC(=O)$-, -OCO_2R^a, $R^aR^bNC(=O)O$-, $R^bOC(=O)N(R^a)$-, R^aR^bN-, $R^aR^bNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^aR^bNC(=O)N(R^b)$-, $R^aR^bNC(=S)N(R^b)$-, -OPO_3R^a, $R^aOC(=S)$-, $R^aC(=S)$-, -SSR^a, $R^aS(=O)$-, $R^aS(=O)_2$-, -NNR^a and -OPO_2R^a; and each R^6 is independently selected from the group consisting of halo, -OR^a, -SR^a, substituted or unsubstituted (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_1-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, heterocycle, hetrocyclyl(C_1-C_8)alkyl, aryl, aryl(C_1-C_8)alkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl, -CO_2R^a, $R^aC(=O)O$-, $R^aC(=O)$-, -OCO_2R^a, $R^aR^bNC(=O)O$-, $R^bOC(=O)N(R^a)$-, R^aR^bN-, $R^aR^bNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^aR^bNC(=O)N(R^b)$-, $R^aR^bNC(=S)N(R^b)$-, -OPO_3R^a, $R^aOC(=S)$-, $R^aC(=S)$-, -SSR^a, $R^aS(=O)$-, -NNR^a and -OPO_2R^a.

65. The compound of Claim 1, wherein the ring comprising –$C(R^3)R^4R^5$ is 2-methylcyclohexan-1-yl, 2,2-dimethylcyclohexan-1-yl, 2-ethylcyclohexan-1-yl, 2,2-diethylcyclohexan-1-yl, 2-tert-butylcyclohexan-1-yl, 2-phenylcyclohexan-1-yl, 3-methylcyclohexan-1-yl, 3-ethylcyclohexan-1-yl, 3,3-dimethylcyclohexan-1-yl, 4-methylcyclohexan-1-yl, 4-ethylcyclohexan-1-yl, 4,4-dimethylcyclohexan-1-yl, 4-tert-butylcyclohexan-1-yl, 4-phenylcyclohexan-1-yl, 3,3,5,5-tetramethylcyclohexan-1-yl, 2,4-dimethylcyclopentan-1-yl, 4-(carboxyl)cyclohexan-1-yl, 4-(carboxymethyl)cyclohexan-1-yl and 4-(carboxyethyl)cyclohexan-1-yl.

66. The compound of Claim 1, wherein the ring comprises -$C(R^3)R^4R^5$ is piperidin-4-yl, 1-carboxypiperiden-4-yl, 1-(methoxycarbonyl)piperidin-4-yl, 1-(ethoxycarbonyl)piperidin-4-yl, 1-(n-propoxycarbonyl)piperidin-4-yl, 1-(2,2-dimethylpropoxycarbonyl)piperidin-4-yl, piperidin-1-yl, 4-carboxypiperiden-1-yl, 4-(methoxycarbonyl)piperidine-1-yl, 4-(ethoxycarbonyl)piperidine-1-yl, 4-(n-propoxy)piperidine-1-yl, 4-(2,2-dimethylpropoxycarbonyl)piperidine-1-yl, piperidin-3-yl, 1-carboxypiperidene-3-yl, 1-(methoxycarbonyl)piperidine-3-yl, 1-(ethoxycarbonyl)piperidine-3-yl, 1-(n-propoxycarbonyl)piperidine-3-yl, 1-(2,2-dimethylpropoxycarbonyl)piperidine-3-yl, 3-carboxypiperidene-1-yl, 3-(methoxycarbonyl)piperidine-1-yl, 3-(ethoxycarbonyl)piperidine-1-yl, 3-(n-propoxycarbonyl)piperidine-1-yl, 3-(2,2-dimethylpropoxycarbonyl)piperidine-1-yl, piperazin-1-yl, 1-caboxypiperazin-4-yl,

1-(methoxycarbonyl)piperazin-4-yl, 1-(ethoxycarbonyl)piperazin-4-yl and 1-(n-propoxycarbonyl)piperazin-4-yl.

67. The compound of Claim 1, wherein the ring comprising $-C(R^3)R^4R^5$ is selected from the group consisting of 2-methylcyclohexan-1-yl, 2,2-dimethylcyclohexan-1-yl, 2-ethylcyclohexan-1-yl, 2,2-diethylcyclohexan-1-yl, 2-tert-butylcyclohexan-1-yl, 2-phenylcyclohexan-1-yl, 3-methylcyclohexan-1-yl, 3-ethylcyclohexan-1-yl, 3,3-dimethylcyclohexan-1-yl, 4-methylcyclohexan-1-yl, 4-ethylcyclohexan-1-yl, 4,4-dimethylcyclohexan-1-yl, 4-tert-butylcyclohexan-1-yl, 4-phenylcyclohexan-1-yl, 3,3,5,5-tetramethylcyclohexan-1-yl, 2,4-dimethylcyclopentan-1-yl, 4-(carboxyl)cyclohexan-1-yl, 4-(carboxymethyl)cyclohexan-1-yl, 4-(carboxyethyl)cyclohexan-1-yl, piperidin-4-yl, 1-(methoxycarbonyl)piperidin-4-yl, 1-(2,2-dimethylpropoxycarbonyl)piperidin-4-yl, piperidin-1-yl, 4-(methoxycarbonyl)piperidine-1-yl, 4-(2,2-dimethylpropoxycarbonyl)piperidine-1-yl, piperidin-3-yl, 1-(methoxycarbonyl)piperidine-3-yl, 1-(2,2-dimethylpropoxycarbonyl)piperidine-3-yl, 3-(methoxycarbonyl)piperidine-1-yl and 3-(2,2-dimethylpropoxycarbonyl)piperidine-1-yl.

68. The compound of Claim 2, wherein Z is a mono-, bicyclic-, tricyclic- or aromatic or non-aromatic (C_3-C_{20})cycloalkyl ring, wherein the ring atoms are optionally interrupted by 1-8 heteroatoms selected from the group consisting of –O–, –S–, –SO–, $–S(O)_2–$ and amino ($–NR^a–$).

69. The compound of Claim 2, wherein R^1 and R^2 are hydrogen, m is 0, 1, 2 or 3 and Z is selected from the group consisting of furan, dihydro-furan, tetrahydrofuran, thiophene, pyrrole, 2*H*-pyrrole, 2-pyrroline, 3-pyrroline, pyrrolidine, 1,3-dioxolane, oxazole, thiazole, imidazole, dihydro-imidazole, 2-imidazoline, imidazolidine, pyrazole, 2-pyrazoline, pyrazolidine, isoxazole, isothiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,3,4-thiadiazole, 2*H*-pyran, 1*H*-tetrazole, 4*H*-pyran, pyridine, dihydro-pyridine, tetrahydro-pyridine, piperidine, 1,4-dioxane, morpholine, 1,4-dithiane, thiomorpholine, pyridazine, pyrimidine, dihydro-pyrimidine, tetrahydro-pyrimidine, hexahydro-pyrimidine, pyrazine, dihydro-pyrazine, tetrahydro-pyrazine, piperazine, 1,3,5-triazine and 1,3,5-trithiane, wherein each Z group is optionally substituted with from 1 to 10 R^a groups.

70. The compound of Claim 3, wherein Z is a mono-, bicyclic-, tricyclic- or aromatic or non-aromatic (C_3-C_{20})cycloalkyl ring, wherein the ring atoms are optionally interrupted by 1-8 heteroatoms selected from the group consisting of –O–, –S–, –SO–, –$S(O)_2$– and amino (–NR^a–).

71. The compound of Claim 3, wherein R^1 and R^2 are hydrogen, m is 0, 1, 2 or 3 and Z is selected from the group consisting of furan, dihydro-furan, tetrahydrofuran, thiophene, pyrrole, 2*H*-pyrrole, 2-pyrroline, 3-pyrroline, pyrrolidine, 1,3-dioxolane, oxazole, thiazole, imidazole, dihydro-imidazole, 2-imidazoline, imidazolidine, pyrazole, 2-pyrazoline, pyrazolidine, isoxazole, isothiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,3,4-thiadiazole, 2*H*-pyran, 1*H*-tetrazole, 4*H*-pyran, pyridine, dihydro-pyridine, tetrahydro-pyridine, piperidine, 1,4-dioxane, morpholine, 1,4-dithiane, thiomorpholine, pyridazine, pyrimidine, dihydro-pyrimidine, tetrahydro-pyrimidine, hexahydro-pyrimidine, pyrazine, dihydro-pyrazine, tetrahydro-pyrazine, piperazine, 1,3,5-triazine and 1,3,5-trithiane, wherein each Z group is optionally substituted with from 1 to 10 R^a groups.

72. A compound selected from the group:

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine;

9-Cyclopropylmethyl-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (1);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-propargyladenine (2);

9-Cyclopentyl-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (3);

9-Acetonitrile-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (4);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-(4-methoxybenzyl)adenine (5);

9-(3,4-Dichlorobenzyl)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (6);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-(4-trifluoromethylbenzyl)adenine (7);

9-(3,5-Dimethyl-isoxazol-4-ylmethyl)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (8);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-[2-(trifluoromethylphenyl)thiazol-4-ylmethyl]adenine (9);

2-{2-[Hydroxy-adamantan-2-yl]ethyn-1-yl}-9-(3-(thiophen-2-yl)prop-2-ynyl)adenine (10);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-methyl-N6-(3-pentyl)adenine (11);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)-9-propyladenine (12);

9-Isobutyl-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (13);

9-Cyclopropylmethyl-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (14);

9-Cyclopentyl-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (15);

9-Allyl-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (16);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)-9-(propargyl)adenine (17);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)-9-(pent-4-yne)adenine (18);

9-(2-Hydroxyethyl)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (19);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-(3-hydroxypropyl)-N6-(3-pentyl)adenine (20);

9-(2-Chloroethyl)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (21);

9-([1,3]-Dioxolan-2-ylmethyl)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (22);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)-9-(tetrahydro-pyran-2-ylmethyl)adenine (23);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)-9-(isopropylcarboxylate)adenine (24);

9-(Acetic acid ethyl ester)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (25);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-(2-oxo-oxazolidin-5-ylmethyl)-N6-(3-pentyl)adenine (26);

9-Benzyl-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (27);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)-9-(pyridin-3-ylmethyl)adenine (28);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-(4-nitrobenzyl)-N6-(3-pentyl)adenine (29);

9-(3,5-Dimethyl-isoxazol-4-ylmethyl)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-pentyl)adenine (30);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-(2-methyl-thiazol-5-ylmethyl)-N6-(3-pentyl)adenine (31);

N6-[(S)-(+)-sec-Butyl]-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-propargyl-adenine (32);

N6-[(s)-(+)-sec-Butyl]-9-(3,5-dimethyl-isoxazol-4-ylmethyl)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}adenine (33);

N6-(2-Diphenylethyl)-2-{2-[1(S)-hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-methyladenine (34);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-[(s)-(-)-alpha-napthalen-1-yl-ethyl]-9-(propargyl)adenine (35);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-(3-methoxybenzyl)-9-(propargyl)adenine (36);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-9-(propargyl)-N6-(pyridin-2-ylmethyl)adenine (37);

2-{2-[1(S)-Hydroxy-3(R)-methyl-1-cyclohexyl]ethyn-1-yl}-N6-[(methyl)(2-phenethyl)]-9- (propargyl)adenine (38);

2-{2-[Hydroxy-adamantan-2-yl]ethyn-1-yl}-9-methyladenine (39);

9-Ethyl-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (40);

2-{2-[Hydroxy-adamantan-2-yl]ethyn-1-yl}-9-propyladenine (41);

9-Hexyl-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (42);

2-{2-[Hydroxy-adamantan-2-yl]ethyn-1-yl}-9-nonyladenine (43);

2-{2-[Hydroxy-adamantan-2-yl]ethyn-1-yl}-9-isobutyl-adenine (44);

9-Cyclopropylmethyl-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (45);

9-Cyclobutylmethyl-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (46);

9-Cyclopentylmethyl-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (47);

9-Cyclohexylmethyl-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (48);

9-Cyclobutyl-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (49);

9-Cyclopentyl-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (50);

2-{2-[Hydroxy-adamantan-2-yl]ethyn-1-yl}-9-propargyl-adenine (51);

2-{2-[Hydroxy-adamantan-2-yl]ethyn-1-yl}-9-(2-hydroxyethyl)adenine (52);

2-{2-[Hydroxy-adamantan-2-yl]ethyn-1-yl}-9-(2-hydroxypropyl)adenine (53);

2-{2-[Hydroxy-norbornan-2-yl]ethyn-1-yl}-9-propargyladenine: Isomer A (60);

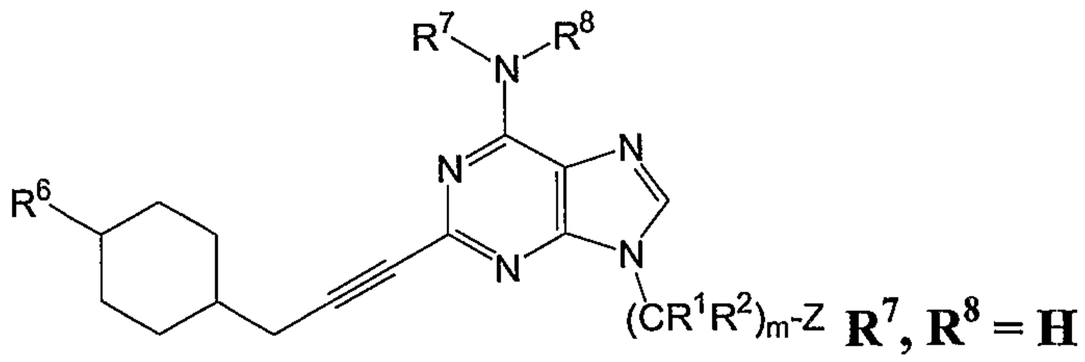
2-{2-[Hydroxy-norbornan-2-yl]ethyn-1-yl}-9-propargyladenine: Isomer B (61);

9-(But-3-ynyl)-2-{2-[hydroxy-adamantan-2-yl]ethyn-1-yl}adenine (62); and

2-{3-[1-(Methoxycarbanoyl)piperidin-4-yl]propyn-1-yl}-9-propargyladenine (63); or a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof.

73. A compound selected from the group in Tables 1 to 7, or a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof:

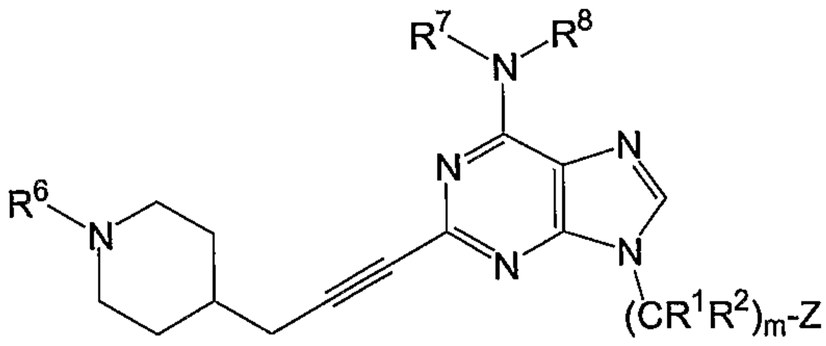
Table 1



Compound	$(CR^1R^2)_m$-Z	R^6
NC100	Propargyl	CH_2OH
NC101	*c*-Pentyl	CH_2OH
NC102	Propargyl	CO_2H
NC103	*c*-Pentyl	CO_2H
NC104	Propargyl	CO_2Me
NC105	*c*-Pentyl	CO_2Me
NC106	Propargyl	CH_2OAc

NC107	*c*-Pentyl	CH_2OAc
NC108	Propargyl	$CH_2N(CH_3)_2$
NC109	*c*-Pentyl	$CH_2N(CH_3)_2$
NC110	Propargyl	$COOCH_2CH_2NHBoc$
NC111	*c*-Pentyl	$COOCH_2CH_2NHBoc$
NC112	Propargyl	$COOCH_2CH_2NH_2$
NC113	*c*-Pentyl	$COOCH_2CH_2NH_2$
NC114	Propargyl	$CONHCH_2CH_3$
NC115	*c*-Pentyl	$CONHCH_2CH_3$
NC116	Propargyl	$CONH_2$
NC117	*c*-Pentyl	$CONH_2$
NC118	Propargyl	CONHMe
NC119	*c*-Pentyl	CONHMe
NC120	Propargyl	Me, cis CO_2Me
NC121	*c*-Pentyl	Me, cis CO_2Me
NC122	Propargyl	Me, trans CO_2Me
NC123	*c*-Pentyl	Me, trans CO_2Me
NC124	Propargyl	CH_2CH_3
NC125	*c*-Pentyl	CH_2CH_3
NC126	Propargyl	H
NC127	*c*-Pentyl	H
NC128	Propargyl	$COCH_3$
NC129	*c*-Pentyl	$COCH_3$
NC130	Propargyl	$CHCH_3(OH)$
NC131	*c*-Pentyl	$CHCH_3(OH)$

Table 2

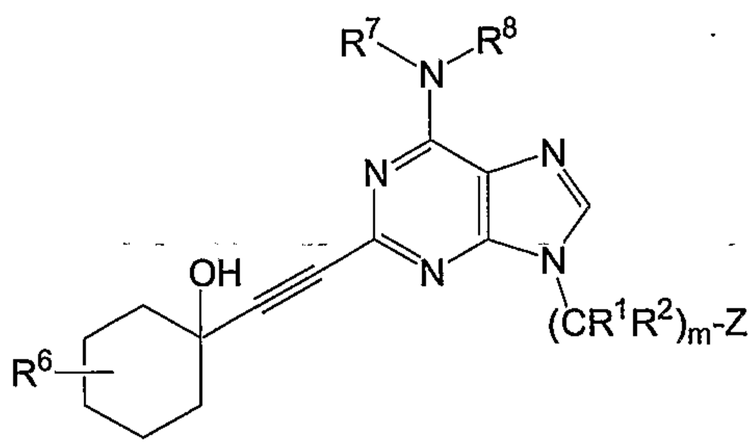


R^7, R^8 = H

Compound	**$(CR^1R^2)_m$-Z**	**R^6**
NC132	Propargyl	H
NC133	*c*-Pentyl	H
NC134	Propargyl	CO_2tBu
NC135	*c*-Pentyl	CO_2tBu
NC136	Propargyl	CO_2Et
NC137	*c*-Pentyl	CO_2Et
NC138	Propargyl	CO_2iBu
NC139	*c*-Pentyl	CO_2iBu
NC140	Propargyl	CO_2iPr
NC141	*c*-Pentyl	CO_2iPr
63	Propargyl	COMe
NC142	*c*-Pentyl	COMe
NC143	Propargyl	$COC(CH_3)_3$

NC144	*c*-Pentyl	$COC(CH_3)_3$
NC145	Propargyl	$COCH_2(CH_3)_3$
NC146	*c*-Pentyl	$COCH_2(CH_3)_3$
NC147	Propargyl	$C(O)N(CH_3)_2$
NC148	*c*-Pentyl	$C(O)N(CH_3)_2$
NC149	Propargyl	$C(O)N(CH_3)Et$
NC150	*c*-Pentyl	$C(O)N(CH_3)Et$
NC142	Propargyl	$C(O)N(CH_3)iPr$
NC143	*c*-Pentyl	$C(O)N(CH_3)iPr$
NC144	Propargyl	$C(O)N(CH_3)iBu$
NC145	*c*-Pentyl	$C(O)N(CH_3)iBu$
NC146	Propargyl	$C(O)NH(CH_3)$
NC147	*c*-Pentyl	$C(O)NH(CH_3)$
NC148	Propargyl	C(O)NH(Et)
NC149	*c*-Pentyl	C(O)NH(Et)
NC150	Propargyl	C(O)NH(iPr)
NC142	*c*-Pentyl	C(O)NH(iPr)
NC143	Propargyl	C(O)NH(iBu)
NC144	*c*-Pentyl	C(O)NH(iBu)

Table 3

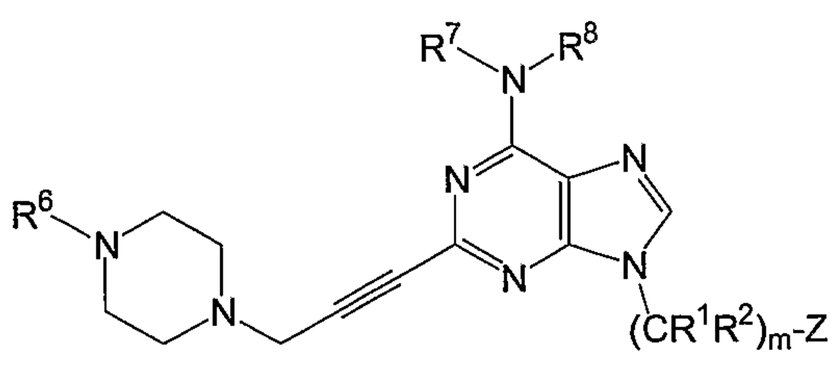


R^7, R^8 = H

Compound	**$(CR^1R^2)_m$-Z**	**R^6**
NC151	Propargyl	H
NC152	*c*-Pentyl	H
NC153	Propargyl	2-CH_3
NC154	*c*-Pentyl	2-CH_3
NC155	Propargyl	2-$C(CH_3)_3$
NC156	*c*-Pentyl	2-$C(CH_3)_3$
NC157	Propargyl	2-C_6H_5
NC158	*c*-Pentyl	2-C_6H_5
2	Propargyl	3-CH_3
3	*c*-Pentyl	3-CH_3
NC159	Propargyl	3-$(CH_3)_2$
NC160	*c*-Pentyl	3-$(CH_3)_2$
NC161	Propargyl	3-CH_2CH_3
NC162	*c*-Pentyl	3-CH_2CH_3
NC163	Propargyl	3-$(CH_3)_2$, 5-$(CH_3)_2$
NC164	*c*-Pentyl	3-$(CH_3)_2$, 5-$(CH_3)_2$
NC165	Propargyl	4-CH_3

NC166	*c*-Pentyl	4-CH_3
NC167	Propargyl	4-C_2H_5
NC168	*c*-Pentyl	4-C_2H_5
NC169	Propargyl	4-$C(CH_3)_3$
NC170	*c*-Pentyl	4-$C(CH_3)_3$
NC171	Propargyl	4-C_6H_5
NC172	*c*-Pentyl	4-C_6H_5

Table 4

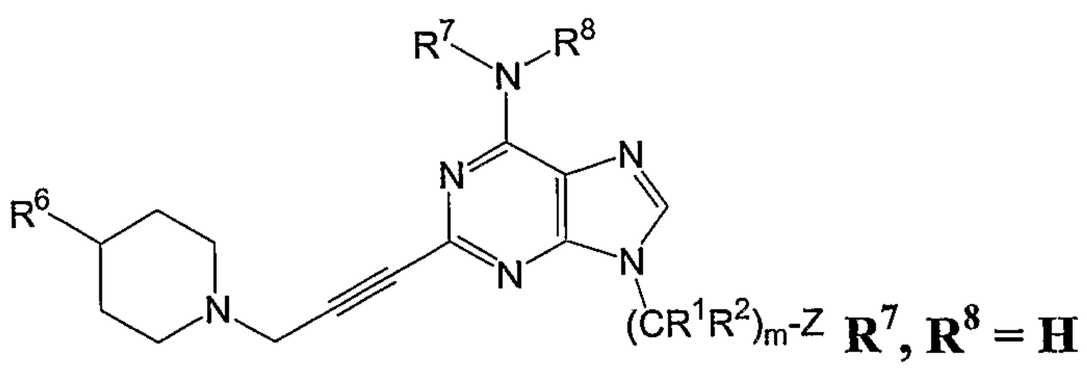


R^7, R^8 = H

Compound	**$(CR^1R^2)_m$-Z**	**R^6**
NC173	Propargyl	H
NC174	*c*-Pentyl	H
NC175	Propargyl	cyclohexyl
NC176	*c*-Pentyl	cyclohexyl
NC177	Propargyl	CO_2Et
NC178	*c*-Pentyl	CO_2Et
NC179	Propargyl	CO_2tBu
NC180	*c*-Pentyl	CO_2tBu
NC181	Propargyl	COMe
NC182	*c*-Pentyl	COMe
NC183	Propargyl	CO_2iBu
NC184	*c*-Pentyl	CO_2iBu
NC185	Propargyl	2-Pyrimidinyl
NC186	*c*-Pentyl	2-Pyrimidinyl
NC187	Propargyl	$COC(CH_3)_3$
NC188	*c*-Pentyl	$COC(CH_3)_3$
NC189	Propargyl	COMe
NC190	*c*-Pentyl	COMe
NC191	Propargyl	$COCH_2(CH_3)_3$
NC192	*c*-Pentyl	$COCH_2(CH_3)_3$
NC193	Propargyl	$COCH_3$
NC194	*c*-Pentyl	$COCH_3$
NC195	Propargyl	$C(O)N(CH_3)_2$
NC196	*c*-Pentyl	$C(O)N(CH_3)_2$
NC197	Propargyl	$C(O)N(CH_3)Et$
NC198	*c*-Pentyl	$C(O)N(CH_3)Et$
NC199	Propargyl	$C(O)N(CH_3)iPr$
NC200	*c*-Pentyl	$C(O)N(CH_3)iPr$
NC201	Propargyl	$C(O)N(CH_3)iBu$
NC202	*c*-Pentyl	$C(O)N(CH_3)iBu$
NC203	Propargyl	$C(O)NH(CH_3)$
NC204	*c*-Pentyl	$C(O)NH(CH_3)$

NC205	Propargyl	C(O)NH(Et)
NC206	*c*-Pentyl	C(O)NH(Et)
NC207	Propargyl	C(O)NH(iPr)
NC208	*c*-Pentyl	C(O)NH(iPr)
NC209	Propargyl	C(O)NH(iBu)
NC210	*c*-Pentyl	C(O)NH(iBu)

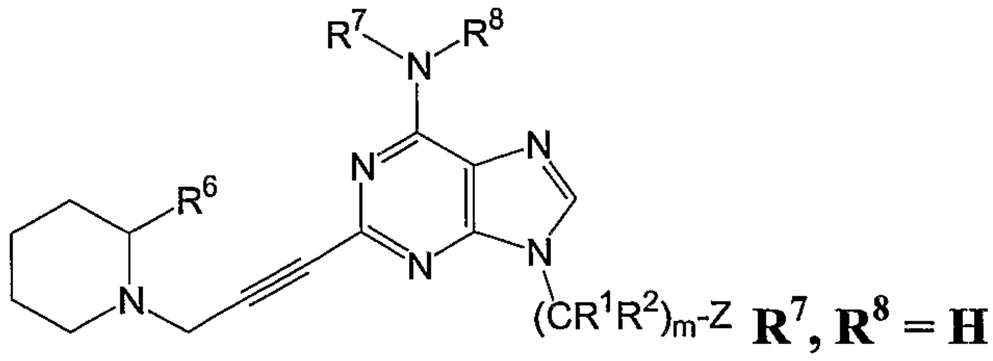
Table 5



R^7, R^8 = H

Compound	**$(CR^1R^2)_m$-Z**	**R^6**
NC211	Propargyl	CH_2OH
NC212	*c*-Pentyl	CH_2OH
NC213	Propargyl	CO_2H
NC214	*c*-Pentyl	CO_2H
NC215	Propargyl	CO_2Me
NC216	*c*-Pentyl	CO_2Me
NC217	Propargyl	CO_2Et
NC218	*c*-Pentyl	CO_2Et
NC219	Propargyl	CH_2OAc
NC220	*c*-Pentyl	CH_2OAc
NC221	Propargyl	$CH_2N(CH_3)_2$
NC222	*c*-Pentyl	$CH_2N(CH_3)_2$
NC223	Propargyl	$COOCH_2CH_2NHBoc$
NC224	*c*-Pentyl	$COOCH_2CH_2NHBoc$
NC225	Propargyl	$COOCH_2CH_2NH_2$
NC226	*c*-Pentyl	$COOCH_2CH_2NH_2$
NC227	Propargyl	$CONHCH_2CH_3$
NC228	*c*-Pentyl	$CONHCH_2CH_3$
NC229	Propargyl	$CONH_2$
NC230	*c*-Pentyl	$CONH_2$
NC231	Propargyl	CONHMe
NC232	*c*-Pentyl	CONHMe
NC233	Propargyl	CH_2CH_3
NC234	*c*-Pentyl	CH_2CH_3
NC235	Propargyl	$COCH_3$
NC236	*c*-Pentyl	$COCH_3$
NC237	Propargyl	$CHCH_3(OH)$
NC238	*c*-Pentyl	$CHCH_3(OH)$

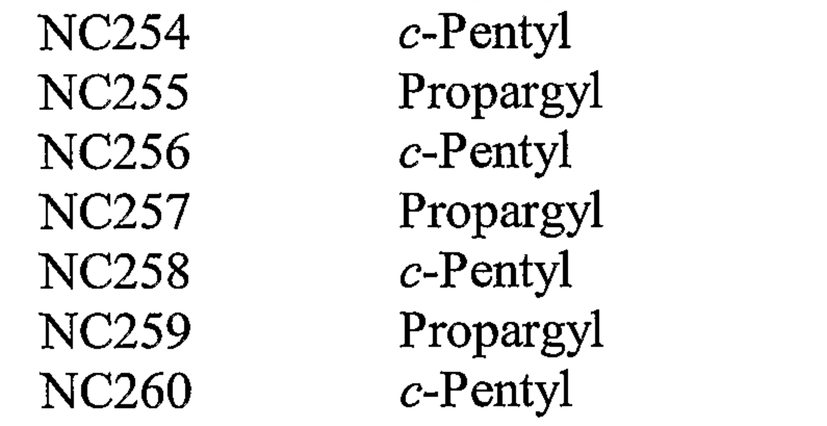
Table 6



$\mathbf{R^7, R^8 = H}$

Compound	$(CR^1R^2)_m$-Z	R^6
NC239	Propargyl	CH_2OH
NC240	*c*-Pentyl	CH_2OH
NC241	Propargyl	CO_2H
NC242	*c*-Pentyl	CO_2H
NC243	Propargyl	CO_2Me
NC244	*c*-Pentyl	CO_2Me
NC245	Propargyl	CH_2OAc
NC246	*c*-Pentyl	CH_2OAc
NC247	Propargyl	$CH_2N(CH_3)_2$
NC248	*c*-Pentyl	$CH_2N(CH_3)_2$
NC249	Propargyl	$COOCH_2CH_2NHBoc$
NC250	*c*-Pentyl	$COOCH_2CH_2NHBoc$
NC251	Propargyl	$COOCH_2CH_2NH_2$
NC252	*c*-Pentyl	$COOCH_2CH_2NH_2$
NC253	Propargyl	$CONHCH_2CH_3$
NC254	*c*-Pentyl	$CONHCH_2CH_3$
NC255	Propargyl	$CONH_2$
NC256	*c*-Pentyl	$CONH_2$
NC257	Propargyl	CONHMe
NC258	*c*-Pentyl	CONHMe
NC259	Propargyl	CH_2CH_3
NC260	*c*-Pentyl	CH_2CH_3
NC261	Propargyl	$COCH_3$
NC262	*c*-Pentyl	$COCH_3$
NC263	Propargyl	$CHCH_3(OH)$
NC264	*c*-Pentyl	$CHCH_3(OH)$

Table 7



$\mathbf{R^7, R^8 = H}$

Compound	$(CR^1R^2)_m$-Z	W	W'	R^6
NC265	Propargyl	CH	CH	CO_2Me
NC266	*c*-Pentyl	CH	N	CO_2Me
NC267	Propargyl	N	CH	CO_2Me

NC268	*c*-Pentyl	N	N	CO_2Me
NC269	Propargyl	CH	CH	CO_2Me
NC270	*c*-Pentyl	CH	N	CO_2Me
NC271	Propargyl	N	CH	CO_2Me
NC272	*c*-Pentyl	N	N	CO_2Me
NC273	Propargyl	CH	CH	CH_2OH
NC274	*c*-Pentyl	CH	N	CH_2OH
NC275	Propargyl	N	CH	CH_2OH
NC276	*c*-Pentyl	N	N	CH_2OH
NC277	Propargyl	CH	CH	CH_2OH
NC278	*c*-Pentyl	CH	N	CH_2OH
NC279	Propargyl	N	CH	CH_2OH
NC280	*c*-Pentyl	N	N	CH_2OH
NC281	Propargyl	CH	CH	CO_2H
NC282	*c*-Pentyl	CH	N	CO_2H
NC283	Propargyl	N	CH	CO_2H
NC284	*c*-Pentyl	N	N	CO_2H
NC285	Propargyl	CH	CH	CO_2H
NC286	*c*-Pentyl	CH	N	CO_2H
NC287	Propargyl	N	CH	CO_2H
NC288	*c*-Pentyl	N	N	CO_2H
NC289	Propargyl	CH	CH	CH_2OAc
NC290	*c*-Pentyl	CH	N	CH_2OAc
NC291	Propargyl	N	CH	CH_2OAc
NC292	*c*-Pentyl	N	N	CH_2OAc
NC293	Propargyl	CH	CH	CH_2OAc
NC294	*c*-Pentyl	CH	N	CH_2OAc
NC295	Propargyl	N	CH	CH_2OAc
NC296	*c*-Pentyl	N	N	CH_2OAc
NC297	Propargyl	CH	CH	$CONH_2$
NC298	*c*-Pentyl	CH	N	$CONH_2$
NC299	Propargyl	N	CH	$CONH_2$
NC300	*c*-Pentyl	N	N	$CONH_2$
NC301	Propargyl	CH	CH	$CONH_2$
NC302	*c*-Pentyl	CH	N	$CONH_2$
NC303	Propargyl	N	CH	$CONH_2$
NC304	*c*-Pentyl	N	N	$CONH_2$
NC305	Propargyl	CH	CH	CONHMe
NC306	*c*-Pentyl	CH	N	CONHMe
NC307	Propargyl	N	CH	CONHMe
NC308	*c*-Pentyl	N	N	CONHMe
NC309	Propargyl	CH	CH	CONHMe
NC310	*c*-Pentyl	CH	N	CONHMe
NC311	Propargyl	N	CH	CONHMe
NC312	*c*-Pentyl	N	N	CONHMe
NC313	Propargyl	CH	CH	CO_2tBu
NC314	*c*-Pentyl	CH	N	CO_2tBu
NC315	Propargyl	N	CH	CO_2tBu

NC316	*c*-Pentyl	N	N	CO_2tBu
NC317	Propargyl	CH	CH	CO_2tBu
NC318	*c*-Pentyl	CH	N	CO_2tBu
NC319	Propargyl	N	CH	CO_2tBu
NC320	*c*-Pentyl	N	N	CO_2tBu
NC321	Propargyl	CH	CH	CO_2Et
NC322	*c*-Pentyl	CH	N	CO_2Et
NC323	Propargyl	N	CH	CO_2Et
NC324	*c*-Pentyl	N	N	CO_2Et
NC325	Propargyl	CH	CH	CO_2Et
NC326	*c*-Pentyl	CH	N	CO_2Et
NC327	Propargyl	N	CH	CO_2Et
NC328	*c*-Pentyl	N	N	CO_2Et
NC329	Propargyl	CH	CH	CO_2iBu
NC330	*c*-Pentyl	CH	N	CO_2iBu
NC331	Propargyl	N	CH	CO_2iBu
NC332	*c*-Pentyl	N	N	CO_2iBu
NC333	Propargyl	CH	CH	CO_2iBu
NC334	*c*-Pentyl	CH	N	CO_2iBu
NC335	Propargyl	N	CH	CO_2iBu
NC336	*c*-Pentyl	N	N	CO_2iBu
NC337	Propargyl	CH	CH	CO_2iPr
NC338	*c*-Pentyl	CH	N	CO_2iPr
NC339	Propargyl	N	CH	CO_2iPr
NC340	*c*-Pentyl	N	N	CO_2iPr
NC341	Propargyl	CH	CH	CO_2iPr
NC342	*c*-Pentyl	CH	N	CO_2iPr
NC343	Propargyl	N	CH	CO_2iPr
NC344	*c*-Pentyl	N	N	CO_2iPr
NC345	Propargyl	CH	CH	COMe
NC346	*c*-Pentyl	CH	N	COMe
NC347	Propargyl	N	CH	COMe
NC348	*c*-Pentyl	N	N	COMe
NC349	Propargyl	CH	CH	COMe
NC350	*c*-Pentyl	CH	N	COMe
NC351	Propargyl	N	CH	COMe
NC352	*c*-Pentyl	N	N	COMe
NC353	Propargyl	CH	CH	$COC(CH_3)_3$
NC354	*c*-Pentyl	CH	N	$COC(CH_3)_3$
NC355	Propargyl	N	CH	$COC(CH_3)_3$
NC356	*c*-Pentyl	N	N	$COC(CH_3)_3$
NC357	Propargyl	CH	CH	$COC(CH_3)_3$
NC358	*c*-Pentyl	CH	N	$COC(CH_3)_3$
NC359	Propargyl	N	CH	$COC(CH_3)_3$
NC360	*c*-Pentyl	N	N	$COC(CH_3)_3$
NC361	Propargyl	CH	CH	$COCH_2(CH_3)_3$
NC362	*c*-Pentyl	CH	N	$COCH_2(CH_3)_3$
NC363	Propargyl	N	CH	$COCH_2(CH_3)_3$

NC364	*c*-Pentyl	N	N	$COCH_2(CH_3)_3$
NC365	Propargyl	CH	CH	$COCH_2(CH_3)_3$
NC366	*c*-Pentyl	CH	N	$COCH_2(CH_3)_3$
NC367	Propargyl	N	CH	$COCH_2(CH_3)_3$
NC368	*c*-Pentyl	N	N	$COCH_2(CH_3)_3$
NC369	Propargyl	CH	CH	$C(O)N(CH_3)_2$
NC370	*c*-Pentyl	CH	N	$C(O)N(CH_3)_2$
NC371	Propargyl	N	CH	$C(O)N(CH_3)_2$
NC372	*c*-Pentyl	N	N	$C(O)N(CH_3)_2$
NC373	Propargyl	CH	CH	$C(O)N(CH_3)_2$
NC374	*c*-Pentyl	CH	N	$C(O)N(CH_3)_2$
NC375	Propargyl	N	CH	$C(O)N(CH_3)_2$
NC376	*c*-Pentyl	N	N	$C(O)N(CH_3)_2$
NC377	Propargyl	CH	CH	$C(O)N(CH_3)Et$
NC378	*c*-Pentyl	CH	N	$C(O)N(CH_3)Et$
NC379	Propargyl	N	CH	$C(O)N(CH_3)Et$
NC380	*c*-Pentyl	N	N	$C(O)N(CH_3)Et$
NC381	Propargyl	CH	CH	$C(O)N(CH_3)Et$
NC382	*c*-Pentyl	CH	N	$C(O)N(CH_3)Et$
NC383	Propargyl	N	CH	$C(O)N(CH_3)Et$
NC384	*c*-Pentyl	N	N	$C(O)N(CH_3)Et$
NC385	Propargyl	CH	CH	$C(O)N(CH_3)iPr$
NC386	*c*-Pentyl	CH	N	$C(O)N(CH_3)iPr$
NC387	Propargyl	N	CH	$C(O)N(CH_3)iPr$
NC388	*c*-Pentyl	N	N	$C(O)N(CH_3)iPr$
NC389	Propargyl	CH	CH	$C(O)N(CH_3)iPr$
NC390	*c*-Pentyl	CH	N	$C(O)N(CH_3)iPr$
NC391	Propargyl	N	CH	$C(O)N(CH_3)iPr$
NC392	*c*-Pentyl	N	N	$C(O)N(CH_3)iPr$
NC393	Propargyl	CH	CH	$C(O)N(CH_3)iBu$
NC394	*c*-Pentyl	CH	N	$C(O)N(CH_3)iBu$
NC395	Propargyl	N	CH	$C(O)N(CH_3)iBu$
NC396	*c*-Pentyl	N	N	$C(O)N(CH_3)iBu$
NC397	Propargyl	CH	CH	$C(O)N(CH_3)iBu$
NC398	*c*-Pentyl	CH	N	$C(O)N(CH_3)iBu$
NC399	Propargyl	N	CH	$C(O)N(CH_3)iBu$
NC400	*c*-Pentyl	N	N	$C(O)N(CH_3)iBu$
NC401	Propargyl	CH	CH	C(O)NH(Et)
NC402	*c*-Pentyl	CH	N	C(O)NH(Et)
NC403	Propargyl	N	CH	C(O)NH(Et)
NC404	*c*-Pentyl	N	N	C(O)NH(Et)
NC405	Propargyl	CH	CH	C(O)NH(Et)
NC406	*c*-Pentyl	CH	N	C(O)NH(Et)
NC407	Propargyl	N	CH	C(O)NH(Et)
NC408	*c*-Pentyl	N	N	C(O)NH(Et)
NC409	Propargyl	CH	CH	C(O)NH(iPr)
NC410	*c*-Pentyl	CH	N	C(O)NH(iPr)
NC411	Propargyl	N	CH	C(O)NH(iPr)

NC412	*c*-Pentyl	N	N	C(O)NH(iPr)
NC413	Propargyl	CH	CH	C(O)NH(iPr)
NC414	*c*-Pentyl	CH	N	C(O)NH(iPr)
NC415	Propargyl	N	CH	C(O)NH(iPr)
NC416	*c*-Pentyl	N	N	C(O)NH(iPr)
NC417	Propargyl	CH	CH	C(O)NH(iBu)
NC418	*c*-Pentyl	CH	N	C(O)NH(iBu)
NC419	Propargyl	N	CH	C(O)NH(iBu)
NC420	*c*-Pentyl	N	N	C(O)NH(iBu)
NC421	Propargyl	CH	CH	C(O)NH(iBu)
NC422	*c*-Pentyl	CH	N	C(O)NH(iBu)
NC423	Propargyl	N	CH	C(O)NH(iBu)
NC424	*c*-Pentyl	N	N	C(O)NH(iBu)
NC425	Propargyl	CH	CH	CH_2OCOCH_3
NC426	*c*-Pentyl	CH	N	CH_2OCOCH_3
NC427	Propargyl	N	CH	CH_2OCOCH_3
NC428	*c*-Pentyl	N	N	CH_2OCOCH_3
NC429	Propargyl	CH	CH	CH_2OCOCH_3
NC430	*c*-Pentyl	CH	N	CH_2OCOCH_3
NC431	Propargyl	N	CH	CH_2OCOCH_3
NC432	*c*-Pentyl	N	N	CH_2OCOCH_3
NC433	Propargyl	CH	CH	CH_2OCOEt
NC434	*c*-Pentyl	CH	N	CH_2OCOEt
NC435	Propargyl	N	CH	CH_2OCOEt
NC436	*c*-Pentyl	N	N	CH_2OCOEt
NC437	Propargyl	CH	CH	CH_2OCOEt
NC438	*c*-Pentyl	CH	N	CH_2OCOEt
NC439	Propargyl	N	CH	CH_2OCOEt
NC440	*c*-Pentyl	N	N	CH_2OCOEt
NC441	Propargyl	CH	CH	$CH_2OCOiPr$
NC442	*c*-Pentyl	CH	N	$CH_2OCOiPr$
NC443	Propargyl	N	CH	$CH_2OCOiPr$
NC444	*c*-Pentyl	N	N	$CH_2OCOiPr$
NC445	Propargyl	CH	CH	$CH_2OCOiPr$
NC446	*c*-Pentyl	CH	N	$CH_2OCOiPr$
NC447	Propargyl	N	CH	$CH_2OCOiPr$
NC448	*c*-Pentyl	N	N	$CH_2OCOiPr$
NC449	Propargyl	CH	CH	$CH_2OCOiBu$
NC450	*c*-Pentyl	CH	N	$CH_2OCOiBu$
NC451	Propargyl	N	CH	$CH_2OCOiBu$
NC452	*c*-Pentyl	N	N	$CH_2OCOiBu$
NC453	Propargyl	CH	CH	$CH_2OCOiBu$
NC454	*c*-Pentyl	CH	N	$CH_2OCOiBu$
NC455	Propargyl	N	CH	$CH_2OCOiBu$
NC456	*c*-Pentyl	N	N	$CH_2OCOiBu$

74. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1, and a pharmaceutically acceptable excipient.

75. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof.

76. A method for stimulating motor activity without dyskinesia in a mammal, comprising administering a therapeutically effective amount of an A_{2A} anatagonist compound of Claim 1 to the mammal in need of such treatment.

77. The method of Claim 76, wherein the therapeutically effective amount is effective to treat ischemia, brain damage induced by ischemia and excitoxicity, Huntington's disease, catalepsy, cancer, drug addiction and withdrawal, Parkinson's disease (drug induced, post-encephalitic, poison induced or post-traumatic induced), acute or chronic pain, narcolepsy and Alzheimer's disease.

78. The method of Claim 76 wherein the therapeutically effective amount is effective to stimulate motor activity for treating a movement disorder, where the disorder is progressive supernuclear palsy, Huntington's disease, multiple system atrophy, corticobasal degeneration, Wilsons disease, Hallerrorden-Spatz disease, progressive pallidal atrophy, Dopa-responsive dystonia-Parkinsonism, spasticity or other disoders of the basal ganglia which result in dyskinesias

79. The method of Claim 76, wherein the compound is used in combination with one or more additional drugs in the treatment of movement disorders (i.e. L-DOPA or dopamine agonist), addiction, or cancer with the components being in the same formulation or in a separate formulation for administration simultaneously or sequentially.

80. The method of Claim 79, wherein the therapeutically effective amount is effective to provide neuroprotection and slow or halt the degeneration of dopaminergic neurons.

81. The method of Claim 76, wherein the therapeutically effective amount is effective to enhance the immune response by increasing the activity of an immune cell in a mammal.

82. The method of Claim 81, wherein the activity is pro-inflammatory cytokine production.

83. The method of Claim 81, wherein the activity of the immune cell results in an increase in inflammation.

84. The method of Claim 81, wherein the mammal is human.