1H-INDAZOLES, BENZOTHIAZOLES, 1,2-BENZOISOXAZOLES, 1,2-BENZOISOTHIAZOLES, AND CHROMONES AND PREPARATION AND USES THEREOF

This application claims the benefit of U.S. provisional application Serial No. 60/568,696, filed May 7, 2004, U.S. provisional application Serial No. 60/574,712, filed May 27, 2004, and U.S. provisional application Serial No. 60/629,469, filed November 10, 2004, the entire disclosures of which are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates generally to the field of ligands for nicotinic acetylcholine receptors (nAChR), activation of nAChRs, and the treatment of disease conditions associated with defective or malfunctioning nicotinic acetylcholine receptors, especially of the brain. Further, this invention relates to novel compounds, which act as ligands for the α7 nAChR subtype, methods of preparing such compounds, compositions comprising such compounds, and methods of use thereof.

BACKGROUND OF THE INVENTION

There are two types of receptors for the neurotransmitter, acetylcholine: muscarinic receptors and nicotinic receptors, based on the selectivity of action of muscarine and nicotine, respectively. Muscarinic receptors are G-protein coupled receptors. Nicotinic receptors are members of the ligand-gated ion channel family. When activated, the conductance of ions across the nicotinic ion channels increases.

Nicotinic alpha-7 receptor protein forms a homo-pentameric channel in vitro that is highly permeable to a variety of cations (e.g., Ca^{++}). Each nicotinic alpha-7 receptor has four transmembrane domains, named M1, M2, M3, and M4. The M2 domain has been suggested to form the wall lining the channel. Sequence alignment shows that nicotinic alpha-7 is highly conserved during evolution. The M2 domain that lines the channel is identical in protein sequence from chicken to human. For discussions of the alpha-7 receptor, see, e.g., Revah et al. (**1991**), *Nature*, 353, 846-849; Galzi et al. (**1992**), *Nature*

359, 500-505; Fucile et al. (**2000**), *PNAS* 97(7), 3643-3648; Briggs et al. (**1999**), *Eur. J. Pharmacol.* 366 (2-3), 301-308; and Gopalakrishnan et al. (**1995**), *Eur. J. Pharmacol.* 290(3), 237-246.

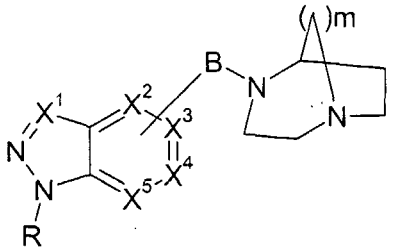
The nicotinic alpha-7 receptor channel is expressed in various brain regions and is believed to be involved in many important biological processes in the central nervous system (CNS), including learning and memory. Nicotinic alpha-7 receptors are localized on both presynaptic and postsynaptic terminals and have been suggested to be involved in modulating synaptic transmission. It is therefore of interest to develop novel compounds, which act as ligands for the α7 nAChR subtype, for the treatment of disease conditions associated with defective or malfunctioning nicotinic acetylcholine receptors.

SUMMARY OF THE INVENTION

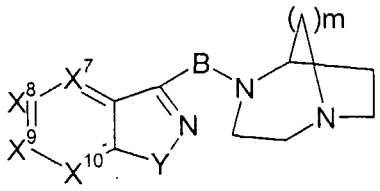
This invention relates to novel compounds, which act as ligands for the α7 nAChR subtype, methods of preparing such compounds, compositions comprising such compounds, and methods of use thereof.

DETAILED DESCRIPTION OF THE INVENTION

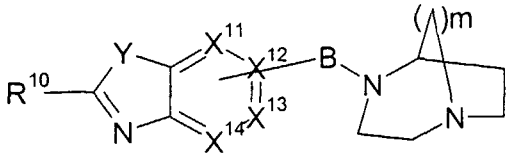
The present invention includes compounds of Formulas I, II, III, IV, V, VI, VII or VIII:



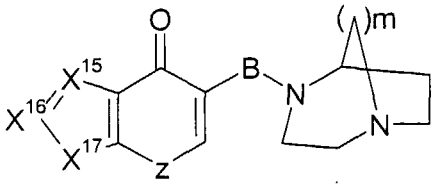
(I)



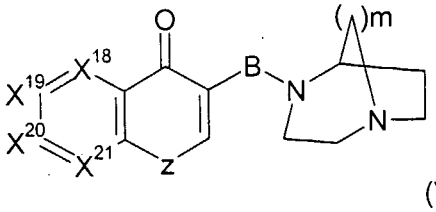
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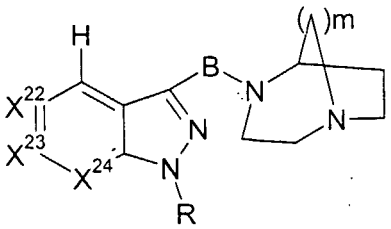
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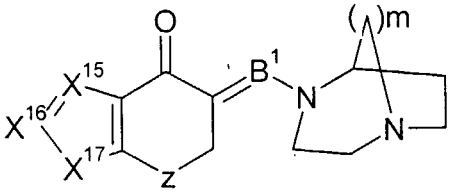
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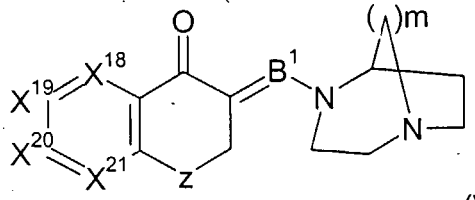
(V)



(VI)



(VII)



(VIII)

wherein

X^1 is CH or CR^1;

X^2 to X^5 are each, independently, N, CH, CR^1, or C-, wherein -C represents the point of attachment of group B, and wherein at most one of X^2 to X^5 is N, and one of X^2 to X^5 is -C (preferably X^3 or X^4), preferably X^1 is CH, or CR^1, X^2 and X^5 are N or CH, and X^3 and X^4 are N, CH, CR^1, or C-;

X^7 to X^{10} are each, independently, N, CH, or CR^2, wherein at most one of X^7 to X^{10} is N;

X^{11} to X^{14} are each, independently N, CH, CR^3, or C-, wherein -C represents the point of attachment of group B, and wherein at most one of X^{11} to X^{14} is N, and one of X^{11} to X^{14} is -C (preferably X^{12} or X^{13});

X^{15} to X^{17} are each, independently N, O, S, CH, or CR^4;

X^{18} to X^{21} are each, independently N, CH, or CR^5, wherein at most one of X^{18} to X^{21} is N;

X^{22} and X^{23} are each, independently, CH or CR^{12}, wherein at least one of X^{22} or X^{23} is CR^{12};

X^{24} is either CH or N;

B is CH_2, C=O, or C=S;

B^1 is CH;

Y is O or S;

Z is O or NR^{11};

m is 1 or 2;

R is H, alkyl having 1 to 4 carbon atoms, halogenated alkyl having 1 to 4 carbon atoms, cycloalkyl having 3 to 7 carbon atoms, cycloalkylalkyl having 4 to 7 carbon atoms, or C_{1-6}alkyl-Ar (e.g., benzyl),

R^1, R^2, R^4 and R^5 are each, independently,

C_{1-6}-alkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., CH_3, C_2H_5, CF_3),

C_{2-6}-alkenyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., C_2H_3, C_3H_5),

C_{2-6}-alkynyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, $Si(R^8)_3$, Ar, Het, or combinations thereof (e.g., C_2H, C_3H_3),

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., cyclopropyl, cyclobutyl, cyclopentyl),

C_{4-10}-cycloalkylalkyl which is unsubstituted or substituted in the cycloalkyl portion one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof, and/or substituted in the alkyl portion one or more times by one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., cyclopentylmethyl, cyclopropylmethyl, etc.),

halogen (e.g., F, Cl, Br, I,),

CN, NO_2, NR^6R^7, SR^6, SOR^6, SO_2R^6, $SO_2NR^6R^7$, $NR^6SO_2R^7$, $CONR^6R^7$, $CSNR^6R^7$, $COOR^6$, NR^6COR^7, NR^6CSR^7, $NR^6CONR^6R^7$, $NR^6CSNR^6R^7$, NR^6COOR^7, NR^6CSOR^7, $OCONR^6R^7$, $OCSNR^6R^7$,

Ar (e.g., phenyl),

Het (e.g., thienyl), or

OR^9 (e.g., hydroxyl, alkoxy, cycloalkyloxy, cycloalkylalkoxy);

R^3 is halogen (e.g., F, Cl, Br, I), OR^{16} (e.g., OCH_3, cyclopropyloxy, cyclopropylmethoxy, OCF_3, $OCHF_2$, hydroxyethoxy), CN, nitro, alkyl having 1 to 4 carbon atoms (e.g., CH_3, C_2H_5), halogenated alkyl having 1 to 4 carbon atoms (e.g., CF_3), cycloalkyl having 3 to 7 carbon atoms (e.g., cyclopropyl, cyclobutyl, cyclopentyl), cycloalkylalkyl having 4 to 7 carbon atoms (e.g., cyclopentylmethyl, cyclopropylmethyl), hydoxyalkyl having 1 to 4 carbon atoms (e.g., hydroxymethyl, hydroxyethyl), NH_2, monoalkylamino having 1 to 4 carbon atoms (e.g., methylamino), dialkylamino wherein each alkyl group independently has 1 to 4 carbon atoms (e.g., dimethylamino), Ar (e.g., phenyl) or Het;

R^6 and R^7 are each independently

H,

C_{1-6}-alkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms (e.g., diethylamino), C_{3-8}-cycloalkyl, Ar, Het, or combinations thereof (e.g., CH_3, C_2H_5, CF_3),

C_{3-6}-alkenyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms (e.g., diethylamino), C_{3-8}-cycloalkyl, Ar, Het, or combinations thereof (e.g., C_2H_3, C_3H_5),

C_{3-6}-alkynyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms (e.g.,

diethylamino), C_{3-8}-cycloalkyl, $Si(R^8)_3$, Ar, Het, or combinations thereof (e.g., C_2H, C_3H_3),

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms (e.g., diethylamino), C_{3-8}-cycloalkyl, Ar, Het, or combinations thereof (e.g., cyclopropyl, cyclobutyl, cyclopentyl),

C_{4-10}-cycloalkylalkyl which is unsubstituted or substituted in the cycloalkyl portion one or more times by F, Cl, Br, I, CN, OR^{16}, monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms (e.g., diethylamino), C_{3-8}-cycloalkyl, Ar, Het, or combinations thereof, and/or substituted in the alkyl portion one or more times by one or more times by F, Cl, Br, I, CN, OR^{16}, monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms (e.g., diethylamino), C_{3-8}-cycloalkyl, Ar, Het, or combinations thereof (e.g., cyclopentylmethyl, cyclopropylmethyl, etc.),

Ar, or

Het;

R^8 is C_{1-6}-alkyl (e.g., CH_3);

R^9 is H,

C_{1-6}-alkyl which is unsubstituted or substituted one or more by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., CH_3, C_2H_5, CF_3),

C_{3-6}-alkenyl which is unsubstituted or substituted one or more by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., C_2H_3, C_3H_5),

C_{3-6}-alkynyl which is unsubstituted or substituted one or more by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., C_2H, C_3H_3),

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., cyclopropyl, cyclobutyl, cyclopentyl),

C_{4-8}-cycloalkylalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., cyclopentylmethyl, cyclopropylmethyl, etc.),

Ar, or

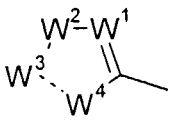
Het;

R^{10} is H, alkyl having 1 to 4 carbon atoms (e.g., CH_3, C_2H_5), halogenated alkyl having 1 to 4 carbon atoms (e.g., CF_3), cycloalkyl having 3 to 7 carbon atoms (e.g., cyclopropyl, cyclobutyl, cyclopentyl), or cycloalkylalkyl having 4 to 7 carbon atoms (e.g., cyclopentylmethyl, cyclopropylmethyl, etc.);

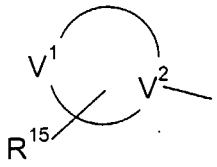
R^{11} is H, alkyl having 1 to 4 carbon atoms (which is unsubstituted or substituted one or more times by halogen, OR^{16}, C_{3-8} cycloalkyl, NR^6R^7,

Ar, or Het), cycloalkyl having 3 to 7 carbon atoms (which is unsubstituted or substituted one or more times by halogen, OR^{16}, NR^6R^7, Ar, or Het), cycloalkylalkyl having 4 to 7 carbon atoms (e.g., cyclopentylmethyl, cyclopropylmethyl, etc.), Ar or Het (e.g., CH_3, C_2H_5, CF_3, cyclopropyl, cyclopentyl, phenyl);

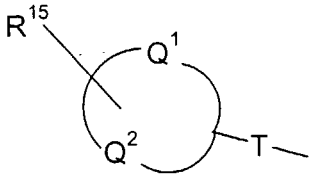
R^{12} is C_{1-6}-alkoxy which is substituted one or more times by F, or is selected from Formulae IX-XI



(IX)



(X)



(XI)

wherein Formula IX represents a 5-membered, unsaturated heterocycle in which the bond between W^2 and W^3 is a single bond and the, Formula X represents a 5-8-membered, heterocycle which is saturated or partially saturated and wherein the heterocyclic ring may be bridged by a divalent alkylene group having 1 to 3 carbon atoms, and Formula XI represents a 5-8-membered, heterocycle which is saturated, partially saturated, or unsaturated and wherein the heterocyclic ring may be bridged by a divalent alkylene group having 1 to 3 carbon atoms;

Q^1 is O, S, N, NR^{13}, or SO_2;

Q^2 is CH, CR^{14}, CHR^{14}, O, S, SO_2, N, or NR^{13};

T is O or NR^{10};

V^1 is O, S, SO_2, N, NR^{13}, CR^{14}, or CHR^{14};

W^1 is N;

W^2 and W^3 are each, independently, O, S, N, NR^{13}, CH, or CR^1, in which the bond between W^2 and W^3 is a single bond and the bond between W^3 and W^4 is a double bond, or the bond between W^2 and W^3 is a double bond and the bond between W^3 and W^4 is a single bond;

W^4 is O, S, N, or NR^{13};

V^2 is C, CH, C-OH, or N;

R^{13} is H,

C_{1-6}-alkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., CH_3, C_2H_5, CF_3),

C_{3-6}-alkenyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., C_2H_3, C_3H_5),

C_{3-6}-alkynyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, $Si(R^8)_3$, Ar, Het, or combinations thereof (e.g., C_2H, C_3H_3),

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., cyclopropyl, cyclobutyl, cyclopentyl),

C_{4-10}-cycloalkylalkyl which is unsubstituted or substituted in the cycloalkyl portion one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof, and/or substituted in the alkyl portion one or more times by one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl (e.g., cyclopentylmethyl, cyclopropylmethyl, etc.), SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., cyclopentylmethyl, cyclopropylmethyl, etc.),

SO_2R^6, $CONR^6R^7$, $CSNR^6R^7$, $COOR^6$, $CSOR^6$, COR^7, CSR^7,

Ar, or

Het;

R^{14} is H,

C_{1-6}-alkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^9, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., CH_3, C_2H_5, CF_3),

C_{2-6}-alkenyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^9, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., C_2H_3, C_3H_5),

C_{2-6}-alkynyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^9, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, $Si(R^8)_3$, Ar, Het, or combinations thereof (e.g., C_2H, C_3H_3),

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^9, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-

cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., cyclopropyl, cyclobutyl, cyclopentyl),

C_{4-10}-cycloalkylalkyl which is unsubstituted or substituted in the cycloalkyl portion one or more times by F, Cl, Br, I, CN, OR^9, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof, and/or substituted in the alkyl portion one or more times by one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., cyclopentylmethyl, cyclopropylmethyl, etc.),

halogen (e.g., F, Cl, Br, I,),

CN, NO_2, NR^6R^7, SR^6, SOR^6, SO_2R^6, $SO_2NR^6R^7$, $NR^6SO_2R^7$, $CONR^6R^7$, $CSNR^6R^7$, $COOR^6$, NR^6COR^7, NR^6CSR^7, $NR^6CONR^6R^7$, $NR^6CSNR^6R^7$, NR^6COOR^7, NR^6CSOR^7, $OCONR^6R^7$, $OCSNR^6R^7$,

Ar,

Het, or

OR^9;

R^{15} is H,

C_{1-6}-alkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., CH_3, C_2H_5, CF_3),

C_{2-6}-alkenyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., C_2H_3, C_3H_5),

C_{2-6}-alkynyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, $Si(R^8)_3$, Ar, Het, or combinations thereof (e.g., C_2H, C_3H_3),

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., cyclopropyl, cyclobutyl, cyclopentyl),

C_{4-10}-cycloalkylalkyl which is unsubstituted or substituted in the cycloalkyl portion one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof, and/or substituted in the alkyl portion one or more times by one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., cyclopentylmethyl, cyclopropylmethyl, etc.),

C_{3-8}-cycloalkyloxy which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., cyclopropyloxy, cyclopentyloxy),

halogen (e.g., F, Cl, Br, I,),

oxo, thio, CN, NO_2, NR^6R^7, SR^6, SOR^6, SO_2R^6, $SO_2NR^6R^7$, $NR^6SO_2R^7$, $CONR^6R^7$, $CSNR^6R^7$, $COOR^6$, NR^6COR^7, NR^6CSR^7, $NR^6CONR^6R^7$, $NR^6CSNR^6R^7$, NR^6COOR^7, NR^6CSOR^7, $OCONR^6R^7$, $OCSNR^6R^7$,

Ar,

Het, or

OR^9;

R^{16} is H,

C_{1-6}-alkyl which is unsubstituted or substituted one or more by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., CH_3, C_2H_5, CF_3),

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., cyclopropyl, cyclobutyl, cyclopentyl), or

C_{4-8}-cycloalkylalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., cyclopentylmethyl, cyclopropylmethyl, etc.);

R^{17} and R^{18} are each independently H, alkyl having 1 to 4 carbon atoms (e.g., CH_3, C_2H_5), halogenated alkyl having 1 to 4 carbon atoms (e.g., CF_3), cycloalkyl having 3 to 7 carbon atoms (e.g., cyclopropyl, cyclobutyl, cyclopentyl), or cycloalkylalkyl having 4 to 7 carbon atoms (e.g., cyclopentylmethyl, cyclopropylmethyl, etc.);

R^{19} is H or CONH-CH_2-Ar;

Ar is an aryl group containing 6 to 10 carbon atoms which is unsubstituted or substituted one or more times by

alkyl having 1 to 8 carbon atoms,
alkoxy having 1 to 8 carbon atoms,
halogen (F, Cl, Br, or I, preferably F or Cl),
amino,
cyano,
hydroxyl,
nitro,
halogenated alkyl having 1 to 8 carbon atoms,
halogenated alkoxy having 1 to 8 carbon atoms,
hydroxyalkyl having 1 to 8 carbon atoms,
hydroxyalkoxy having 2 to 8 carbon atoms,
alkenyloxy having 3 to 8 carbon atoms,
monoalkylamino having 1 to 8 carbon atoms,
dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms,
carboxy,
alkoxycarbonyl,
alkylaminocarbonyl,
acylamido (e.g., acetamido),
acyloxy (e.g., acetoxy),
alkylthio having 1 to 8 carbon atoms,
alkylsulphinyl having 1 to 8 carbon atoms,
alkylsulphonyl having 1 to 8 carbon atoms,
sulfo,
sulfonylamino,
Het,

cycloalkylamino wherein the cycloalkyl group has 3 to 7 C atoms and is optionally substituted by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

aryloxy wherein the aryl portion contains 6 to 10 carbon atoms (e.g., phenyl, naphthyl, biphenyl) and is optionally substituted by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

arylthio wherein the aryl portion contains 6 to 10 carbon atoms (e.g., phenyl, naphthyl, biphenyl) and is optionally substituted by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

cycloalkyloxy wherein the cycloalkyl group has 3 to 7 C atoms and is optionally substituted by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio, or

combinations thereof; and

Het is a heterocyclic group (e.g., furyl, thienyl, methylthienyl, bithienyl, benzylprazolyl, thiazolyl, imidazolyl, methylimidazolyl, pyrrolidinyl, morpholinyl, thiomorpholinyl), which is fully saturated, partially saturated or fully unsaturated, having 5 to 10 ring atoms in which at least 1 ring atom is a N, O or S atom, which is unsubstituted or substituted one or more times by

alkyl having 1 to 8 carbon atoms,
alkoxy having 1 to 8 carbon atoms,
halogen (F, Cl, Br, or I, preferably F or Cl),
amino,
cyano,
hydroxyl,
nitro,
halogenated alkyl having 1 to 8 carbon atoms,
halogenated alkoxy having 1 to 8 carbon atoms,
hydroxyalkyl having 1 to 8 carbon atoms,
hydroxyalkoxy having 2 to 8 carbon atoms,
alkenyloxy having 3 to 8 carbon atoms,
monoalkylamino having 1 to 8 carbon atoms,
dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms,
carboxy,
alkoxycarbonyl,
alkylaminocarbonyl,
acylamido (e.g., acetamido),
acyloxy (e.g., acetoxy),
alkylthio having 1 to 8 carbon atoms,
alkylsulphinyl having 1 to 8 carbon atoms,
alkylsulphonyl having 1 to 8 carbon atoms,
sulfo,
oxo,

sulfonylamino,

cycloalkylamino wherein the cycloalkyl group has 3 to 7 carbon atoms and is optionally substituted by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

aryl containing 6 to 10 carbon atoms (e.g., phenyl, naphthyl, biphenyl) and is optionally substituted by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

aryl-alkylene group (e.g., benzyl, phenethyl, phenpropyl) wherein the aryl portion contains 6 to 10 carbon atoms and the alkylene portion contains 1 to 4 carbon atoms and is unsubstituted or substituted one or more times by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 C atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

aryloxy wherein the aryl portion contains 6 to 10 carbon atoms (e.g., phenyl, naphthyl, biphenyl) and is optionally substituted by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

arylthio wherein the aryl portion contains 6 to 10 carbon atoms (e.g., phenyl, naphthyl, biphenyl) and is optionally substituted by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

cycloalkyloxy wherein the cycloalkyl group has 3 to 7 carbon atoms and is optionally substituted by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 C carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

heterocyclic group, which is fully saturated, partially saturated or fully unsaturated, having 5 to 10 ring atoms in which at least 1 ring atom is a N, O or S atom, which is unsubstituted or substituted one or more times by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio, or combinations thereof; and

pharmaceutically acceptable salts thereof.

According to a further aspect of the invention, the compounds are selected from Formulas I-VI, wherein

R is H, and

Het is a heterocyclic group (e.g., furyl, thienyl, methylthienyl, bithienyl, benzylprazolyl, thiazolyl, imidazolyl, methylimidazolyl, pyrrolidinyl, morpholinyl, thiomorpholinyl), which is fully saturated, partially saturated or fully unsaturated, having 5 to 10 ring atoms in which at least 1 ring atom is a N, O or S atom, which is unsubstituted or substituted one or more times by

alkyl having 1 to 8 carbon atoms,
alkoxy having 1 to 8 carbon atoms,
halogen (F, Cl, Br, or I, preferably F or Cl),
amino,
cyano,
hydroxyl,
nitro,
halogenated alkyl having 1 to 8 carbon atoms,
halogenated alkoxy having 1 to 8 carbon atoms,
hydroxyalkyl having 1 to 8 carbon atoms,
hydroxyalkoxy having 2 to 8 carbon atoms,
alkenyloxy having 3 to 8 carbon atoms,
monoalkylamino having 1 to 8 carbon atoms,
dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms,
carboxy,
alkoxycarbonyl,
alkylaminocarbonyl,
acylamido (e.g., acetamido),
acyloxy (e.g., acetoxy),
alkylthio having 1 to 8 carbon atoms,
alkylsulphinyl having 1 to 8 carbon atoms,
alkylsulphonyl having 1 to 8 carbon atoms,
sulfo,
sulfonylamino,

cycloalkylamino wherein the cycloalkyl group has 3 to 7 carbon atoms and is optionally substituted by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

aryl containing 6 to 10 carbon atoms (e.g., phenyl, naphthyl, biphenyl) and is optionally substituted by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

aryl-alkylene group (e.g., benzyl, phenethyl, phenpropyl) wherein the aryl portion contains 6 to 10 carbon atoms and the alkylene portion contains 1 to 4 carbon atoms and is unsubstituted or substituted one or more times by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 C atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

aryloxy wherein the aryl portion contains 6 to 10 carbon atoms (e.g., phenyl, naphthyl, biphenyl) and is optionally substituted by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

arylthio wherein the aryl portion contains 6 to 10 carbon atoms (e.g., phenyl, naphthyl, biphenyl) and is optionally substituted by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

cycloalkyloxy wherein the cycloalkyl group has 3 to 7 carbon atoms and is optionally substituted by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 C carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

heterocyclic group, which is fully saturated, partially saturated or fully unsaturated, having 5 to 10 ring atoms in which at least 1 ring atom is a N, O or S atom, which is unsubstituted or substituted one or more times by halogen (F, Cl, Br, or I, preferably F or Cl), alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio, or combinations thereof;

and pharmaceutically acceptable salts thereof.

According to a further aspect of the invention, the compounds of Formulas I-VI are selected from Formulas I-V, wherein R is H, and R^1, R^2, R^4 and R^5 are each, independently,

C_{1-6}-alkyl (e.g., CH_3) which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{2-6}-alkenyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{2-6}-alkynyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, $Si(R^8)_3$, Ar, Het, or combinations thereof,

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{4-10}-cycloalkylalkyl which is unsubstituted or substituted in the cycloalkyl portion one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof, and/or substituted in the alkyl portion one or more times by one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof (e.g., cyclopentylmethyl, cyclopropylmethyl, etc.),

C_{3-8}-cycloalkyloxy which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

halogen (e.g., F, Cl, Br, I,),

CN, NO_2, NR^6R^7, SR^6, SOR^6, SO_2R^6, $SO_2NR^6R^7$, $NR^6SO_2R^7$, $CONR^6R^7$, $CSNR^6R^7$, $COOR^6$, NR^6COR^7, NR^6CSR^7, $NR^6CONR^6R^7$, $NR^6CSNR^6R^7$, NR^6COOR^7, NR^6CSOR^7, $OCONR^6R^7$, $OCSNR^6R^7$,

Ar,

Het, or

OR^9;

R^3 is halogen (e.g., F, Cl, Br, I), OH, CN, nitro, alkyl having 1 to 4 carbon atoms, halogenated alkyl having 1 to 4 carbon atoms (e.g., CF_3), cycloalkyl having 3 to 7 carbon atoms, cycloalkylalkyl having 4 to 7 carbon atoms, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), cycloalkoxy having 3 to 7 carbon atoms, cycloalkylalkoxy having 4 to 7 carbon atoms, halogenated alkoxy having 1 to 4 carbon atoms (e.g., OCF_3, $OCHF_2$), hydoxyalkyl having 1 to 4 carbon atoms, hydroxyalkoxy having 2 to 4 carbon atoms, NH_2, monoalkylamino having 1 to 4 carbon atoms, dialkylamino wherein each alkyl group independently has 1 to 4 carbon atoms, Ar or Het;

R^6 and R^7 are each independently

H,

C_{1-6}-alkyl (e.g., CH_3) which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms (e.g., diethylamino), C_{3-8}-cycloalkyl, Ar, Het, or combinations thereof,

C_{2-6}-alkenyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms (e.g., diethylamino), C_{3-8}-cycloalkyl, Ar, Het, or combinations thereof,

C_{2-6}-alkynyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms (e.g., diethylamino), C_{3-8}-cycloalkyl, $Si(R^8)_3$, Ar, Het, or combinations thereof,

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms (e.g., diethylamino), C_{3-8}-cycloalkyl, $Si(R^8)_3$, Ar, Het, or combinations thereof,

C_{4-10}-cycloalkylalkyl which is unsubstituted or substituted in the cycloalkyl portion one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms (e.g., diethylamino), C_{3-8}-cycloalkyl, $Si(R^8)_3$, Ar, Het, or combinations thereof, and/or substituted in the alkyl portion one or more

times by one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms (e.g., diethylamino), C_{3-8}-cycloalkyl, $Si(R^8)_3$, Ar, Het, or combinations thereof (e.g., cyclopentylmethyl, cyclopropylmethyl, etc.),

Ar, or

Het;

R^9 is H,

C_{1-6}-alkyl (e.g., CH_3) which is unsubstituted or substituted one or more by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{3-6}-alkenyl which is unsubstituted or substituted one or more by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), $NR^{13}R^{14}$, SH, SR^{13}, SOR^{13}, C_{3-8}-cycloalkyl, SO_2R^{13}, $SO_2NR^{13}R^{14}$, Ar, Het, or combinations thereof,

C_{3-6}-alkynyl which is unsubstituted or substituted one or more by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{4-8}-cycloalkylalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms (e.g., OCH_3), NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

Ar, or

Het; and

R^{11} is H, alkyl having 1 to 4 carbon atoms (which is unsubstituted or substituted one or more times by halogen, OH, alkoxy having 1 to 4 carbon atoms, C_{3-8} cycloalkyl, NR^6R^7, Ar, or Het), cycloalkyl having 3 to 7 carbon atoms (which is unsubstituted or substituted one or more times by halogen, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, Ar, or Het), Ar or Het.

According to a further aspect of the invention, the compounds are selected from Formulas I, II, IV and V, and at least one of R^1, R^2, R^4 and R^5 is C_{1-6}-alkyl which is substituted at least one time by OR^{16}, C_{2-6}-alkenyl which is substituted at least one time by OR^{16}, C_{2-6}-alkynyl which is substituted at least one time by OR^{16}, C_{3-8}-cycloalkyl which is substituted at least one time by OR^{16}, or C_{4-10}-cycloalkylalkyl which is substituted at least one time by OR^{16}, and R^{16} is other than H or C_{1-4}-alkyl.

According to a further aspect of the invention, the compounds are selected from Formula III, R^3 is OR^{16}, and R^{16} is other than H, C_{1-4}-alkyl, halogenated C_{1-4}-alkyl, C_{3-7}-cycloalkyl or C_{4-8}-cycloalkylalkyl.

According to a further aspect of the invention, the compounds are selected from Formulas I, II, IV and V and at least one of R^6 and R^7 is C_{1-6}-alkyl which is substituted at least one time by OR^{16}, C_{2-6}-alkenyl which is substituted at least one time by OR^{16}, C_{2-6}-

alkynyl which is substituted at least one time by OR^{16}, C_{3-8}-cycloalkyl which is substituted at least one time by OR^{16}, or C_{4-10}-cycloalkylalkyl which is substituted at least one time by OR^{16}, and R^{16} is other than H or C_{1-4}-alkyl.

According to a further aspect of the invention, the compounds are selected from Formulas I, II, IV and V and at least one R^9 is C_{1-6}-alkyl which is substituted at least one time by OR^{16}, C_{2-6}-alkenyl which is substituted at least one time by OR^{16}, C_{2-6}-alkynyl which is substituted at least one time by OR^{16}, C_{3-8}-cycloalkyl which is substituted at least one time by OR^{16}, or C_{4-10}-cycloalkylalkyl which is substituted at least one time by OR^{16}, and R^{16} is other than H or C_{1-4}-alkyl.

According to a further aspect of the invention, the compounds are selected from formula IV, Z is NR^{11}, R^{11} is C_{1-4}-alkyl which is substituted at least one time by OR^{16}, or C_{3-7}-cycloalkyl which is substituted at least one time by OR^{16}, and R^{16} is other than H or C_{1-4}-alkyl.

According to a further aspect of the invention, R^{12}, in addition to being C_{1-6}-alkoxy which is substituted one or more times by F or being selected from Formulae IX-XI , can also be NHR^8 (e.g., R^8 is C_{2-6}-alkyl), $NR^{17}CO\text{-}R^{10}$, $NR^{17}SO_2\text{-Het}$, $NR^{17}CO\text{-}O\text{-}CH_2\text{-Ar}$, $NR^{17}CONH\text{-}R^{10}$, or $NR^{17}CONR^{18}\text{-}CH_2\text{-Ar}$. Thus, for example, R^{12} can be selected from NHR^8 (e.g., R^8 is C_{2-6}-alkyl), $NR^{17}CO\text{-}O\text{-}CH_2\text{-Ar}$, $NR^{17}CONH\text{-}R^{10}$, and $NR^{17}CONR^{18}\text{-}CH_2\text{-Ar}$. In addition, R^{12} can be selected from $NR^{17}CO\text{-}O\text{-}CH_2\text{-Ar}$, $NR^{17}CONH\text{-}R^{10}$, or $NR^{17}CONR^{18}\text{-}CH_2\text{-Ar}$. In these embodiments, R^{17} and R^{18} are each independently H, alkyl having 1 to 4 carbon atoms (e.g., CH_3, C_2H_5), halogenated alkyl having 1 to 4 carbon atoms (e.g., CF_3), cycloalkyl having 3 to 7 carbon atoms (e.g., cyclopropyl, cyclobutyl, cyclopentyl), or cycloalkylalkyl having 4 to 7 carbon atoms (e.g., cyclopentylmethyl, cyclopropylmethyl, etc.). Further, R^1 (in addition to being unsubstituted or substituted C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{4-10}-cycloalkylalkyl, halogen, CN, NO_2, NR^6R^7, SR^6, SOR^6, SO_2R^6, $SO_2NR^6R^7$, $NR^6SO_2R^7$, $CONR^6R^7$, $CSNR^6R^7$, $COOR^6$, NR^6COR^7, NR^6CSR^7, $NR^6CONR^6R^7$, $NR^6CSNR^6R^7$, NR^6COOR^7, NR^6CSOR^7, $OCONR^6R^7$, $OCSNR^6R^7$, Ar, Het, or OR^9) can also be $-COR^{11}$

(e.g., -CO-C_{3-7}cycloalkyl) -$CONR^{10}R^{11}$ (e.g., -$CONHC_{3-8}$cycloalkyl) or -$CONHR^{10}(C_{1-6}$alkyl)Ar. Compounds which have an R^{12} and/or R^{1} group in accordance with these definitions include:

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-*N*-(4-fluorobenzyl)-5-({[(4-fluorobenzyl)amino]carbonyl}amino)-1*H*-indazole-1-carboxamide hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-*N*-(4-fluorobenzyl)-5-({[(4-fluorobenzyl)amino]carbonyl}amino)-1*H*-indazole-1-carboxamide,

Benzyl [3-(1,3-diazabicyclo[3.2.2]non-3-ylcarbonyl)-1*H*-indazol-5-yl]carbamate hydroformate,

Benzyl [3-(1,3-diazabicyclo[3.2.2]non-3-ylcarbonyl)-1*H*-indazol-5-yl]carbamate,

N-[1-(Cyclopropylcarbonyl)-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]cyclopropanecarboxamide hydroformate

N-[1-(Cyclopropylcarbonyl)-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]cyclopropanecarboxamide,

N-[3-(1,3-Diazabicyclo[3.2.2]non-3-ylcarbonyl)-1*H*-indazol-5-yl]-*N'*-(3-methoxybenzyl)urea hydroformate,

N-[3-(1,3-Diazabicyclo[3.2.2]non-3-ylcarbonyl)-1*H*-indazol-5-yl]-N'-(3-methoxybenzyl)urea,

N-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]-1-methyl-1*H*-imidazole-4-sulfonamide hydroformate,

N-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]-1-methyl-1*H*-imidazole-4-sulfonamide,

N-[3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]cyclopropanecarboxamide hydroformate,

N-[3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]cyclopropanecarboxamide,

N-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]-*N'*-(4-fluorobenzyl)urea hydroformate,

N-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]-N'-(4-fluorobenzyl)urea,

N-Cyclopentyl-*N'*-[3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]urea hydroformate,

N-Cyclopentyl-N'-[3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]urea,

N-Cyclopentyl-5-{[(cyclopentylamino)carbonyl]amino}-3-(1,4-diazabicyclo-[3.2.2]non-4-ylcarbonyl)-1*H*-indazole-1-carboxamide hydroformate,

N-Cyclopentyl-5-{[(cyclopentylamino)carbonyl]amino}-3-(1,4-diazabicyclo-[3.2.2]non-4-ylcarbonyl)-1*H*-indazole-1-carboxamide,

N-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1H-indazol-5-yl]pyrrolidine-1-carboxamide hydroformate,

N-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1H-indazol-5-yl]pyrrolidine-1-carboxamide,

Benzyl [1-benzyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]carbamate hydroformate, and

Benzyl [1-benzyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]carbamate.

Alkyl throughout means a straight-chain or branched-chain aliphatic hydrocarbon radical having preferably 1 to 4 carbon atoms, unless otherwise indicated. Suitable alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, and tert-butyl. The alkyl group can also be substituted.

Alkenyl throughout means a straight-chain or branched-chain alkyl radical having preferably 2 to 6 carbon atoms, unless otherwise indicated, wherein at least one CH_2CH_2 group is replaced by CH=CH. Suitable alkenyl groups include ethenyl, propenyl, butenyl, etc. The alkenyl group can also be substituted.

Alkynyl throughout means a straight-chain or branched-chain alkyl radical having preferably 2 to 6 carbon atoms, unless otherwise indicated, wherein at least one CH_2CH_2 group is replaced by C≡C. Suitable alkynyl groups include ethynyl, propynyl, butynyl, etc. The alkynyl group can also be substituted.

Alkoxy means alkyl-O- groups in which the alkyl portion preferably has 1 to 4 carbon atoms, unless otherwise indicated. Suitable alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, and sec-butoxy. The alkoxy group can also be substituted. For example, the alkoxy group may be substituted one or more times by F (e.g., OCF3, and $OCHF_2$).

Cycloalkyl means a cyclic, bicyclic or tricyclic saturated hydrocarbon radical having 3 to 8 carbon atoms, unless otherwise indicated. Suitable cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Other suitable cycloalkyl groups include spiropentyl, bicyclo[2.2.1]heptyl, and bicyclo[2.2.2]octyl.

The cycloalkyl groups can be substituted by, for example, F, Cl, Br, C_{1-4}-alkyl, C_{1-4}-alkoxy, hydroxyl, amino, monoalkylamino having 1 to 4 carbon atoms, and/or dialklyamino in which each alkyl group has 1 to 4 carbon atoms.

Cycloalkylalkyl refers to cycloalkyl-alkyl radicals in which the cycloalkyl and alkyl portions are in accordance with previous discussions. Suitable examples include cyclopropylmethyl and cyclopentylmethyl.

Cycloalkyloxy refers to cycloalkyl-oxy radicals in which the cycloalkyl portion is in accordance with previous discussions. Suitable examples include cyclopropyloxy and cyclopentyloxy.

Aryl, as a group or substituent per se or as part of a group or substituent, refers to an aromatic carbocyclic radical containing 6 to 10 carbon atoms, unless indicated otherwise. Suitable aryl groups include phenyl, napthyl and biphenyl. Substituted aryl groups include the above-described aryl groups which are substituted one or more times by halogen, alkyl, hydroxy, alkoxy, nitro, methylenedioxy, ethylenedioxy, amino, alkylamino, dialkylamino, hydroxyalkyl, hydroxyalkoxy, carboxy, cyano, acyl, alkoxycarbonyl, alkylthio, alkylsulphinyl, alkylsulphonyl, phenoxy, and acyloxy (e.g., acetoxy).

Arylalkyl refers to an aryl-alkyl radical in which the aryl and alkyl portions are in accordance with the previous descriptions. Suitable examples include benzyl, 1-phenethyl, 2-phenethyl, phenpropyl, phenbutyl, phenpentyl, and napthylmethyl.

Heterocyclic groups refer to saturated, partially saturated and fully unsaturated heterocyclic groups having one, two or three rings and a total number of 5 to 10 ring atoms wherein at least one of the ring atoms is an N, O or S atom. Preferably, the heterocyclic group contains 1 to 3 hetero-ring atoms selected from N, O and S. Suitable saturated and partially saturated heterocyclic groups include, but are not limited to tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, oxoazolinyl, isoxazolinyl and the like. Suitable heteroaryl groups include but are not limited to furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyridyl, pyrimidinyl, benzopyranyl, indolyl, quinolinyl, isoquinolinyl, naphthyridinyl and the like. Other examples of suitable heterocyclic groups, are 2-quinolinyl, 1,3-benzodioxyl, 2-thienyl, 2-benzofuranyl, 2-benzothiophenyl, 3-thienyl, 2,3-dihydro-5-benzofuranyl, 4-indoyl, 4-pyridyl, 3-quinolinyl, 4-quinolinyl, 1,4-benzodioxan-6-yl, 3-indoyl, 2-pyrrolyl, benzopyran-6-yl, 5-indolyl, 1,5-benzoxepin-8-yl, 3-pyridyl, 6-coumarinyl, 5-benzofuranyl, 2-isoimidazol-4-yl, 3-pyrazolyl, 3-carbazolyl, 2-thiazolyl, 2-oxazolyl, 1-imidazolyl, and 2-imidazolyl.

Substituted heterocyclic groups refer to the heterocyclic groups described above, which are substituted in one or more places by, for example, halogen, aryl, alkyl, hydroxy, alkoxy, cyano, trifluoromethyl, nitro, oxo, amino, alkylamino, and dialkylamino.

Radicals which are substituted one or more times preferably have 1 to 3 substituents, especially 1 or 2 substituents of the exemplified substituents. Halogenated radicals such as halogenated alkyls are preferably fluorinated and include perhalo radicals such as trifluoromethyl.

According to a further aspect of the invention the compounds are selected from formulas I-VIII, except that the following compounds are excluded:
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-*N*-(3-methoxybenzyl)-5-({[(3-methoxybenzyl)amino]carbonyl}amino)-1*H*-indazole-1-carboxamide and pharmaceutically acceptable salts thereof,
3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-8-(methoxy)-4*H*-chromen-4-one and pharmaceutically acceptable salts thereof,
N,1-Dibutyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-amine and pharmaceutically acceptable salts thereof, or
N-Butyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-amine and pharmaceutically acceptable salts thereof.

According to a further aspect of the invention the compounds are selected from formulas I-VIII, except that the following compounds are excluded:
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-methoxy-4*H*-chromen-4-one and pharmaceutically acceptable salts thereof,
5-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,3-benzothiazole and pharmaceutically acceptable salts thereof,
6-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,3-benzothiazole and pharmaceutically acceptable salts thereof,
6-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazole and pharmaceutically acceptable salts thereof,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-methoxyquinolin-4(1H)-one and pharmaceutically acceptable salts thereof,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-7-methoxyquinolin-4(1*H*)-one and pharmaceutically acceptable salts thereof,
N,N,1-Tributyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-amine and pharmaceutically acceptable salts thereof, and
5-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazole and pharmaceutically acceptable salts thereof.

In accordance with a further aspect of the invention, preferred R groups include halogens (R^1 to R^5, R^{14} and R^{15}), nitro (R^1 to R^5, R^{14} and R^{15}), NR^6R^7 (R^1, R^2, R^4, R^5, R^{14} and R^{15}), amino (R^1 to R^5, R^{14} and R^{15}), alkylamino (R^1 to R^5, R^{14} and R^{15}), dialkylamino (R^1 to R^5, R^{14} and R^{15}), phenyl which is unsubstituted or substituted (R^1, R^2, R^4 to R^7, R^9, R^{11}, and R^{13} to R^{15}), $NR^6CONR^6R^7$ such as phenylurea (R^1, R^2, R^4, R^5, R^{14} and R^{15}), hydroxyl (R^1 to R^5, R^{14} and R^{15}), alkoxy (R^1 to R^5, R^{14} and R^{15}), halogenated alkoxy (R^1 to R^5, R^{14} and R^{15}), and alkylsuflonamide (R^1, R^2, R^4, R^5, R^{14} and R^{15}) (e.g., bromo, nitro, amino, phenylurea, trifluoromethoxy, methoxy, methansulfonamide, hydroxyl, etc.)

In accordance with a further aspect of the invention, preferred groups for the heterocyclic groups of Formulas IX to XI include thiazolyl, substituted thiazolyl, thiazolylamino, substituted thiazolylamino, oxazolyl, substituted oxazolyl, imidazolyl, substituted imidazolyl, pyranyl, substituted pyranyl, piperidinyl, substituted piperidinyl, pyrrolydinyl, substituted pyrrolydinyl, pyrrolydinyloxy and substituted pyrrolydinyloxy (e.g., 5-methyl-1,3-thiazol-2-yl, 4-methyl-1,3-thiazol-2-yl, 1,3-thiazol-2-yl, 1,3-oxazol-2-yl, 1,3-imidazol-2-yl, 5-methyl-1,3-oxazol-2-yl, 4-methyl-1,3-oxazol-2-yl, pyran-4-yl, piperidin-4-yl, pyrrolidin-3-yl, pyrrolidin-3-yloxy, 3-hydroxypyrrolidin-1-yl, 1,3-thiazol-2-ylamino, etc.).

In accordance with a further aspect of the invention, R in Formulas I and VI is preferably H.

In accordance with a further aspect of the invention, B in Formulas II and VI is preferably C=O. In Formula V, B is preferably CH_2 or C=O.

In accordance with a further aspect of the invention, Z in Formulas IV and V is preferably O or NH.

In accordance with a further aspect of the invention, Y in Formula II is preferably S.

In accordance with a further aspect of the invention, the subscript "m" is preferably 2.

In accordance with a further aspect of the invention, preferred R^{12} groups of Formula IX are oxazolyl, thiazolyl, 4-methylthiazolyl, and 5-methylthiazolyl.

In accordance with a further aspect of the invention, preferred R^{12} groups of Formula X are tetrahydropyran and dihydropyran. Other preferred R^{12} groups of Formula X include 3-methylimidazolidin-2-one and 3-isopropyl-imidazolidin-2-one. A further preferred R^{12} group is halogenated alkoxy, especially OCF_3 and $OCHF_2$.

In accordance with a further aspect of the invention, preferred R^2 groups are OCH_3, OCF_3, ethoxy, cyclopropylmethoxy, and cyclopropyl.

In accordance with a further aspect of the invention, R^5 is preferably OCH_3.

In accordance with a further aspect of the invention, the compounds of Formula VI are prerferred.

According to a further compound and/or method aspect of the invention, the compounds are selected from:

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-thiazol-2-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-thiazol-2-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(trifluoromethoxy)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(trifluoromethoxy)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-oxazol-2-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-oxazol-2-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-thiazol-2-yl)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-thiazol-2-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-methoxy-1,2-benzisothiazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-methoxy-1,2-benzisothiazole,
4-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazole hydroformate, and
4-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazole; and
pharmaceutically acceptable salts thereof.

According to a further compound and/or method aspect of the invention, the compounds are selected from:
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-thiazol-2-yl)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-thiazol-2-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(trifluoromethoxy)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(trifluoromethoxy)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-oxazol-2-yl)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-oxazol-2-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-thiazol-2-yl)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-thiazol-2-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-methoxy-1,2-benzisothiazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-methoxy-1,2-benzisothiazole,
4-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazole hydroformate, and
4-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazole; and
pharmaceutically acceptable salts thereof.

According to a further compound and/or method aspect of the invention, the compounds are selected from:
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-4*H*-chromen-4-one hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-4*H*-chromen-4-one,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate, and
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole; and
pharmaceutically acceptable salts thereof.

According to a further compound and/or method aspect of the invention, the compounds are selected from:

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisoxazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisoxazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-thiazol-2-yl)-1*H*-indazole hydrochloride,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-thiazol-2-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(ethoxy)-1,2-benzisothiazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(ethoxy)-1,2-benzisothiazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1,2-benzisothiazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1,2-benzisothiazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-7-(methoxy)-1,2-benzisothiazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-7-(methoxy)-1,2-benzisothiazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-5-(methoxy)-4*H*-chromen-4-one,

3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-6-(methoxy)-4*H*-chromen-4-one hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-6-(methoxy)-4*H*-chromen-4-one,
3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-7-(methoxy)-4*H*-chromen-4-one,
6-(Cyclopropylmethoxy)-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole,
6-Cyclopropyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole hydroformate,
6-Cyclopropyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate,
and
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole; and
pharmaceutically acceptable salts thereof.

According to a further compound and/or method aspect of the invention, the compounds are selected from:
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisoxazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisoxazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-thiazol-2-yl)-1*H*-indazole hydrochloride,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-thiazol-2-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(ethoxy)-1,2-benzisothiazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(ethoxy)-1,2-benzisothiazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1,2-benzisothiazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1,2-benzisothiazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-7-(methoxy)-1,2-benzisothiazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-7-(methoxy)-1,2-benzisothiazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-5-(methoxy)-4*H*-chromen-4-one,

3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-6-(methoxy)-4*H*-chromen-4-one hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-6-(methoxy)-4*H*-chromen-4-one,

3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-7-(methoxy)-4*H*-chromen-4-one,

6-(Cyclopropylmethoxy)-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole,

6-Cyclopropyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole hydroformate,

6-Cyclopropyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate, and

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole; and

pharmaceutically acceptable salts thereof.

According to a further compound and/or method aspect of the invention, the compounds are selected from:

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(methoxy)-1,2-benzisothiazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(methoxy)-1,2-benzisothiazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-5-(methoxy)-4*H*-chromen-4-one hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-7-(methoxy)-4*H*-chromen-4-one hydroformate,

6-Bromo-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole hydroformate,

6-Bromo-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole,

1-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazol-6-yl]-3-isopropylimidazolidin-2-one hydroformate,

1-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazol-6-yl]-3-isopropylimidazolidin-2-one,

1-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazol-6-yl]-3-methylimidazolidin-2-one hydroformate,

1-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazol-6-yl]-3-methylimidazolidin-2-one,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-oxazol-2-yl)-1H-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-oxazol-2-yl)-1H-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-oxazol-2-yl)-1*H*-indazole hydrochloride,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(difluoromethoxy)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(difluoromethoxy)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(difluoromethoxy)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(difluoromethoxy)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(tetrahydro-2*H*-pyran-4-yloxy)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(tetrahydro-2*H*-pyran-4-yloxy)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(3,6-dihydro-2*H*-pyran-4-yl)-1H-indazole hydrochloride,

(3*E*)-3-(1,4-Diazabicyclo[3.2.2]non-4-ylmethylene)-6-methoxy-2,3-dihydro-4*H*-chromen-4-one hydroformate,

(3*E*)-3-(1,4-Diazabicyclo[3.2.2]non-4-ylmethylene)-6-methoxy-2,3-dihydro-4*H*-chromen-4-one,

(3*E*)-3-(1,4-Diazabicyclo[3.2.2]non-4-ylmethylene)-5-methoxy-2,3-dihydro-4*H*-chromen-4-one hydroformate,

(3*E*)-3-(1,4-Diazabicyclo[3.2.2]non-4-ylmethylene)-5-methoxy-2,3-dihydro-4*H*-chromen-4-one,

(3*E*)-3-(1,4-Diazabicyclo[3.2.2]non-4-ylmethylene)-7-methoxy-2,3-dihydro-4*H*-chromen-4-one hydroformate, and

(3*E*)-3-(1,4-Diazabicyclo[3.2.2]non-4-ylmethylene)-7-methoxy-2,3-dihydro-4*H*-chromen-4-one;

and pharmaceutically acceptable salts thereof.

Preferred aspects include pharmaceutical compositions comprising a compound of this invention and a pharmaceutically acceptable carrier and, optionally, another active agent as discussed below; a method of stimulating or activating inhibiting alpha-7 nicotinic receptors, e.g., as determined by a conventional assay or one described herein, either *in vitro* or *in vivo* (in an animal, e.g., in an animal model, or in a mammal or in a human); a method of treating a neurological syndrome, e.g., loss of memory, especially long-term memory, cognitive impairment or decline, memory impairment, etc. method of treating a disease state modulated by nicotinic alpha-7 activity, in a mammal, e.g., a human, e.g., those mentioned herein.

The compounds of the present invention may be prepared conventionally. Some of the known processes that can be used are described below. All starting materials are known or can be conventionally prepared from known starting materials.

The synthesis of similar compounds is disclosed in copending applications Serial No. 10/669,645, filed September 25, 2003, Serial No. 11/018,429, filed December 22, 2004, and Serial No. 11/111,958, filed April 22, 2005, the entire disclosures of which are hereby incorporated by reference.

Acids that were used in the preparation of the bicyclobase amides were commercially available or were prepared by known procedures described in the literature or as described below. For example, chromone-3-carboxylic acid was commercially available. Positional isomers of indazole carboxylic acid were prepared from the requisite bromo-2-methylanilines by diazotization followed by metal-halogen exchange and trapping with carbon dioxide (US 6,313,110 B1 and Sun, J.H.; Teleha, C.A.; Yan, J.S.; Rodgers, J.D.; Nugiel, D.A. *J. Org. Chem.* **1997**, *62*, 5627-5629). A variety of the simple substituted indazole-3-acids, such as the bromoindazole acids, were prepared from the corresponding isatins by basic hydrolysis, diazotization, and reduction (Snyder, H.R.; et al. *J. Am. Chem. Soc.* **1952**, *74*, 2009).

Some substituted indazole-3-acids were prepared by modifying existing indazole acids or esters. For example, 5-nitroindazole-3-acid was prepared by nitration of indazole-3-acid (Kamm, O.; Segur, J.B. *Org. Syn. Coll. Vol I.* **1941**, 372). Some non-aromatic heterocyclic derivatives were prepared from the bromides by metal-halogen exchange, trapping of indazole aryllithiums with ketones, followed by reduction or acid mediated elimination. Aromatic substituted indazole-3-acids were prepared from the bromides via palladium mediated cross-coupling with boronic acids or aryl zinc reagents (Reeder, M.R.; et. al. *Org. Proc. Res. Devel.* **2003**, *7*, 696).

Some substituted indazole-3-acids were prepared from simple benzene derivatives. For example, 5-difluoromethoxyindazole-3-acid was prepared from 3-

bromo-4-nitrophenol by reaction with ethyl difluoroacetate, reaction with diethyl malonate, decarboxylative saponification, esterification, reduction of the nitro group, and diazotization. 6-Difluoromethoxyindazole-3-acid was prepared in a similar manner from 2-bromo-5-difluoromethoxynitrobenzene. The 2-bromo-5-difluoromethoxynitrobenzene used in that preparation was prepared from 4-nitrophenol by ether formation, nitro reduction with concomitant protection as the amide, nitration, amide hydrolysis, and a Sandmeyer reaction with copper (I) bromide.

The benzisoxazole- and benzisoxazolecarboxylic acids were prepared using similar strategies outlined for the indazole acids. For example, ethyl 6-bromobenzisoxazole-3-carboxylate was prepared from 2,5-dibromonitrobenzene by reaction with diethyl malonate, saponification and decarboxylation, and reaction with isoamylnitrite. Ethyl benzisoxazole-3-carboxylate was obtained by hydrogenolysis of the 6-bromo derivative. 3-Benzisothiazolecarboxylic acid was prepared from thiophenol by reaction with oxalyl chloride and aluminum chloride followed by treatment with hydroxylamine, hydrogen peroxide, and sodium hydroxide.

The bicycloamines that were used in the preparation of the bicyclobase amides were prepared by known procedures described in the literature. For example, 1,4-diazabicyclo[3.2.2]nonane was prepared from 3-quinuclidinone hydrochloride according to the procedure outlined in WO 2004/076453 A1.

The bicyclobase amide was prepared by the coupling reaction of acids with the bicycloamine and HOBt and EDCI or HBTU in DMF, or by converting the acids to the corresponding acid chloride and then reaction with the bicycloamine (Macor, J.E.; et.al. *Bioorg. Med. Chem. Lett.* **2001**, *9*, 319-321). The couplings were generally performed at room temperatures for 18-24 hours. Bicyclobase methylenamine analogs were prepared by reductive amination using commercially available aldehydes. 5-Methoxychromone-3-carboxaldehyde was purchased from Indofine Chemical Company (Hillsborough, NJ). The resultant adducts was isolated and purified by standard techniques, such as chromatography or recrystallization, practiced by those skilled in the art

The nicotinic ligands were, alternatively, prepared by modification of other nicotinic ligands. For example, the 6-(3-isopropylimidazolidin-2-one) ligand was prepared from the corresponding bromide ligand by a palladium-catalyzed cross-coupling reaction. Other halogen-substituted ligands served as precursors for modified ligands where appropriate. As a final example, urea analogs were prepared from aniline substituted analogs.

One of ordinary skill in the art will recognize that compounds of Formulas I-VIII can exist in different tautomeric and geometrical isomeric forms. All of these compounds, including *cis* isomers, *trans* isomers, diastereomic mixtures, racemates, nonracemic mixtures of enantiomers, substantially pure, and pure enantiomers, are within the scope of the present invention. Substantially pure enantiomers contain no more than 5% w/w of the corresponding opposite enantiomer, preferably no more than 2%, most preferably no more than 1%.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (e.g., chiral HPLC columns), with or without conventional derivation, optimally chosen to maximize the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Diacel, e.g., Chiracel OD and Chiracel OJ among many others, all routinely selectable. Enzymatic separations, with or without derivitization, are also useful. The optically active compounds of Formulas I-VIII can likewise be obtained by utilizing optically active

starting materials in chiral synthesis processes under reaction conditions which do not cause racemization.

In addition, one of ordinary skill in the art will recognize that the compounds can be used in different enriched isotopic forms, e.g., enriched in the content of ^{2}H, ^{3}H, ^{11}C, ^{13}C and/or ^{14}C. In one particular embodiment, the compounds are deuterated. Such deuterated forms can be made the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997. As described in U.S. Patent Nos. 5,846,514 and 6,334,997, deuteration can improve the efficacy and increase the duration of action of drugs.

Deuterium substituted compounds can be synthesized using various methods such as described in: Dean, Dennis C.; Editor. Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development. [In: Curr., Pharm. Des., 2000; 6(10)] (**2000**), 110 pp. CAN 133:68895 AN 2000:473538 CAPLUS; Kabalka, George W.; Varma, Rajender S. The synthesis of radiolabeled compounds via organometallic intermediates. Tetrahedron (**1989**), 45(21), 6601-21, CODEN: TETRAB ISSN:0040-4020. CAN 112:20527 AN 1990:20527 CAPLUS; and Evans, E. Anthony. Synthesis of radiolabeled compounds, J. Radioanal. Chem. (**1981**), 64(1-2), 9-32. CODEN: JRACBN ISSN:0022-4081, CAN 95:76229 AN 1981:476229 CAPLUS.

Where applicable, the present invention also relates to useful forms of the compounds as disclosed herein, such as pharmaceutically acceptable salts or prodrugs of all the compounds of the present invention for which salts or prodrugs can be prepared. Pharmaceutically acceptable salts include those obtained by reacting the main compound, functioning as a bas with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid, succinic acid, citric acid, formic acid, hydrobromic acid, benzoic acid, tartaric acid, fumaric acid, salicylic acid, mandelic acid, and carbonic acid. Pharmaceutically acceptable salts also include those in which the main compound functions as an acid and is reacted with an appropriate base to form, e.g., sodium,

potassium, calcium, magnesium, ammonium, and choline salts. Those skilled in the art will further recognize that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts can be prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

The following are further examples of acid salts that can be obtained by reaction with inorganic or organic acids: acetates, adipates, alginates, citrates, aspartates, benzoates, benzenesulfonates, bisulfates, butyrates, camphorates, digluconates, cyclopentanepropionates, dodecylsulfates, ethanesulfonates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, fumarates, hydrobromides, hydroiodides, 2-hydroxy-ethanesulfonates, lactates, maleates, methanesulfonates, nicotinates, 2-naphthalenesulfonates, oxalates, palmoates, pectinates, persulfates, 3-phenylpropionates, picrates, pivalates, propionates, succinates, tartrates, thiocyanates, tosylates, mesylates and undecanoates.

Preferably, the salts formed are pharmaceutically acceptable for administration to mammals. However, pharmaceutically unacceptable salts of the compounds are suitable as intermediates, for example, for isolating the compound as a salt and then converting the salt back to the free base compound by treatment with an alkaline reagent. The free base can then, if desired, be converted to a pharmaceutically acceptable acid addition salt.

The compounds of the invention can be administered alone or as an active ingredient of a formulation. Thus, the present invention also includes pharmaceutical compositions of compounds of Formulas I-VIII, containing, for example, one or more pharmaceutically acceptable carriers.

Numerous standard references are available that describe procedures for preparing various formulations suitable for administering the compounds according to the invention. Examples of potential formulations and preparations are contained, for

example, in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (current edition); Pharmaceutical Dosage Forms: Tablets (Lieberman, Lachman and Schwartz, editors) current edition, published by Marcel Dekker, Inc., as well as Remington's Pharmaceutical Sciences (Arthur Osol, editor), 1553-1593 (current edition).

In view of their alpha-7 stimulating activity and, preferably their high degree of selectivity, the compounds of the present invention can be administered to anyone needing stimulation of alpha-7 receptors. Administration may be accomplished according to patient needs, for example, orally, nasally, parenterally (subcutaneously, intraveneously, intramuscularly, intrasternally and by infusion) by inhalation, rectally, vaginally, topically and by ocular administration.

Various solid oral dosage forms can be used for administering compounds of the invention including such solid forms as tablets, gelcaps, capsules, caplets, granules, lozenges and bulk powders. The compounds of the present invention can be administered alone or combined with various pharmaceutically acceptable carriers, diluents (such as sucrose, mannitol, lactose, starches) and excipients known in the art, including but not limited to suspending agents, solubilizers, buffering agents, binders, disintegrants, preservatives, colorants, flavorants, lubricants and the like. Time release capsules, tablets and gels are also advantageous in administering the compounds of the present invention.

Various liquid oral dosage forms can also be used for administering compounds of the inventions, including aqueous and non-aqueous solutions, emulsions, suspensions, syrups, and elixirs. Such dosage forms can also contain suitable inert diluents known in the art such as water and suitable excipients known in the art such as preservatives, wetting agents, sweeteners, flavorants, as well as agents for emulsifying and/or suspending the compounds of the invention. The compounds of the present invention may be injected, for example, intravenously, in the form of an isotonic sterile solution. Other preparations are also possible.

Suppositories for rectal administration of the compounds of the present invention can be prepared by mixing the compound with a suitable excipient such as cocoa butter, salicylates and polyethylene glycols. Formulations for vaginal administration can be in the form of a pessary, tampon, cream, gel, paste, foam, or spray formula containing, in addition to the active ingredient, such suitable carriers as are known in the art.

For topical administration the pharmaceutical composition can be in the form of creams, ointments, liniments, lotions, emulsions, suspensions, gels, solutions, pastes, powders, sprays, and drops suitable for administration to the skin, eye, ear or nose. Topical administration may also involve transdermal administration via means such as transdermal patches.

Aerosol formulations suitable for administering via inhalation also can be made. For example, for treatment of disorders of the respiratory tract, the compounds according to the invention can be administered by inhalation in the form of a powder (e.g., micronized) or in the form of atomized solutions or suspensions. The aerosol formulation can be placed into a pressurized acceptable propellant.

The compounds can be administered as the sole active agent or in combination with other pharmaceutical agents such as other agents used in the treatment of cognitive impairment and/or memory loss, e.g., other α-7 agonists, PDE4 inhibitors, calcium channel blockers, muscarinic m1 and m2 modulators, adenosine receptor modulators, amphakines NMDA-R modulators, mGluR modulators, dopamine modulators, serotonin modulators, canabinoid modulators, and cholinesterase inhibitors (e.g., donepezil, rivastigimine, and glanthanamine). In such combinations, each active ingredient can be administered either in accordance with their usual dosage range or a dose below their usual dosage range.

The compounds of the invention can be used in conjunction with "positive modulators" which enhance the efficacy of nicotinic receptor agonists. See, e.g., the positive modulators disclosed in WO 99/56745, WO 01/32619, and WO 01/32622. Such

combinational therapy can be used in treating conditions/diseases associated with reduced nicotinic transmission.

Further the compounds may be used in conjunction with compounds that bind to Aβ peptides and thereby inhibit the binding of the peptides to α7nAChr subtypes. See, e.g., WO 99/62505.

The present invention further includes methods of treatment that involve activation of α-7 nicotinic receptors. Thus, the present invention includes methods of selectively activating/stimulating α-7 nicotinic receptors in a patient (e.g., a mammal such as a human) wherein such activation/stimulation has a therapeutic effect, such as where such activation may relieve conditions involving neurological syndromes, such as the loss of memory, especially long-term memory. Such methods comprise administering to a patient (e.g., a mammal such as a human), an effective amount of a compound of Formulas I-VIII, alone or as part of a formulation, as disclosed herein.

In accordance with a method aspect of the invention, there is provided a method of treating a patient (e.g., a mammal such as a human) suffering from a disease state (e.g., memory impairment) comprising administering to the patient a compound according to Formulas I-VIII. Preferably, the disease state involves decreased nicotinic acetylcholine receptor activity.

In accordance with a method aspect of the invention there is provided a method for the treatment or prophylaxis of a disease or condition resulting from dysfunction of nicotinic acetylcholine receptor transmission in a patient (e.g., a mammal such as a human) comprising administering an effective amount of a compound according to Formulas I-VIII.

In accordance with a method aspect of the invention there is provided a method for the treatment or prophylaxis of a disease or condition resulting from defective or malfunctioning nicotinic acetylcholine receptors, particularly α7nACh receptors, in a

patient (e.g., a mammal such as a human) comprising administering an effective amount of a compound according to Formulas I-VIII.

In accordance with a method aspect of the invention there is provided a method for the treatment or prophylaxis of a disease or condition resulting from suppressed nicotinic acetylcholine receptor transmission in a patient (e.g., a mammal such as a human) comprising administering an amount of a compound according to Formulas I-VIII effective to activate α7nACh receptors.

In accordance with another method aspect of the invention there is provided a method for the treatment or prophylaxis of a psychotic disorder, a cognition impairment (e.g., memory impairment), or neurodegenerative disease in a patient (e.g., a mammal such as a human) comprising administering an effective amount of a compound according to Formulas I-VIII.

In accordance with another method aspect of the invention there is provided a method for the treatment or prophylaxis of a disease or condition resulting from loss of cholinergic synapses in a patient (e.g., a mammal such as a human) comprising administering an effective amount of a compound according to Formulas I-VIII.

In accordance with another method aspect of the invention there is provided a method for the treatment or prophylaxis of a neurodegenerative disorder by activation of α7nACh receptors in a patient (e.g., a mammal such as a human) comprising administering an effective amount of a compound according to Formulas I-VIII.

In accordance with another method aspect of the invention there is provided a method for protecting neurons in a patient (e.g., a mammal such as a human) from neurotoxicity induced by activation of α7nACh receptors comprising administering an effective amount of a compound according to Formulas I-VIII.

In accordance with another method aspect of the invention there is provided a method for the treatment or prophylaxis of a neurodegenerative disorder by inhibiting the binding of Aβ peptides to α7nACh receptors in a patient (e.g., a mammal such as a human) comprising administering an effective amount of a compound according to Formulas I-VIII.

In accordance with another method aspect of the invention there is provided a method for protecting neurons in a patient (e.g., a mammal such as a human) from neurotoxicity induced by Aβ peptides comprising administering an effective amount of a compound according to Formulas I-VIII.

In accordance with another method aspect of the invention there is provided a method for alleviating inhibition of cholinergic function induced by Aβ peptides in a patient (e.g., a mammal such as a human) comprising administering an effective amount of a compound according to Formulas I-VIII.

A subject or patient in whom administration of the therapeutic compound is an effective therapeutic regimen for a disease or disorder is preferably a human, but can be any animal, including a laboratory animal in the context of a clinical trial or screening or activity experiment. Thus, as can be readily appreciated by one of ordinary skill in the art, the methods, compounds and compositions of the present invention are particularly suited to administration to any animal, particularly a mammal, and including, but by no means limited to, humans, domestic animals, such as feline or canine subjects, farm animals, such as but not limited to bovine, equine, caprine, ovine, and porcine subjects, wild animals (whether in the wild or in a zoological garden), research animals, such as mice, rats, rabbits, goats, sheep, pigs, dogs, cats, etc., avian species, such as chickens, turkeys, songbirds, etc., i.e., for veterinary medical use.

The compounds of the present invention are nicotinic alpha-7 ligands, preferably agonists, especially partial agonists, for the alpha-7 nicotinic acetylcholine receptor. Assays for determining nicotinic acetylcholine activity are known within the art. See,

e.g., Davies, A.R., et al., Characterisation of the binding of [3H]methyllycaconitine: a new radioligand for labelling alpha 7-type neuronal nicotinic acetylcholine receptors. Neuropharmacology, 1999. 38(5): p. 679-90. As agonists for α7nACh receptors, the compounds are useful in the prophylaxis and treatment of a variety of diseases and conditions associated with the central nervous system. Nicotinic acetylcholine receptors are ligand-gastrol ion-channel receptors that are composed of five subunit proteins which form a central ion-conducting pore. Presently, there are eleven known neuronal nACh receptor subunits (α2 - α9 and β2 - β4). There are also five further subunits expressed in the peripheral nervous system (α1, β1, γ, δ, ε).

The nACh receptor subtypes can be homopentameric or heteropentameric. The subtype which has received considerable attention is the homopentameric α7 receptor subtype formed from five α7 subunits. The α7nACh receptors exhibit a high affinity for nicotine (agonist) and for α-bungarotoxin (antagonist). Studies have shown the α7nACh receptor agonists can be useful in the treatment of psychotic diseases, neurodegenerative diseases, and cognitive impairments, among other things. While nicotine is a known agonist, there is a need for the development of other α7nACh receptor agonists, especially selective agonists, which are less toxic or exhibit fewer side effects than nicotine.

The compound anabaseine, i.e., 2-(3-pyridyl)-3,4,5,6-tetrahydropyridine is a naturally occurring toxin in certain marine worms (nemertine worms) and ants. See, e.g., Kem et al., Toxicon, 9:23, **1971**. Anabaseine is a potent activator of mammalian nicotinic receptors. See, e.g., Kem, Amer. Zoologist, 25, 99, **1985**. Certain anabaseine analogs such as anabasine and DMAB (3-[4-(dimethylamino)benzylidene]-3,4,5,6-tetrahydro-2',3'-bipyridine) are also known nicotinic receptor agonists. See, e.g., US 5,602,257 and WO 92/15306. One particular anabaseine analog, (E-3-[2,4-dimethoxy-benzylidene]-anabaseine, also known as GTS-21 and DMXB (see, e.g., US 5,741,802), is a selective partial α7nACh receptor agonist that has been studied extensively. For example, abnormal sensory inhibition is a sensory processing deficit in schizophrenics

and GTS-21 has been found to increase sensory inhibition through interaction with α7nACh receptors. See, e.g., Stevens et al., Psychopharmacology, 136: 320-27 (1998).

Another compound which is known to be a selective α7nACh receptor agonist is Tropisetron, i.e., 1αH, 5αH-tropan-3α-yl indole-3-carboxylate. See J. E. Macor et al., The 5-HT3-Antagonist Tropisetron (ICS 205-930) is a Potent and Selective A7 Nicotinic Receptor Partial Agonist. *Bioorg. Med. Chem. Lett.* 2001, 319-321).

Agents that bind to nicotinic acetylcholine receptors have been indicated as useful in the treatment and/or prophylaxis of various diseases and conditions, particularly psychotic diseases, neurodegenerative diseases involving a dysfunction of the cholinergic system, and conditions of memory and/or cognition impairment, including, for example, schizophrenia, anxiety, mania, depression, manic depression [examples of psychotic disorders], Tourette's syndrome, Parkinson's disease, Huntington's disease [examples of neurodegenerative diseases], cognitive disorders (such as Alzheimer's disease, Lewy Body Dementia, Amyotrophic Lateral Sclerosis, memory impairment, memory loss, cognition deficit, attention deficit, Attention Deficit Hyperactivity Disorder), and other uses such as treatment of nicotine addiction, inducing smoking cessation, treating pain (i.e., analgesic use), providing neuroprotection, and treating jetlag. See, e.g., WO 97/30998; WO 99/03850; WO 00/42044; WO 01/36417; Holladay et al., J. Med. Chem., 40:26, 4169-94 (**1997**); Schmitt et al., Annual Reports Med. Chem., Chapter 5, 41-51 (**2000**); Stevens et al., Psychopharmatology, (**1998**) 136: 320-27; and Shytle et al., Molecular Psychiatry, (**2002**), 7, pp. 525-535.

Thus, in accordance with the invention, there is provided a method of treating a patient, especially a human, suffering from psychotic diseases, neurodegenerative diseases involving a dysfunction of the cholinergic system, and conditions of memory and/or cognition impairment, including, for example, schizophrenia, anxiety, mania, depression, manic depression [examples of psychotic disorders], Tourette's syndrome, Parkinson's disease, Huntington's disease [examples of neurodegenerative diseases], and/or cognitive disorders (such as Alzheimer's disease, Lewy Body Dementia,

Amyotrophic Lateral Sclerosis, memory impairment, memory loss, cognition deficit, attention deficit, Attention Deficit Hyperactivity Disorder) comprising administering to the patient an effective amount of a compound according to Formulas I-VIII.

Neurodegenerative disorders included within the methods of the present invention include, but are not limited to, treatment and/or prophylaxis of Alzheimer's diseases, Pick's disease, diffuse Lewy Body disease, progressive supranuclear palsy (Steel-Richardson syndrome), multisystem degeneration (Shy-Drager syndrome), motor neuron diseases including amyotrophic lateral sclerosis, degenerative ataxias, cortical basal degeneration, ALS-Parkinson's-Dementia complex of Guam, subacute sclerosing panencephalitis, Huntington's disease, Parkinson's disease, synucleinopathies, primary progressive aphasia, striatonigral degeneration, Machado-Joseph disease/spinocerebellar ataxia type 3, olivopontocerebellar degenerations, Gilles De La Tourette's disease, bulbar, pseudobulbar palsy, spinal muscular atrophy, spinobulbar muscular atrophy (Kennedy's disease), primary lateral sclerosis, familial spastic paraplegia, Werdnig-Hoffmann disease, Kugelberg-Welander disease, Tay-Sach's disease, Sandhoff disease, familial spastic disease, Wohlfart-Kugelberg-Welander disease, spastic paraparesis, progressive multifocal leukoencephalopathy, prion diseases (such as Creutzfeldt-Jakob, Gerstmann-Sträussler-Scheinker disease, Kuru and fatal familial insomnia), and neurodegenerative disorders resulting from cerebral ischemia or infarction including embolic occlusion and thrombotic occlusion as well as intracranial hemorrhage of any type (including, but not limited to, epidural, subdural, subarachnoid and intracerebral), and intracranial and intravertebral lesions (including, but not limited to, contusion, penetration, shear, compression and laceration).

In addition, α7nACh receptor agonists, such as the compounds of the present invention can be used to treat age-related dementia and other dementias and conditions with memory loss including age-related memory loss, senility, vascular dementia, diffuse white matter disease (Binswanger's disease), dementia of endocrine or metabolic origin, dementia of head trauma and diffuse brain damage, dementia pugilistica and frontal lobe dementia. See, e.g., WO 99/62505. Thus, in accordance with the invention, there is

provided a method of treating a patient, especially a human, suffering from age-related dementia and other dementias and conditions with memory loss comprising administering to the patient an effective amount of a compound according to Formulas I-VIII.

Thus, in accordance with a further embodiment, the present invention includes methods of treating patients suffering from memory impairment due to, for example, mild cognitive impairment due to aging, Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeld-Jakob disease, depression, aging, head trauma, stroke, CNS hypoxia, cerebral senility, multiinfarct dementia and other neurological conditions, as well as HIV and cardiovascular diseases, comprising administering an effective amount of a compound according to Formulas I-VIII.

Amyloid precursor protein (APP) and Aβ peptides derived therefrom, e.g., $A\beta_{1-40}$, $A\beta_{1-42}$, and other fragments, are known to be involved in the pathology of Alzhemier's disease. The $A\beta_{1-42}$ peptides are not only implicated in neurotoxicity but also are known to inhibit cholinergic transmitter function. Further, it has been determined that Aβ peptides bind to α7nACh receptors. Thus, agents which block the binding of the Aβ peptides to α-7 nAChRs are useful for treating neurodegenerative diseases. See, e.g., WO 99/62505. In addition, stimulation α7nACh receptors can protect neurons against cytotoxicity associated with Aβ peptides. See, e.g., Kihara, T. et al., Ann. Neurol., **1997**, 42, 159.

Thus, in accordance with an embodiment of the invention there is provided a method of treating and/or preventing dementia in an Alzheimer's patient which comprises administering to the subject a therapeutically effective amount of a compound according to Formulas I-VIII to inhibit the binding of an amyloid beta peptide (preferably, $A\beta_{1-42}$) with nACh receptors, preferable α7nACh receptors, most preferably, human α7nACh receptors (as well as a method for treating and/or preventing other clinical manifestations of Alzheimer's disease that include, but are not limited to, cognitive and language deficits, apraxias, depression, delusions and other neuropsychiatric symptoms and signs, and movement and gait abnormalities).

The present invention also provides methods for treating other amyloidosis diseases, for example, hereditary cerebral angiopathy, nonneuropathic hereditary amyloid, Down's syndrome, macroglobulinemia, secondary familial Mediterranean fever, Muckle-Wells syndrome, multiple myeloma, pancreatic- and cardiac-related amyloidosis, chronic hemodialysis anthropathy, and Finnish and Iowa amyloidosis.

In addition, nicotinic receptors have been implicated as playing a role in the body's response to alcohol ingestion. Thus, agonists for α7nACh receptors can be used in the treatment of alcohol withdrawal and in anti-intoxication therapy. Thus, in accordance with an embodiment of the invention there is provided a method of treating a patient for alcohol withdrawal or treating a patient with anti-intoxication therapy comprising administering to the patient an effective amount of a compound according to Formulas I-VIII.

Agonists for the α7nACh receptor subtypes can also be used for neuroprotection against damage associated with strokes and ischemia and glutamate-induced excitotoxicity. Thus, in accordance with an embodiment of the invention there is provided a method of treating a patient to provide for neuroprotection against damage associated with strokes and ischemia and glutamate-induced excitotoxicity comprising administering to the patient an effective amount of a compound according to Formulas I-VIII.

As noted above, agonists for the α7nACh receptor subtypes can also be used in the treatment of nicotine addiction, inducing smoking cessation, treating pain, and treating jetlag, obesity, diabetes, and inflammation. Thus, in accordance with an embodiment of the invention there is provided a method of treating a patient suffering from nicotine addiction, pain, jetlag, obesity and/or diabetes, or a method of inducing smoking cessation in a patient comprising administering to the patient an effective amount of a compound according to Formulas I-VIII.

The inflammatory reflex is an autonomic nervous system response to an inflammatory signal. Upon sensing an inflammatory stimulus, the autonomic nervous system responds through the vagus nerve by releasing acetylcholine and activating nicotinic α7 receptors on macrophages. These macrophages in turn release cytokines. Dysfunctions in this pathway have been linked to human inflammatory diseases including rheumatoid arthritis, diabetes and sepsis. Macrophages express the nicotinic α7 receptor and it is likely this receptor that mediates the cholinergic anti-inflammatory response. Therefore, compounds with affinity for the α7nACh receptor on macrophages may be useful for human inflammatory diseases including rheumatoid arthritis, diabetes and sepsis. See, e.g., Czura, C J et al., J. Intern. Med., **2005,** 257(2), 156-66.

Thus, in accordance with an embodiment of the invention there is provided a method of treating a patient (e.g., a mammal, such as a human) suffering from an inflammatory disease, such as, but not limited to, rheumatoid arthritis, diabetes or sepsis, comprising administering to the patient an effective amount of a compound according to Formulas I-VIII.

In addition, due to their affinity to α7nACh receptors, labeled derivatives of the compounds of Formulas I-VIII (e.g., C^{11} or F^{18} labeled derivatives), can be used in neuroimaging of the receptors within, e.g., the brain. Thus, using such labeled agents in vivo imaging of the receptors can be performed using, e.g., PET imaging.

The condition of memory impairment is manifested by impairment of the ability to learn new information and/or the inability to recall previously learned information. Memory impairment is a primary symptom of dementia and can also be a symptom associated with such diseases as Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeld-Jakob disease, HIV, cardiovascular disease, and head trauma as well as age-related cognitive decline.

Thus, in accordance with an embodiment of the invention there is provided a method of treating a patient suffering from, for example, mild cognitive impairment

(MCI), vascular dementia (VaD), age-associated cognitive decline (AACD), amnesia associated w/open-heart-surgery, cardiac arrest, and/or general anesthesia, memory deficits from early exposure of anesthetic agents, sleep deprivation induced cognitive impairment, chronic fatigue syndrome, narcolepsy, AIDS-related dementia, epilepsy-related cognitive impairment, Down's syndrome, Alcoholism related dementia, drug/substance induced memory impairments, Dementia Puglistica (Boxer Syndrome), and animal dementia (e.g., dogs, cats, horses, etc.) comprising administering to the patient an effective amount of a compound according to Formulas I-VIII.

The dosages of the compounds of the present invention depend upon a variety of factors including the particular syndrome to be treated, the severity of the symptoms, the route of administration, the frequency of the dosage interval, the particular compound utilized, the efficacy, toxicology profile, pharmacokinetic profile of the compound, and the presence of any deleterious side-effects, among other considerations.

The compounds of the invention can be administered to patients, e.g., mammals, particularly humans, at typical dosage levels customary for α-7 nicotinic receptor agonists such as the known α-7 nicotinic receptor agonist compounds mentioned above. For example, the compounds can be administered, in single or multiple doses, by oral administration at a dosage level of, for example, 0.0001-10 mg/kg/day, e.g., 0.01-10 mg/kg/day. Unit dosage forms can contain, for example, 1-200 mg of active compound. For intravenous administration, the compounds can be administered in single or multiple dosages.

In carrying out the procedures of the present invention it is of course to be understood that reference to particular buffers, media, reagents, cells, culture conditions and the like are not intended to be limiting, but are to be read so as to include all related materials that one of ordinary skill in the art would recognize as being of interest or value in the particular context in which that discussion is presented. For example, it is often possible to substitute one buffer system or culture medium for another and still achieve similar, if not identical, results. Those of skill in the art will have sufficient knowledge of

such systems and methodologies so as to be able, without undue experimentation, to make such substitutions as will optimally serve their purposes in using the methods and procedures disclosed herein.

The compounds of the invention also are useful as intermediates for making other compounds of the inventive genus. Thus, for example, compounds exhibiting relatively low activity are also useful for preparing other compounds within the inventive genus.

The present invention will now be further described by way of the following non-limiting examples. In applying the disclosure of these examples, it should be kept clearly in mind that other and different embodiments of the methods disclosed according to the present invention will no doubt suggest themselves to those of skill in the relevant art.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius; and, unless otherwise indicated, all parts and percentages are by weight.

The entire disclosures of all applications, patents and publications, cited above and below, are hereby incorporated by reference.

Using the following procedures and further procedures described below, the following compounds in Examples 1-54 were prepared.

EXAMPLES

All spectra were recorded at 300 MHz on a Bruker Instruments NMR unless otherwise stated. Coupling constants (*J*) are in Hertz (Hz) and peaks are listed relative to TMS (δ 0.00 ppm). Microwave reactions were performed using a Personal Chemistry Optimizer™ microwave reactor in 2.5 mL or 5 mL Personal Chemistry microwave reactor vials. All reactions were performed at 200 °C for 600 s with the fixed hold time ON unless otherwise stated. Sulfonic acid ion exchange resins (SCX) were purchased

from Varian Technologies. Analytical HPLC was performed on 4.6 mm x 100 mm Xterra RP_{18} 3.5 μ columns using a gradient of 20/80 to 80/20 water (0.1% formic acid)/acetonitrile (0.1% formic acid) over 6 min. Preparative HPLC was performed on 30 mm x 100 mm Xtera Prep RP_{18} 5 μ columns using an 8 min gradient of 95/5 to 20/80 water (0.1% formic acid)/acetonitrile (0.1% formic acid). Hydrochloride salts of the bicycle amides were prepared by adding an ethereal solution of hydrochloric acid to a methanolic solution of the bicyclic amide, followed by isolation of the resulting precipitate.

Representative Procedures.

I. Acid Syntheses

Procedure 1

Procedure 1 provides a preparation of substituted benzisothiazole-3-carboxylic acids from the corresponding thiophenols.

To a solution of 3-methoxythiophenol (26.7 mmol) in ether (20 mL) was added oxalyl chloride (43 mmol) dropwise. The mixture was heated at reflux for 1.5 h, cooled to rt, and concentrated *in vacuo*. The resulting yellow oil was dissolved in dichloromethane (50 mL), cooled to 0 °C, and was treated with aluminum chloride (32.0 mmol) in portions. The mixture was heated at reflux for 30 min, cooled to rt, and poured onto ice water with stirring. The organic layer was separated and successively washed with saturated, aqueous sodium bicarbonate, water, and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by chromatography (4/1 ethyl acetate/hexane) which provided 6-methoxy-1-benzothiophene-2,3-dione (47%) as an orange solid.

To a mixture of the dione (0.44 mmol) in 30% aqueous solution of ammonium hydroxide (2.0 mL) was added 35% aqueous solution hydrogen peroxide (0.2 mL) and the reaction mixture was maintained for 12 h. The precipitated pink solids were isolated

by filtration, washed with water, and dried under high vacuum to afford 6-methoxybenzisothiazole-3-carboxamide (42%).

To a solution of the amide (5.46 mmol) in methanol (100 mL) was added 10 N sodium hydroxide (12 mL). The mixture was heated at reflux for 12 h, cooled to rt, and was acidified to pH < 2 by the slow addition of conc. hydrochloric acid. The organic layer was extracted with dichloromethane (2 x) and was dried over sodium sulfate. The crude product was purified by chromatography (300/50/1 dichloromethane/methanol/formic acid) to provide 6-methoxy-1,2-benzisothiazole-3-carboxylic acid (89%) as a pink solid. The acid was coupled with 1,4-diazabicyclo[3.2.2]nonane according to procedure A.

The following acids were prepared by this method:

1,2-Benzisothiazole-3-carboxylic acid.
6-Methoxy-1,2-benzisothiazole-3-carboxylic acid.
6-Ethoxy-1,2-benzisothiazole-3-carboxylic acid
6-Trifluoromethoxy-1,2-benzisothiazole-3-carboxylic acid
6-Bromo-1,2-benzisothiazole-3-carboxylic acid
7-Methoxy-1,2-benzisothiazole-3-carboxylic acid

Procedure 2

Procedure 2 provides a method for the conversion of substituted isatins to the corresponding indazole-3-carboxylic acids.

The conversion of the substituted isatins to the corresponding indazole-3-carboxylic acids is essentially the same method as described for indazole-3-carboxylic acid: Snyder, H.R., et. al., *J. Am. Chem. Soc.* **1952**, *74*, 2009. The substituted isatin (22.1 mmol) was diluted with 1 N sodium hydroxide (24 mL) and was heated at 50 °C for 30 min. The burgundy solution was allowed to cool to rt and was maintained for 1h. The reaction mixture was cooled to 0 °C and was treated with a 0 °C solution of sodium nitrite

(22.0 mmol) in water (5.5 mL). This solution was added through a pipet submerged below the surface of a vigorously stirred solution of sulfuric acid (2.3 mL) in water (45 mL) at 0 °C. The addition took 15 min and the reaction was maintained for an additional 30 min. A cold (0 °C) solution of tin (II) chloride dihydrate (52.7 mmol) in concentrated hydrochloric acid (20 mL) was added to the reaction mixture over 10 min and the slurry was maintained for 60 min. The precipitated solids were isolated by filtration, washed with water, and dried to give a quantitative mass balance. The solid was recrystallized from acetic acid (20 mL/g) to provide the acid as a light yellow solid. . The acid was coupled with 1,4-diazabicyclo[3.2.2]nonane according to procedure A.

The following acids were prepared according to this method:

5-Bromo-1*H*-indazole-3-carboxylic acid.

5-Methoxy-1*H*-indazole-3-carboxylic acid.

5-(Trifluoromethoxy)-1*H*-indazole-3-carboxylic acid.

Procedure 3

Procedure 3 provides a method for the preparation of 5-nitroindazole-3-acid from indazole-3-acid.

The conversion of ethyl indazole-3-acid to 5-nitroindazole-3-carboxylic acid is essentially the same method as described for methyl 3-nitrobenzoic acid: Kamm, O.; Segur, J.B. *Org. Syn. Coll. Vol 1.* **1941**, 372. Ethyl indazole-3-carboxylate (73.7 mmol) was dissolved in 20 mL concentrated sulfuric acid and the reaction mixture was cooled to 0 °C. A mixture of concentrated sulfuric acid (12 mL) and 70% nitric acid (12 mL) was added dropwise over the course of 1 h. The mixture was stirred for an additional 1 h at 0 °C and was poured onto of crushed ice (200 g). The solid was collected by vacuum filtration, washed with several portions of water and dried *in vacuo*. The dried solid was suspended in 250 mL acetonitrile and the mixture was heated at reflux for 2 h. The mixture was allowed to cool to room temperature and the solid was collected and dried *in vacuo* to provide ethyl 5-nitroindazole-3-carboxylate (53%) as a colorless solid. The

ester was added to a solution of 10 N sodium hydroxide and the suspension was warmed to 60 °C. After 2 h the solution was allowed to cool to room temperature and was acidified to pH ~ 2. The precipitated solids were collected by filtration, washed with water, and dried to provide the acid as a light yellow solid. The acid was coupled with 1,4-diazabicyclo[3.2.2]nonane according to procedure A.

Procedure 4

Procedure 4 provides a method for the coupling between the brominated carboxylic esters and zinc reagents to form alkyl- and aryl-substituted derivatives.

A 5 mL microwave reaction vessel was charged with bis(triphenylphosphine)palladium (II) chloride (0.030 mmol, 0.1 eq) and the bromo ester (0.30 mmol). The vessel was evacuated and back-filled with argon gas. In a separate reaction vessel, solution of the Grignard (1.2 mmol, 4 eq) was added to a 0.5 M solution of zinc chloride (1.2 mmol, 4 eq) in tetrahydrofuran at rt. The suspension was maintained for 30 min and the entire contents were transferred to the reaction vessel via cannula. The vessel was sealed and subjected to microwave irradiation at 100 °C for 600 sec. The reaction was quenched with acetic acid (0.5 mL) and concentrated. The residue was diluted with saturated sodium bicarbonate and extracted with 9/1 dichloromethane/methanol (5 x 40 mL). The combined organic layers were dried (sodium sulfate) and concentrated. The residue was purified by chromatography (1/1 to 0/1 hexane/ethyl acetate) to provide the ester. The ester was added to a solution of 2 N sodium hydroxide and the suspension was warmed to 60 °C. After 2 h the solution was allowed to cool to room temperature and was acidified to pH ~ 2. The precipitated solids were collected by filtration, washed with water, and dried to provide the acid as an off-white to light yellow solid. The acid was coupled with 1,4-diazabicyclo[3.2.2]nonane according to procedure A.

The Grignard reagent of thiazole is commercially available. Alternatively, the aryllithium and the corresponding arylzinc reagent can be generated according to the

procedure outlined by Reeder, M.R.; et. al. *Org. Proc. Res. Devel.* **2003**, *7*, 696. The zinc reagents of oxazole, and related reagents were prepared according to this procedure.

The following acids were prepared according to this method:

5-(1,3-Thiazol-2-yl)-1*H*-indazole-3-carboxylic acid.
6-(1,3-Thiazol-2-yl)-1*H*-indazole-3-carboxylic acid.
5-(1,3-Oxazol-2-yl)-1*H*-indazole-3-carboxylic acid.
6-(1,3-Oxazol-2-yl)-1*H*-indazole-3-carboxylic acid.
6-(4-Methyl-1,3-thiazol-2-yl)-1*H*-indazole-3-carboxylic acid.
6-(5-Methyl-1,3-thiazol-2-yl)-1*H*-indazole-3-carboxylic acid.
5-(4-Methyl-1,3-thiazol-2-yl)-1*H*-indazole-3-carboxylic acid.
5-(5-Methyl-1,3-thiazol-2-yl)-1*H*-indazole-3-carboxylic acid.
6-Cyclopropyl-1,2-benzisothiazole-3-carboxylic acid.

Procedure 5

Procedure 5 provides a method for the preparation of indazole carboxylic acids from bromomethylanilines. (See, George V. DeLucca, U.S. Patent No. 6,313,110.)

To a cooled (water/ice bath) solution of bromomethylaniline (1.00 equiv.) in chloroform (1.5 mL/mol) was added acetic anhydride (2.27 equiv.) maintaining the temperature below 40 °C. The mixture was stirred at room temperature for 1 h. Potassium acetate (0.29 eq) was added followed by isoamyl nitrite (2.15 equiv.). The reaction mixture was heated overnight to reflux. Volatiles were removed on vacuum rotary evaporator. Water (0.65 L/mol) was added to the residue and the mixture was again concentrated in vacuum. Hydrochloric acid (11 N, 1 L/mol) was added to the residue and the mixture was vigorously stirred and heated to 50 °C for 2 h. The mixture was cooled to room temperature and pH was adjusted to 10 with 50% aqueous sodium hydroxide while maintaining the temperature below 25 °C. The mixture was diluted with water (0.65 L/mol) and extracted with ethyl acetate (2 x 1.2 L/mol). The combined extracts were washed with brine (1 L/mol) and dried over anhydrous sodium sulfate. The organic

solution was filtered through a plug of silica gel. The plug was further eluted with ethyl acetate. The solvent was removed on vacuum rotary evaporator, and the residue was triturated with heptane (1 L/mol). The solid material was collected by filtration, rinsed with heptane, and dried to provide the bromoindazole in 60-70% yield.

To a solution of the bromoindazole (1.00 equiv.) in anhydrous THF (7 L/mol) was added sodium hydride (60% in mineral oil, 1.11 equiv.) in several portions at room temperature. The resulting solution was stirred 30 min at room temperature then cooled in dry ice/acetone bath. *sec*-Butyllithium (1.3 M in cyclohexane, 2.11 equiv.) was added to the reaction mixture maintaining the temperature below –50 °C. The mixture was stirred 2 h at –50 °C. Anhydrous carbon dioxide was bubbled through the reaction mixture at temperature below –40 °C for 1 h. The reaction was allowed to reach room temperature while keeping steady flow of carbon dioxide through the mixture. Brine (6 L/mol) was added and pH of the mixture was adjusted to 5 with concd. hydrochloric acid. The mixture was extracted with warm ethyl acetate (3 x 8 L/mol). The combined extracts were washed with small volume of brine, dried over anhydrous sodium sulfate and concentrated. The product was purified by chromatography on silica gel or by crystallization to provide the acid in 30-60% yield. The acid was coupled with 1,4-diazabicyclo[3.2.2]nonane according to procedure A.

The following acid was prepared by this method:

1*H*-Indazole-4-carboxylic acid.

Procedure 6:

Procedure 6 details the preparation of benzisoxazole-3-carboxylic acid from 2,5-dibromonitrobenzene.

Diethyl malonate (12.6 g, 79 mmol) was added to a suspension of sodium hydride (3.16 g, 132 mmol) in dimethylsulfoxide (60 ml) over 30 min. The temperature of the reaction rose to 60 °C and the mixture clarified. 1,4-Dibromo-2-nitrobenzene (10 g, 36.0

mmol) was added and the solution was maintained for 2 h at 100 °C. The reaction mixture was allowed to cool to rt and was poured into ice (300g-400g). The precipitated solids were isolated by filtration and dried to provide 11.0 g of the product (89%).

The ester (11.0 g, 32.0 mmol) was diluted with a 2 N solution of sodium hydroxide (32 mL, 63 mmol) and the reaction mixture was maintained at room temperature for 16 h. The aqueous layer was extracted with dichloromethane (20 mL) and was acidified. The precipitated solids were isolated by filtration and dried to provide 7.00 g of the acid (89%).

Sulfuric acid (1 mL) was added to a solution of the acid (7.00 g, 27.0 mmol) in ethanol (60 ml). The reaction mixture was warmed to reflux, maintained for 2 h, and was concentrated under reduce pressure. The residue was partitioned between ethyl acetate (250 mL) and saturated sodium carbonate (50 mL) and the organic layer was washed with saturated sodium carbonate (50 mL) and brine (50 mL). The organic layer was dried (sodium sulfate) and concentrated to provide 8.00 g (98%) of the ester as a liquid.

Under N_2 atmosphere, sodium ethylate was formed with sodium (33.5 g, 1.46 mol) in ethanol (1.0 L).

Isoamylnitrite (225 mL) was added to a solution of the ester (420 g, 1.46 mol) in ethanol (3 L) in a 10 L three-necked round bottom flask and the mixture was warmed to 60 °C. A solution of sodium ethoxide, prepared from sodium metal (33.5 g, 1.46 mmol) in ethanol (1 L) was added dropwise and the reaction mixture was maintained for 2 h. The reaction mixture was allowed to cool to rt and was neutralized with 2 N hydrochloric acid. The reaction mixture was extracted with ethyl acetate (4 x 2L) and the combined organic layers were washed with water (2 x 1 L) and brine (2 x 1 L) and dried (sodium sulfate). The residue was purified by chromatography (1/1 to 0/1 hexane/ethyl acetate) to provide 110 g of the product (28%).

10% Palladium on carbon (1.5g) and triethylamine (7.5 g, 82.4 mmol) were added to a solution of ethyl 6-bromobenzisoxazole-3-carboxylate (20g, 0.081mol) in ethanol (300ml) at 0 °C under an atmosphere of nitrogen. The nitrogen atmosphere was removed by evacuation and replaced with hydrogen gas, and the reaction mixture was maintained for 1 hour. The hydrogen atmosphere was removed by evacuation and replaced with nitrogen gas, and the palladium removed by filtration through Celite. The filter cake was washed with ethanol (3 x 50 mL) and the filtrates were concentrated. The residue was dissolved in dichloromethane (200 mL) and the solution was washed with water (4 x 50 mL), dried (sodium sulfate) and evaporated to provide 13.0 g of the product as a yellow solid (96%). The ester was saponified using sodium hydroxide to provide the acid. The acid was coupled with 1,4-diazabicyclo[3.2.2]nonane according to procedure A.

Literature reference: Angell, R.M.; Baldwin, I.R.; Bamborough, P.; Deboeck, N.M.; Longstaff, T.; Swanson, S., WO 04/010995 A1

The following acid was prepared using this method:

1,2-Benzisoxazole-3-carboxylic acid.

Procedure 7

Procedure 7 provides a method for the trapping of indazole aryllithiums with ketones and the coupling with 3-aminoquinuclidine to form heterocyclic derivatives.

tert-Butyl 6-bromoindazole-3-carboxylate was prepared from the acid by reaction with a 2-fold excess of di-*tert*-butyldicarbonate followed by treatment with sodium hydroxide. To a suspension of sodium hydride (60% mineral oil dispersion) (4.8 mmol) in tetrahydrofuran (40 mL) at 0 °C was slowly added a solution of *tert*-butyl 6-bromoindazole-3-carboxylate (4.0 mmol) in tetrahydrofuran (4 mL). After stirring for 0.5 h at 0 °C, the mixture was cooled to –78 °C and a 1.7 M solution of *tert*-butyllithium in pentane (5.1 mmol) was added. After 0.5 h at –78 °C, a solution of tetrahydropyran-4-one (5 mmol) in tetrahydrofuran (1 mL) was added dropwise. The mixture was stirred at

–78 °C for 1 h and warmed to 0 °C. The reaction mixture was quenched with saturated aqueous ammonium chloride and the mixture was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was separated, washed with brine (50 mL), dried (magnesium sulfate), and concentrated. The residue was purified by chromatography (70/30 ethyl acetate/hexanes) to yield 6-(4-hydroxytetrahydropyran-4-yl)-1*H*-indazole-3-carboxylic acid tert-butyl ester (68%) as a colorless solid.

6-(4-Hydroxytetrahydropyran-4-yl)-1*H*-indazole-3-carboxylic acid *tert*-butyl ester (0.86 mmol) was dissloved in trifluoroacetic acid (3 mL) and the mixture was maintained at room temperature for 16 h. The solvent was removed *in vacuo* and the residue was triturated with ethyl acetate to provide 6-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole-3-carboxylic acid (76%).

6-(4-Hydroxytetrahydropyran-4-yl)-1*H*-indazole-3-carboxylic acid *tert*-butyl ester (1.0 mmol) was taken up in trifluoroacetic acid (5 mL), triethylsilane (2 mL), and dichloromethane (3 mL) and the mixture was refluxed for 16 h. The solvent was removed *in vacuo* and the residue was triturated with ethyl acetate to provide 6-(tetrahydropyran-4-yl)-1*H*-indazole-3-carboxylic acid (60%) as a tan solid.

The acids were coupled with 1,4-diazabicyclo[3.2.2]nonane according to procedure A.

The following acids were prepared using this method:

5-(3,6-Dihydro-2*H*-pyran-4-yl)-1*H*-indazole-3-carboxylic acid.
6-(3,6-Dihydro-2*H*-pyran-4-yl)-1*H*-indazole-3-carboxylic acid.
5-(Tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole-3-carboxylic acid.
6-(Tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole-3-carboxylic acid.

Procedure 8:

Procedure 8 provides a method for the preparation of 6-nitroindazole-3-acid and the coupling with bicyclobases to form nitro-substituted derivatives.

A 5 mL microwave reaction vessel was charged with 3-iodo-6-nitroindazole (1 mmol), copper (I) cyanide (2 mmol) and *N,N*-dimethylformamide (3 mL). The vessel was sealed and subjected to microwave irradiation at 185 °C for 600 sec. The reaction mixture was partitioned between ethyl acetate (100 mL) and water (100 mL) and the mixture was filtered through Celite. The organic layer was collected, washed with brine, dried (magnesium sulfate), and concentrated to give 122 mg of a 10/1 mixture of 3-cyano-6-nitroindazole and 6-nitroindazole as a yellow solid. The 10/1 mixture of 3-cyano-6-nitroindazole and 6-nitroindazole was dissolved in 10 N sodium hydroxide and the bright orange solution was heated at 100 °C for 1 h. The mixture was allowed to cool to room temperature and carefully acidified (pH = 1) with 3 N hydrochloric acid. The solid was isolated and triturated with EtOAc to provide 51mg of 6-nitroindazole-3-carboxylic acid as a brown solid. The acid was coupled with 1,4-diazabicyclo[3.2.2]nonane according to procedure A.

The following acid was prepared using this method:

6-Nitro-1*H*-indazole-3-carboxylic acid.

Procedure 9:

Procedure 9 provides a method for the preparation of 5-difluoromethoxyindazole-3-acid from 3-bromo-4-nitrophenol.

3-Bromo-4-nitrophenol (10.0 mmol) was added to a suspension of sodium hydroxide (29.0 mmol) in *N,N*-dimethylformamide (15 mL) and the suspension was maintained for 15 min at rt. The reaction mixture was cooled to 0 °C and was treated with ethyl chlorodifluoroacetate (20.0 mmol). The reaction mixture was heated at 70 °C for 16 h and was concentrated. The residue was diluted with ice water (200 mL) and was extracted with ethyl acetate (3x100 mL). The combined organic layers were dried

(magnesium sulfate) and concentrated to provide the difluoromethyl ether in 75% yield as a yellow oil.

Diethyl malonate (328 mmol) was added dropwise to a suspension of sodium hydride (328 mmol) in dimethylsulfoxide (40 mL) at 0 °C. The reaction mixture was warmed to 60 °C and maintained for 0.5 h. A solution of the difluoromethyl ether (149 mmol) in dimethylsulfoxide (80 mL) was added dropwise and the reaction mixture was heated at 100 °C for 5 h. The cooled solution was poured onto ice water, and the aqueous layer was extracted with dichloromethane (3x100 mL). The combined organic layers were dried (magnesium sulfate) and concentrated to give the crude diester in 112% yield as an oil. The diester (167 mmol), sodium hydroxide (500 mmol), and water (335 mL) were combined and heated at 60 °C for 1 h. The reaction mixture was allowed to cool to rt and the aqueous layer was washed with dichloromethane (3x100 mL). The pH of the aqueous layer was cautiously adjusted to 1 with concentrated hydrochloric acid and the reaction mixture was heated at 60 °C for 1 h. The suspension was cooled to 5 °C and the solids were collected by filtration and dried to provide the acid in 61% yield.

Acetyl chloride (203 mmol) was added dropwise to ethanol (300 mL) at 0 °C. After 0.5 h, the acid (101 mmol) was added and the reaction mixture was heated at reflux for 15 h. The reaction mixture was concentrated and the residue was partitioned between dichloromethane (200 mL) and saturated sodium bicarbonate (100 mL). The aqueous layer was further extracted with dichloromethane (2x200 mL) and the combined organic layers were dried (magnesium sulfate) and concentrated to provide the ester in 60% yield as a brown oil.

The ester (60.4 mmol) was dissolved in ethanol (103 mL), diluted with water (71 mL), and was treated with ammonium chloride (243 mmol) and iron powder (301 mmol). The reaction mixture was heated at reflux for 10 minutes and the suspension was filtrated through Celite and the filter cake was washed with ethanol three times. The filtrate was concentrated, the residue was suspended in 2 N hydrochloric acid and was stirred vigorously for 0.5 h. The aqueous layer was washed with ethyl acetate (3x50mL) and the

pH adjusted to 9-10 with 5 M sodium hydroxide. The aqueous layer was extracted with chloroform (3x100mL) and the combined organic layers were dried (magnesium sulfate). Acetic anhydride (392 mmol), isoamyl nitrite (291 mmol), and potassium acetate (51.0 mmol) were added to the organic layer and the suspension was heated at reflux for 16 h. The solution was evaporated and the residue was partitioned between saturated sodium bicarbonate (50 mL) and dichloromethane (100 mL). The aqueous layer was further extracted with dichloromethane (2x100 mL) and the combined organic layers were dried (magnesium sulfate) and concentrated to provide the *N*-acetylindazole ester in 79% yield as a brown oil.

The ester (63.8 mmol), sodium hydroxide (193 mmol), and water (65 mL) were combined and the reaction was maintained for 24 h at 60 °C. After cooling to rt, the aqueous layer was washed with dichloromethane (3x50mL). The aqueous layer was adjusted to pH 1 with concentrated hydrochloric acid. The precipitated solids were collected by filtration, washed with water and dichloromethane, and dried to provide the acid in 27% yield. The acid was coupled with 1,4-diazabicyclo[3.2.2]nonane according to procedure A.

The following acids were prepared according to this method:

5-(Difluoromethoxy)-1*H*-indazole-3-carboxylic acid.

Procedure 10:

Procedure 10 provides a method for the preparation of 6-difluoromethoxyindazole-3-acid from 4-nitrophenol.

4-Nitrophenol (162 mmol) was added to a suspension of sodium hydroxide (485 mmol) in *N,N*-dimethylformamide (150 mL) and the suspension was maintained for 15 min at rt. The reaction mixture was cooled to 0 °C and was treated with ethyl chlorodifluoroacetate (329 mmol). The reaction mixture was heated at 70 °C for 16 h and was concentrated. The residue was diluted with ice water (200 mL) and was extracted

with ethyl acetate (3x100 mL). The combined organic layers were dried (magnesium sulfate) and concentrated to provide the difluoromethyl ether in 59% yield as a yellow oil.

The nitro ether (149 mmol) was dissolved in ethanol (37.5 mL), diluted with water (25 mL), and was treated with ammonium chloride (84.7 mmol) and iron powder (105 mmol). The reaction mixture was heated at reflux for 30 minutes and the suspension was filtered through Celite. The filter cake was washed with ethanol three times and the combined filtrates were concentrated. The residue was dissolved in water and the pH adjusted to 9-10 with 5 M sodium hydroxide. The aqueous layer was extracted with ethyl acetate (3x100mL) and the combined organic layers were dried (magnesium sulfate) and concentrated to a yellow oil. The oil was dissolved in acetic anhydride (23.5 mmol) and the reaction mixture was maintained at rt for 16 h. The reaction mixture was diluted with water (50 mL) and was neutralized with solid sodium bicarbonate. The precipitated solids were isolated by filtration, washed with water, and dried to provide the acetamide in 62% yield as a light yellow solid.

Acetic anhydride (19.6 mmol) was added to a solution of the acetamide (13.2 mmol) in chloroform (20 mL) and the reaction mixture was warmed to reflux. Fuming nitric acid (16.0 mmol) was added dropwise and the reaction mixture was maintained at reflux for 30 min. The cooled solution was diluted with water (20 mL) and the aqueous layer was extracted with dichloromethane (3x10mL). The combined organic layers were dried (magnesium sulfate) and concentrated to provide the nitro-amide in 83% yield.

The amide (11.0 mmol), sodium hydroxide (43.8 mmol), and water (10 mL) were combined and the reaction mixture was maintained for 1.5 hour at 60 °C. the reaction was allowed to cool to rt and the precipitated solids were isolated by filtration, and washed with water, and dried to provide the aniline in 98% yield as a light yellow solid.

The aniline (15.7 mmol) was mixed with 40% hydrobromic acid (14.3 g) and water (10 mL) and the reaction mixture was warmed to 80-90 °C in order to completely

dissolve the aniline. The reaction mixture was cooled to 0 °C and a solution of sodium nitrite (23.2 mmol) in water (5.3 mL) was added during a 15 min period. The solution was maintained for 40 minutes at 0-5 °C and filtered. Copper (I) bromide (18.8 mmol) was dissolved in 40% hydrobromic acid (21 mL) and was cooled to 0 °C. The solution of the diazo salt was added slowly to the copper solution and the mixture was maintained for 30 min at 0-10 °C. The reaction mixture was heated at 60 °C for 30 min and then at 100 °C for 10 min to ensure completion. The reaction mixture was allowed to cool to rt and was extracted with dichloromethane (3x40mL). The combined organic layers were washed with 1 M sodium hydroxide, water, 1 N hydrochloric acid, and water. The organic layer was dried (magnesium sulfate) and concentrated to provide the nitro bromide in 76% yield as a light yellow solid.

Diethyl malonate (25.7 mmol) was added dropwise to a suspension of sodium hydride (25.8 mmol) in dimethylsulfoxide (5 mL) at 0 °C. The reaction mixture was warmed to 60 °C and maintained for 30 min. A solution of the nitro bromide (11.7 mmol) in dimethylsulfoxide (7 mL) was added dropwise and the reaction mixture was heated at 100 °C for 5 h. The cooled solution was poured onto ice water and the aqueous layer was extracted with dichloromethane (3x100 mL). The combined organic layers were dried (magnesium sulfate) and concentrated to give the crude diester as an oil. The diester (11.7 mmol), sodium hydroxide (35 mmol), and water (20 mL) were combined and heated at 60 °C for 1 h. The reaction mixture was allowed to cool to rt and the aqueous layer was washed with dichloromethane (3x100 mL). The pH of the aqueous layer was cautiously adjusted to 1 with concentrated hydrochloric acid and the reaction mixture was heated at 60 °C for 1 h. The suspension was cooled to 0 °C and the solids were collected by filtration and dried to provide the acid in 64% yield.

Acetyl chloride (15.3 mmol) was added dropwise to ethanol (50 mL) at 0 °C. After 30 min, the acid (7.69 mmol) was added and the reaction mixture was heated at reflux for 15 h. The reaction mixture was concentrated and the residue was partitioned between dichloromethane (20 mL) and saturated sodium bicarbonate (10 mL). The aqueous layer was further extracted with dichloromethane (2x20 mL) and the combined

organic layers were dried (magnesium sulfate) and concentrated to provide the ester in 94% yield as a brown oil.

Acetic anhydride (6.0 mL) was added to a suspension of the ester (3.64 mmol), and acetic acid (7.0 mL) at 0 °C. Zinc dust (14.6 mmol) was added in portions over 15 min and the reaction mixture was maintained for 30 min at 0 °C and then for 1.5 h at rt. Additional zinc powder (6.15 mmol) was added and the reaction maintained for 3 h. The suspension was filtered through Celite and the filtrate was concentrated. The residue was partitioned between saturated sodium bicarbonate (10 mL) and ethyl acetate (20 mL). The aqueous layer was further extracted with ethyl acetate (3x20mL) and the combined organic layers were dried (magnesium sulfate) and concentrated to provide the acetamide in 92% yield as a brown oil.

Acetic anhydride (13.7 mmol), isoamyl nitrite (13.7 mmol), and potassium acetate (2.04 mmol) were added to a solution of the acetamide (3.92 mmol) in chloroform (20 mL) and the suspension was heated at reflux for 16 h. The solution was evaporated and the residue was partitioned between saturated sodium bicarbonate (10 mL) and dichloromethane (20 mL). The aqueous layer was further extracted with dichloromethane (2x20 mL) and the combined organic layers were dried (magnesium sulfate) and concentrated to provide the crude *N*-acetylindazole ester as a brown oil.

The ester (3.36 mmol), sodium hydroxide (10 mmol) and water (5 mL) were combined and the reaction was maintained for 24 h at 60 °C. After cooling to rt, the aqueous layer was washed with dichloromethane (3x30mL). The aqueous layer was adjusted to pH 1 with concentrated hydrochloric acid and the precipitated solids were collected by filtration, washed with water and dichloromethane, and dried to provide the acid in 26% yield. The acid was coupled with 1,4-diazabicyclo[3.2.2]nonane according to procedure A.

The following acids were prepared according to this method:

6-(Difluoromethoxy)-1*H*-indazole-3-carboxylic acid.

Procedure 11:

Procedure 11 provides a method for the preparation of alkoxy indazole acids from the corresponding benzyloxy indazole esters using Mitsunobu conditions.

Diisopropyl azodicarboxylate (0.618 mmol) was added dropwise to a solution of ethyl 5-hydroxy-1-(2-trimethylsilanylethoxymethyl)-1*H*-indazole-3-carboxylate (0.594 mmol), 1-methyl-3-pyrrolidinol (0.594 mmol), and triphenylphosphine (0.594 mmol) in tetrahydrofuran (3.6 mL). The reaction was maintained for 16 h and was concentrated. The residue was purified by chromatography (100/0 to 90/10 ethyl acetate/[70/30/2 ethyl acetate/methanol/dimethylethylamine] to provide the ether product in 49% yield. The ester was saponified to provide the acid which was coupled with 1,4-diazabicyclo[3.2.2]nonane according to procedure A.

The following acids were prepared using this method:

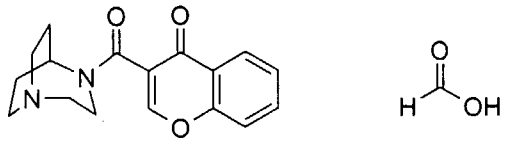
5-(Tetrahydro-2*H*-pyran-4-yloxy)-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-indazole-3-carboxylic acid.

II. Coupling and Derivatization Procedures

Representative Procedure A.

Procedure A provides a method for the coupling between bicyclobases and carboxylic acids to form carboxamide derivatives.

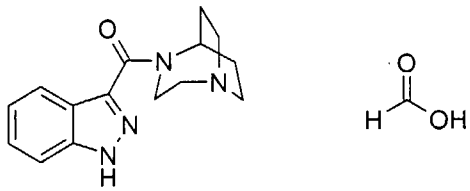
Example 1: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-4*H*-chromen-4-one hydroformate.



N,N-Diisopropylethylamine (2.01 mmol) was added to a solution of the carboxylic acid (0.502 mmol), 1,4-diazabicyclo[3.2.2]nonane (0.502 mmol) and HATU (0.603 mmol) in N,N-dimethylformamide (5 mL) at 25 °C, and the reaction mixture was maintained for 10 h. The reaction mixture was loaded on a SCX column, washed with methanol, and the product was eluted using a 2N solution of ammonia in methanol. The residue was purified by preparative HPLC to provide the product in 25 % yield. ^{1}H NMR (CD_3OD) δ 8.48 (s, 1 H), 8.43 (s, 1 H), 8.19 (dd, J = 9.0, 1.6, 1 H), 7.86 (td, J = 7.2, 1.7, 1 H), 7.62 (d, J = 8.5, 1 H), 7.56 (td, J = 7.1, 1.0, 1 H), 4.20 (m, 1 H), 3.83 (m, 2 H), 3.61-3.42 (m, 6 H), 2.40-2.12 (m, 4 H); LC/MS (EI) t_R 1.76 min, m/z 299 (M^++1).

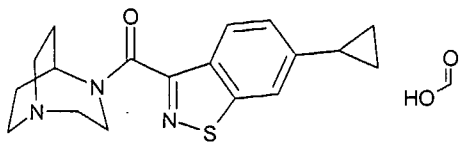
Using this general procedure the following compounds were prepared:

Example 2: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazole hydroformate.



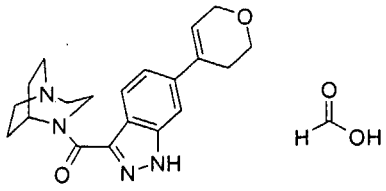
Prepared by Procedure A in 29 % yield. LC/MS (EI) t_R 2.4 min, m/z 271 (M^++1).

Example 3: 6-Cyclopropyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole hydroformate.



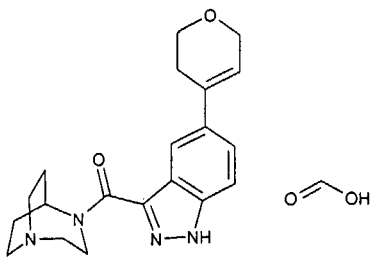
Prepared by Procedure A in 70 % yield. LC/MS (EI) t_R 4.75 min, *m/z* 328 (M^++1).

Example 4: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate.



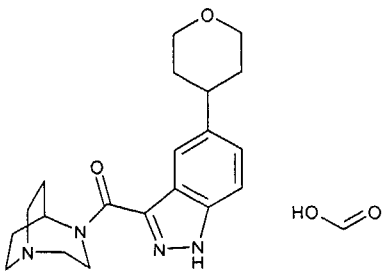
Prepared by Procedure A in 20 % yield. LC/MS (EI) t_R 2.43 min, *m/z* 353 (M^++1).

Example 5: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate.



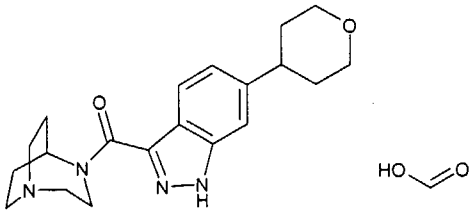
Prepared by Procedure A in 20 % yield. LC/MS (EI) t_R 2.42 min, *m/z* 353 (M^++1).

Example 6: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate.



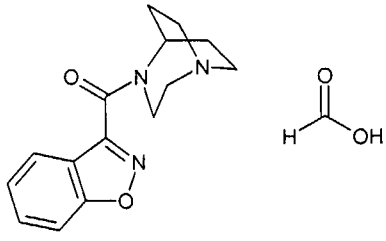
Prepared by Procedure A in 20 % yield. LC/MS (EI) t_R 2.41 min, *m/z* 355 (M^++1).

Example 7: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate.



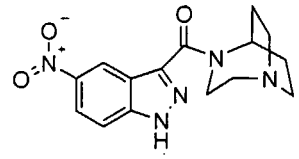
Prepared by Procedure A in 20 % yield. LC/MS (EI) t_R 2.44 min, *m/z* 355 (M^++1).

Example 8: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisoxazole hydroformate.



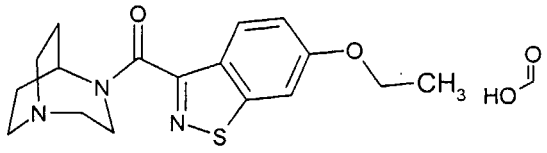
Prepared by Procedure A in 20 % yield. LC/MS (EI) t_R 3.78 min, *m/z* 272 (M^++1).

Example 9: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(nitro)-1*H*-indazole.



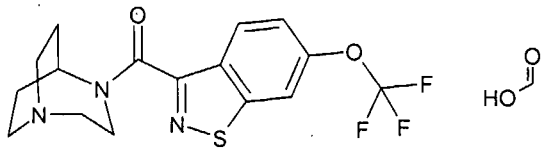
Prepared by Procedure A in 60 % yield. LC/MS (EI) t_R 1.33 min, *m/z* 316 (M^++1).

Example 10: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(ethoxy)-1,2-benzisothiazole hydroformate.



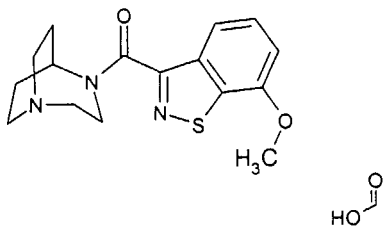
Prepared by Procedure A in 70 % yield. LC/MS (EI) t_R 3.44 min, *m/z* 331 (M^++1).

Example 11: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1,2-benzisothiazole hydroformate.



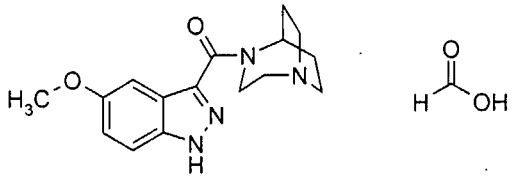
Prepared by Procedure A in 70 % yield. LC/MS (EI) t_R 4.41 min, *m/z* 372 (M^++1).

Example 12: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-7-(methoxy)-1,2-benzisothiazole hydroformate.



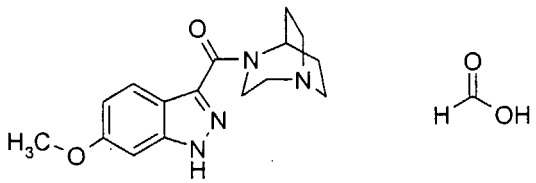
Prepared by Procedure A in 66 % yield. LC/MS (EI) t_R 2.94 min, *m/z* 318 (M^++1).

Example 13: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(methoxy)-1*H*-indazole hydroformate.



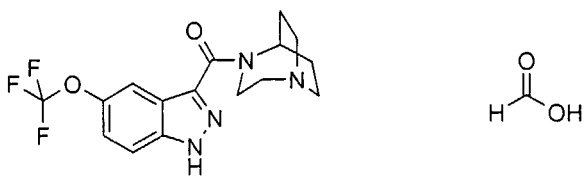
Prepared by Procedure A in 60 % yield. LC/MS (EI) t_R 3.55 min, *m/z* 301 (M^++1).

Example 14: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(methoxy)-1*H*-indazole hydroformate.



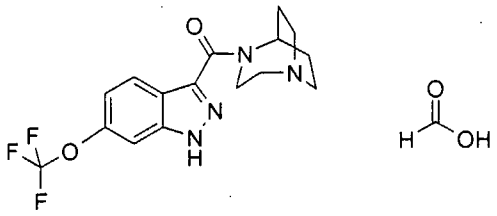
Prepared by Procedure A in 20 % yield. LC/MS (EI) t_R 3.02 min, *m/z* 301 (M^++1).

Example 15: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(trifluoromethoxy)-1*H*-indazole hydroformate.



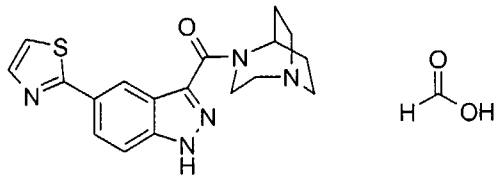
Prepared by Procedure A in 40 % yield. LC/MS (EI) t_R 4.42 min, *m/z* 355 (M^++1).

Example 16: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1*H*-indazole hydroformate.



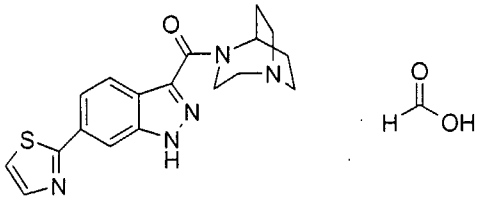
Prepared by Procedure A in 30 % yield. LC/MS (EI) t_R 4.33 min, *m/z* 355 (M^++1).

Example 17: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-thiazol-2-yl)-1*H*-indazole hydroformate.



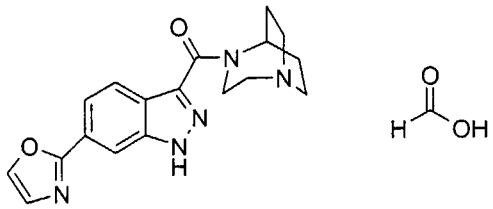
Prepared by Procedure A in 80 % yield. LC/MS (EI) t_R 3.18 min, *m/z* 354 (M^++1).

Example 18: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-thiazol-2-yl)-1*H*-indazole hydroformate.



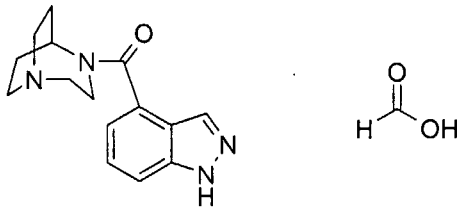
Prepared by Procedure A in 20 % yield. LC/MS (EI) t_R 2.45 min, *m/z* 354 (M^++1).

Example 19: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-oxazol-2-yl)-1*H*-indazole hydroformate.



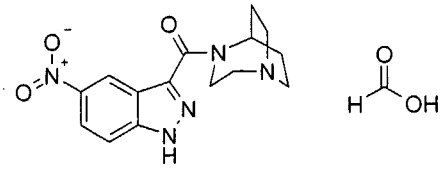
Prepared by Procedure A in 20 % yield. LC/MS (EI) t_R 2.45 min, *m/z* 338 (M^++1).

Example 20: 4-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazole hydroformate.



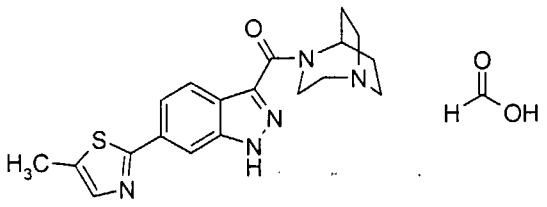
Prepared by Procedure A in 74 % yield. LC/MS (EI) t_R 1.61 min, *m/z* 272 (M^++1).

Example 21: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(nitro)-1*H*-indazole hydroformate.



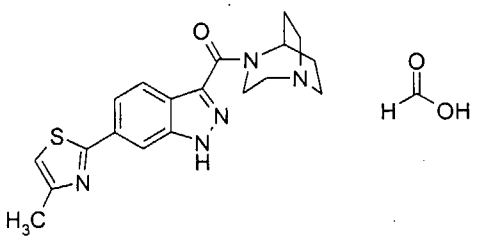
Prepared by Procedure A in 60 % yield. LC/MS (EI) t_R 1.32 min, *m/z* 316 (M^++1).

Example 22: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate.



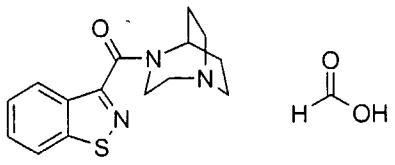
Prepared by Procedure A in 20 % yield. LC/MS (EI) t_R 3.55 min, *m/z* 368 (M^++1).

Example 23: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate.



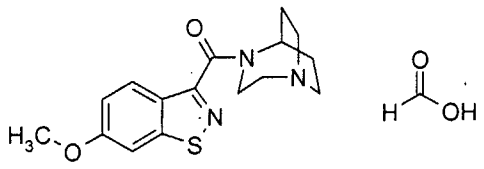
Prepared by Procedure A in 20 % yield. LC/MS (EI) t_R 3.20 min, *m/z* 368 (M^++1).

Example 24: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole hydroformate.



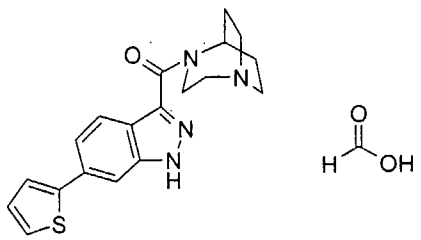
Prepared by Procedure A in 80 % yield. LC/MS (EI) t_R 2.44 min, *m/z* 288 (M^++1).

Example 25: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(methoxy)-1,2-benzisothiazole hydroformate.



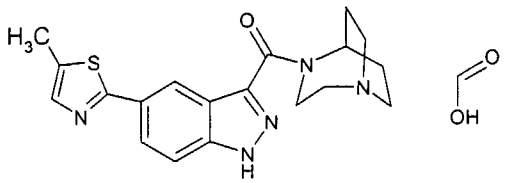
Prepared by Procedure A in 70 % yield. LC/MS (EI) t_R 3.82 min, *m/z* 318 (M^++1).

Example 26: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(2-thienyl)-1*H*-indazole hydroformate.



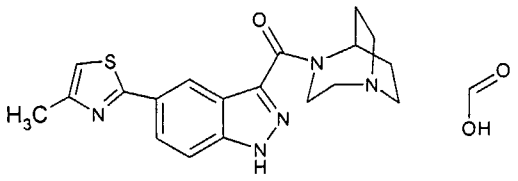
Prepared by Procedure A in 20 % yield. LC/MS (EI) t_R 3.78 min, *m/z* 353 (M^++1).

Example 27: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate.



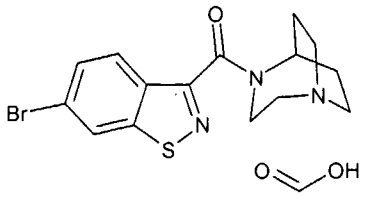
Prepared by Procedure A in 20 % yield. LC/MS (EI) t_R 3.24 min, *m/z* 368 (M^++1).

Example 28: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate.



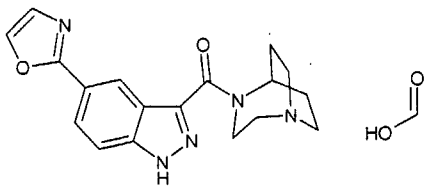
Prepared by Procedure A in 20 % yield. LC/MS (EI) t_R 3.03 min, *m/z* 368 (M^++1).

Example 29: 6-Bromo-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole hydroformate



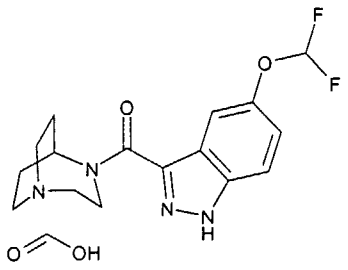
Prepared by Procedure A in 64% yield. LC/MS (EI) t_R 3.69 min, *m/z* 367 (M^++1).

Example 30: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-oxazol-2-yl)-1*H*-indazole hydroformate



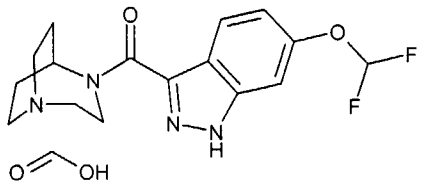
Prepared by Procedure A in 20 % yield. LC/MS (EI) t_R 2.5 min, *m/z* 338 (M^++1).

Example 31: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(difluoromethoxy)-1*H*-indazole hydroformate



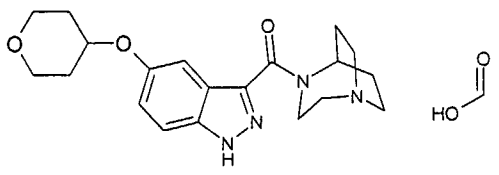
Prepared by Procedure A in 6 % yield. LC/MS (EI) t_R 4.62 min, *m/z* 337 (M^++1).

Example 32: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(difluoromethoxy)-1*H*-indazole hydroformate



Prepared by Procedure A in 6 % yield. LC/MS (EI) t_R 2.13 min, *m/z* 337 (M^++1).

Example 33: 3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(tetrahydro-2*H*-pyran-4-yloxy)-1*H*-indazole hydroformate

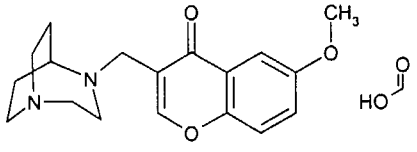
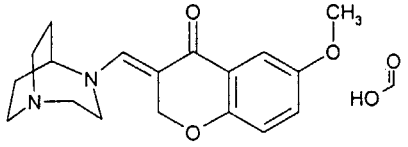


Prepared by Procedure A, followed by exposure to aquesous hydrochloric acid, in 17 % yield. LC/MS (EI) t_R 4.27 min, *m/z* 370 (M^++1).

Representative Procedure B.

Procedure **B** provides a method for the coupling between bicyclobase amines and carboxaldehydes to form tertiary amine derivatives.

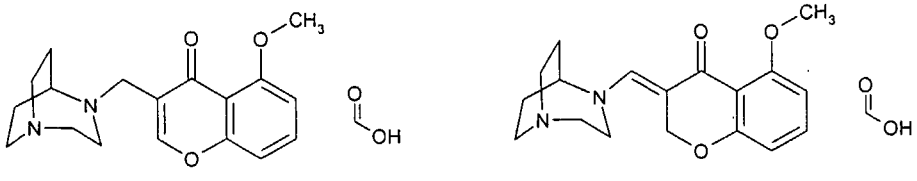
Example 34: Mixture of 3-(1,4-diazabicyclo[3.2.2]non-4-yl-methyl)-6-(methoxy)-4*H*-chromen-4-one hydroformate and (3*E*)-3-(1,4-diazabicyclo[3.2.2]non-4-ylmethylene)-6-methoxy-2,3-dihydro-4*H*-chromen-4-one hydroformate.

Sodium cyanoborohydride (0.0980 mmol) was added to a solution of 6-methoxy-4-oxo-4*H*-chromene-3-carbaldehyde (0.490 mmol), and 1,4-diazabicyclo[3.2.2] nonane (0.490 mmol) in methanol (3.00 mL), and the reaction mixture was maintained for 10 h. The reaction mixture was transferred to a SCX column, washed with methanol, and the product was eluted using a 2N solution of ammonia in methanol. The residue was purified by preparative HPLC to provide the product in 4 % yield, as a mixture of the 1,2 and 1,4 reduction products. ^{1}H NMR (CD_3OD) δ 8.27 (s, 0.5 H), 8.21 (s, 0.5 H), 7.56 (d, J = 9.0, 0.5 H), 7.54 (d, J = 2.9, 0.5 H), 7.38 (dd, J = 9.0, 3.0, 0.5 H), 6.89 (d, J = 2.9, 0.5 H), 6.76 (dd, J = 8.9, 2.9, 0.5 H), 6.68 (d, J = 8.9, 0.5 H), 4.87 (s, 1 H), 4.27-4.22 (m, 0.5 H), 4.07-4.01 (m, 0.5 H), 3.89 (s, 1.5 H), 3.77 (s, 1.5 H), 3.46-3.29 (m, 3.5 H), 3.11-2.46 (m, 3.5 H), 2.53-2.19 (m, 3 H), 2.09-1.93 (m, 3 H); LC/MS (EI) t_R 1.55 min, *m/z* 315 (M^++1).

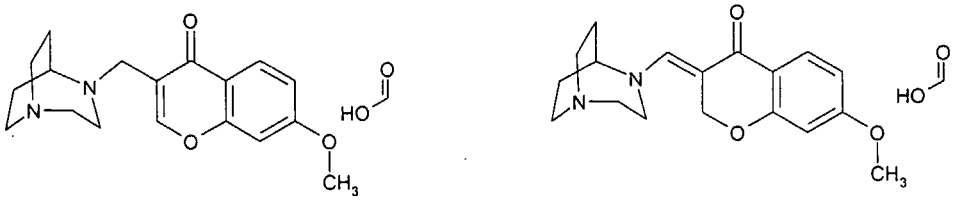
Using this general procedure the following compounds were prepared:

Example 35: Mixture of 3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-5-(methoxy)-4*H*-chromen-4-one hydroformate and (3*E*)-3-(1,4-Diazabicyclo[3.2.2]non-4-ylmethylene)-5-methoxy-2,3-dihydro-4*H*-chromen-4-one hydroformate.



Prepared by Procedure B in 4 % yield. LC/MS (EI) t_R 1.35 min, *m/z* 315 (M^++1).

Example 36: Mixture of 3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-7-(methoxy)-4*H*-chromen-4-one hydroformate and (3*E*)-3-(1,4-Diazabicyclo[3.2.2]non-4-ylmethylene)-7-methoxy-2,3-dihydro-4*H*-chromen-4-one hydroformate.

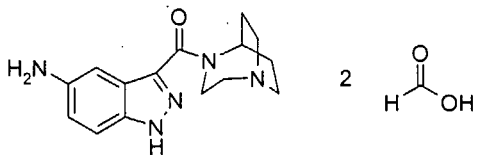


Prepared by Procedure B in 3 % yield. LC/MS (EI) t_R 1.51 min, *m/z* 315 (M^++1).

Representative Procedure C.

Procedure C provides a method for the reduction of nitro bicyclobase carboxamides to form aniline derivatives.

Example 37: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1H-indazol-5-amine dihydroformate.

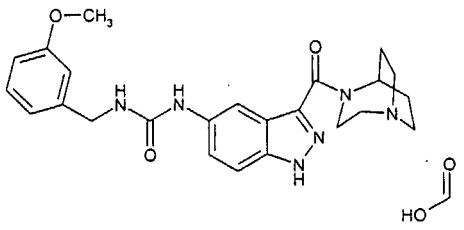


10% Palladium on charcoal (200 mg) was added to a solution of (1,4-Diaza-bicyclo[3.2.2]non-4-yl)- (5-nitro-1H-indazol-3-yl)-methanone (3.8 mmol) in methanol (100 mL). The reaction mixture was maintained under an atmosphere of hydrogen gas (60 psi) for 16 h. The catalyst was then removed by filtration (Celite), the filter cake was washed with methanol, and the combined filtrates were concentrated to provide the product in 89% yield. ^{1}H NMR (CD_3OD) δ 8.30 (s, 1 H), 7.52 (s, 2 H), 4.30 (m, 2 H), 4.20 (m, 1 H), 3.50-3.30 (m, 6 H), 2.40-2.20 (m, 2 H), 2.20-1.90 (m, 2 H); LC/MS (EI) t_R 1.53 min, *m/z* 286 (M^++1).

Representative Procedure D.

Procedure **D** provides a method for the coupling between amino bicyclobase carboxamides and isocyanates to form urea derivatives.

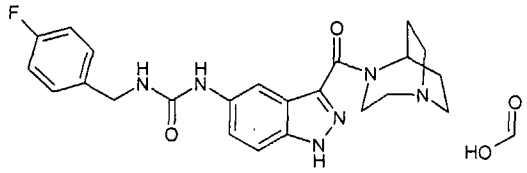
Example 38: *N*-[3-(1,3-Diazabicyclo[3.2.2]non-3-ylcarbonyl)-1*H*-indazol-5-yl]-*N'*-(3-methoxybenzyl)urea hydroformate.



3-Methoxybenzyl isocyanate (0.53 mmol) was added to a solution of the amine (100 mg, 0.4 mmol) in pyridine (4 mL), and the resulting mixture was maintained at rt for 16 h. The reaction mixture was concentrated and the residue was purified by preparative HPLC to provide the product in 60% yield and the bis-acylated product in 20% yield. ^{1}H NMR (CD_3OD) δ 8.35 (broad, 2 H), 8.07 (s, 1 H), 7.51 (d, J = 9.0, 1 H), 7.43 (d, J = 9.0, 1 H), 7.24 (dd, J = 6.0, 9.0, 1 H), 6.92 (m, 2 H), 6.79 (m, 1 H), 4.55 (m, 2 H), 4.35 (s, 2 H), 3.75 (s, 3 H), 3.60-3.40 (m, 6 H), 2.50-2.30 (m, 2 H), 2.30-2.10 (m, 2 H); LC/MS (EI) t_R 3.99 min, *m/z* 449 (M^++1).

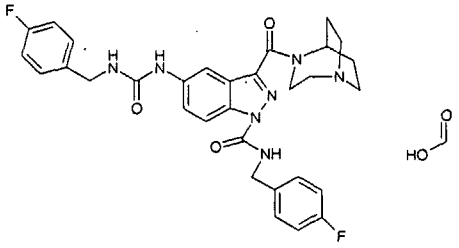
Using this general procedure the following compounds were prepared:

Example 39: ***N*-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]-*N'*-(4-fluorobenzyl)urea hydroformate.**



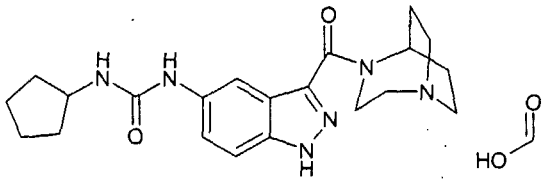
Prepared by Procedure D in 30 % yield. LC/MS (EI) t_R 3,52 min, *m/z* 437 (M^++1).

Example 40: **3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-*N*-(4-fluorobenzyl)-5-({[(4-fluorobenzyl)amino]carbonyl}amino)-1*H*-indazole-1-carboxamide hydroformate.**



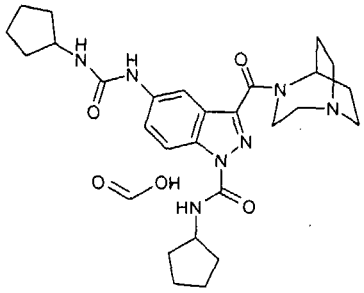
Prepared by Procedure D in 10 % yield. LC/MS (EI) t_R 4.19 min, *m/z* 599 (M^++1).

Example 41: *N*-Cyclopentyl-*N'*-[3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]urea hydroformate.



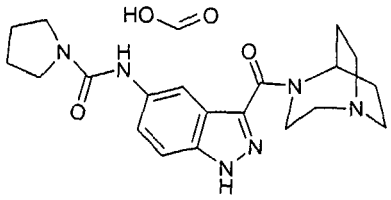
Prepared by Procedure D in 40 % yield. LC/MS (EI) t_R 3.01 min, *m/z* 397 (M^++1).

Example 42: *N*-Cyclopentyl-5-{[(cyclopentylamino)carbonyl]amino}-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazole-1-carboxamide hydroformate



Prepared by Procedure D in 10 % yield. LC/MS (EI) t_R 4.16 min, *m/z* 508 (M^++1).

Example 43: *N*-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1H-indazol-5-yl]pyrrolidine-1-carboxamide hydroformate

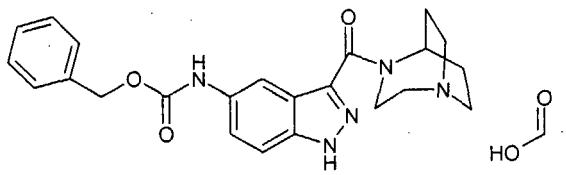


Prepared by Procedure D in 50 % yield. LC/MS (EI) t_R 2.44 min, *m/z* 383 (M^++1).

Representative Procedure E.

Procedure **E** provides a method for the coupling between amino bicyclobase carboxamides and chloroformates to form carbamate derivatives.

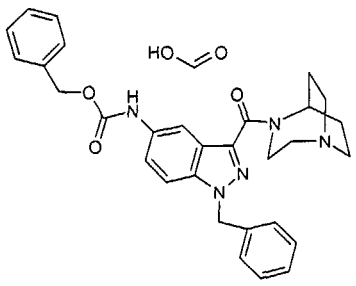
Example 44: Benzyl [3-(1,3-Diazabicyclo[3.2.2]non-3-ylcarbonyl)-1*H*-indazol-5-yl]carbamate hydroformate.



Benzyl chloroformate (0.56 mmol) was added to a solution of the amine (0.4 mmol) in pyridine (4 mL), and the reaction mixture was maintained at rt for 16 h. The reaction mixture was concentrated, and the residue was purified by preparative HPLC to provide the the product in 30% yield, the bis-acylated product in 10% yield, and the N-(1)-benzylated product (Example 45) in 5% yield. ^{1}H NMR (CD_3OD) δ 8.35 (broad, 2 H), 7.60-7.30 (m, 7 H), 5.20 (s, 1 H), 4.60 (m, 2 H), 4.25 (m, 1 H), 3.70-3.40 (m, 6 H), 2.50-2.30 (m, 2 H), 2.30-2.10 (m, 2 H); LC/MS (EI) t_R 3.74 min, *m/z* 420(M^++1).

Using this general procedure the following compounds were prepared:

Example 45: Benzyl [1-benzyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]carbamate hydroformate

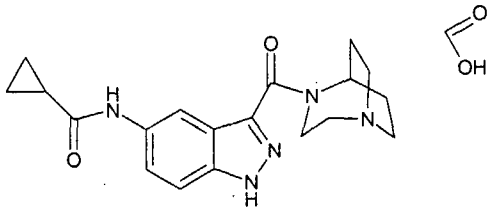


Prepared by Procedure E in 5 % yield. LC/MS (EI) t_R 4.06 min, *m/z* 510 (M^++1).

Representative Procedure F.

Procedure **F** provides a method for the coupling between amino bicyclobase carboxamides and acid chlorides to form amide derivatives.

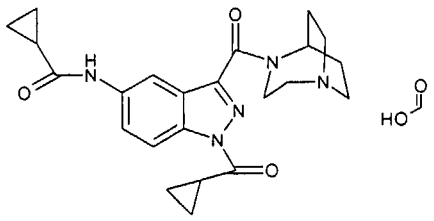
Example 46: *N*-[1-(Cyclopropylcarbonyl)-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]cyclopropanecarboxamide hydroformate.



Cyclopropanecarbonyl chloride (0.4 mmol) was added to a solution of 3-(2-azabicyclo[3.2.2]non-2-ylcarbonyl)-1*H*-indazol-5-amine (0.4 mol) in pyridine (4 mL), and the reaction mixture was maintained at rt for 16 h. The reaction mixture was concentrated, and the residue was purified by preparative HPLC to provide the product in 50% yield, and the bis acylated product in 20% yield. ^{1}H NMR (CD_3OD) δ 8.31 (s, 1 H), 8.29 (s, 1 H), 7.55 (s, 1 H), 4.50 (m, 2 H), 4.30 (m, 1 H), 3.70-3.50 (m, 6 H), 2.50-2.30 (m, 2 H), 2.30-2.10 (m, 2 H), 1.85 (m, 1 H), 0.97 (m, 2 H), 0.88 (m, 2 H); LC/MS (EI) t_R 2.41 min, *m/z* 354 (M^++1).

Using this general procedure the following compounds were prepared:

Example 47: *N*-[1-(Cyclopropylcarbonyl)-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]cyclopropanecarboxamide hydroformate.

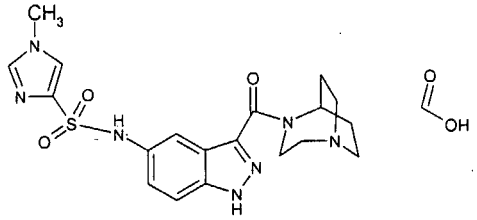


Prepared by Procedure F in 20 % yield. LC/MS (EI) t_R 3.60 min, *m/z* 423 (M^++1).

Representative Procedure G.

Procedure **G** provides a method for the coupling between amino bicyclobase carboxamides and sulfonyl chlorides to form sulfonamide derivatives.

Example 48: *N*-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-yl]-1-methyl-1*H*-imidazole-4-sulfonamide hydroformate.

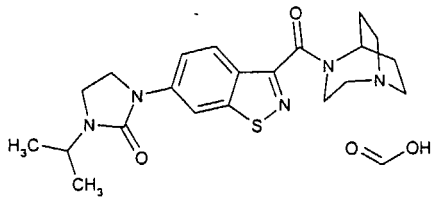


1-Methylimidazole-4-sulphonyl chloride (0.4 mmol) was added to a solution of 3-(2-azabicyclo[3.2.2]non-2-ylcarbonyl)-1*H*-indazol-5-amine (0.4 mol) in pyridine (4 mL), and the reaction mixture maintained at rt for 16 h. The reaction mixture was concentrated, and the residue purified by preparative HPLC to provide the product in 50% yield. ^{1}H NMR (CD_3OD) δ 8.39 (s, 1 H), 7.85 (broad, 1 H), 7.67 (s, 1 H), 7.58 (s, 1 H), 7.28 (d, *J* = 9.0, 1 H), 7.27 (d, *J* = 9.0, 1 H), 4.50 (m, 2 H), 4.30 (m, 1 H), 3.65 (s, 3 H), 3.50-3.30 (m, 6 H), 2.50-2.30 (m, 2 H), 2.30-2.10 (m, 2 H); LC/MS (EI) t_R 1.72 min, *m/z* 431 (M^++1).

Representative Procedure H.

Procedure **H** provides a method for the coupling between brominated bicyclobase carboxamides and monosubstituted cyclic ureas to form urea derivatives.

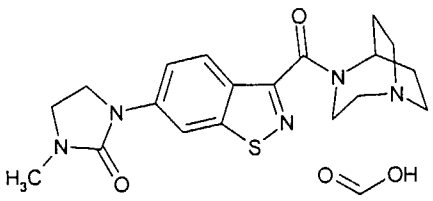
Example 49: 1-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazol-6-yl]-3-isopropylimidazolidin-2-one hydroformate



A mixture of toluene (8 mL) and (*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.2 mmol) was degassed with nitrogen for 4 minutes, then heated at 80 °C until the (*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl dissolved completely. The solution was allowed to cool to rt and palladium acetate (0.09 mmol) was added. The mixture was stirred until the palladium acetate completely dissolved. The resultant yellow solution was added to a mixture of 6-bromo-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole (0.33 mmol), 1-isopropylimidazolidin-2-one (0.5 mmol) and cesium carbonate (0.39 mmol) under a nitrogen atmosphere. The reaction mixture was subjected to microwave radiation at 150 °C for 360 s. The inorganic precipitates were removed by filtration, and the filtrate was concentrated. The residue was purified by preparative HPLC to provide the product in 75% yield. ^{1}H NMR (CD_3OD) δ 8.17 (s, 1 H), 8.03-7.93 (m, 2 H), 4.30-4.05 (m, 2 H), 3.92 (t, J = 7.14, 2 H), 3.70 (t, J = 5.7, 2 H), 3.54 (t, J = 7.1, 2 H), 3.20-3.00 (m, 6 H), 1.22 (d, J = 6.78, 3 6 H); LC/MS (EI) t_R 3.10 min, *m/z* 415 (M^++1).

Using this general procedure the following compounds were prepared:

Example 50: 1-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazol-6-yl]-3-methylimidazolidin-2-one hydroformate

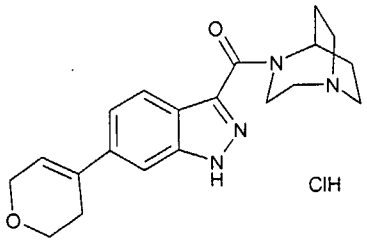


Prepared by Procedure H in 69 % yield. LC/MS (EI) t_R 2.47 min, *m/z* 386 (M^++1).

Representative Procedure I.

Procedure **I** provides a method for the coupling between bicyclobases and carboxylic acids to form carboxamide derivatives and the transformation of these derivatives to their hydrochloric acid salt.

Example 51: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(3,6-dihydro-2H-pyran-4-yl)-1H-indazole hydrochloride



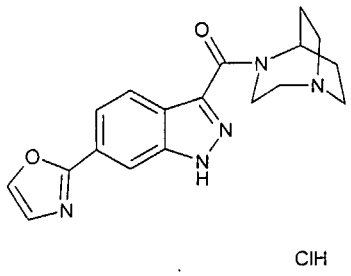
N,*N*-Diisopropylethylamine (7.0 mL) was added to a solution of 6-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole-3-carboxylic acid (11.9 mmol) and 1,4-diazabicyclo[3.2.2]nonane (10.0 mmol) in *N*,*N*-dimethylformamide (80 mL) and tetrahydrofuran (60 mL). After 15 minutes, *N*,*N*,*N*',*N*'-tetramethyl-O-(7-azabenzotriazol-

1-yl)uronium hexafluorophosphate (12.1 mmol) was added, and the reaction mixture was maintained at rt for 36 h, and was concentrated to a brown sludge. The residue was diluted with 9/1 dichloromethane/methanol (100 mL) and was washed with 2/1 saturated sodium bicarbonate/water (25 mL). The aqueous layer was back-extracted with 9/1 dichloromethane/methanol (4 x 50 mL). The combined organic layers were dried over sodium sulfate, treated with silica gel (15 g) and concentrated. The residue was purified by chromatography using a gradient of 50/50 to 0/100 ethyl acetate/(70/30/1) ethylacetate/methanol/ammonium hydroxide).

The free base was suspended in ethanol/ethyl acetate (4/1, 100 mL) and was warmed to the boiling point. The reaction mixture was cooled to room temperature and acetyl chloride (505 uL) was added dropwise, resulting in the immediate formation of a precipitate. After 1 h, the precipitated solids were collected, dried, and then recrystallized from boiling methanol (60 mL). The product was further purified by suspending the solid in 95/5 ethanol/water, warming the heterogeneous mixture to 100 °C, and allowing the supsendion to cool to rt. The solids were isolated by filtration, washed with cold ethanol, and dried to provide the analytically pure product in 57% yield. ^{1}H NMR (CD_3OD) δ 7.57 (d, J = 8.7, 1 H), 7.28 (s, 1H), 7.18 (d, J = 8.6, 1 H), 6.06 (s, 1 H), 4.76 (m, 1 H), 4.14-4.05 (two m, rotomers, 4 H), 3.76 (t, J = 5.3, 2 H), 3.54-3.34 (two m, rotomers, 6 H), 2.31-1.92 (three m, 6 H) ; LC/MS (EI) t_R 2.68 min, m/z 353 (M^++1).

Using this general procedure the following compounds were prepared:

Example 52: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-oxazol-2-yl)-1H-indazole hydrochloride

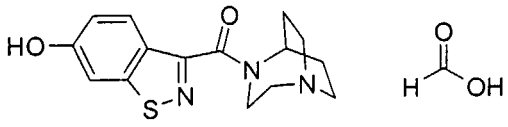


Prepared by Procedure I in 20 % yield. LC/MS (EI) t_R 2.53 min, *m/z* 338 (M^++1).

Representative Procedure J

Procedure J provides a method for the demethylation of aryl ethers to provide phenols.

Example 53: 3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazol-6-ol hydroformate.

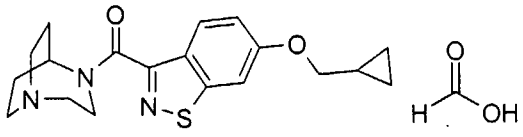


A 1.0 M solution of boron tribromide in dichloromethane (10 mL) was added to a suspension of (1,4-diazabicyclo[3.2.2]non-4-yl)-(6-methoxybenzo[d]isothiazol-3-yl)methanone (2.06 mmol) in 1,2-dichloroethane (20 mL). The suspension was heated at 50 °C for 16 h and was allowed to cool to rt. The reaction mixture was quenched with methanol (50 mL) and concentrated to dryness. The residue was diluted with methanol, and loaded on a SCX column. The column was washed with methanol (50 mL), 2 M ammonia in methanol (60 mL) and the amonia wash was concentrated. The residue was purified by chromotography [1/1 to 0/1 ethyl acetate/(70/30/1 ethyl acetate/methanol/ammonium hydroxide)] followed by preparative HPLC to provide the product in 21% yield. ^{1}H NMR (CD_3OD) δ 8.35 (s, 1 H), 8.01 and 8.00 (two d, J = 8.9, 1 H), 7.37 (d, J = 1.9, 1 H), 7.05 and 7.04 (two dd, J = 8.9, 2.2, 1 H), 4.99 (m, 1 H), 4.47 (m, 0.3 H), 4.25 (m, 0.7 H), 4.07 (m, 1.3 H), 3.64 (m, 0.3 H), 3.53-3.34 (m, 5 H), 2.45-2.27 (m, 2 H), 2.26-2.04 (m, 2 H); LC/MS (EI) t_R 2.47 min, *m/z* 304 (M^++1).

Representative Procedure K

Procedure **K** provides a method for the coupling between phenols and alcohols to form ether analogs.

Example 54: 6-(Cyclopropylmethoxy)-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole hydroformate.



Diisopropyl azodicarboxylate (0.396 mmol) was added dropwise to a solution of 3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazol-6-ol (0.359 mmol), cyclopropyl carbinol (0.432 mmol), and triphenylphosphine (0.541 mmol) in tetrahydrofuran (2.2 mL). The reaction mixture was maintained at rt for 16 h, and then the reaction mixture was concentrated. The residue was purified by chromatography using a gradient of 50/50 to 0/100 ethyl acetate/[(70/30/1) ethylacetate/methanol/ammonium hydroxide)]. The compound was further purified by preparative HPLC to provide the product in 39% yield. ^{1}H NMR (CD_3OD) δ 8.06 and 8.05 (two d, J = 9.0 ea, 1 H), 7.56 (d, J = 1.8, 1 H), 7.14 and 7.13 (two dd, J = 8.7, 2.2 ea, 1 H), 5.00 (m, 0.79 H), 4.50 (m, 0.34 H), 4.25 (t, J = 5.6, 0.68 H), 4.09 (t, J = 5.6, 1.34 H), 3.95 (d, J = 6.9, 2 H), 3.63 (t, J = 5.7, 0.70 H), 3.62-3.36 (m, 5 H), 2.45-2.37 (m, 2 H), 2.26-2.02 (two m, 2 H), 1.37-1.27 (m, 1 H), 0.69-0.62 (m, 2 H), 0.42-0.37 (m, 2H); LC/MS (EI) t_R 3.91 min, m/z 358 (M^++1).

The following compounds could not be prepared using the procedures set forth above. However, it is believed that these compounds may be prepared using alternate conventional synthetic procedures well known to those of ordinary skill in the art.

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-*N*-(3-methoxybenzyl)-5-({[(3-methoxybenzyl)amino]carbonyl}amino)-1*H*-indazole-1-carboxamide and pharmaceutically acceptable salts thereof,

3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-8-(methoxy)-4*H*-chromen-4-one and pharmaceutically acceptable salts thereof,

N,1-Dibutyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-amine and pharmaceutically acceptable salts thereof, or

N-Butyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-amine and pharmaceutically acceptable salts thereof.

Example 55: [^{3}H] MLA binding

Materials:

Rat Brain: Pel-Freez Biologicals, CAT No. 56004-2

Protease inhibitor cocktail tablet: Roche, CAT No. 1697498

Membrane preparation

Rat brains in 20 vol (w/v) of ice-cold 0.32 M sucrose with protease inhibitors (one tablet per 50 ml,) were homogenized with a polytron for 10 sec at setting 11, then centrifuged 10 min at 1000 g, 4 °C. The supernatant was centrifuged again for 20 min at 20,000 g, 4 °C. The pellets were resuspended in binding buffer (200 mM TRIS-HCl, 20 mM HEPES, pH 7.5, 144 mM NaCl, 1.5 mM KCl, 1 mM $MgSO_4$, 2 mM $CaCl_2$, 0.1% (w/v) BSA) and stored membrane prep at –80 °C.

For saturation assay, the 200 µl assay mixture in binding buffer contains 200 µg of membrane protein, 0.2 to 44 nM of [^{3}H] MLA. The nonspecific binding was defined using 1 µM MLA. Competition assay was carried out with 2 nM [^{3}H] MLA and a desirable range of compounds. The assay mixture was incubated at 22 °C for 2 hours, then harvested with GF/B filter presoaked with 0.3% PEI in binding buffer using Tomtec harvester. The filter was washed three times with binding buffer and the radioactivity was counted with Trilux.

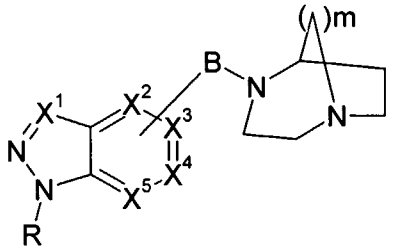
Binding affinities for the preferred compounds of the invention were 5 nM to 21 µM, especially 5 nM to 2.5 µM.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

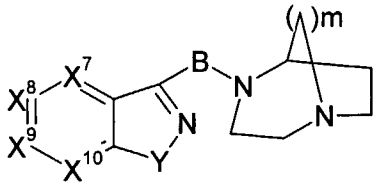
While the invention has been illustrated with respect to the production of particular compounds, it is readily apparent to those of ordinary skill in the art that variations and modifications of the invention can be made without departing from the spirit or scope of the invention.

We Claim:

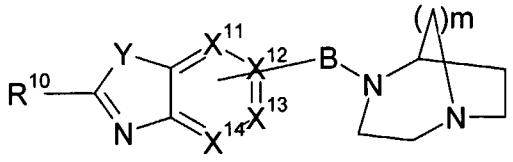
1. A compound selected from Formulas I, II, III, IV, V, VI, VII and VIII:



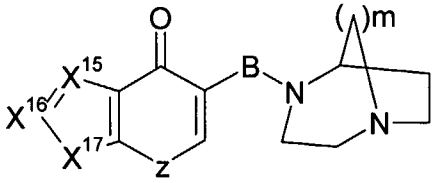
(I)



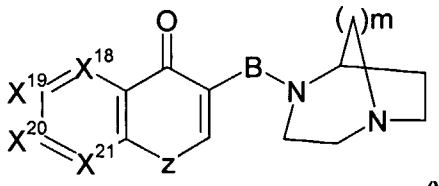
(II)



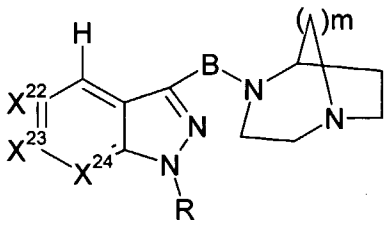
(III)



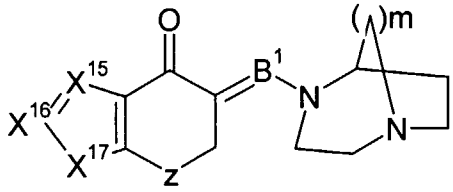
(IV)



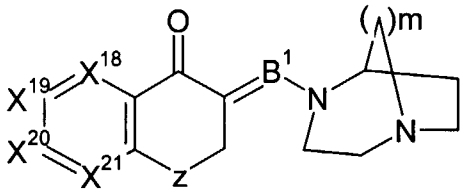
(V)



(VI)



(VII)



(VIII)

wherein

X^1 is CH or CR^1;

X^2 to X^5 are each, independently, N, CH, CR^1, or C-, wherein -C represents the point of attachment of group B, and wherein at most one of X^2 to X^5 is N, and one of X^2 to X^5 is -C;

X^7 to X^{10} are each, independently, N, CH, or CR^2, wherein at most one of X^7 to X^{10} is N;

X^{11} to X^{14} are each, independently N, CH, CR^3, or C-, wherein -C represents the point of attachment of group B, and wherein at most one of X^{11} to X^{14} is N, and one of X^{11} to X^{14} is -C;

X^{15} to X^{17} are each, independently N, O, S, CH, or CR^4;

X^{18} to X^{21} are each, independently N, CH, or CR^5, wherein at most one of X^{18} to X^{21} is N;

X^{22} and X^{23} are each, independently, CH or CR^{12}, wherein at least one of X^{22} or X^{23} is CR^{12};

X^{24} is either CH or N;

B is CH_2, C=O, or C=S;

B^1 is CH;

Y is O or S;

Z is O or NR^{11};

m is 1 or 2;

R is H, alkyl having 1 to 4 carbon atoms, halogenated alkyl having 1 to 4 carbon atoms, cycloalkyl having 3 to 7 carbon atoms, cycloalkylalkyl having 4 to 7 carbon atoms, or C_{1-6}alkyl-Ar,

R^1, R^2, R^4 and R^5 are each, independently,

C_{1-6}-alkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{2-6}-alkenyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{2-6}-alkynyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, $Si(R^8)_3$, Ar, Het, or combinations thereof,

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{4-10}-cycloalkylalkyl which is unsubstituted or substituted in the cycloalkyl portion one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof, and/or substituted in the alkyl portion one or more times by one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

halogen,

CN, NO_2, NR^6R^7, SR^6, SOR^6, SO_2R^6, $SO_2NR^6R^7$, $NR^6SO_2R^7$, $CONR^6R^7$, $CSNR^6R^7$, $COOR^6$, NR^6COR^7, NR^6CSR^7, $NR^6CONR^6R^7$, $NR^6CSNR^6R^7$, NR^6COOR^7, NR^6CSOR^7, $OCONR^6R^7$, $OCSNR^6R^7$,

Ar,

Het, or

OR^9;

R^3 is halogen, OR^{16}, CN, nitro, alkyl having 1 to 4 carbon atoms, halogenated alkyl having 1 to 4 carbon atoms, cycloalkyl having 3 to 7 carbon atoms, cycloalkylalkyl having 4 to 7 carbon atoms, hydoxyalkyl having 1 to 4 carbon atoms, NH_2, monoalkylamino having 1 to 4 carbon atoms, dialkylamino wherein each alkyl group independently has 1 to 4 carbon atoms, Ar or Het;

R^6 and R^7 are each independently

H,

C_{1-6}-alkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms, C_{3-8}-cycloalkyl, Ar, Het, or combinations thereof,

C_{3-6}-alkenyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, monoalkylamino having 1 to 6 carbon atoms,

dialkylamino wherein each alkyl group has 1 to 6 carbon atoms, C_{3-8}-cycloalkyl, Ar, Het, or combinations thereof,

C_{3-6}-alkynyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms, C_{3-8}-cycloalkyl, $Si(R^8)_3$, Ar, Het, or combinations thereof,

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms, C_{3-8}-cycloalkyl, Ar, Het, or combinations thereof,

C_{4-10}-cycloalkylalkyl which is unsubstituted or substituted in the cycloalkyl portion one or more times by F, Cl, Br, I, CN, OR^{16}, monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms, C_{3-8}-cycloalkyl, Ar, Het, or combinations thereof, and/or substituted in the alkyl portion one or more times by one or more times by F, Cl, Br, I, CN, OR^{16}, monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms, C_{3-8}-cycloalkyl, Ar, Het, or combinations thereof,

Ar, or

Het;

R^8 is C_{1-6}-alkyl;

R^9 is H,

C_{1-6}-alkyl which is unsubstituted or substituted one or more by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{3-6}-alkenyl which is unsubstituted or substituted one or more by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{3-6}-alkynyl which is unsubstituted or substituted one or more by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{4-8}-cycloalkylalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

Ar, or

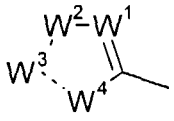
Het;

R^{10} is H, alkyl having 1 to 4 carbon atoms, halogenated alkyl having 1 to 4 carbon atoms, cycloalkyl having 3 to 7 carbon atoms, or cycloalkylalkyl having 4 to 7 carbon atoms;

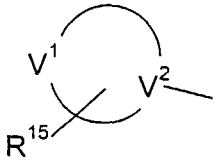
R^{11} is H, alkyl having 1 to 4 carbon atoms which is unsubstituted or substituted one or more times by halogen, OR^{16}, C_{3-8} cycloalkyl, NR^6R^7, Ar, or Het, cycloalkyl having 3 to 7 carbon atoms which is unsubstituted

or substituted one or more times by halogen, OR^{16}, NR^6R^7, Ar, or Het, cycloalkylalkyl having 4 to 7 carbon atoms, Ar or Het;

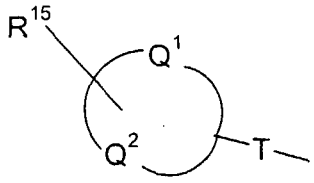
R^{12} is C_{1-6}-alkoxy which is substituted one or more times by F, or is selected from Formulae IX-XI



(IX)



(X)



(XI)

wherein Formula IX represents a 5-membered, unsaturated heterocycle in which the bond between W^2 and W^3 is a single bond and the, Formula X represents a 5-8-membered, heterocycle which is saturated or partially saturated and wherein the heterocyclic ring may be bridged by a divalent alkylene group having 1 to 3 carbon atoms, and Formula XI represents a 5-8-membered, heterocycle which is saturated, partially saturated, or unsaturated and wherein the heterocyclic ring may be bridged by a divalent alkylene group having 1 to 3 carbon atoms;

Q^1 is O, S, N, NR^{13}, or SO_2;

Q^2 is CH, CR^{14}, CHR^{14}, O, S, SO_2, N, or NR^{13};

T is O or NR^{10};

V^1 is O, S, SO_2, N, NR^{13}, CR^{14}, or CHR^{14};

W^1 is N;

W^2 and W^3 are each, independently, O, S, N, NR^{13}, CH, or CR^1, in which the bond between W^2 and W^3 is a single bond and the bond between W^3 and W^4 is a double bond, or the bond between W^2 and W^3 is a double bond and the bond between W^3 and W^4 is a single bond;

W^4 is O, S, N, or NR^{13};

V^2 is C, CH, C-OH, or N;

R^{13} is H,

C_{1-6}-alkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{3-6}-alkenyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{3-6}-alkynyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, $Si(R^8)_3$, Ar, Het, or combinations thereof,

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{4-10}-cycloalkylalkyl which is unsubstituted or substituted in the cycloalkyl portion one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof, and/or substituted in the alkyl portion one or

more times by one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

SO_2R^6, $CONR^6R^7$, $CSNR^6R^7$, $COOR^6$, $CSOR^6$, COR^7, CSR^7,

Ar, or

Het;

R^{14} is H,

C_{1-6}-alkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^9, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{2-6}-alkenyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^9, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{2-6}-alkynyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^9, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, $Si(R^8)_3$, Ar, Het, or combinations thereof,

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^9, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{4-10}-cycloalkylalkyl which is unsubstituted or substituted in the cycloalkyl portion one or more times by F, Cl, Br, I, CN, OR^9, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or

combinations thereof, and/or substituted in the alkyl portion one or more times by one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

halogen,

CN, NO_2, NR^6R^7, SR^6, SOR^6, SO_2R^6, $SO_2NR^6R^7$, $NR^6SO_2R^7$, $CONR^6R^7$, $CSNR^6R^7$, $COOR^6$, NR^6COR^7, NR^6CSR^7, $NR^6CONR^6R^7$, $NR^6CSNR^6R^7$, NR^6COOR^7, NR^6CSOR^7, $OCONR^6R^7$, $OCSNR^6R^7$,

Ar,

Het, or

OR^9;

R^{15} is H,

C_{1-6}-alkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{2-6}-alkenyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{2-6}-alkynyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, $Si(R^8)_3$, Ar, Het, or combinations thereof,

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{4-10}-cycloalkylalkyl which is unsubstituted or substituted in the cycloalkyl portion one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof, and/or substituted in the alkyl portion one or more times by one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{3-8}-cycloalkyloxy which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OR^{16}, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

halogen,

oxo, thio, CN, NO_2, NR^6R^7, SR^6, SOR^6, SO_2R^6, $SO_2NR^6R^7$, $NR^6SO_2R^7$, $CONR^6R^7$, $CSNR^6R^7$, $COOR^6$, NR^6COR^7, NR^6CSR^7, $NR^6CONR^6R^7$, $NR^6CSNR^6R^7$, NR^6COOR^7, NR^6CSOR^7, $OCONR^6R^7$, $OCSNR^6R^7$,

Ar,

Het, or

OR^9;

R^{16} is H,

C_{1-6}-alkyl which is unsubstituted or substituted one or more by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof, or

C_{4-8}-cycloalkylalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof;

R^{17} and R^{18} are each independently H, alkyl having 1 to 4 carbon atoms, halogenated alkyl having 1 to 4 carbon atoms, cycloalkyl having 3 to 7 carbon atoms, or cycloalkylalkyl having 4 to 7 carbon atoms;

R^{19} is H or CONH-CH_2-Ar;

Ar is an aryl group containing 6 to 10 carbon atoms which is unsubstituted or substituted one or more times by

alkyl having 1 to 8 carbon atoms,
alkoxy having 1 to 8 carbon atoms,
halogen,
amino,
cyano,
hydroxyl,
nitro,
halogenated alkyl having 1 to 8 carbon atoms,
halogenated alkoxy having 1 to 8 carbon atoms,

hydroxyalkyl having 1 to 8 carbon atoms,
hydroxyalkoxy having 2 to 8 carbon atoms,
alkenyloxy having 3 to 8 carbon atoms,
monoalkylamino having 1 to 8 carbon atoms,
dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms,
carboxy,
alkoxycarbonyl,
alkylaminocarbonyl,
acylamido,
acyloxy,
alkylthio having 1 to 8 carbon atoms,
alkylsulphinyl having 1 to 8 carbon atoms,
alkylsulphonyl having 1 to 8 carbon atoms,
sulfo,
sulfonylamino,
Het,

cycloalkylamino wherein the cycloalkyl group has 3 to 7 C atoms and is optionally substituted by halogen, alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

aryloxy wherein the aryl portion contains 6 to 10 carbon atoms and is optionally substituted by halogen, alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

arylthio wherein the aryl portion contains 6 to 10 carbon atoms and is optionally substituted by halogen, alkyl having 1 to 8 carbon atoms,

halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

cycloalkyloxy wherein the cycloalkyl group has 3 to 7 C atoms and is optionally substituted by halogen, alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio, or combinations thereof; and

Het is a heterocyclic group, which is fully saturated, partially saturated or fully unsaturated, having 5 to 10 ring atoms in which at least 1 ring atom is a N, O or S atom, which is unsubstituted or substituted one or more times by

alkyl having 1 to 8 carbon atoms,
alkoxy having 1 to 8 carbon atoms,
halogen,
amino,
cyano,
hydroxyl,
nitro,
halogenated alkyl having 1 to 8 carbon atoms,
halogenated alkoxy having 1 to 8 carbon atoms,
hydroxyalkyl having 1 to 8 carbon atoms,
hydroxyalkoxy having 2 to 8 carbon atoms,
alkenyloxy having 3 to 8 carbon atoms,
monoalkylamino having 1 to 8 carbon atoms,
dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms,
carboxy,

alkoxycarbonyl,

alkylaminocarbonyl,

acylamido (e.g., acetamido),

acyloxy (e.g., acetoxy),

alkylthio having 1 to 8 carbon atoms,

alkylsulphinyl having 1 to 8 carbon atoms,

alkylsulphonyl having 1 to 8 carbon atoms,

sulfo,

oxo,

sulfonylamino,

cycloalkylamino wherein the cycloalkyl group has 3 to 7 carbon atoms and is optionally substituted by halogen, alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

aryl containing 6 to 10 carbon atoms and is optionally substituted by halogen, alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

aryl-alkylene group wherein the aryl portion contains 6 to 10 carbon atoms and the alkylene portion contains 1 to 4 carbon atoms and is unsubstituted or substituted one or more times by halogen, alkyl having 1 to 8 C atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

aryloxy wherein the aryl portion contains 6 to 10 carbon atoms and is optionally substituted by halogen, alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

arylthio wherein the aryl portion contains 6 to 10 carbon atoms and is optionally substituted by halogen, alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

cycloalkyloxy wherein the cycloalkyl group has 3 to 7 carbon atoms and is optionally substituted by halogen, alkyl having 1 to 8 C carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

heterocyclic group, which is fully saturated, partially saturated or fully unsaturated, having 5 to 10 ring atoms in which at least 1 ring atom is a N, O or S atom, which is unsubstituted or substituted one or more times by halogen, alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio, or combinations thereof; and

pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein said compound is of Formula I.

3. A compound according to claim 1, wherein said compound is of Formula II.

4. A compound according to claim 1, wherein said compound is of Formula III.

5. A compound according to claim 1, wherein said compound is of Formula IV.

6. A compound according to claim 1, wherein said compound is of Formula V.

7. A compound according to claim 1, wherein said compound is of Formula VI.

8. A compound according to claim 1, wherein said compound is of Formula VII.

9. A compound according to claim 1, wherein said compound is of Formula VIII.

10. A compound according to claim 1, wherein R in Formulas I and VI is H.

11. A compound according to claim 1, wherein said compound is selected from formula I-VI in which

R is H, and

Het is a heterocyclic group, which is fully saturated, partially saturated or fully unsaturated, having 5 to 10 ring atoms in which at least 1 ring atom is a N, O or S atom, which is unsubstituted or substituted one or more times by

alkyl having 1 to 8 carbon atoms,

alkoxy having 1 to 8 carbon atoms,

halogen,

amino,
cyano,
hydroxyl,
nitro,
halogenated alkyl having 1 to 8 carbon atoms,
halogenated alkoxy having 1 to 8 carbon atoms,
hydroxyalkyl having 1 to 8 carbon atoms,
hydroxyalkoxy having 2 to 8 carbon atoms,
alkenyloxy having 3 to 8 carbon atoms,
monoalkylamino having 1 to 8 carbon atoms,
dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms,
carboxy,
alkoxycarbonyl,
alkylaminocarbonyl,
acylamido,
acyloxy,
alkylthio having 1 to 8 carbon atoms,
alkylsulphinyl having 1 to 8 carbon atoms,
alkylsulphonyl having 1 to 8 carbon atoms,
sulfo,
sulfonylamino,

cycloalkylamino wherein the cycloalkyl group has 3 to 7 carbon atoms and is optionally substituted by halogen, alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

aryl containing 6 to 10 carbon atoms which is optionally substituted by halogen, alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the

alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

aryl-alkylene group wherein the aryl portion contains 6 to 10 carbon atoms and the alkylene portion contains 1 to 4 carbon atoms and is unsubstituted or substituted one or more times by halogen, alkyl having 1 to 8 C atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

aryloxy wherein the aryl portion contains 6 to 10 carbon atoms and is optionally substituted by halogen, alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

arylthio wherein the aryl portion contains 6 to 10 carbon atoms and is optionally substituted by halogen, alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

cycloalkyloxy wherein the cycloalkyl group has 3 to 7 carbon atoms and is optionally substituted by halogen, alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio,

heterocyclic group, which is fully saturated, partially saturated or fully unsaturated, having 5 to 10 ring atoms in which at least 1 ring atom is a N, O or S atom, which is unsubstituted or substituted one or more times by halogen, alkyl having 1 to 8 carbon atoms, halogenated alkyl having 1 to 8 carbon atoms, alkoxy

having 1 to 4 carbon atoms, amino, monoalkylamino wherein the alkyl portion has 1 to 8 carbon atoms, dialkylamino wherein the alkyl portions each have 1 to 8 carbon atoms, COR^9, CSR^9, cyano, hydroxyl, nitro, oxo, or thio, or combinations thereof;

and pharmaceutically acceptable salts thereof.

12. A compound according to claim 1, wherein said compound is selected from formulas I-V, wherein

R is H, and

R^1, R^2, R^4 and R^5 are each, independently

C_{1-6}-alkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{2-6}-alkenyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{2-6}-alkynyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, $Si(R^8)_3$, Ar, Het, or combinations thereof,

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{4-10}-cycloalkylalkyl which is unsubstituted or substituted in the cycloalkyl portion one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof, and/or substituted in the alkyl portion one or more times by one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{3-8}-cycloalkyloxy which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

halogen,

CN, NO_2, NR^6R^7, SR^6, SOR^6, SO_2R^6, $SO_2NR^6R^7$, $NR^6SO_2R^7$, $CONR^6R^7$, $CSNR^6R^7$, $COOR^6$, NR^6COR^7, NR^6CSR^7, $NR^6CONR^6R^7$, $NR^6CSNR^6R^7$, NR^6COOR^7, NR^6CSOR^7, $OCONR^6R^7$, $OCSNR^6R^7$,

Ar,

Het, or

OR^9;

R^3 is halogen, OH, CN, nitro, alkyl having 1 to 4 carbon atoms, halogenated alkyl having 1 to 4 carbon atoms, cycloalkyl having 3 to 7 carbon atoms, cycloalkylalkyl having 4 to 7 carbon atoms, alkoxy having 1 to 4 carbon atoms, cycloalkoxy having 3 to 7 carbon atoms, cycloalkylalkoxy having 4 to 7 carbon atoms, halogenated alkoxy having 1 to 4 carbon atoms,

hydoxyalkyl having 1 to 4 carbon atoms, hydroxyalkoxy having 2 to 4 carbon atoms, NH_2, monoalkylamino having 1 to 4 carbon atoms, dialkylamino wherein each alkyl group independently has 1 to 4 carbon atoms, Ar or Het;

R^6 and R^7 are each independently

H,

C_{1-6}-alkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms, C_{3-8}-cycloalkyl, Ar, Het, or combinations thereof,

C_{2-6}-alkenyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms, C_{3-8}-cycloalkyl, Ar, Het, or combinations thereof,

C_{2-6}-alkynyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms, C_{3-8}-cycloalkyl, $Si(R^8)_3$, Ar, Het, or combinations thereof,

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms, C_{3-8}-cycloalkyl, $Si(R^8)_3$, Ar, Het, or combinations thereof,

C_{4-10}-cycloalkylalkyl which is unsubstituted or substituted in the cycloalkyl portion one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms, C_{3-8}-cycloalkyl, $Si(R^8)_3$, Ar, Het, or combinations thereof, and/or substituted in the alkyl portion one or more times by one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, monoalkylamino having 1 to 6 carbon atoms, dialkylamino wherein each alkyl group has 1 to 6 carbon atoms, C_{3-8}-cycloalkyl, $Si(R^8)_3$, Ar, Het, or combinations thereof,

Ar, or

Het;

R^9 is H,

C_{1-6}-alkyl which is unsubstituted or substituted one or more by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{3-6}-alkenyl which is unsubstituted or substituted one or more by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, $NR^{13}R^{14}$, SH, SR^{13}, SOR^{13}, C_{3-8}-cycloalkyl, SO_2R^{13}, $SO_2NR^{13}R^{14}$, Ar, Het, or combinations thereof,

C_{3-6}-alkynyl which is unsubstituted or substituted one or more by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, SH, SR^6, SOR^6, C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{3-8}-cycloalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

C_{4-8}-cycloalkylalkyl which is unsubstituted or substituted one or more times by F, Cl, Br, I, CN, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, SH, SR^6, SOR^6, unsubstituted C_{3-8}-cycloalkyl, SO_2R^6, $SO_2NR^6R^7$, Ar, Het, or combinations thereof,

Ar, or

Het; and

R^{11} is H,

alkyl having 1 to 4 carbon atoms which is unsubstituted or substituted one or more times by halogen, OH, alkoxy having 1 to 4 carbon atoms, C_{3-8} cycloalkyl, NR^6R^7, Ar, or Het,

cycloalkyl having 3 to 7 carbon atoms which is unsubstituted or substituted one or more times by halogen, OH, alkoxy having 1 to 4 carbon atoms, NR^6R^7, Ar, or Het,

Ar, or

Het.

13. A compound according to claim 1, wherein said compound is selected from formulas I, II, IV and V, and at least one of R^1, R^2, R^4 and R^5 is C_{1-6}-alkyl which is substituted at least one time by OR^{16}, C_{2-6}-alkenyl which is substituted at least one time

by OR^{16}, C_{2-6}-alkynyl which is substituted at least one time by OR^{16}, C_{3-8}-cycloalkyl which is substituted at least one time by OR^{16}, or C_{4-10}-cycloalkylalkyl which is substituted at least one time by OR^{16}, and R^{16} is other than H or C_{1-4}-alkyl.

14. A compound according to claim 1, wherein said compound is of formula III, R^3 is OR^{16}, and R^{16} is other than H, C_{1-4}-alkyl, halogenated C_{1-4}-alkyl, C_{3-7}-cycloalkyl or C_{4-8}-cycloalkylalkyl.

15. A compound according to claim 1, wherein said compound is selected from formulas I, II, IV and V, and at least one of R^6 and R^7 is C_{1-6}-alkyl which is substituted at least one time by OR^{16}, C_{2-6}-alkenyl which is substituted at least one time by OR^{16}, C_{2-6}-alkynyl which is substituted at least one time by OR^{16}, C_{3-8}-cycloalkyl which is substituted at least one time by OR^{16}, or C_{4-10}-cycloalkylalkyl which is substituted at least one time by OR^{16}, and R^{16} is other than H or C_{1-4}-alkyl.

16. A compound according to claim 1, wherein said compound is selected from formulas I, II, IV and V, and at least one R^9 is C_{1-6}-alkyl which is substituted at least one time by OR^{16}, C_{2-6}-alkenyl which is substituted at least one time by OR^{16}, C_{2-6}-alkynyl which is substituted at least one time by OR^{16}, C_{3-8}-cycloalkyl which is substituted at least one time by OR^{16}, or C_{4-10}-cycloalkylalkyl which is substituted at leastone time by OR^{16}, and R^{16} is other than H or C_{1-4}-alkyl.

17. A compound according to claim 1, wherein said compound is of formula IV, Z is NR^{11}, R^{11} is C_{1-4}-alkyl which is substituted at least one time by OR^{16} or C_{3-7}-cycloalkyl which is substituted at least one time by OR^{16}, and R^{16} is other than H or C_{1-4}-alkyl.

18. A compound according to claim 1, wherein

R^1, R^2, R^4, R^5, R^{14}, and R^{15} are each, independently, halogen, nitro, NR^6R^7, amino, alkylamino, dialkylamino, unsubstituted or substituted phenyl, $NR^6CONR^6R^7$, hydroxyl, alkoxy, halogenated alkoxy, or alkylsulfonamide;

R^3 is halogen, nitro, amino, alkylamino, dialkylamino, hydroxyl, alkoxy, or halogenated alkoxy; and

R^6, R^7, R^9, and R^{11} are each, independently, unsubstituted or substituted phenyl.

19. A compopund according to claim 1, wherein Ar is in each case phenyl, napthyl or biphenyl, which is unsubstituted or substituted one or more times by halogen, alkyl, hydroxy, alkoxy, nitro, methylenedioxy, ethylenedioxy, amino, alkylamino, dialkylamino, hydroxyalkyl, hydroxyalkoxy, carboxy, cyano, acyl, alkoxycarbonyl, alkylthio, alkylsulphinyl, alkylsulphonyl, phenoxy, or acyloxy.

20. A compopund according to claim 1, wherein Het is in each case tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, oxoazolinyl, isoxazolinyl, furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyridyl, pyrimidinyl, benzopyranyl, indolyl, quinolinyl, isoquinolinyl or naphthyridinyl, which is unsubstituted or substituted one or more times by halogen, aryl, alkyl, hydroxy, alkoxy, cyano, trifluoromethyl, nitro, oxo, amino, alkylamino, or dialkylamino.

21. A compound according to claim 1, wherein Het is in each case 2-quinolinyl, 1,3-benzodioxyl, 2-thienyl, 2-benzofuranyl, 2-benzothiophenyl, 3-thienyl, 2,3-dihydro-5-benzofuranyl, 4-indoyl, 4-pyridyl, 3-quinolinyl, 4-quinolinyl, 1,4-benzodioxan-6-yl, 3-indoyl, 2-pyrrolyl, benzopyran-6-yl, 5-indolyl, 1,5-benzoxepin-8-yl, 3-pyridyl, 6-coumarinyl, 5-benzofuranyl, 2-isoimidazol-4-yl, 3-pyrazolyl, 3-carbazolyl, 2-thiazolyl, 2- oxazolyl, 1-imidazolyl, or 2-imidazolyl, which is unsubstituted or substituted one or more times by halogen, aryl, alkyl, hydroxy, alkoxy, cyano, trifluoromethyl, nitro, oxo, amino, alkylamino, or dialkylamino.

22. A compound according to claim 1, wherein the heterocyclic groups of Formulas IX-XI are selected from thiazolyl, substituted thiazolyl, thiazolylamino, substituted thiazolylamino, oxazolyl, substituted oxazolyl, imidazolyl, substituted imidazolyl, pyranyl, substituted pyranyl, piperidinyl, substituted piperidinyl, pyrrolydinyl, substituted pyrrolydinyl, pyrrolydinyloxy, and substituted pyrrolydinyloxy.

23. A compound according to claim 14, wherein the heterocyclic groups of Formulas IX-XI are selected from 5-methyl-1,3-thiazol-2-yl, 4-methyl-1,3-thiazol-2-yl, 1,3-thiazol-2-yl, 1,3-oxazol-2-yl, 1,3-imidazol-2-yl, 5-methyl-1,3-oxazol-2-yl, 4-methyl-1,3-oxazol-2-yl, pyran-4-yl, piperidin-4-yl, pyrrolidin-3-yl, pyrrolidin-3-yloxy, 3-hydroxypyrrolidin-1-yl, and 1,3-thiazol-2-ylamino.

24. A compound according to claim 1, wherein said compound is selected from formulas II and VI, and B is C=O.

25. A compound according to claim 1, wherein said compound is of formula V, and B is CH_2 or C=O.

26. A compound according to claim 1, wherein said compound is selcted from formulas IV and V, and Z is O or NH.

27. A compound according to claim 1, wherein said compound is of formula II and Y is S.

28. A compound according to claim 1, wherein m is 2.

29. A compound according to claim 1, wherein R^{12} is of Formula **IX**, and is oxazolyl, thiazolyl, 4-methylthiazolyl, or 5-methylthiazolyl.

30. A compound according to claim 1, wherein R^{12} is of Formula **X** and is tetrahydropyran and dihydropyran.

31. A compound according to claim 1, wherein R^{12} is of Formula **X** and is 3-methyl-imidazolidin-2-one or 3-isopropyl-imidazolidin-2-one.

32. A compound according to claim 1, wherein R^{12} is halogenated alkoxy.

33. A compound according to claim 1, wherein R^2 is OCH_3, OCF_3, ethoxy, cyclopropylmethoxy, or cyclopropyl.

34. A compound according to claim 1, wherein R^5 is OCH_3.

35. A compound according to claim 1, wherein said compound is of Formula VI.

36. A compound according to claim 1, wherein said compound is not:
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-*N*-(3-methoxybenzyl)-5-({[(3-methoxybenzyl)amino]carbonyl}amino)-1*H*-indazole-1-carboxamide and pharmaceutically acceptable salts thereof,
3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-8-(methoxy)-4*H*-chromen-4-one and pharmaceutically acceptable salts thereof,
N,1-Dibutyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-amine and pharmaceutically acceptable salts thereof, or
N-Butyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-amine and pharmaceutically acceptable salts thereof.

37. A compound according to claim 36, wherein said compound is not:
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-methoxy-4*H*-chromen-4-one and pharmaceutically acceptable salts thereof,
5-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,3-benzothiazole and pharmaceutically acceptable salts thereof,

6-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,3-benzothiazole and pharmaceutically acceptable salts thereof,

6-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazole and pharmaceutically acceptable salts thereof,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-methoxyquinolin-4(1H)-one and pharmaceutically acceptable salts thereof,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-7-methoxyquinolin-4(1*H*)-one and pharmaceutically acceptable salts thereof,

N,N,1-Tributyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazol-5-amine and pharmaceutically acceptable salts thereof, and

5-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazole and pharmaceutically acceptable salts thereof.

38. A compound according to claim 1, wherein said compound is selected from:

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-thiazol-2-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-thiazol-2-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(trifluoromethoxy)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(trifluoromethoxy)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-oxazol-2-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-oxazol-2-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-thiazol-2-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-thiazol-2-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-methoxy-1,2-benzisothiazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-methoxy-1,2-benzisothiazole,
4-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazole hydroformate, and
4-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazole; and
pharmaceutically acceptable salts thereof.

39. A compound according to claim 1, wherein said compound is selected from:
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-4*H*-chromen-4-one hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-4*H*-chromen-4-one,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate, and
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole; and
pharmaceutically acceptable salts thereof.

40. A compound according to claim 1, wherein said compound is selected from:
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisoxazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisoxazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-thiazol-2-yl)-1*H*-indazole hydrochloride,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-thiazol-2-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(ethoxy)-1,2-benzisothiazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(ethoxy)-1,2-benzisothiazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1,2-benzisothiazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1,2-benzisothiazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-7-(methoxy)-1,2-benzisothiazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-7-(methoxy)-1,2-benzisothiazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-5-(methoxy)-4*H*-chromen-4-one,

3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-6-(methoxy)-4*H*-chromen-4-one hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-6-(methoxy)-4*H*-chromen-4-one,

3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-7-(methoxy)-4*H*-chromen-4-one,

6-(Cyclopropylmethoxy)-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole,
6-Cyclopropyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole hydroformate,
6-Cyclopropyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate, and
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole; and
pharmaceutically acceptable salts thereof.

41. A compound according to claims 1, wherein said compound is selected from:
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(methoxy)-1,2-benzisothiazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(methoxy)-1,2-benzisothiazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-5-(methoxy)-4*H*-chromen-4-one hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-7-(methoxy)-4*H*-chromen-4-one hydroformate,
6-Bromo-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole hydroformate,
6-Bromo-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole,
1-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazol-6-yl]-3-isopropylimidazolidin-2-one hydroformate,
1-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazol-6-yl]-3-isopropylimidazolidin-2-one,
1-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazol-6-yl]-3-methylimidazolidin-2-one hydroformate,
1-[3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazol-6-yl]-3-methylimidazolidin-2-one,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-oxazol-2-yl)-1H-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-oxazol-2-yl)-1H-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-oxazol-2-yl)-1*H*-indazole hydrochloride,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(difluoromethoxy)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(difluoromethoxy)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(difluoromethoxy)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(difluoromethoxy)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(tetrahydro-2*H*-pyran-4-yloxy)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(tetrahydro-2*H*-pyran-4-yloxy)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(3,6-dihydro-2*H*-pyran-4-yl)-1H-indazole hydrochloride,

(3*E*)-3-(1,4-diazabicyclo[3.2.2]non-4-ylmethylene)-6-methoxy-2,3-dihydro-4*H*-chromen-4-one hydroformate,

(3*E*)-3-(1,4-diazabicyclo[3.2.2]non-4-ylmethylene)-6-methoxy-2,3-dihydro-4*H*-chromen-4-one,

(3*E*)-3-(1,4-Diazabicyclo[3.2.2]non-4-ylmethylene)-5-methoxy-2,3-dihydro-4*H*-chromen-4-one hydroformate,

(3*E*)-3-(1,4-Diazabicyclo[3.2.2]non-4-ylmethylene)-5-methoxy-2,3-dihydro-4*H*-chromen-4-one,

(3*E*)-3-(1,4-Diazabicyclo[3.2.2]non-4-ylmethylene)-7-methoxy-2,3-dihydro-4*H*-chromen-4-one hydroformate, and

(3*E*)-3-(1,4-Diazabicyclo[3.2.2]non-4-ylmethylene)-7-methoxy-2,3-dihydro-4*H*-chromen-4-one;

and pharmaceutically acceptable salts thereof.

42. A pharmaceutical composition comprising a compound according to any one of claims 1 to 41 and a pharmaceutically acceptable carrier.

43. A method of selectively activating/stimulating α-7 nicotinic receptors in a patient wherein such activation/stimulation has a therapeutic effect, comprising administering to the patient in need thereof an effective amount of a compound according to any one of claims 1 to 41.

44. A method of treating a patient suffering from a psychotic disease, a neurodegenerative disease involving a dysfunction of the cholinergic system, and/or a condition of memory and/or cognition impairment, comprising administering to the patient an effective amount of a compound according to any one of claims 1 to 41.

45. A method according to claim 44, wherein said patient is suffering from schizophrenia, anxiety, mania, depression, manic depression, Tourette's syndrome, Parkinson's disease, Huntington's disease, Alzheimer's disease, Lewy Body Dementia, Amyotrophic Lateral Sclerosis, memory impairment, memory loss, cognition deficit, attention deficit, and/or Attention Deficit Hyperactivity Disorder.

46. A method of treating a patient suffering from dementia and/or another condition with memory loss, comprising administering to the patient an effective amount of a compound according to any one of claims 1 to 41.

47. A method of treating a patient suffering from memory impairment due to mild cognitive impairment due to aging, Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeld-Jakob disease, depression, aging, head trauma, stroke, CNS hypoxia, cerebral senility, multiinfarct dementia, HIV and/or cardiovascular disease comprising administering to the patient an effective amount of a compound according to any one of claims 1 to 41.

48. A method of treating and/or preventing dementia in an Alzheimer's patient comprising administering to the patient a therapeutically effective amount of a compound according to any one of claims 1 to 41 to inhibit the binding of an amyloid beta peptide with nACh receptors.

49. A method of treating a patient for alcohol withdrawal or treating a patient with anti-intoxication therapy comprising administering to the patient an effective amount of a compound according to any one of claims 1 to 41.

50. A method of treating a patient to provide for neuroprotection against damage associated with strokes and ischemia and glutamate-induced excitotoxicity comprising administering to the patient an effective amount of a compound according to any one of claims 1 to 41.

51. A method of treating a patient suffering from nicotine addiction, pain, jetlag, obesity and/or diabetes, comprising administering to the patient an effective amount of a compound according to any one of claims 1 to 41.

52. A method of inducing smoking cessation in a patient comprising administering to the patient an effective amount of a compound according to any one of claims 1 to 41.

53. A method of treating a patient suffering from mild cognitive impairment (MCI), vascular dementia (VaD), age-associated cognitive decline (AACD), amnesia associated with open-heart-surgery, cardiac arrest, general anesthesia, memory deficits from exposure to anesthetic agents, sleep deprivation induced cognitive impairment, chronic fatigue syndrome, narcolepsy, AIDS-related dementia, epilepsy-related cognitive impairment, Down's syndrome, Alcoholism related dementia, drug/substance induced memory impairments, Dementia Puglistica (Boxer Syndrome), or animal dementia comprising administering to the patient an effective amount of a compound according to any one of claims 1 to 41.

54. A method for treating loss of memory comprising administering to a patient in need thereof an effective amount of a compound according to any one of claims 1 to 41.

55. A method for treating a patient suffering from memory impairment comprising administering to the patient a compound according to according to any one of claims 1 to 41.

56. A method according to claim 55, wherein said memory impairment is due to decreased nicotinic acetylcholine receptor activity.

57. A method for the treatment or prophylaxis of a disease or condition resulting from dysfunction of nicotinic acetylcholine receptor transmission in a patient comprising administering to the patient an effective amount of a compound according to any one of claims 1 to 41.

58. A method for the treatment or prophylaxis of a disease or condition resulting from defective or malfunctioning nicotinic acetylcholine receptors in a patient comprising administering to the patient an effective amount of a compound according to any one of claims 1 to 41.

59. A method for the treatment or prophylaxis of a disease or condition resulting from suppressed nicotinic acetylcholine receptor transmission in a patient comprising administering to the patient an effective amount of a compound according to any one of claims 1 to 41.

60. A method for the treatment or prophylaxis of a disease or condition resulting from loss of cholinergic synapses in a patient comprising administering to the patient an effective amount of a compound according to any one of claims 1 to 41.

61. A method for protecting neurons in a patient from neurotoxicity induced by activation of α7nACh receptors comprising administering to said patient an effective amount of a compound according to any one of claims 1 to 41.

62. A method for the treatment or prophylaxis of a neurodegenerative disorder by inhibiting the binding of Aβ peptides to α7nACh receptors in a patient, comprising administering to said patient an effective amount of a compound according to any one of claims 1 to 41.

63. A method for treating a patient suffering from an inflammatory disease, comprising administering to said patient an effective amount of a compound according to any one of claims 1 to 41.

64. A method according to claim 63, wherein said inflammatory disease is rheumatoid arthritis, diabetes or sepsis.

65. A method for selectively activating/stimulating α-7 nicotinic receptors in a patient wherein such activation/stimulation has a therapeutic effect, comprising administering to the patient in need thereof an effective amount of a compound selected from:

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-thiazol-2-yl)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-thiazol-2-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(trifluoromethoxy)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(trifluoromethoxy)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-oxazol-2-yl)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-oxazol-2-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-thiazol-2-yl)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(1,3-thiazol-2-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1*H*-indazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-methoxy-1,2-benzisothiazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-methoxy-1,2-benzisothiazole,
4-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazole hydroformate, and
4-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1*H*-indazole; and
pharmaceutically acceptable salts thereof.

66. A method for selectively activating/stimulating α-7 nicotinic receptors in a patient wherein such activation/stimulation has a therapeutic effect, comprising administering to the patient in need thereof an effective amount of a compound selected from:
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisoxazole hydroformate,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisoxazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-thiazol-2-yl)-1*H*-indazole hydrochloride,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(1,3-thiazol-2-yl)-1*H*-indazole,
3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(3,6-dihydro-2*H*-pyran-4-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(5-methyl-1,3-thiazol-2-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(ethoxy)-1,2-benzisothiazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(ethoxy)-1,2-benzisothiazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1,2-benzisothiazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-6-(trifluoromethoxy)-1,2-benzisothiazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-7-(methoxy)-1,2-benzisothiazole hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-7-(methoxy)-1,2-benzisothiazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-5-(methoxy)-4*H*-chromen-4-one,

3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-6-(methoxy)-4*H*-chromen-4-one hydroformate,

3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-6-(methoxy)-4*H*-chromen-4-one,

3-(1,4-Diazabicyclo[3.2.2]non-4-yl-methyl)-7-(methoxy)-4*H*-chromen-4-one,

6-(Cyclopropylmethoxy)-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole,

6-Cyclopropyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole hydroformate,

6-Cyclopropyl-3-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1,2-benzisothiazole,

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole hydroformate,

and

3-(1,4-Diazabicyclo[3.2.2]non-4-ylcarbonyl)-5-(4-methyl-1,3-thiazol-2-yl)-1*H*-indazole;

and

pharmaceutically acceptable salts thereof.

67. A method according to any one of claims 43 to 66, wherein said patient is a human.