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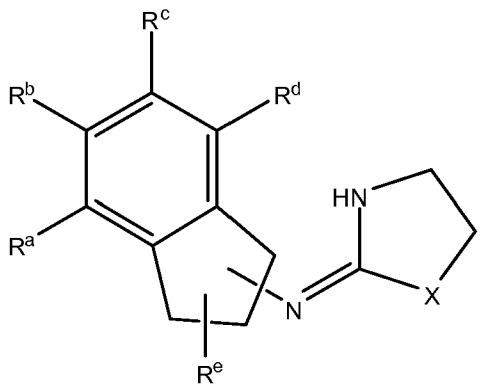
(54) Title: THERAPEUTIC COMPOUNDS



(57) Abstract: Disclosed herein is a compound having a structure (I), compositions, methods, and medicaments related thereto are also disclosed.

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THERAPEUTIC COMPOUNDS

By Inventors

Ken Chow, Wenkui K. Fang, Evelyn G. Corpuz, Dario G. Gomez, Santosh C. Sinha, Smita S. Bhat, Todd M. Heidelbaugh, and Daniel W. Gil

CROSS-REFERENCE

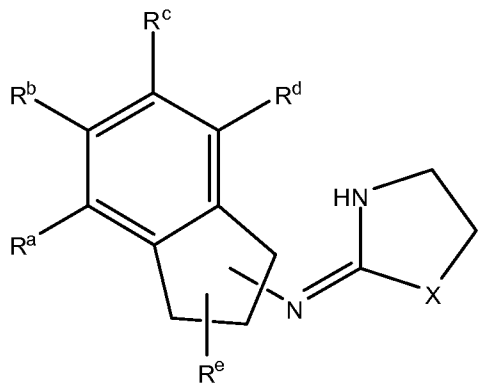
[1] This application claims the benefit of U.S. Provisional Application serial number 60/955,964, filed August 15, 2007, which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[2] There is a continuing need for alpha adrenergic compounds for treating pain, glaucoma and other conditions.

DESCRIPTION OF THE INVENTION

[3] Disclosed herein is a compound having a structure



wherein X is O, S, or NH;

R^a, R^b, R^c, and R^d are stable moieties independently consisting of: from 0 to 4 carbon atoms, from 0 to 10 hydrogen atoms, from 0 to 2 oxygen atoms, from 0 to 1 sulfur atoms, from 0 to 1 nitrogen atoms, from 0 to 3 fluorine atoms, from 0 to 1 chlorine atoms, and from 0 to 1 bromine atoms; and

R^e is H or C_{1-4} alkyl.

[4] These compounds are useful for the treatment of pain, glaucoma, and the reduction of intraocular pressure. The compound is incorporated into a dosage form or a medicament and administered to the mammal in need thereof. For example, a liquid composition may be administered as an eye drop for the treatment of glaucoma or lowering intraocular pressure. A solid dosage form may also be administered orally for any of these conditions. Other types of dosage forms and medicaments are well known in the art, and may also be used here.

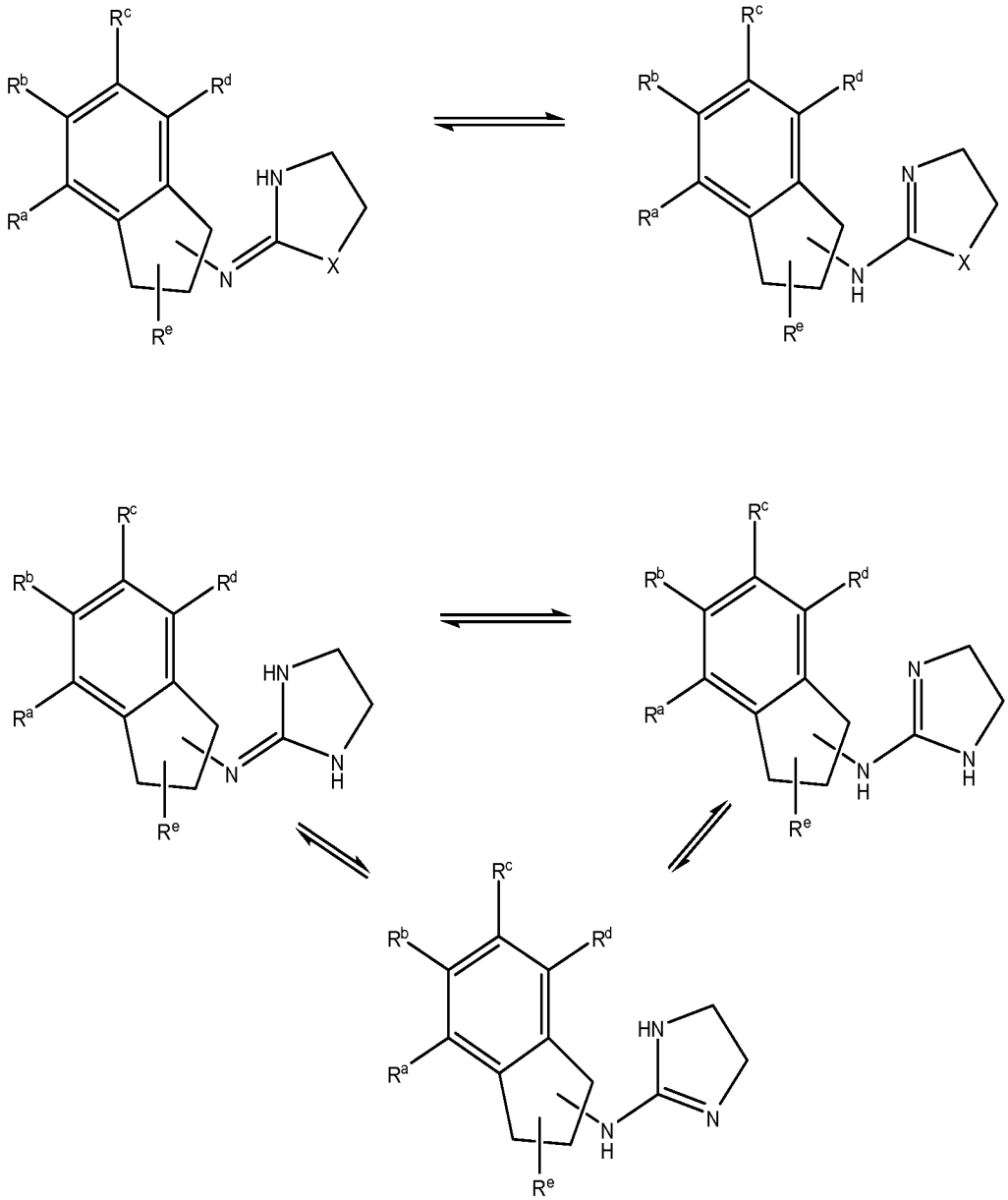
[5] For the purposes of this disclosure, "treat," "treating," or "treatment" refer to the use of a compound, composition, therapeutically active agent, or drug in the diagnosis, cure, mitigation, treatment, prevention of disease or other undesirable condition.

[6] Unless otherwise indicated, reference to a compound should be construed broadly to include pharmaceutically acceptable salts, prodrugs, tautomers, alternate solid forms, and non-covalent complexes of a chemical entity of the depicted structure or chemical name.

[7] A pharmaceutically acceptable salt is any salt of the parent compound that is suitable for administration to an animal or human. A pharmaceutically acceptable salt also refers to any salt which may form *in vivo* as a result of administration of an acid, another salt, or a prodrug which is converted into an acid or salt. A salt comprises one or more ionic forms of the compound, such as a conjugate acid or base, associated with one or more corresponding counter-ions. Salts can form from or incorporate one or more deprotonated acidic groups (e.g. carboxylic acids), one or more protonated basic groups (e.g. amines), or both (e.g. zwitterions).

[8] A prodrug is a compound which is converted to a therapeutically active compound after administration. While not intending to limit the scope of the invention, conversion may occur by hydrolysis of an ester group or some other biologically labile group. Prodrug preparation is well known in the art. For example, "Prodrugs and Drug Delivery Systems," which is a chapter in Richard B. Silverman, *Organic Chemistry of Drug Design and Drug Action*, 2d Ed., Elsevier Academic Press: Amsterdam, 2004, pp. 496-557, provides further detail on the subject.

[9] Tautomers are isomers that are in rapid equilibrium with one another. For example, tautomers may be related by transfer of a proton, hydrogen atom, or hydride ion. Examples of tautomers are depicted below.

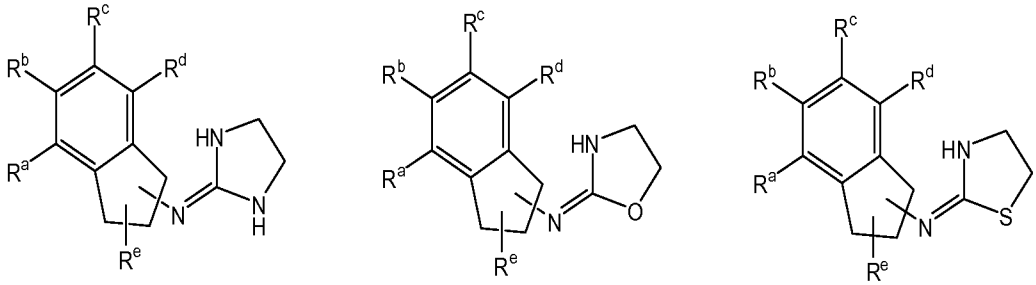


[10] Unless stereochemistry is explicitly depicted, a structure is intended to include every possible stereoisomer, both pure or in any possible mixture.

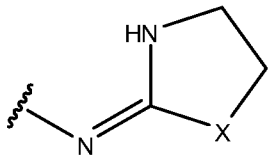
[11] Alternate solid forms are different solid forms than those that may result from practicing the procedures described herein. For example, alternate solid forms may be polymorphs, different kinds of amorphous solid forms, glasses, and the like.

[12] Non-covalent complexes are complexes that may form between the compound and one or more additional chemical species that do not involve a covalent bonding interaction between the compound and the additional chemical species. They may or may not have a specific ratio between the compound and the additional chemical species. Examples might include solvates, hydrates, charge transfer complexes, and the like.

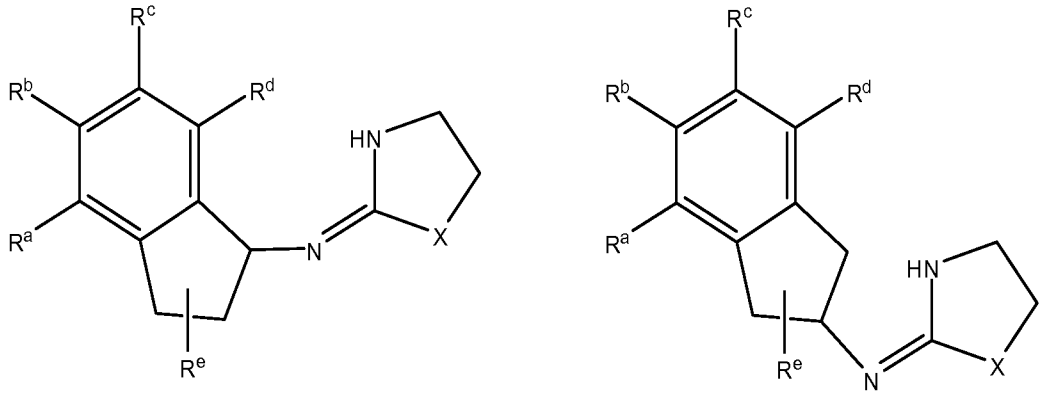
[13] X is O, S, or NH. Thus, compounds of any of the structures depicted below are contemplated.



[14] The part of the compound:



attaches to one of the non-aromatic carbons of the ring system. In other words, the compounds having the structures depicted below are contemplated.



[15] R^a, R^b, R^c, and R^d are stable moieties independently consisting of: from 0 to 4 carbon atoms, from 0 to 10 hydrogen atoms, from 0 to 2 oxygen atoms, from 0 to 1

sulfur atoms, from 0 to 1 nitrogen atoms, from 0 to 3 fluorine atoms, from 0 to 1 chlorine atoms, and from 0 to 1 bromine atoms.

[16] Subject to the constraints described herein (e.g. limits on the number of atoms), examples of R^a, R^b, R^c, and R^d include, but are not limited to:

[17] Hydrocarbyl, meaning a moiety consisting of carbon and hydrogen only, including, but not limited to:

a. alkyl, meaning hydrocarbyl having no double or triple bonds, including, but not limited to:

- linear alkyl, e.g. methyl, ethyl, *n*-propyl, *n*-butyl, etc.,
- branched alkyl, e.g. *iso*-propyl, *t*-butyl and other branched butyl isomers, etc.,
- cycloalkyl, e.g. cyclopropyl, cyclobutyl, etc.,
- combinations of linear, branched, and/or cycloalkyl;

b. alkenyl, e.g. hydrocarbyl having 1 or more double bonds, including linear, branched, or cycloalkenyl

c. alkynyl, e.g. hydrocarbyl having 1 or more triple bonds, including linear, branched, or cycloalkynyl;

d. combinations of alkyl, alkenyl, and/or akynyl

[18] alkyl-CN, such as $-CH_2$-CN, -$(CH_2)_2$-CN; -$(CH_2)_3$-CN, and the like;

[19] hydroxyalkyl, i.e. alkyl-OH, such as hydroxymethyl, hydroxyethyl, and the like;

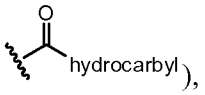
[20] ether substituents, including -O-alkyl, alkyl-O-alkyl, and the like;

[21] thioether substituents, including -S-alkyl, alkyl-S-alkyl, and the like;

[22] amine substituents, including -NH_2, -NH-alkyl,-N-alkyl^{1}alkyl^2 (i.e., alkyl^1 and alkyl^2 are the same or different, and both are attached to N), alkyl-NH_2, alkyl-NH-alkyl, alkyl-N-alkyl^{1}alkyl^2, and the like;

[23] aminoalkyl, meaning alkyl-amine, such as aminomethyl (-CH_2-amine), aminoethyl, and the like;

[24] ester substituents, including -CO_2-alkyl, -CO_2-phenyl, etc.;

[25] other carbonyl substituents, including aldehydes; ketones, such as acyl (i.e. ), and the like; in particular, acetyl, propionyl, and benzoyl substituents are contemplated;

[26] fluorocarbons or hydroflourocarbons such as $-CF_3$, $-CH_2CF_3$, etc.; and

[27] -CN;

[28] combinations of the above are also possible, subject to the constraints defined;

[29] Alternatively, a substituent may be -F, -Cl, -Br, or -I.

[30] In particular, alkyl having from 1 to 4 carbon atoms is contemplated;

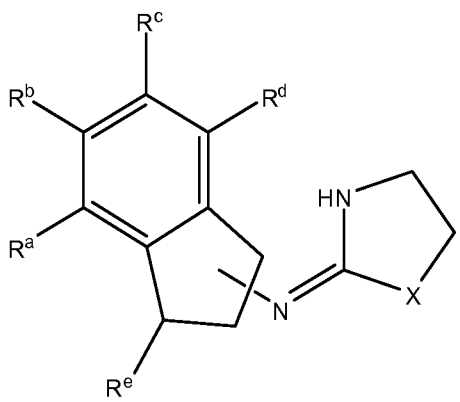
[31] R^a, R^b, R^c, and R^d are stable, i.e. they are stable enough to be stored in a bottle at room temperature under a normal atmosphere for at least 12 hours, or stable enough to be useful for any purpose disclosed herein.

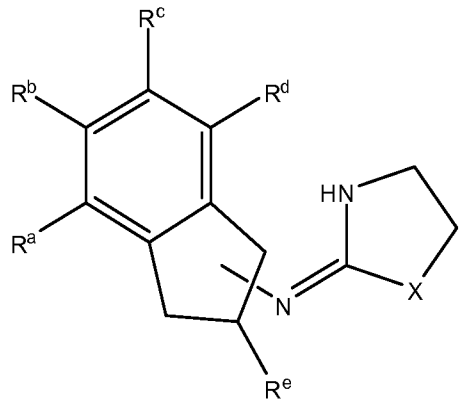
[32] If R^a, R^b, R^c, or R^d is a salt, for example of a carboxylic acid or an amine, the counter-ion of said salt, i.e. the ion that is not covalently bonded to the remainder of the molecule is not counted for the purposes of the number of atoms in the moiety. Thus, for example, the salt $-CO_2^-Na^+$ consists of 1 carbon and 2 oxygen atoms, i.e. sodium is not counted. In another example, the salt $-NH(Me)_2^+Cl^-$ consists of 2 carbon atoms, 1 nitrogen atom, and 7 hydrogen atoms, i.e. chlorine is not counted.

[33] In another embodiment, R^a, R^b, R^c, and R^d are independently –H, alkyl having from 1 to 4 carbon atoms, -F, -Cl, -Br, $-CH_2OH$, an amine having from 0 to 4 carbon atoms, $-CH_2CN$, $-CF_3$, or acyl having from 1 to 4 carbon atoms.

[34] In another embodiment, R^a, R^b, R^c, and R^d are independently –H, –F, -Cl, -Br, $-CH_3$, $-NHCH_3$, or $-CF_3$.

[35] R^e is H or C_{1-4} alkyl, i.e. methyl, ethyl, *n*-propyl, *iso*-propyl, and the butyl isomers. R^e attaches to one of the non-aromatic carbons of the ring system. Thus, compounds having any of the structures depicted below are contemplated.





[36] In another embodiment X is O.

[37] In another embodiment X is S.

[38] In another embodiment X is NH.

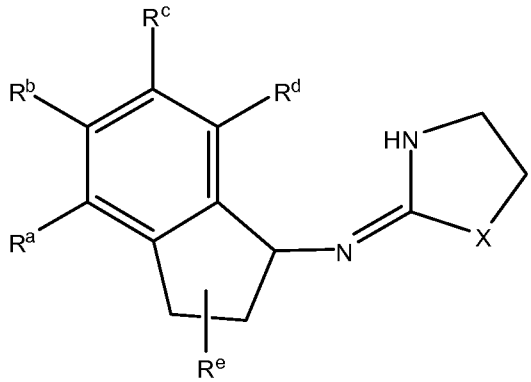
[39] In another embodiment R^a, R^b, R^c, and R^d are independently selected from H, methyl, ethyl, C_3 alkyl, and C_4 alkyl, F, Cl, Br, $-CH_2OH$, $-CH_2NH_2$, $-CHNH(C_{1-4}$ alkyl), $-CN(C_{1-4}$ alkyl$)_2$, $-CH_2CN$, and CF_3.

[40] In another embodiment R^a, R^b, R^c, and R^d are independently selected from H, methyl, ethyl, F, Cl, Br, $-CH_2CN$, and CF_3.

[41] In another embodiment R^e is H.

[42] In another embodiment R^e is methyl.

[43] In another embodiment, the compound has a structure



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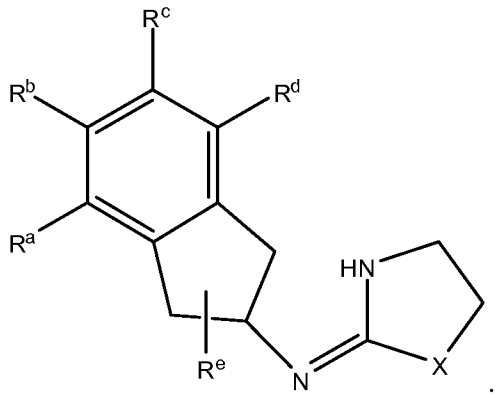
[44] In another embodiment, the compound has a structure



[45] Another embodiment is method of reducing intraocular pressure comprising administering a compound disclosed herein to a mammal in need thereof.

[46] Another embodiment is method of treating pain comprising administering a compound disclosed herein to a mammal in need thereof.

[47] Other useful compounds include:

[(1R)-(4,5-Dihydro-1H-imidazol-2-yl)-(4-methyl-indan-1-yl)]-amine;

[(1S)-(4,5-Dihydro-1H-imidazol-2-yl)-(4-methyl-indan-1-yl)]-amine;

(4,5-Dihydro-1H-imidazol-2-yl)-(6-methyl-indan-1-yl)-amine;

(4-Bromo-indan-1-yl)-(4,5-dihydro-1H-imidazol-2-yl)-amine;

[(1S)-(4,5-Dihydro-1H-imidazol-2-yl)-indan-1-yl] amine;

(4,5-Dihydro-1H-imidazol-2-yl)-indan-1-yl-amine;

(4,5-Dihydro-1H-imidazol-2-yl)-indan-2-yl-amine;

(4,5-Dihydro-oxazol-2-yl)-(4-methyl-indan-1-yl)-amine;

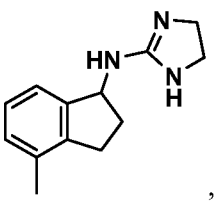
(4,5-Dihydro-thiazol-2-yl)-(4-methyl-indan-1-yl)-amine;

(4,5-Dihydro-thiazol-2-yl)-(3-methyl-indan-1-yl)-amine;

(4,5-Dihydro-oxazol-2-yl)-(3-methyl-indan-1-yl)-amine; and

(4,5-Dihydro-thiazol-2-yl)-indan-1-yl-amine.

[48] One embodiment is a compound having a structure selected from: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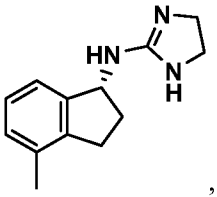
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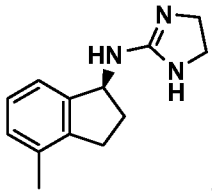
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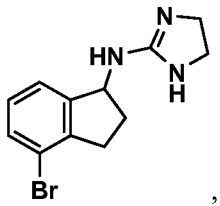
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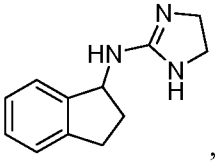
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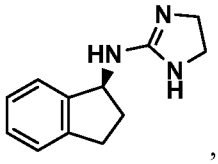
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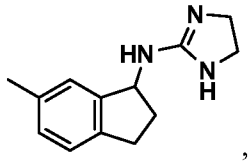
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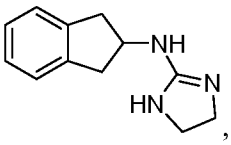
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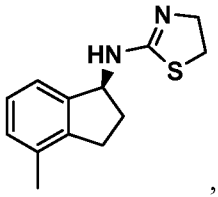
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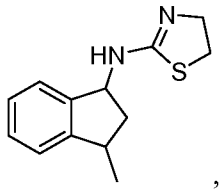
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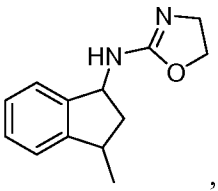
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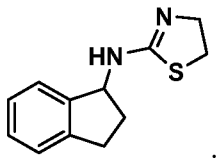
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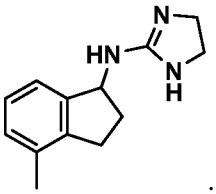
[49] Another embodiment is a compound having the formula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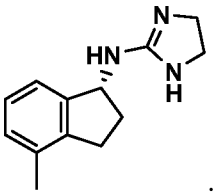
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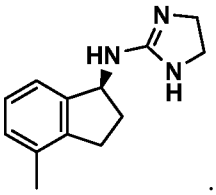
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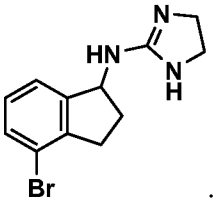
[52] Another embodiment is a compound having the formula



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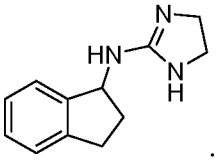

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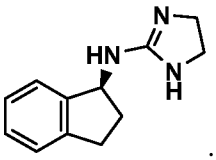
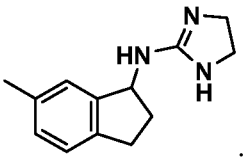
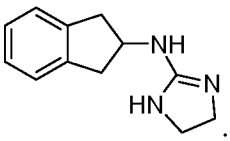


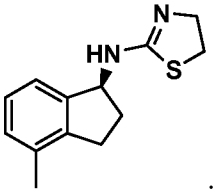
[55] Another embodiment is a compound having the formula



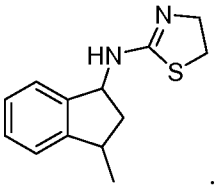
[56] Another embodiment is a compound having the formula



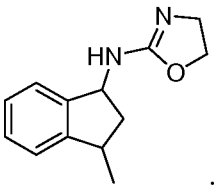
[57] Another embodiment is a compound having the formula



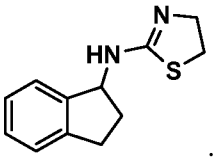
[58] Another embodiment is a compound having the formula



[59] Another embodiment is a compound having the formula



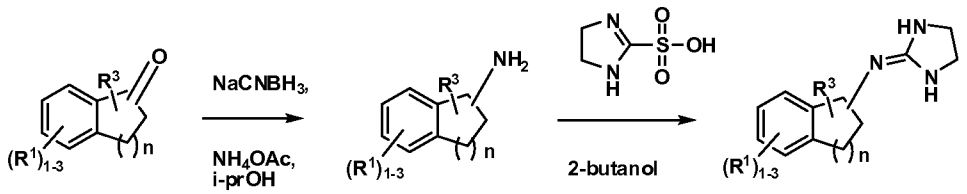
[60] Another embodiment is a compound having the formula



[61] Synthetic Methods

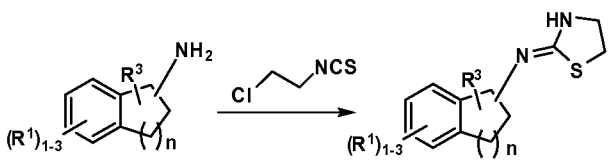
[62] Reaction Scheme A, B, and C illustrate general methods for obtaining the amino-imidazolines, amino-oxazolines and amino-thiazolines.

Reaction Scheme A



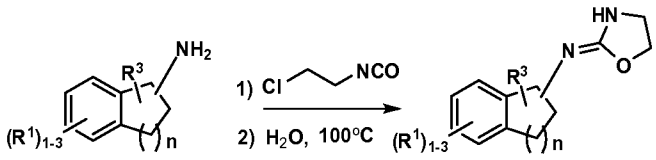
Formula 1 Formula 2 Formula 3

Reaction Scheme B



Formula 4 Formula 5

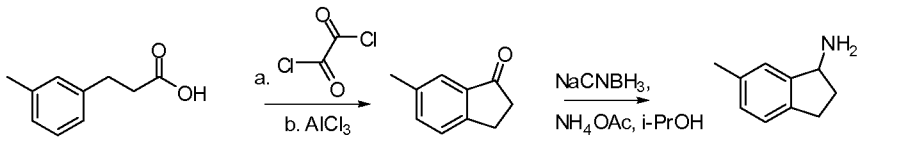
Reaction Scheme C



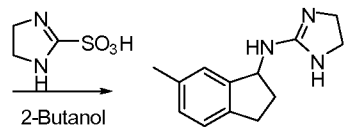
Formula 6 Formula 7

Example A

Method A: Procedure for the preparation of (4,5-dihydro-1H-imidazol-2-yl)-(6-methyl-indan-1-yl)-amine, (083)



Intermediate 1 Intermediate 2 Intermediate 3



083

A solution of 3-*m*-tolyl-propionic acid **(Intermediate 1)** (5.0 g, 29.5 mmol) in dichloromethane was treated with oxalyl chloride (4.5 g, 3.09 mL , 41.09 mmol) at rt and stirred for 2 h at rt. The mixture was concentrated and dissolved in dichloromethane and aluminum chloride (6.28 g, 37.62 mmol) was added in portions. The mixture was quenched with ice. The residue was isolated in a typical aqueous workup to give 6-methyl-indan-1-one **(Intermediate 2)**, (crude).

6-Methyl-indan-1-one, **(Intermediate 2)** (3.0 g, 20.0 mmol) in isopropanol (20 mL) was treated with sodiumcyanoborohydride(9.01 g, 143.5 mmol) and ammonium acetate (47.4 g, 615 mmol) and the reaction was refluxed for 16 hours. The mixture was cooled to room temperature and basified with sodium hydroxide (10

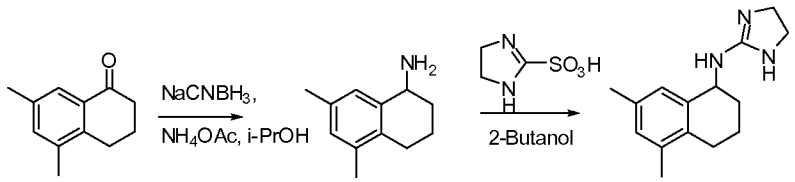
mL). The residue was isolated in a typical aqueous workup to give, 6-methyl-indan-1-ylamine **(Intermediate 3)**.

A mixture of 6-methyl-indan-1-ylamine (300 mg, 2.05 mmol) **(Intermediate 3)** and 4, 5-dihydro-1H-imidazole-2-sulfonic acid (339 mg, 2.2 mmol) in 2-butanol (10 mL) was refluxed for 16 h. The mixture was evaporated under reduced pressure. This material was purified by chromatography on silica gel with 5% NH_3-MeOH: CH_2Cl_2 to (4,5-dihydro-1H-imidazol-2-yl)-(6-methyl-indan-1-yl)-amine (**083**) 152 mg (34%).

^{1}**HNMR** (CD_3OD, 300MHz): δ = 7.32 (s, 1H), 7.24 (dd, J = 4.5, 13.2 Hz, 2H), 4.76-4.37 (m, 1H), 3.80 (s, 4H), 3.15-3.16 (m, 1H), 2.65-3.10 (m, 1H), 2.64-2.93 (m, 1H), 2.12-2.05 (m, 1H), 2.39 (s, 3H).

Example B

Method B: Procedure for the preparation of (4,5-dihydro-1H-imidazol-2-yl)-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-amine (**904**)



Intermediate 4 **Intermediate 5** **Intermediate 6**

904

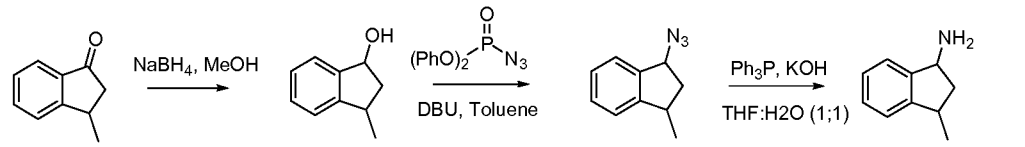
A solution of 5,7-dimethyl-3,4-dihydro-2H-naphthalen-1-one (commercially available, 12.3 g, 28.3 mmol) - **(Intermediate 4)** in isopropanol (100 mL) was treated with sodium cyanoborohydride (9.01 g, 143.5 mmol) and ammonium acetate (47.4 g, 615 mmol), and the reaction mixture was refluxed for 16 hours. The mixture was basified with sodium hydroxide (10 mL). The residue was isolated in a typical

aqueous workup to give (6.5 g, 37.1 mmol) **(Intermediate 5).** A mixture of (500 mg, 5.7 mmol) **(Intermediate 5)** and 4, 5-dihydro-1H-imidazole-2-sulfonic acid (940 mg, 6.3 mmol) in 2-butanol (30 mL) was refluxed for 24 h. The mixture was evaporated under reduced pressure. This material was purified by chromatography on silica gel with 5% NH_3-MeOH:CH_2Cl_2 to give (90 mg, 3.7 mmol,36%) of (4,5-dihydro-1H-imidazol-2-yl)-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-amine (**904**).

Following a procedure similar to that for **904** afforded **631, 659, 629, 659, 323, 522, 380, 523, and 380**.

Example C

Method C: Procedure for the preparation of:



Intermediate 7 **Intermediate 8** **Intermediate 9** **Intermediate 10**

Sodium borohydride (1.3 g, 34.36 mmol, 1.0 eq) was added to a cooled (0 °C) solution of 3-methyl-2,3-dihydro-1H-inden-1-one **(Intermediate 7)** (5.0 g, 34.2 mmol) in MeOH. The reaction mixture was stirred for 1 hour after which it was quenched with saturated NH_4Cl. The resulting mixture was extracted with Et_2O (3x 50 mL), and the combined organic extracts was washed with H_2O (3x 50 mL), brine (1x 50 mL), dried over $MgSO_4$ and concentrated to give 3-methyl-2,3-dihydro-1H-inden-1-ol **(Intermediate 8)** which was purified by column chromatography using hexane:EtOAc (4:1) as eluant.

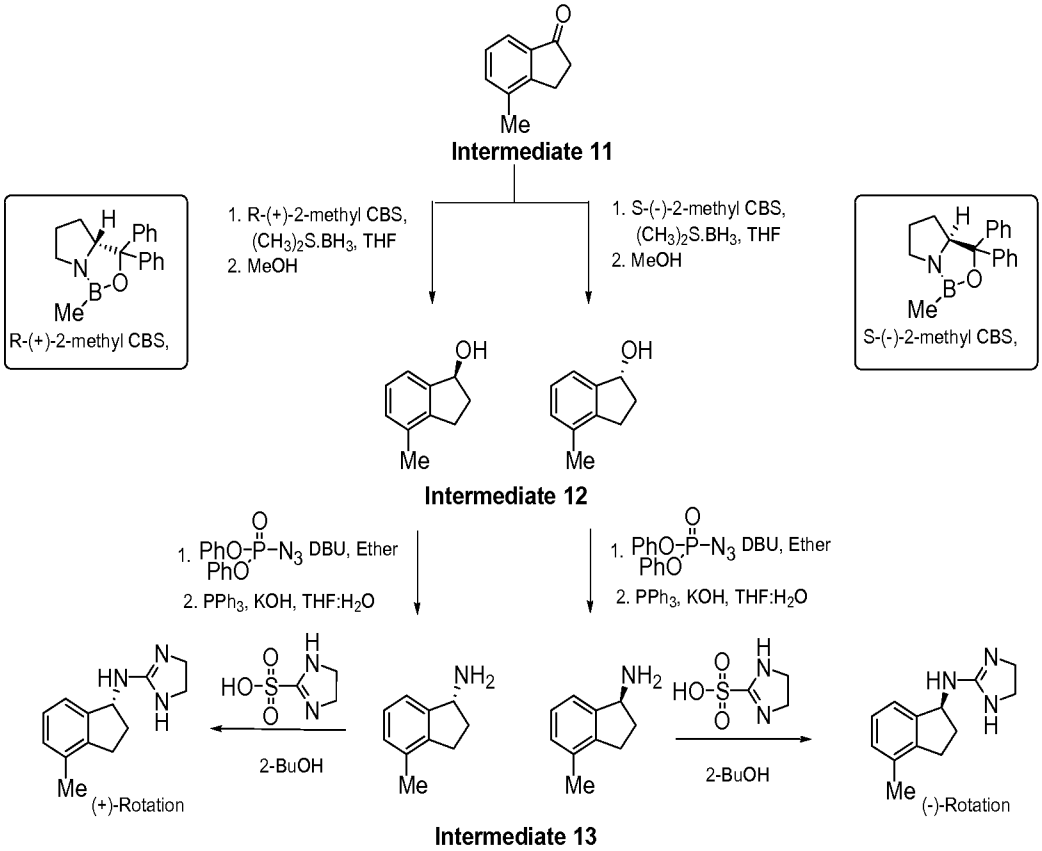
Diphenylphosphoryl azide (10.40 mL, 48.26 mmol, 1.5 eq) was added to a cooled (0 °C) solution of of 3-methyl-2,3-dihydro-1H-inden-1-ol **(Intermediate 8)** (4.77 g, 32.2 mmol) in toluene. The resulting mixture was stirred for a few minutes and 7.22 mL (1.5 eq) of DBU was added slowly. After stirring the reaction mixture overnight, it was diluted with toluene and washed with H_2O (3x 50 mL), brine (1x 50

mL), dried over $MgSO_4$ and concentrated to give 1-azido-3-methyl-2,3-dihydro-1H-indene **(Intermediate 9)** which was purified by column chromatography using hexane:EtOAc (4:1) as eluant.

To a solution of of 1-azido-3-methyl-2,3-dihydro-1H-indene **(Intermediate 9)** (5.53 g, 32.0 mmol) in THF:H_2O (1:1) was added triphenyl phosphine (8.5 g, 1.01 eq) followed by KOH (1.8 g, 1.0 eq) and the resulting mixture was stirred overnight. The reaction mixture was then diluted with H_2O and slowly acidified with HCl and the aqueous layer was washed with Et_2O (3x 50 mL). The aqueous layer was then basified with NaOH (pH 14), extracted with Et_2O (3x 50 mL), and the combined extracts was washed with H_2O (1x 25 mL), brine (1x 25 mL), dried over K_2CO_3 and concentrated to give 3-methyl-2,3-dihydro-1H-inden-1-amine **(Intermediate 10)**, (4.47 g, 95% yield).

Example D

Method D: Procedure for the preparation of (R)- and (S)-4,5-dihydro-1H-imidazol-2-yl)-(4-methyl-indan-1-yl)]-amine (348 and 349) – optically pure enantiomers:



To a solution of 4-methyl indanone (5.0 g, 34.2 mmol) **Intermediate 11** in anhydrous tetrahydrofuran (100 mL), the catalyst, R-(+)-2-methyl CBS. (5.1 mL, 5.1 mmol) was added. The reaction mixture was cooled to -18 °C and BH_3·SMe (4.78 mL, 23.94 mmol) was added slowly followed by the addition of methanol (40 mL). The reaction was warmed to rt and stirred for 14 hours. The mixture was evaporated under reduced pressure to afford (5.03 g) of **Intermediate 12**.

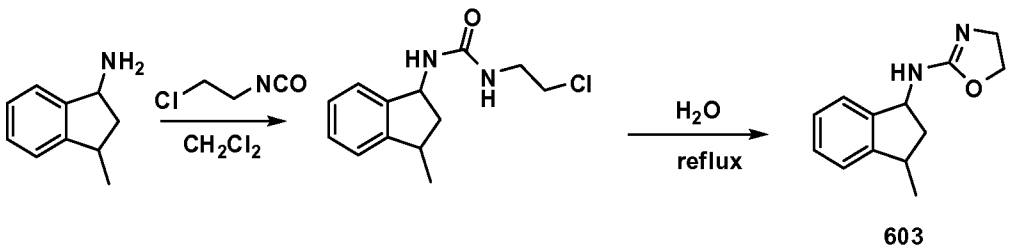
A solution of **Intermediate 13** (2.0 g, 13.6 mmol) and diphenyl phoshoryl azide (3.52 mL, 16.32 mmol) in toluene (50 mL), was cooled to 0 °C and DBU (2.44ml, 16.32 mmol) was added. The reaction mixture was stirred for 7 hours. The mixture was quenched with water. The residue was isolated in a typical aqueous workup to yield the intermediate azide. The azide (1.6g , 9.3 mmol) was dissolved in tetrahydrofuran (20 mL) and treated with triphenyl phosphine (2.46 g, 9.39 mmol)

followed by the addition of potassium hydroxide (526 mg, 9.39 mmol) and water (5 mL). The reaction mixture was stirred at rt. overnight. The aqueous layer was basified with potassium hydroxide to pH 14, followed by an aqueous workup and concentrated under reduced pressure. The product was further purified with an acid/base workup to afford (1.35 g) of **Intermediate 13**.

A mixture of **(Intermediate 13) (250 mgs, 1.7 mmol)** and 4, 5-dihydro-1H-imidazole-2-sulfonic acid
(292 mg, 1.87mmol) in 2-butanol (30 mL) was refluxed for 24 h. The mixture was evaporated under reduced pressure. This material was purified by chromatography on silica gel with 5% NH_3-MeOH: CH_2Cl_2 to give 4, 5-dihydro-1H-imidazol-2-yl)-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-amine(**348**) respectively.

Example E

Method E: Procedure for the preparation of (4,5-Dihydro-oxazol-2-yl)-(3-methyl-indan-1-yl)-amine **603**:



603

Intermediate 14 Intermediate 15 Intermediate 16

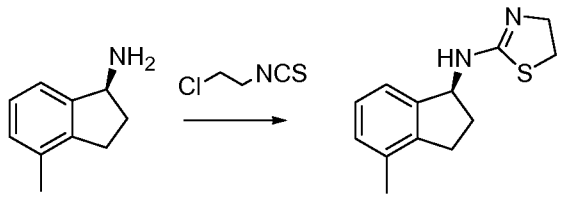
3-Methyl-indan-1-ylamine **(Intermediate 14)** (0.44 g, 3.0 mmol) in dichloromethane (10 mL) was added chloroethylisocyanate (0.32 mL, 3.3 mmol). The solution was stirred at room temperature for 1.5 hour, and quenched with water. The aqueous layer was extracted with dichloromethane (3 x 50). The pooled organic layer was dried over magnesium sulfate. The mixture was filtered. The filtrate was added silica gel, and the solvents were removed under vacuum. Purification by

chromatography on silica gel (2 to 10% methanol in dichloromethane) gave a crude material, which was recrystalized in methanol/water to give **Intermediate 15**.

Intermediate 15 was refluxed in H_2O (60 mL) for 1 hour. After cooling to room temperature, the reaction was basified with NaOH (pH 14), extracted in Ethyl acetate (3 x 50 mL). The pooled organic layers were washed with brine and dried over magnesium sulphate to give **603**.

Example F

Method F: Procedure for the preparation of (4, 5-Dihydro-thiazol-2-yl)-(4-methyl-indan-1-yl)-amine **770**:



Intermediate 17 **Intermediate 18**

1-(2,3-dichlorophenyl)-2-(pyridin-4-yl)ethanamine **(Intermediate 17)** (0.44 g, 3.0 mmol) in dichloromethane (10 mL) was added chloroethylisocyanate (0.32 mL, 3.3 mmol). The solution was stirred at room temperature for 1.5 hour, and quenched with water. The aqueous layer was extracted with dichloromethane (3x). The pooled organic layer was dried over magnesium sulfate. The mixture was filtered. The filtrate was added silica gel, and the solvents were removed under vacuum. Purification by chromatography on silica gel (2 to 10% methanol in dichloromethane) gave a crude material, which was recrystalized in methanol/water to give (4,5-dihydro-thiazol-2-yl)-(4-methyl-indan-1-yl)-amine **770** as a solid (129 mg, 0.55 mmol, 81% yield).

The following compounds have been synthesized by one of the methods described above:

(4, 5-Dihydro-1H-imidazol-2-yl)-(4-methyl-indan-1-yl)-amine, 629:

Method B:

^{1}HNMR (CD_3OD, 500MHz): δ = 7.08-7.15 (m, 3H), 4.99 (t, *J* = 7.5 Hz, 1H), 3.68 (s, 4H), 2.97-3.02 (m, 1H), 2.77-2.81 (m, 1H), 2.55-2.62 (m, 1H).

[(1R)-(4, 5-Dihydro-1H-imidazol-2-yl)-(4-methyl-indan-1-yl)]-amine, 348:

Method D:

^{1}HNMR (CD_3OD, 500MHz): δ = 7.08-7.15 (m, 3H), 4.99 (t, *J* = 7.5 Hz, 1H), 3.68 (s, 4H), 2.97-3.02 (m, 1H), 2.77-2.81 (m, 1H), 2.55-2.62 (m, 1H).

[(1S)-(4, 5-Dihydro-1H-imidazol-2-yl)-(4-methyl-indan-1-yl)]-amine, 349:

Method D:

^{1}HNMR (CD_3OD, 500MHz): δ = 7.08-7.15 (m, 3H), 4.99 (t, *J* = 7.5 Hz, 1H), 3.68 (s, 4H), 2.97-3.02 (m, 1H), 2.77-2.81 (m, 1H), 2.55-2.62 (m, 1H).

(4-Bromo-indan-1-yl)- (4, 5-dihydro-1H-imidazol-2-yl)-amine, 631:

Method B:

^{1}HNMR (DMSO, 300MHz): δ = 7.6 (d, *J* = 6 Hz, 1H), 7.20-7.40 (m, 2H), 5.05-5.20 (m, 1H), 3.65 (s, 4H), 2.70-3.05 (m, 2H), 2.50-2.60 (m, 1H), 1.6-2.0 (m, 1H).

(4, 5-Dihydro-1H-imidazol-2-yl)-indan-1-yl-amine, 523:

Method B:

^{1}HNMR (DMSO, 300MHz); δ 7.31 - 7.25 (m, 4 H), 5.02 (t, *J* = 7.08 Hz, 1 H), 3.66 (m, 4H), 2.95 – 2.98 (m, 1 H), 2.81 - 2.85 (m, 1 H), 2.48-2.53 (m, 1 H), 1.84-1.91 (m, 1 H).

[(1S (4, 5-Dihydro-1H-imidazol-2-yl)-indan-1-yl] amine, 380:

Method B:

^{1}HNMR (CD_3OD, 500MHz): δ = 7.22-7.40 (m, 4 H), 5.02 (t, *J* = 7.08 Hz, 1 H), 3.74 (s, 4H), 2.83-3.16, (m, 1 H), 2.53-2.71 (m, 2 H), 1.95-1.99 (m, 1 H).

(4, 5-Dihydro-1H-imidazol-2-yl)-(6-methyl-indan-1-yl)-amine, 083:

Method A:

^{1}HNMR (CD_3OD, 300MHz): δ = 7.32 (s, 1H), 7.24 (dd, *J* = 4.5, 13.2 Hz, 2H), 4.76-4.37 (m, 1H), 3.80 (s, 4H), 3.15-3.16 (m, 1H), 2.65-3.10 (m, 1H), 2.64-2.93 (m, 1H), 2.12-2.05 (m, 1H), 2.39 (s, 3H).

(4, 5-Dihydro-1H-imidazol-2-yl)-indan-2-yl-amine, 522:

Method B:

^{1}HNMR (DMSO, 300MHz): δ = 7.26-7.28 (m, 4H), 4.24-4.30 (m, 1H), 3.62 (s, 4H), 3.34 (dd, *J* = 6 Hz, 15 Hz, 2H,), 3.20 (dd, *J* = 9 Hz, 18 Hz, 2H).

(4,5-Dihydro-1H-imidazol-2-yl)-(1,2,3,4-tetrahydro-naphthalen-1-yl)amine, 639:

Method B:

^{1}HNMR (CD_3OD, 300MHz): δ = 7.26-7.14 (m, 4H), 4.65 (t, *J* = 6.0 Hz, 1H), 3.74 (s, 4H), 2.65-2.90 (m, 2H), 1.86-2.08 (m, 3H), 1.42-1.47 (m, 1H).

[(1S (4,5-Dihydro-1H-imidazol-2-yl)-(1,2,3,4-tetrahydro-naphthalen-1-yl)] amine, 323 :

Method B:

^{1}HNMR (CD_3OD, 500MHz): δ = 7.06 - 7.37 (m, 4H), 4.65 (t , *J* = 5.0 Hz, 1H), 3.74 (s, 4H), 2.72-2.98 (m, 2H), 1.77-2.23 (m, 3H), 1.44-1.48 (m, 1H).

(4, 5-Dihydro-1H-imidazol-2-yl)-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-amine,

904:

Method B:

^{1}HNMR (CD_3OD, 500MHz): δ = 6.94 (d, 2H), 4.61-4.67 (m, 1H), 3.90 (s, 4H), 2.63-2.60 (m, 2H), 1.82-1.98 (m, 4H), 2.28 (s, 3H), 2.28 (s, 3H).

(4, 5-Dihydro-oxazol-2-yl)-(4-methyl-indan-1-yl)-amine, 770:

Method E:

^{1}HNMR (CD_3OD, 300MHz): δ = 7.13-7.19 (m, 3H), 5.20 (t, *J* = 10 Hz, 1H), 4.06-4.93 (m, 2H), 3.60-3.63 (m, 2H), 3.00-3.06 (m, 1H), 2.83-2.88 (m, 1H), 2.60-2.67 (m, 1H), 2.30 (s, 3H), 1.99-2.05 (m, 1H) .

(4, 5-Dihydro-thiazol-2-yl)-(4-methyl-indan-1-yl)-amine, 075:

Method F:

^{1}HNMR ($CDCl_3$, 500MHz): δ = 6.97-7.19 (m, 3H), 5.50 (t , *J* = 10 Hz, 1H), 3.30-3.41 (m, 2H), 3.19-3.22 (m, 1H), 3.02-3.07 (m, 1H), 2.68-2.74 (m, 1H), 2.81-2.84 (m, 1H), 2.19 (s, 3H), 1.85-1.88 (m, 1H) .

(4, 5-Dihydro-thiazol-2-yl)- (3-methyl-indan-1-yl)-amine, 604:

Method F:

^{1}HNMR (DMSO, 500MHz): δ = 7.38 (d, *J* = 10 Hz, 1H), 7.12-7.26 (m, 3H), 5.28 (t, *J* = 10 Hz , 1H), 3.90-3.93 (m, 2H), 3.28-3.36 (m, 3H), 2.14-2.16 (m, 1H), 1.97-2.13 (m, 1H), 1.25 (d, 3H, *J* = 10 Hz) .

(4, 5-Dihydro-oxazol-2-yl)-(3-methyl-indan-1-yl)-amine , 603:

Method E:

^{1}HNMR (DMSO, 500MHz): δ = 7.34 (d, *J* = 10 Hz, 1H), 7.16-7.21 (m, 3H), 5.04(t, *J* = 10 Hz , 1H), 4.16 (t, *J* = 5 Hz , 1H), 3.59-3.63 (m, 3H), 3.29 (m, 1H), 2.08-2.10 (m, 1H), 1.94-1.90 (m, 1H), 1.17 (d, 3H, *J* = 5 Hz) .

(4, 5-Dihydro-thiazol-2-yl)-indan-1-yl-amine, 524:

Method F:

^{1}HNMR ($CDCl_3$, 300MHz): δ = 6.89-7.34 (m, 4H), 5.21 (s, *J* = 4.5 Hz, 1H), 4.01-4.07 (m, 2H), 3.34-3.39 (m, 2H), 2.82-2.96 (m, 2H), 2.59-2.67 (m, 1H), 1.91-1.99 (m, 1H).

(4, 5-Dihydro-oxazol-2-yl)-(5,6,7,8-tetrahydro-quinolin-8-yl)-amine, 747:

Method E:

^{1}HNMR ($CDCl_3$, 300MHz): δ = 8.42 (d, *J* = 6 Hz, 1H), 7.42 (d, *J* = 6 Hz, 1H), 7.13 (dd, *J* = 6, 9 Hz, 1H), 4.88-4.69 (m, 3H), 3.99-3.85 (m, 2H), 2.95-2.87 (m, 1H), 2.80-2.71 (m, 1H), 2.30-2.23 (m, 1H), 2.08-2.01 (m, 2H), 1.89-1.77 (m, 1H).

(4, 5-Dihydro-oxazol-2-yl)-(5,6,7,8-tetrahydro-quinoxalin-5-yl)-amine, 772:

Method E:

^{1}HNMR (CD_3OD, 500MHz): δ = 8.43 (dd, *J* = 5, 15 Hz, 2H), 4.79 (t, *J* = 5 Hz, 1H), 4.39-4.32 (m, 2H), 3.77 (t, *J* = 10 Hz, 2H), 3.06-2.93 (m, 3H), 2.21-2.19 (m, 1H), 2.01-1.96 (m, 2H).

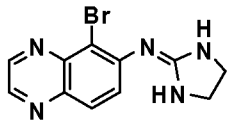
[63] Biological Data

[64] Receptor Selection and Amplification Technology (RSAT) assay

[65] The RSAT assay measures a receptor-mediated loss of contact inhibition that results in selective proliferation of receptor-containing cells in a mixed population of confluent cells. The increase in cell number is assessed with an appropriate transfected marker gene such as β-galactosidase, the activity of which can be easily measured in a 96-well format. Receptors that activate the G protein, Gq, elicit this response. Alpha2 receptors, which normally couple to Gi, activate the RSAT response when coexpressed with a hybrid Gq protein that has a Gi receptor recognition domain, called Gq/i5.

[66] NIH-3T3 cells are plated at a density of 2x106 cells in 15 cm dishes and maintained in Dulbecco's modified Eagle's medium supplemented with 10% calf serum. One day later, cells are cotransfected by calcium phosphate precipitation with mammalian expression plasmids encoding p-SV-β-galactosidase (5-10 μg), receptor (1-2 μg) and G protein (1-2 μg). 40 μg salmon sperm DNA may also be included in the transfection mixture. Fresh media is added on the following day and 1-2 days later, cells are harvested and frozen in 50 assay aliquots. Cells are thawed and 100 μl added to 100 μl aliquots of various concentrations of drugs in triplicate in 96-well dishes. Incubations continue 72-96 hr at 37 °C. After washing with phosphate-buffered saline, β-galactosidase enzyme activity is determined by adding 200 μl of the chromogenic substrate (consisting of 3.5 mM o-nitrophenyl-β-D-galactopyranoside and 0.5% nonidet P-40 in phosphate buffered saline), incubating overnight at 30 °C and measuring optical density at 420 nm. The absorbance is a measure of enzyme activity, which depends on cell number and reflects a receptor-mediated cell proliferation. The efficacy or intrinsic activity is calculated as a ratio of the maximal effect of the drug to the maximal effect of a standard full agonist for each receptor subtype. Brimonidine, also called UK14304, the chemical structure of which is shown below, is used as the standard agonist for the $alpha_{2A}$, $alpha_{2B}$ and $alpha_{2C}$

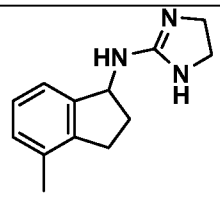
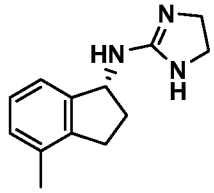
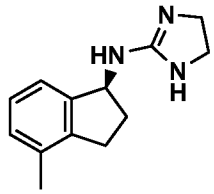
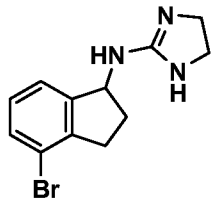
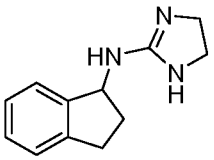
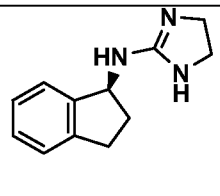
receptors. The EC_{50} is the concentration at which the drug effect is half of its maximal effect.

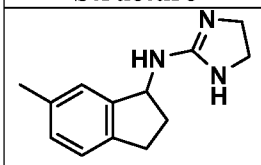
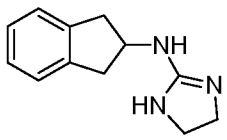
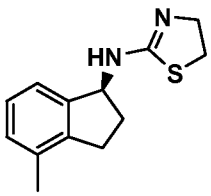
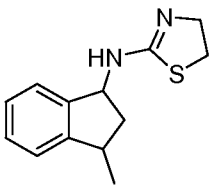
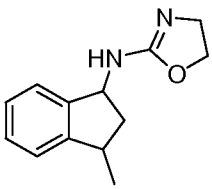
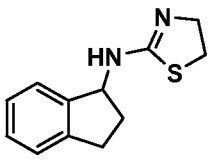


[67] **Brimonidine**

[68] The results of the RSAT assay with several exemplary compounds of the invention are disclosed in **Table 1** above together with the chemical formulas of these exemplary compounds. EC_{50} values are nanomolar. ND stands for "not determinable" at concentrations less than 10 micromolar. IA stands for "intrinsic activity."

Table 1

Structure	Alpha 2B	Alpha 2C	Alpha 2A
 629	5.7 (98)	429 (38)	nd (20)
 348	33.4 (106)	nd (11)	nd (11)
 349	4.5 (125)	82 (62)	nd (16)
 631	12.2 (71)	nd (12)	nd (7)
 523	17 (93)	207 (46)	nd (3)
 380	43 (82)	nd (11)	nd (4)

Structure	Alpha 2B	Alpha 2C	Alpha 2A
 083	473 (34)	nd (7)	nd (7)
 522	61 (36)	nd (5)	nd (5)
 075	3.4 (138)	23 (96)	143 (57)
 604	10 (99)	86 (41)	180 (25)
 603	2.2 (112)	19.8 (50)	7 (25)
 524	7.5 (107)	54 (102)	nd (14)

[69] Methods of formulating these compounds are well known in the art. For example, United States Patent No. 7,141,597 (especially column 10, line 27 to column

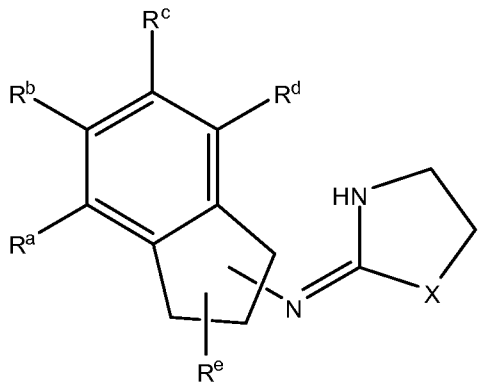
14, line 47) contains information that may be used for general guidance. Similar relevant information is also available in numerous other sources. The biological activity of the compounds disclosed herein (e.g. Table 1) may be used for additional general guidance on dosage, depending on the particular use of a compound.

[70] The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. Similarly, different pharmaceutical compositions may be prepared and used with substantially the same result. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the claims.

CLAIMS

What is claimed is:

1. A method of treating pain comprising administering a compound to a mammal in need thereof, said compound having a structure



wherein X is O, S, or NH;

n is 2 or 3;

R^a, R^b, R^c, and R^d are stable moieties independently consisting of: from 0 to 4 carbon atoms, from 0 to 10 hydrogen atoms, from 0 to 2 oxygen atoms, from 0 to 1 sulfur atoms, from 0 to 1 nitrogen atoms, from 0 to 3 fluorine atoms, from 0 to 1 chlorine atoms, and from 0 to 1 bromine atoms; and

R^e is H or C_{1-4} alkyl.

2. The method of claim 1 wherein X is O.

3. The method of claim 1 wherein X is S.

4. The method of claim 1 wherein X is NH.

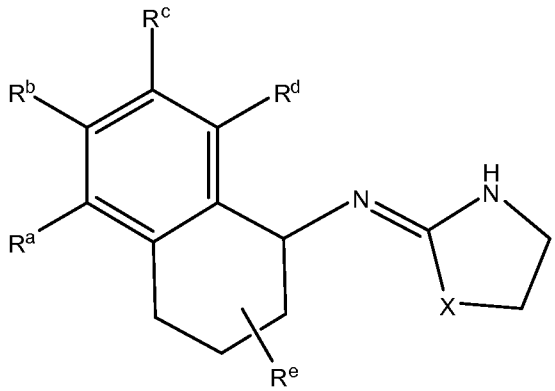
5. The method of claim 1 wherein R^a, R^b, R^c, and R^d are independently selected from H, methyl, ethyl, C_3 alkyl, and C_4 alkyl, F, Cl, Br, $-CH_2OH$, $-CH_2NH_2$, $-CHNH(C_{1-4}$ alkyl), $-CN(C_{1-4}$ alkyl$)_2$, $-CH_2CN$, and CF_3.

6. The method of claim 1 wherein R^a, R^b, R^c, and R^d are independently selected from H, methyl, ethyl, F, Cl, Br, $-CH_2CN$, and CF_3.

7. The method of claim 5 wherein R^e is H.

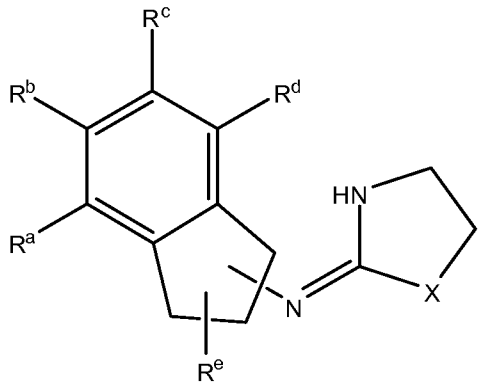
8. The method of claim 5 wherein R^e is methyl.

9. The method of claim 2, said compound having a structure



10. The method of claim 1 wherein the pain is allodynia.

11. A method of reducing intraocular pressure comprising administering a compound to a mammal in need thereof, said compound having a structure



wherein X is O, S, or NH;

n is 2 or 3;

R^a, R^b, R^c, and R^d are stable moieties independently consisting of: from 0 to 4 carbon atoms, from 0 to 10 hydrogen atoms, from 0 to 2 oxygen atoms, from 0 to 1 sulfur atoms, from 0 to 1 nitrogen atoms, from 0 to 3 fluorine atoms, from 0 to 1 chlorine atoms, and from 0 to 1 bromine atoms; and

R^e is H or C_{1-4} alkyl.

12. The method of claim 1 wherein X is O.

13. The method of claim 1 wherein X is S.

14. The method of claim 1 wherein X is NH.

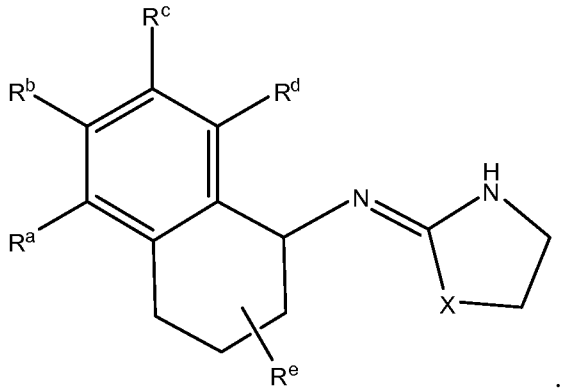
15. The method of claim 1 wherein R^a, R^b, R^c, and R^d are independently selected from H, methyl, ethyl, C_3 alkyl, and C_4 alkyl, F, Cl, Br, $-CH_2OH$, $-CH_2NH_2$, $-CHNH(C_{1-4}$ alkyl), $-CN(C_{1-4}$ alkyl$)_2$, $-CH_2CN$, and CF_3.

16. The method of claim 1 wherein R^a, R^b, R^c, and R^d are independently selected from H, methyl, ethyl, F, Cl, Br, $-CH_2CN$, and CF_3.

17. The method of claim 5 wherein R^e is H.

18. The method of claim 5 wherein R^e is methyl.

19. The method of claim 2, said compound having a structure



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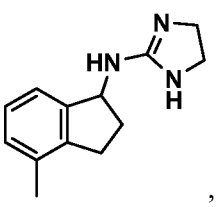
20. A compound having a structure selected from: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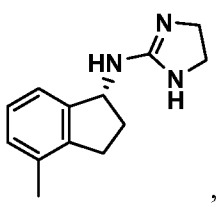
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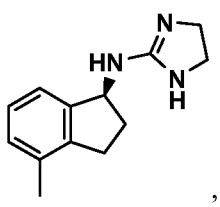
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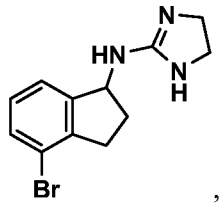
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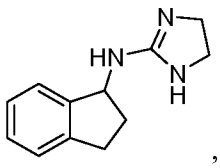
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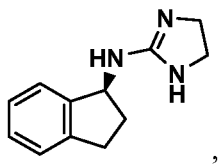
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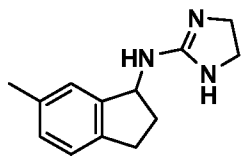
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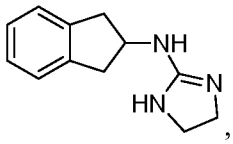
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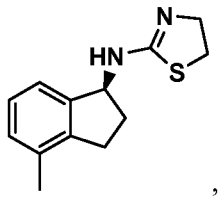
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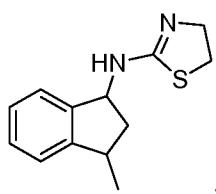
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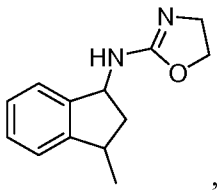
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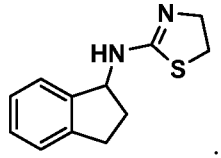
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/073108

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D233/50 C07D263/28 C07D277/18 A61K31/4168 A61K31/421
A61K31/426 A61P25/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2008/115141 A (ALBIREO AB [SE]; BERGMAN ROLF [SE]; CALAZA-CABANAS ISABEL [SE]; JOHANS) 25 September 2008 (2008-09-25) abstract page 2, line 23 - line 25 page 9, line 10 - line 11 page 24; example 6 page 26; example 10 claims	1-11,20
P,X	WO 2007/093292 A (BAYER CROPSCIENCE AG [DE]; DIXSON JOHN A [US]; DUGAN BENJAMIN J [US];) 23 August 2007 (2007-08-23) page 37; example 35; tables I-1 page 48; example 5; tables I-2	20
P,A	examples claims	1-11

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 November 2008	20/11/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Stix-Malaun, Elke

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/020377 A (SYNGENTA PARTICIPATIONS AG [CH]; SYNGENTA LTD [GB]; O'SULLIVAN ANTHONY) 22 February 2007 (2007-02-22) abstract page 57; examples XXVII-67,68 page 69; examples XXVII-472	20
A	examples claims	1-11
X	EP 0 251 453 A (BEECHAM GROUP PLC [GB]) 7 January 1988 (1988-01-07)	11,20
Y	page 2, paragraph 3 page 20; example 2 page 24; example 8 claims	1-10
X	WONG WAI C ET AL: "A convenient synthesis of 2-amino-2-oxazolines and their pharmacological evaluation at cloned human alpha adrenergic receptors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 4, no. 19, 1 January 1994 (1994-01-01), pages 2317-2322, XP002443801 ISSN: 0960-894X	9
Y	abstract page 2317, last paragraph page 2320; example 9	1,11,20
X	US 4 256 755 A (SMITH JR DEWEY H) 17 March 1981 (1981-03-17)	9
Y	abstract column 3 - column 4; table 1; compound claims	1,11,20
X	US 3 636 219 A (CULIK RUDOLF ET AL) 18 January 1972 (1972-01-18)	9
Y	abstract column 1, paragraph 3 column 10; example 9 claims	1,11,20
Y	NAKAYAMA ET AL: "Pharmacological effects of 2-(1,2,3,4-tetrahydro-1-naphthylamino)-2-imidazoline hydrochloride. II. Teratogenic activities on mice and rats" CA HOST- CA, 1966, XP002501874 abstract	1-11,20

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/073108

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2 870 159 A (BLOOM BARRY M) 20 January 1959 (1959-01-20) column 1 column 6; example II column 10; example XXIII claims	1-11,20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/073108

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008115141 A	25-09-2008	NONE	
WO 2007093292 A	23-08-2007	AR 059492 A1	09-04-2008
		AU 2007214826 A1	23-08-2007
		EP 1986498 A2	05-11-2008
		UY 30148 A1	28-09-2007
WO 2007020377 A	22-02-2007	AR 057088 A1	14-11-2007
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EP 0251453 A	07-01-1988	AU 600939 B2	30-08-1990
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		PT 84818 A	01-06-1987
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US 2870159 A	20-01-1959	NONE	