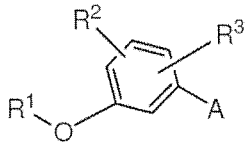
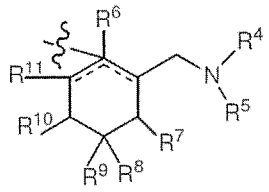
WE CLAIM:

1. A compound, or salt thereof, of formula I:



I

wherein A is



R^1 is hydrogen, C_1–C_5 alkyl, C_1–C_5 haloalkyl, C_1–C_5 alkanol, –(C_1–C_5 alkyl)phenyl, or phenyl, or a group of the formula –C(O)-R^{12}, where R^{12} ~~may be~~ is C_1–C_5 alkyl, C_1–C_5 alkoxy, C_1–C_5 haloalkyl, C_1–C_5 alkanol, –(C_1–C_5 alkyl)phenyl, or phenyl;

R^2 is hydrogen, C_1–C_5 alkyl, C_1–C_5 alkoxy, halogen, C_1–C_5 haloalkyl, or C_1–C_5 haloalkoxy;

R^3 is hydrogen, C_1–C_5 alkyl, C_1–C_5 alkoxy, halogen, C_1–C_5 haloalkyl, or C_1–C_5 haloalkoxy;

R^4 is hydrogen, C_1–C_5 alkyl, or –(C_1–C_5 alkyl)phenyl;

R^5 is hydrogen, C_1–C_5 alkyl, or –(C_1–C_5 alkyl)phenyl;

R^6 is hydrogen, hydroxy, or is absent;

R^7 is hydrogen;

R^8 is hydrogen or methyl;

R^9 is hydrogen or methyl;

R^{10} is hydrogen;

R^{11} is hydrogen or C_1–C_5 alkyl;

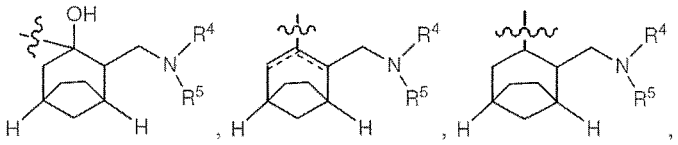
provided that one of I), II), and III) is present, wherein I), II) and III) are:

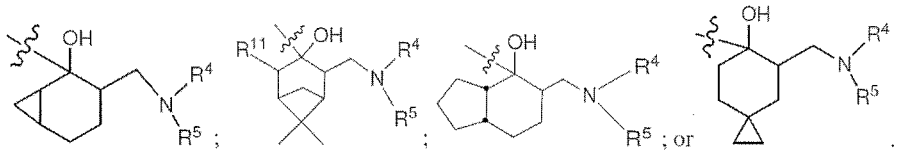
~~or A)~~ I) R^7 and R^{10} combine to form –CH_2- or –$(CH_2)_2$-;

~~or B~~) II) R^8 and R^9 combine to form a cyclopropyl group with the carbon to which they are attached; and

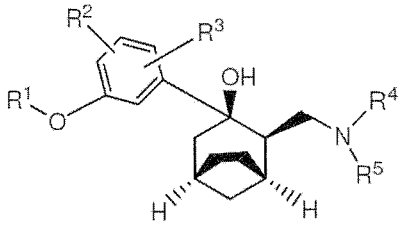
~~or C~~) III) R^{10} and R^{11} combine to form $-CH_2-$ or $-(CH_2)_3-$~~, wherein one of A, B, or C is present~~.

2. The compound, or salt thereof, of claim 1 wherein A is selected from





3. The compound of claim 2 of the formula Ia:



Ia,

or a salt thereof.

4. The compound of claim 2 wherein it is

2-dimethylaminomethyl-3-(3-methoxy-phenyl)-bicyclo[3.2.1]octan-3-ol;

2-dimethylaminomethyl-3-(3-fluoro-5-methoxy-phenyl)-bicyclo[3.2.1]octan-3-ol;

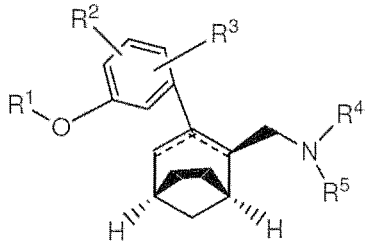
2-dimethylaminomethyl-3-(5-methoxy-2-trifluoromethoxy-phenyl)-bicyclo[3.2.1]octan-3

-ol; 2-dimethylaminomethyl-3-(2-fluoro-5-methoxy-phenyl)-bicyclo[3.2.1]octan-3-ol;
2-dimethylaminomethyl-3-(4-fluoro-3-methoxy-phenyl)-bicyclo[3.2.1]octan-3-ol;
2-dimethylaminomethyl-3-(2-fluoro-3-methoxy-phenyl)-bicyclo[3.2.1]octan-3-ol;
2-dimethylaminomethyl-3-(3-methoxy-5-methyl-phenyl)-bicyclo[3.2.1]octan-3-ol;
3-(2-chloro-5-methoxy-phenyl)-2-dimethylaminomethyl-bicyclo[3.2.1]octan-3-ol;
3-(3-chloro-5-methoxyphenyl)-2-dimethylaminomethyl-bicyclo[3.2.1]octan-3-ol;
2-dimethylaminomethyl-3-(5- methoxy-2-methyl-phenyl)-bicyclo[3.2.1]octan-3-ol;
2-dimethylaminomethyl-3-(3-methoxy-4- methyl-phenyl)-bicyclo[3.2.1]octan-3-ol;
2-dimethylaminomethyl-3-(3-hydroxy-phenyl)-bicyclo[3.2.1]octan-3-ol;
2-dimethylaminomethyl-3-(2-fluoro-5-hydroxy-phenyl)-bicyclo[3.2.1]octan-3-ol;
2-dimethylaminomethyl-3-(3-fluoro-5-hydroxy-phenyl)-bicyclo[3.2.1]octan-3-ol;
2-dimethylaminomethyl-3-(3-hydroxy-5-trifluoromethyl-phenyl)-bicyclo[3.2.1]octan-3-ol;
2-dimethylaminomethyl-3-(5-hydroxy-2-trifluoromethoxy-phenyl)-bicyclo[3.2.1]octan-3-ol;
2-dimethylaminomethyl-3-(3-hydroxy-4-trifluoromethyl-phenyl)-bicyclo[3.2.1]octan-3- ol;
2-dimethylaminomethyl-3-(4-fluoro-3-hydroxy-phenyl)-bicyclo[3.2.1]octan-3-ol;
2-dimethylaminomethyl-3-(2-fluoro-3-hydroxy-phenyl)-bicyclo[3.2.1]octan-3-ol;
2-dimethylaminomethyl-3-(3-hydroxy-5-methyl-phenyl)-bicyclo[3.2.1]octan-3-ol;
3-(2-chloro-5-hydroxy-phenyl)-2-dimethylaminomethyl-bicyclo[3.2.1]octan-3-ol;
3-(3-chloro-5-hydroxy-phenyl)-2-dimethylaminomethyl-bicyclo[3.2.1]octan-3-ol;
2-dimethylaminomethyl-3-(5-hydroxy-2-methyl-phenyl)-bicyclo[3.2.1]octan-3-ol;
2-dimethylaminomethyl-3-(3-hydroxy-4-methyl-phenyl)-bicyclo[3.2.1]octan-3-ol;
3-(3,4-difluoro-5-hydroxy-phenyl)-2-dimethylaminomethyl-bicyclo[3.2.1]octan-3-ol;
2-dimethylaminomethyl-3-(2-fluoro-5-hydroxy-phenyl)-bicyclo[3.2.1]octan-3-ol;
2,2-dimethyl-propionic acid 3-(2-dimethylaminomethyl-3-hydroxy-~~bicycle~~ bicyclo[3.2.1]oct-3-yl)-4-fluoro-phenyl ester;
benzoic acid 3-(2-dimethylaminomethyl-3-hydroxy-bicyclo[3.2.1]oct-3-yl)-4-fluoro-phenyl ester;
2,2-dimethyl-propionic acid 3-(2-dimethylaminomethyl-3-hydroxy-bicyclo[3.2.1]oct-3-yl)-phenyl ester;
benzoic acid 3-(2-dimethylaminomethyl-3-hydroxy-bicyclo[3.2.1]oct-3-yl)-phenyl ester;

2,2-dimethyl-propionic acid 3-(2-dimethylaminomethyl-3-hydroxy-bicyclo[3.2.1]oct-3-yl)-5-fluoro-phenyl ester; or

benzoic acid 3-(2-dimethylaminomethyl-3-hydroxy-bicyclo[3.2.1]oct-3-yl)-5-fluoro-phenyl ester; or a salt thereof.

5. The compound of claim 2 of the formula Ib:



Ib_2

or a salt thereof.

6. The compound of claim 2 wherein it is
3-(4-dimethylaminomethyl-bicyclo[3.2.1]oct-2-en-3-yl)-phenol;

[3-(3-methoxy-phenyl)-bicyclo[3.2.1]oct-3-en-2-ylmethyl]-dimethyl-amine;

[3-(5-methoxy-2-trifluoromethoxy-phenyl)-bicyclo[3.2.1]oct-3-en-2-ylmethyl]-dimethyl-amine;

3-(4-dimethylaminomethyl-bicyclo[3.2.1]oct-2-en-3-yl)-4-trifluoromethoxy-phenol;

[3-(3-fluoro-5-methoxy-phenyl)-bicyclo[3.2.1]oct-3-en-2-ylmethyl]-dimethyl-amine;

3-(4-dimethylaminomethyl-bicyclo[3.2.1]oct-2-en-3-yl)-5-fluoro-phenol;

[3-(2-fluoro-5-methoxy-phenyl)-bicyclo[3.2.1]oct-3-en-2-ylmethyl]-dimethyl-amine;

3-(4-dimethylaminomethyl-bicyclo[3.2.1]oct-2-en-3-yl)-4-fluoro-phenol;

[3-(3-methoxy-5-methyl-phenyl)-bicyclo[3.2.1]oct-3-en-2-ylmethyl]-dimethyl-amine;

3-(4-dimethylaminomethyl-bicyclo[3.2.1]oct-2-en-3-yl)-5-methyl-phenol;

3-chloro-5-(4-dimethylaminomethyl-bicyclo[3.2.1]oct-2-en-3-yl)-phenol;

[3-(5-methoxy-2-methyl-phenyl)-bicyclo[3.2.1]oct-3-en-2-ylmethyl]-dimethyl-amine;

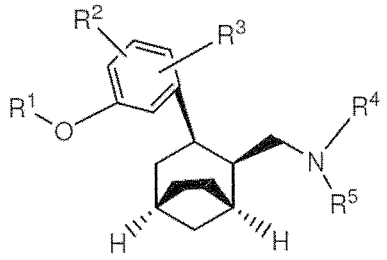
3-(4-dimethylaminomethyl-bicyclo[3.2.1]oct-2-en-3-yl)-4-methyl-phenol;

4-chloro-3-(4-dimethylaminomethyl-bicyclo[3.2.1]oct-2-en-3-yl)-phenol;

2,2-dimethyl-propionic acid 3-(4-dimethylaminomethyl-bicyclo[3.2.1]oct-2-en-3-yl)-phenyl ester;

benzoic acid 3-(4-dimethylaminomethyl-bicyclo[3.2.1]oct-2-en-3-yl)-phenyl ester;
2,2-dimethyl-~~propionicacid~~propionic acid 3-(4-dimethylaminomethyl-bicyclo[3.2.1]oct-2-en-3-yl)-5-fluorophenyl ester;
isobutyric acid 3-(4-dimethylaminomethyl-bicyclo[3.2.1]oct-2-en-3-yl)-5-fluoro-phenyl ester;
2,2-dimethyl-propionic acid 3-(4-dimethylaminomethyl-bicyclo[3.2.1]oct-2-en-3-yl) -4-fluoro-phenyl ester; or
isobutyric acid 3-(4-dimethylaminomethyl-bicyclo[3.2.1]oct-2-en-3-yl)-4-fluoro-phenyl ester; or a salt thereof.

7. The compound of claim 2 wherein it is of the formula Ic:



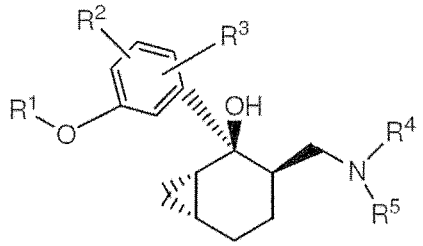
Ic,

or a salt thereof.

8. The compound of claim 2 wherein it is:
3-(2-dimethylaminomethyl-bicyclo[3.2.1]oct-3-yl)-phenol;
[3-(3-methoxy-phenyl)-bicyclo[3.2.1]oct-2-ylmethyl]-dimethyl-amine;
3-(2-dimethylaminomethyl-bicyclo[3.2.1]oct-3-yl)-5-fluoro-phenol;
[3-(3-fluoro-5-methoxy-phenyl)-bicyclo[3.2.1]oct-2-ylmethyl]-dimethyl-amine;
3-(2-dimethylaminomethyl-bicyclo[3.2.1]oct-3-yl)-4-fluoro-phenol;
[3-(2-fluoro-5-methoxy-phenyl)-bicyclo[3.2.1]oct-2-ylmethyl]-dimethyl-amine;
3-(2-dimethylaminomethyl-bicyclo[3.2.1]oct-3-yl)-5-methyl-phenol;
[3-(3-methoxy-5-methyl-phenyl)-bicyclo[3.2.1]oct-2-ylmethyl]-dimethyl-amine;
2,2-dimethyl-propionic acid 3-(2-dimethylaminomethyl-bicyclo[3.2.1]oct -3-yl)-phenyl ester;
benzoic acid 3-(2-dimethylaminomethyl-bicyclo[3.2.1]oct-3-yl)-phenyl ester;

2,2-dimethyl-propionic acid 3-(2-dimethylaminomethyl-bicyclo[3.2.1]oct-3-yl)-5-fluoro-phenyl ester;
isobutyric acid 3-(2-dimethylaminomethyl-bicyclo[3.2.1]oct-3-yl)-5-fluoro-phenyl ester;
2,2-dimethyl-propionic acid 3-(2-dimethylaminomethyl-bicyclo[3.2.1]oct-3-yl)-4-fluoro-phenyl ester;
or isobutyric acid 3-(2-dimethylaminomethyl-bicyclo[3.2.1]oct-3-yl)-4-fluoro-phenyl ester;
or a salt thereof.

9. The compound of claim 2 wherein it is of the formula Id:

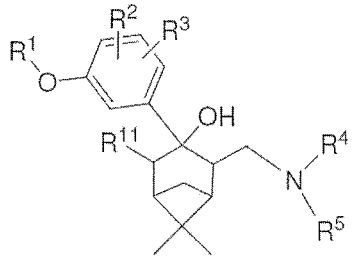


Id

or a salt thereof.

10. The compound of claim 2 wherein it is
3-dimethylaminomethyl-2-(3-hydroxy-phenyl)-bicyclo[4.1.0]heptan-2-ol;
3-dimethylaminomethyl-2-(3-methoxy-phenyl)-bicyclo[4.1.0]heptan-2-ol;
3-dimethylaminomethyl-2-(3-fluoro-5-methoxy-phenyl)-bicyclo[4.1.0]heptan-2-ol;
3-dimethylaminomethyl-2-(5-methoxy-2-methyl-phenyl)-bicyclo[4.1.0]heptan-2-ol;
3-dimethylaminomethyl-2-(3-methoxy-phenyl)-5,5-dimethyl-bicyclo[4.1.0]heptan-2-ol;
3-dimethylaminomethyl-2-(3-hydroxy-phenyl)-5,5-dimethyl-bicyclo[4.1.0]heptan-2-ol;
3-dimethylaminomethyl-2-(3-fluoro-5-hydroxy-phenyl)-bicyclo[4.1.0] heptan-2-ol;
3-dimethylaminomethyl-2-(2-fluoro-5-hydroxy-phenyl)-bicyclo[4.1.0]heptan-2-ol;
3-dimethylaminomethyl-2-(3-hydroxy-5-methyl-phenyl)-bicyclo[4.1.0]heptan-2-ol;
2,2-dimethyl-propionic acid 3-(3-dimethylaminomethyl-2-hydroxy-bicyclo[4.1.0]hept-2-yl)-5-fluoro-phenyl ester; or
2,2-dimethyl-propionic acid 3-(3-dimethylaminomethyl-2-hydroxy-bicyclo[4.1.0]hept-2-yl) -4-fluoro-phenyl ester; or a salt thereof.

11. The compound of claim 2 wherein it is of the formula Ie:

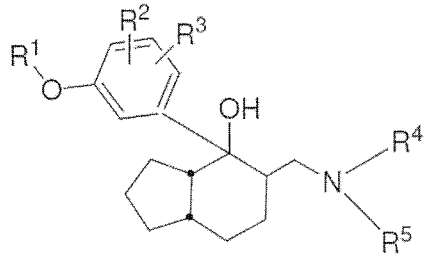


Ie,

or a salt thereof.

12. The compound of claim 11 wherein it is
(1R,2R,3S,4S,5S)-3-(3-hydroxyphenyl)-2,6,6-trimethyl-4-((methyl(phenethyl)amino)methyl)bicyclo[3.1.1]heptan-3-ol;
(1R,2R,3S,4S,5S)-3-(3-methoxyphenyl)-2,6,6-trimethyl-4-((methyl(phenethyl)amino)methyl)bicyclo[3.1.1]heptan-3-ol;
(1S,2S,3R,4R,5R)-3-(3-hydroxyphenyl)-2,6,6-trimethyl-4-((methyl(phenethyl)amino)methyl)bicyclo[3.1.1]heptan-3-ol;
(1S,2S,3R,4R,5R)-3-(3-methoxyphenyl)-2,6,6-trimethyl-4-((methyl(phenethyl)amino)methyl)bicyclo[3.1.1]heptan-3-ol; or a salt thereof.

13. The compound of claim 2 wherein it is of the formula If:



If,

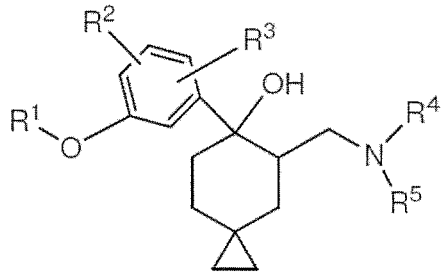
or a salt thereof.

14. The compound of claim 13 wherein it is 5-((dimethylamino)methyl)- 4-(3-hydroxyphenyl)octahydro-1H-inden-4-ol, or a salt thereof.

15. The compound of claim 2 wherein it is
(+)-(1S,2R,3R,5R)-2- ((dimethylamino)methyl)-3-(3-hydroxyphenyl)bicyclo[3.2.1]octan-3-ol;
(-)-(1R,2S,3S,5S)-2-((dimethylamino)methyl)-3-(3-hydroxyphenyl)bicyclo[3.2.1]octan-3-

ol;
(S)-3-((1S,2R,3R,5R)-2- ((dimethylamino)methyl)-3-hydroxybicyclo[3.2.1]octan-3-yl)phenyl 2-phenylpropanoate hydrochloride;
(S)-3-(1R,2S,3S,5S)-2-((dimethylamino)methyl)-3-hydroxybicyclo[3.2.1]octan-3-yl)phenyl 2-phenylpropanoate hydrochloride;
3-(4-dimethylaminomethyl-bicyclo[3.2.1]oct-2- en-3-yl)-phenol;
3-((1S,5R)-2-((dimethylamino)methyl)bicyclo[3.2.1]oct-2-en-3-yl)phenol; ~~and salts~~ or a salt thereof.

16. A compound of claim 2 wherein it is of the formula Ig:



Ig,

or a salt thereof.

17. The compound of claim 16 where it is 5-dimethylaminomethyl-6-(2- fluoro-5-hydroxy-phenyl)-spiro[2.5]octan-6-ol, or a salt thereof.

18. The compound of claim 4 wherein it is 2-dimethylaminomethyl-3- (3-methoxy-5-methyl-phenyl)-bicyclo[3.2.1]octan-3-ol, or a salt thereof.

19. The compound of claim 4 wherein it is 2-dimethylaminomethyl-3- (3-hydroxy-5-methyl-phenyl)-bicyclo[3.2.1]octan-3-ol, or a salt thereof.

20. The compound of claim 10 wherein it is 3-dimethylaminomethyl-2-(3-fluoro-5-hydroxy-phenyl)-bicyclo[4.1.0]heptan-2-ol, or a salt thereof.

21. The compound of claim 10 wherein it is 3-dimethylaminomethyl-2-(2-fluoro-5-hydroxy-phenyl)-bicyclo[4.1.0]heptan-2-ol, or a salt thereof.

22. The compound of claim 10 wherein it is 2,2-dimethyl-propionic acid 3-(3-dimethylaminomethyl-2-hydroxy-bicyclo[4.1.0]hept-2-yl)-5-fluoro-phenyl ester, or a salt thereof.

23. The compound of claim 10 wherein it is 2,2-dimethyl-propionic acid 3-(3-dimethylaminomethyl-2-hydroxy-bicyclo[4.1.0]hept-2-yl)-4-fluoro-phenyl ester, or a salt thereof.

24. The compound of any one of claims 18-23, wherein it is the hydrochloride salt thereof.

25. A pharmaceutical formulation comprising a compound of any of claims 1-24 and one or more pharmaceutically acceptable carriers.

26. The pharmaceutical formulation of claim 25 wherein it further comprises at least one additional active ingredient.

27. The pharmaceutical formulation of claim 25 wherein it is a human pharmaceutical formulation.

28. The pharmaceutical formulation of claim 25 wherein it is a veterinary pharmaceutical formulation.

29. Use of an effective amount of a compound of any of claims 1 through 24 in the manufacture of a medicament for controlling pain in a mammal.

30. The use of claim 29 wherein the medicament comprises at least one other active ingredient.

31. The use of claim 29 or claim 30, wherein said mammal is a human.

32. The use of claim 29 or claim 30, wherein said mammal is a companion animal.

33. The use of claim 32, wherein said companion animal is a dog or cat.

34. A compound or salt according to any one of claims 1 to 24 for use in therapy.

35. The ~~A~~ compound or salt according to claim 34, wherein the use in therapy comprises ~~any one of claims 1 to 24 for use in~~ controlling pain.