

CONVENTION

AUSTRALIA

Patents Act 1990

660609

NOTICE OF ENTITLEMENT

We, NOVO NORDISK A/S of Novo Alle, DK-2880 Bagsvaerd, Denmark state the following in connection with Australian Application No. 75744/91:

1. The nominated person is the assignee of the actual inventor.
2. The nominated person is the applicant of the basic application listed in the declaration under Article 8 of the PCT.
3. The basic application is the application first made in a Convention country in respect of the invention.

Dated: 10 September 1992

By PHILLIPS ORMONDE & FITZPATRICK
Patent Attorneys for the Applicant
By:

David B Fitzpatrick

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To: The Commissioner of Patents

Our Ref: 304375

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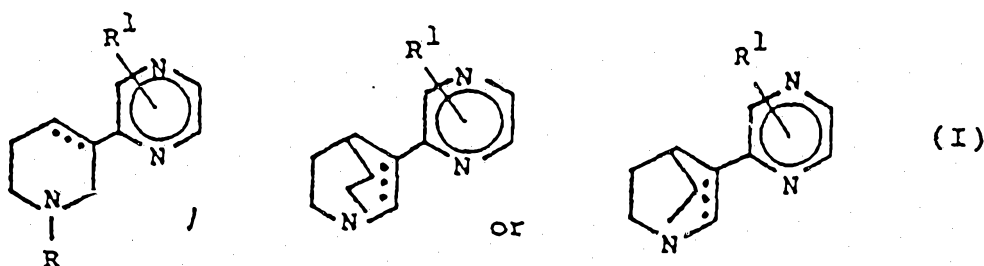
AU9175744

(12) PATENT ABRIDGMENT (11) Document No. AU-B-75744/91
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 660609

- (54) Title
AZACYCLIC OR AZABICYCLIC COMPOUNDS, THEIR PREPARATION AND USE
- International Patent Classification(s)
(51)⁵ C07D 453/02 C07D 401/04 C07D 471/08 A61K 031/495
- (21) Application No. : 75744/91 (22) Application Date : 20.03.91
- (87) PCT Publication Number : WO91/14686
- (30) Priority Data
- | | | |
|-------------|-----------|--------------|
| (31) Number | (32) Date | (33) Country |
| 0727/90 | 21.03.90 | DK DENMARK |
- (43) Publication Date : 21.10.91
- (44) Publication Date of Accepted Application : 06.07.95
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- (56) Prior Art Documents
AU 28834/89 C07D 401/04
AU 60830/90 C07D 453/02
AU 27798/89 C07D 453/02

- (57) The novel compounds are useful as stimulants of the cognitive function of the fore-brain and hippocampus of mammals and especially in the treatment of Alzheimer's disease.

Claim



wherein R is methyl and R^1 is in the 3-position of the pyrazinyl moiety and is halogen, $S-R^2$ or $O-R^2$ wherein R^2 is straight or branched C_{1-15} -alkyl unsubstituted or substituted with one or more halogen atoms or R^3-O-R^4 wherein R^3 and R^4 independently are straight or branched C_{1-15} -alkyl, --- is HC-CH or $\text{C}=\text{C}$, or a salt thereof with a pharmaceutically-acceptable acid.

OPI DATE 21/10/91

APPLN. ID

75744 / 91

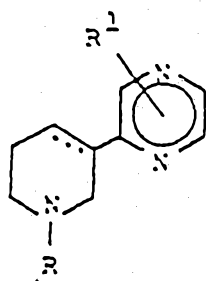
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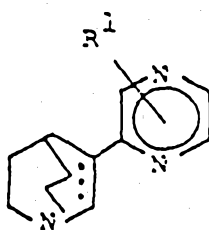
PCT NUMBER PCT/DK91/00087

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

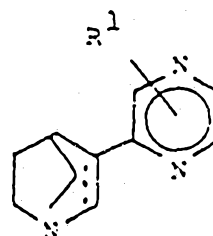
(51) International Patent Classification ⁵ : C07D 453/02, 401/04, 471/08 A61K 31/495	A1	(11) International Publication Number: WO 91/14686 (43) International Publication Date: 3 October 1991 (03.10.91)
(21) International Application Number: PCT/DK91/00087 (22) International Filing Date: 20 March 1991 (20.03.91) (30) Priority data: 0727/90 21 March 1990 (21.03.90) DK (71) Applicant: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK). (72) Inventor: WARD, John, S. ; 241 E. Brunswick Avenue, In- dianapolis, IN 46227 (US). (74) Agent: LEHMANN & REE; Frederiksberg Allé 26, DK- 1820 Frederiksberg C (DK).		(81) Designated States: AT (European patent), AU, BE (Euro- pean patent), CA, CH (European patent), DE (Euro- pean patent), DK (European patent), ES (European pa- tent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, PL, SE (European patent). Published With international search report. 660609

(54) Title: AZACYCLIC OR AZABICYCLIC COMPOUNDS, THEIR PREPARATION AND USE

(A)



(B)



(C)

(I)

(57) Abstract

The present invention relates to therapeutically active azacyclic or azabicyclic compounds of formula (I), a method of preparing the same and to pharmaceutical compositions comprising the compounds. The novel compounds are useful as stimulants of the cognitive function of the forebrain and hippocampus of mammals and especially in the treatment of Alzheimer's disease. (A), (B) or (C), wherein R and R¹ are as defined in claim 1.

Azacyclic or azabicyclic compounds,
their preparation and use

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The present invention relates to therapeutically active azacyclic or azabicyclic compounds, a method of preparing the same and to pharmaceutical compositions comprising the compounds. The novel compounds are useful
10 as stimulants of the cognitive function of the forebrain and hippocampus of mammals and especially in the treatment of Alzheimer's disease.

Due to the in general improved health situation in the
15 western world, elderly-related diseases are much more common now than in the past and are likely to be even more common in the future.

One of the elderly-related symptoms is a reduction of the
20 cognitive functions. This symptom is especially pronounced in the pathophysiological disease known as Alzheimer's disease. This disease is combined with, and also most likely caused by, a up to 90% degeneration of the muscarinic cholinergic neurons in nucleus basalis, which is part of sub-
25 stantia innominata. These neurons project to the prefrontal cortex and hippocampus and have a general stimulatory effect on the cognitive functions of the forebrain as well as of hippocampus, namely learning, association, consolidation, and recognition.

30

It is a characteristic of Alzheimer's disease that although the cholinergic neurons degenerate, then the postsynaptic muscarinic receptors in the forebrain and hippocampus still exist. Therefore muscarinic cholinergic M_1 agonists and
35 M_2 antagonists are useful in the treatment of Alzheimer's disease and in improving the cognitive functions of elderly people.

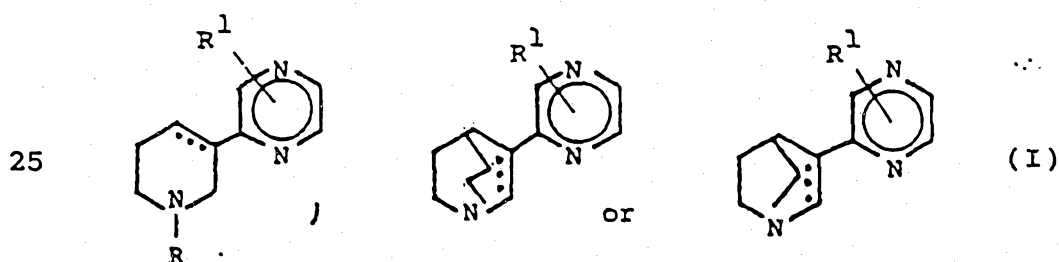
It is well known that arecoline (methyl 1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate) is such a cholinergic agonist.

- 5 Arecoline however has a very short biological half life and a small separation between central and peripheral muscarinic effects. Furthermore arecoline is a rather toxic compound.

10 EP-A-327155 discloses a class of compounds which includes pyrazines substituted with a non-aromatic azacyclic or azabicyclic ring system which stimulate central muscarinic acetylcholine receptors and therefore are useful in the treatment of neurological and mental illnesses.

- 15 It is an object of the invention to provide new muscarinic cholinergic compounds.

The novel compounds of the invention are heterocyclic compounds having the formula I selected from the group consisting of



- 30 wherein R is methyl and R^1 is in the 3-position of the pyrazinyl moiety and is halogen, $S-R^2$ or $O-R^2$ wherein R^2 is straight or branched C_{1-7} -alkyl unsubstituted or substituted with one or more halogen atoms or R^3-O-R^4 wherein R^3 and R^4 independently are straight or branched C_{1-15} -alkyl,

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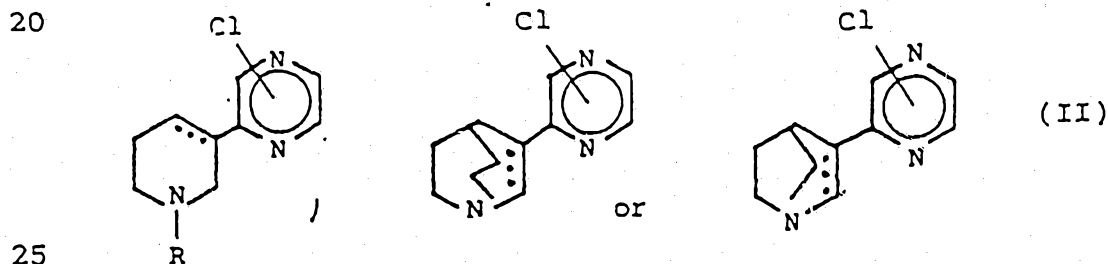
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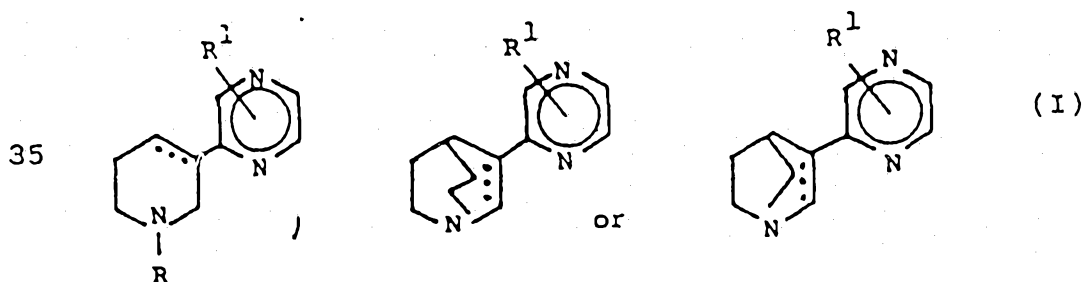
$\text{---}\text{---}\text{---}$ is HC-CH or C=C , or a salt thereof with a pharmaceutically acceptable acid.

Examples of such salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically-acceptable inorganic or organic acid addition salt.

The invention also relates to a method of preparing the above mentioned compounds, which comprises reacting a compound of formula II selected from the group consisting of



wherein R and $\text{---}\text{---}\text{---}$ have the meanings defined above with a reactive derivative to form a compound of formula I selected from the group consisting of



wherein R, R¹ and $\text{>}\cdots\text{<}$ have the meanings defined above.

The pharmacological properties of the compounds of the invention can be illustrated by determining their capability to
5 inhibit the specific binding of ³H-Oxotremorine-M (³H-Oxo).

³H-Oxo labels muscarinic receptor in the CNS (with a preference for agonist domains of the receptors). Three different sites are labelled by ³H-Oxo. These sites have affinity of 1.8, 20 and 3000 nM, respectively. Using the present experimental conditions only the high and medium affinity sites are determined.
10

The inhibitory effects of compounds on ³H-Oxo binding reflects the affinity for muscarinic acetylcholine receptors.
15

All preparations are performed at 0-4°C unless otherwise indicated. Fresh cortex (0.1-1 g) from male Wistar rats (150-250 g) is homogenized for 5-10 s in 10 ml 20 mM Hepes pH: 7.4, with an Ultra-Turrax homogenizer. The homogenizer is rinsed with 10 ml of buffer and the combined suspension centrifuged for 15 min at 40,000 × g. The pellet is washed three times with buffer. In each step the pellet is homogenized as before in 2×10 ml of buffer and centrifuged for
20
25 10 min at 40,000 × g.

The final pellet is homogenized in 20 mM Hepes pH: 7.4 (100 ml per g of original tissue) and used for binding assay. Aliquots of 0.5 ml is added 25 µl of test solution and 25 µl of ³H-Oxotremorine (1.0 nM, final concentration) mixed and incubated for 30 min at 25°C. Non-specific binding is determined in triplicate using arecoline (1 µg/ml, final concentration) as the test substance. After incubation samples are added 5 ml of ice-cold buffer and poured directly onto Whatman GF/C glass fiber filters under suction and immediately washed 2 times with 5 ml of ice-cold buffer. The amount of radioactivity on the filters are deter-
30
35

mined by conventional liquid scintillation counting. Specific binding is total binding minus non specific binding.

Test substances are dissolved in 10 ml water (if necessary heated on a steambath for less than 5 minutes) at a concentration of 2.2 mg/ml. 25-75% inhibition of specific binding must be obtained before calculation of IC_{50} .

The test value will be given as IC_{50} (the concentration (nM) of the test substance which inhibits the specific binding of ^3H -Oxo by 50%).

IC_{50} = (applied test substance concentration)

15

$$x \frac{1}{\frac{C_o}{C_x} - 1} \text{ nM}$$

20

where C_o is specific binding in control assays and C_x is the specific binding in the test assay. (The calculations assume normal mass-action kinetics).

Test results obtained by testing some compounds of the present invention will appear from the following table 1.

30

35

TABLE 1

5	Compound No.	Inhibition in vitro OXO BINDING (nM)
10	3	17
	4	20
	5	99
	6	276
	13	72
15	14	235
	15	4
	16	10
	17	18
	20	130
20	21	5
	24	490
	25	6
	27	46
	28	5.6
25	34	19
	36	13
	37	23
	38	9
	39	0.7
	40	2

30

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, or cap-

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sules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective muscarinic cholinergic agonistic amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing ten (10) milligrams of the active ingredient or, more broadly, one (1) to hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of this invention can thus be used for the formulation of pharmaceutical preparations, e.g. for oral and parenteral administration to mammals including humans, in accordance with conventional methods of galenic pharmacy.

Conventional excipients are such pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral or enteral application which do not deleteriously react with the active compounds.

Examples of such carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

5

Ampoules are convenient unit dosage forms.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch, are particularly suitable for oral application. A syrup, elixir of the like can be used in cases where a sweetened vehicle can be employed.

15 Generally, the compounds of this invention are dispensed in unit form comprising 1-100 mg in a pharmaceutically acceptable carrier per unit dosage.

20 The dosage of the compounds according to this invention is 1-100 mg/day, preferably 10-70 mg/day, when administered to patients, e.g. humans, as a drug.

A typical tablet which may be prepared by conventional
25 tableting techniques contains:

	Active compound	5.0 mg
	Lactosum	67.8 mg Ph.Eur.
	Avicel [®]	31.4 mg
30	Amberlite [®]	1.0 mg
	Magnesii stearas	0.25 mg Ph.Eur.

Due to the high muscarinic cholinergic receptor agonistic activity, the compounds of the invention are extremely useful in the treatment symptoms related to a reduction of the cognitive functions of the brain of mammals, when administered in an amount effective for stimulating the cognitive

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functions of the forebrain and hippocampus. The important stimulating activity of the compounds of the invention includes both activity against the patophysiological disease, Alzheimer's disease as well as against normal degeneration of brain function. The compounds of the invention may accordingly be administered to a subject, e.g., a living animal body, including a human, in need of stimulation of the cognitive functions of the forebrain and hippocampus, and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof (such as the hydrobromide, hydrochloride, or sulfate, in any event prepared in the usual or conventional manner, e.g., evaporation to dryness of the free base in solution together with the acid), ordinarily concurrently, simultaneously, or together with a pharmaceutically-acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parenteral (including subcutaneous) route, in an effective forebrain and hippocampus stimulating amount, and in any event an amount which is effective for improving the cognitive function of mammals due to their muscarinic cholinergic receptor agonistic activity. Suitable dosage ranges are 1-100 milligrams daily, 10-100 milligrams daily, and especially 30-70 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

Elemental analysis are indicated only by the symbols of the elements after the empirical formula and are within 0.4% of the theoretical values. Melting points were determined on a Mel-Temp apparatus and are uncorrected. HPLC separations were performed on a Waters PrepLC/500A using PrepPAK-500 silica gel cartridges with the solvents specified. Radial chromatography was performed on a Chromatotron

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Model 7924T using Analtech Precast Rotors made of Silica Gel GF and eluting with the solvents specified. TLC was carried out on Merck F254 silica gel plates. All reactions, exclusive of extraction procedures, were conducted under an Ar atmosphere. NMR measurements were made with a QE300 using the solvents described.

The invention will now be described in further detail with reference to the following examples:

EXAMPLE 1

3-(3-Chloropyrazinyl)-1-methyl-3-piperidinol (1)

A solution of 7.2 ml 2,2,6,6-tetramethylpiperidine (0.034 mol) in 300 ml of dry THF was cooled to -8°C as 25 ml of 1.6 M butyllithium (0.04 mol) in hexane was added dropwise. The reaction was stirred 20 min then cooled to -77°C . A solution of 2.9 ml of 2-chloropyrazine (0.031 mol) in 5 ml of THF was added dropwise to the reaction. After another 15 min, 3.5 g of 1-methylpiperidin-3-one (0.035 mol) in 10 ml of THF was added dropwise. After the addition, the reaction was stirred 1.5 h followed by addition of a mixture of 8 ml of concentrated HCl and 4 ml of ethanol. The cooling was removed and when the temperature had reached -15°C , 20 ml of 5 N NaOH was added. The volatile organics were evaporated and the aqueous residue was extracted 4X with 30 ml of CH_2Cl_2 . The extracts were washed with brine, dried and the solvent evaporated to give a brown solid that was dissolved in 300 ml of ether and filtered. The ether was evaporated and the residue recrystallized from hexane to give 3.77 g of (1), 53% yield, mp $111-112^{\circ}\text{C}$. NMR ppm (CDCl_3) 1.7-2.2 (5H, m), 2.4 (3H, s), 2.7 (1H, d), 2.85-3.05 (2H, m), 4.4 (1H, bs), 8.35 (1H, d), 8.5 (1H, d). Anal. $\text{C}_{10}\text{H}_{14}\text{ClN}_3\text{O}$, requires C: 52.7%; H: 6.20; N:

18.46%. Found C: 52.64; H: 6.21; N: 18.21%.

3-(3-Methoxypyrazinyl)-1,2,5,6-tetrahydro-1-methylpyridine ethandioate (2)

5

A mixture of 0.32 g of (1) (0.0014 mol) and 10 ml of thionyl chloride was heated to reflux for 1.5 h. The excess thionyl chloride was evaporated, the residue
10 treated with ice-water and made basic with saturated aqueous K_2CO_3 . The mixture was extracted 3X with 25 ml of CH_2Cl_2 , the extracts washed with brine, dried, and the solvent evaporated. The residue was dissolved in 5 ml of methanol and added to 25 ml of methanol that had
15 reacted with 0.35 g of Na (0.015 mol). The reaction was heated to reflux for 1.5 h. The solvent was evaporated, the residue was treated with ice-water and the mixture extracted 3X with 25 ml of CH_2Cl_2 . The extracts were washed with brine, dried, and the solvent evaporated to
20 give a dark liquid, 0.15 g. The liquid was dissolved in ethyl acetate and treated with oxalic acid to give 0.05 g of (2) after recrystallization from ethyl acetate, mp 150-151°C. NMR ppm (D_2O) 2.6-2.9 (2H, m), 3.1 (3H, s), 3.3 (1H, m), 3.65 (1H, m), 4.0 (3H, s), 4.05 (1H, dd),
25 4.35 (1H, d), 6.95 (1H, bs), 8.07 (1H, d), 8.1 (1H, d). Anal. $C_{11}H_{15}N_3O-C_2H_2O_4$ requires C: 52.88; H: 5.80; N: 14.23%. Found C: 52.66; H: 5.94; N: 14.04%.

30 3-(3-Butyloxypyrazinyl)-1,2,5,6-tetrahydro-1-methylpyridine ethanedioate (3)

A mixture of 0.5 g of (1) (0.0022 mol) and 10 ml of thionyl chloride was stirred for 1.5 h. The solvent was
35 evaporated, the residue treated with ice-water, and the mixture made basic with saturated aqueous K_2CO_3 . The mixture was extracted 3X with 25 ml of CH_2Cl_2 , the

extracts washed with brine, dried, and the solvent evaporated. The residue was dissolved in a small amount of butanol and added to 25 ml of butanol that had reacted with 0.5 g of Na (0.022 mol). The reaction was heated to reflux for 2.5 h. After evaporation of the solvent, the residue was treated with ice-water and 3 ml of concentrated HCl. The mixture was extracted 2X with ether. The aqueous solution was made basic with 5 N NaOH, extracted 3X with 25 ml of CH₂Cl₂, the extracts washed with brine, dried, and the solvent evaporated. The brown liquid residue was purified by HPLC eluting with an 8 L gradient starting with CH₂Cl₂ and going to 10% methanol to give 0.1 g of a yellow liquid. The oxalate salt (3), 0.08 g, crystallized from ethyl acetate, mp 160-161.5°C. NMR of the free base, ppm (CDCl₃) 1.0 (3H, t), 1.55 (2H, m), 1.85 (2H, m), 2.5 (5H, bs+s), 2.63 (2H, t), 3.5 (2H, m), 4.4 (2H, t), 7.1 (1H, m), 7.9 (1H, d), 8.1 (1H, d). Anal. C₁₄H₂₁N₃O-C₂H₂O₄ requires C: 56.96; H: 6.87; N: 12.45%. Found C: 56.59; H: 7.12; N: 12.34%.

3-(3-Hexyloxypyrazinyl)-1,2,5,6-tetrahydro-1-methylpyridine diethanoate (4)

25

A mixture of 0.75 g of (1) (0.0033 mol) and 5 ml of thionyl chloride was stirred for 1 h followed by evaporation of the solvent. The residue was treated with ice-water, made basic with saturated aqueous K₂CO₃, and extracted 3X with CH₂Cl₂. The extracts were washed with brine, dried, and the solvent evaporated. The residue was dissolved in a small amount of hexanol and added to 25 ml of hexanol that had reacted with 0.5 g of Na (0.022 mol). The reaction was heated to 120°C for 2 h followed by evaporation of the solvent. The residue was treated with 10 ml of 5 N HCl and the remaining hexanol was azeotroped off with water. The residue was made basic

with 5 N NaOH and extracted 3X with 25 ml of CH_2Cl_2 . The extracts were washed with brine, dried, and the solvent evaporated. The residue was purified by HPLC eluting with an 8 L gradient starting with CH_2Cl_2 and going to 10% methanol-1% NH_4OH to give 0.32 g of brown liquid. The oxalate salt (4), 0.34 g, crystallized from ethyl acetate, mp 154-155°C. NMR of the free base, ppm (CDCl_3) 0.95 (3H, t), 1.3-1.55 (6H, m), 1.85 (2H, m), 2.5 (5H, bs+s), 2.65 (2H, t), 4.4 (2H, t), 7.1 (1H, m), 7.9 (1H, d), 8.1 (1H, d). Anal. $\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}-\text{C}_2\text{H}_2\text{O}_4$ requires C: 59.16; H: 7.45; N: 11.50%. Found C: 58.91; H: 7.34; N: 11.26%.

3-(3-(2-Methoxyethoxy)pyrazinyl)-1,2,5,6-tetrahydro-1-methylpyridine ethanedioate (5)

A mixture of 0.8 g of (1) (0.0035 mol) and 6 ml of thionyl chloride was stirred for 1 h followed by evaporation of the solvent. The residue was treated with ice-water, made basic with saturated aqueous K_2CO_3 , and extracted 3X with 25 ml of CH_2Cl_2 . The extracts were washed with brine, dried, and the solvent evaporated. The residue was dissolved in a small amount of 2-methoxyethanol and added to 25 ml of 2-methoxyethanol that had reacted with 0.5 g of Na (0.022 mol). The reaction was heated to 100°C for 2 h, followed by evaporation of the solvent. The residue was treated with ice-water and extracted 3X with 25 ml of CH_2Cl_2 . The extracts were washed with brine, dried, and the solvent evaporated. The residue was purified by HPLC eluting with an 8 L gradient starting with CH_2Cl_2 and going to 10% methanol to give 0.31 g of a yellow liquid. The oxalate salt (5), 0.26 g, crystallized from ethyl acetate, mp 149.5-150.5°C. NMR of the free base, ppm (CDCl_3) 2.5 (5H, bs + s), 2.65 (2H, t), 3.45 (3H, s), 3.5 (2H, m), 3.8 (2H, t), 4.55 (2H, t), 7.15 (1H, m), 7.9 (1H, d), 8.1 (1H, d). Anal. $\text{C}_{13}\text{H}_{19}\text{N}_3\text{O}_2-\text{C}_2\text{H}_2\text{O}_4$ requires C:

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53.09; H: 6.24; N: 12.38%. Found C: 53.09; H: 6.29; N: 12.37%.

5 3-(3-Chloropyrazinyl)-1,2,5,6-tetrahydro-1-methylpyridine
ethanedioate (6)

10 A solution of 10 ml of thionyl chloride was cooled to 0°C
as 1 g of (1) (0.0044 mol) was added. Cooling was removed
and the reaction stirred 2 h. The solvent was evaporated,
the residue treated with ice-water, and the mixture made
basic with saturated aqueous K₂CO₃. The mixture was ex-
tracted 3X with 25 ml of CH₂Cl₂, the extracts washed with
brine, dried, and the solvent evaporated. The residue was
15 purified by HPLC eluting with an 8 L gradient starting
with CH₂Cl₂ and going to 7.5% methanol-1% NH₄OH to give
0.43 g of an orange liquid. The oxalate salt (6), 0.26 g,
crystallized from isopropanol, mp 110-111°C. NMR ppm (D₂O)
2.75 (2H, m), 3.05 (3H, s), 3.35 (1H, m), 3.65 (1H, m),
20 4.05 (1H, m), 4.25 (1H, d), 6.62 (1H, bs), 8.38 (1H, d),
8.55 (1H, d). Anal. C₁₀H₁₂ClN₃-C₂H₂O₄ requires C: 48.09;
H: 4.71; N: 14.02%. Found C: 48.06; H: 4.76; N: 13.86%.

25 3-(3-Heptyloxypyrazinyl)-1,2,5,6-tetrahydro-1-methyl-
pyridine ethanedioate (17)

30 A mixture of 0.9 g of (1) (0.0039 mol) and 6 ml of thionyl
chloride was stirred for 1 h followed by evaporation of
the solvent. The residue was treated with ice-water, made
basic with saturated aqueous K₂CO₃, and extracted 3X with
25 ml of CH₂Cl₂. The extracts were washed with brine,
dried, and the solvent evaporated. The residue was dis-
solved in a small amount of heptanol and added to 35 ml
35 of heptanol that had reacted with 0.5 g of Na (0.022 mol).
The reaction was heated to 100°C for 2 h, cooled to ambi-
ent temperature and treated with 6 ml of 5 N HCl. The hep-

tanol was azeotroped off with water the aqueous residue made basic with saturated aqueous K_2CO_3 and then extracted 3X with 25 ml of CH_2Cl_2 . The extracts were washed with brine, dried, and the solvent evaporated. The residue was
5 purified by HPLC eluting with an 8 L gradient starting with CH_2Cl_2 and going to 10% methanol to give 0.43 g of yellow liquid that crystallized from ethyl acetate as the oxalate salt (17), 0.41 g, mp 125-127°C. NMR of free base, ppm ($CDCl_3$) 0.9 (3H, t), 1.22-1.52 (8H, m), 1.82 (2H, m),
10 2.5 (5H, bs), 2.62 (2H, t), 3.5 (2H, m), 4.4 (2H, t), 7.1 (1H, m), 7.9 (1H, d), 8.05 (1H, d). Anal. $C_{17}H_{27}N_3O \cdot C_2H_2O_4$ requires C: 60.14; H: 7.70; N: 11.07%. Found C: 59.92; H: 7.61; N: 10.94%.

15 3-(3-Ethoxypyrazinyl)-1,2,5,6-tetrahydro-1-methylpyridine ethandioate (32)

A mixture of 1.1 g (0.0048 mol) of 3-(3-chloropyrazinyl)-1-methyl-3-piperidinol (1) and 7 ml of thionyl
20 chloride was stirred for 1 h at ambient temperature. Excess thionyl chloride was evaporated, the residue was treated with ice-water, and the solution made basic with 5N NaOH. The mixture was extracted 3X with 25
25 ml of CH_2Cl_2 , the extracts dried, and the solvent evaporated. The residue was dissolved in 5 ml of anhydrous ethanol and added to a solution of sodium ethoxide prepared from 0.7 g (0.03 mol) of sodium and
35 35 ml of anhydrous ethanol. The solution was heated to reflux for 2 h, the reaction cooled to ambient temperature, and 5 ml of water was added. The solvents were evaporated, the residue dissolved in water, and the mixture extracted 3X with 25 ml of CH_2Cl_2 . The extracts were dried and the solvent was evaporated. The
residue was purified by radial chromatography eluting with 5% ethanol/ 0.5% $NH_4OH/CHCl_3$ and the desired product converted to the oxalate salt (32), that crystal-

lized from ethyl acetate with 0.25 mol of water, 0.55 g, 38% yield, mp 133-135°C. NMR ppm(CDCl₃) 1.45 (3H, t), 2.62 (1H, bm), 2.75-3.2 (5H, m), 3.5-3.95 (2H, m), 4.3-4.75 (3H, m), 4.8-5.3 (2H, m), 7.38 (1H, m), 7.98 (1H, d), 8.05 (1H, d). Anal. C₁₂H₁₇N₃O-C₂H₂O₄-0.25 H₂O requires C: 53.58; H: 6.26; N: 13.39%. Found C: 53.80; H: 6.15; N: 13.08%.

3-(3-Propyloxypyrazinyl)-1,2,5,6-tetrahydro-1-methylpyridine ethandioate (33)

A mixture of 1 g (0.0044 mol) of (1) and 7 ml of thionyl chloride was stirred 1 h, the excess thionyl chloride was evaporated, and the residue was treated with ice-water. The solution was made basic with 5 N NaOH and the mixture extracted 3X with 25 ml of CH₂Cl₂. The solvent was evaporated from the dried extracts, the residue dissolved in 5 ml of 1-propanol, and the solution added to a solution of sodium propoxide prepared from 0.7 g (0.03 mol) of sodium and 35 ml of 1-propanol. The mixture was heated to reflux for 2 h, the reaction was cooled to ambient temperature, 5 ml of water added, and the solvents evaporated. The residue was treated with water and extracted 3X with 25 ml of CH₂Cl₂. The extracts were dried and the solvent evaporated to give a brown liquid that was purified by radial chromatography eluting with 5% ethanol/ 0.5% NH₄OH/CHCl₃. The oxalate salt (33) crystallized from ethyl acetate to give 0.38 g, 27% yield, of white solid, mp 146-147°C. NMR ppm(CDCl₃) 1.05 (3H, t), 1.87 (2H, m), 2.75-2.92 (2H, m), 3.0 (3H, s), 3.2-3.55 (2H, m) 4.0-4.4 (4H, m), 7.38 (1H, m), 7.97 (1H, d), 8.06 (1H, d). Anal. C₁₃H₁₉N₃O-C₂H₂O₄ requires C: 55.72; H: 6.56; N: 12.99%. Found C: 55.52; H: 6.42; N: 13.02%.

3-(3-Pentyloxypyrazinyl)-1,2,5,6-tetrahydro-1-methyl-

pyridine ethandioate (34)

A mixture of 1 g (0.0044 mol) of (1) and 7 ml of thionyl chloride was stirred 1 h, the excess thionyl chloride was evaporated, and the residue was treated with ice-water. The solution was made basic with 5 N NaOH and the mixture extracted 3X with 25 ml of CH_2Cl_2 . The solvent was evaporated from the dried extracts, the residue was dissolved in 5 ml of 1-pentanol, and the solution added to a solution of sodium pentoxide prepared from 0.7 g (0.03 mol) of sodium and 35 ml of 1-pentanol. After heating at 100°C for 2 h, the reaction was cooled to ambient temperature, 35 ml of 1N HCl was added and the excess pentanol evaporated. The residue was dissolved in water, the solution made basic with 5 N NaOH, and the mixture extracted 3X with 25 ml of CH_2Cl_2 . The solvent was evaporated from the dried extracts and the residue purified by radial chromatography eluting with 5% ethanol/ 0.5% NH_4OH / CHCl_3 . The oxalate salt (34), 0.52 g, 34% yield crystallized from ethyl acetate, mp 151-152°C. NMR ppm- (CDCl_3) 0.94 (3H, t), 1.43 (4H, m), 1.84 (2H, m), 2.7-2.9 (2H, m), 2.99 (3H, s), 3.2-3.55 (2H, m), 4.0-4.43 (4H, m), 7.38 (1H, m), 7.97 (1H, d), 8.06 (1H, d). Anal. $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O} \cdot \text{C}_2\text{H}_2\text{O}_4$ requires C: 58.11; H: 7.17; N: 11.96%. Found C: 57.93; H: 7.20; N: 12.09%.

3-(3-Hexylthiopyrazinyl)-1,2,5,6-tetrahydro-1-methylpyridine hydrochloride (35)

A mixture of 1.1 g (0.0048 mol) of (1) and 7 ml of thionyl chloride was stirred 1 h, the excess thionyl chloride was evaporated, and the residue was treated with ice-water. The solution was made basic with 5 N NaOH and the mixture extracted 3X with 25 ml of

CH₂Cl₂. The solvent was evaporated from the dried extracts, the residue was dissolved in 10 ml of THF, and the solution was added to a suspension of sodium hexylthiolate in THF prepared from 0.21 g (0.0091 mol) NaH, 2 ml (0.014 mol) hexanethiol, and 30 ml of THF. The reaction was heated to reflux for 20 min followed by distillation of most of the THF from the reaction mixture. The solvents were evaporated, the residue treated with water, and the mixture extracted 3X with 25 ml of CH₂Cl₂. The solvent was evaporated from the dried extracts and the residue purified by radial chromatography eluting with 5% ethanol/ 0.5% NH₄OH/-CHCl₃. The hydrochloride salt (35), 0.33 g, 21% yield crystallized from ethyl acetate as a white solid, mp 120.5-122°C. NMR ppm(CDCl₃) 0.9 (3H, t), 1.31 (4H, m), 1.44 (2H, m), 1.67 (2H, m), 2.6-2.7 (1H, m), 2.96 (3H, d), 3.05-3.22 (4H, m), 3.54-3.64 (1H, m), 3.72-3.8 (1H, m), 4.4-4.45 (1H, d), 6.8 (1H, m), 8.15 (1H, d), 8.28 (1H, d). Anal. C₁₆H₂₅N₃S-HCl requires C: 58.61; H: 7.99; N: 12.81%. Found C: 58.48; H: 7.93; N: 12.84%.

3-(3-Pentylthiopyraziny1)-1,2,5,6-tetrahydro-1-methylpyridine hydrochloride (36)

25

A mixture of 1 g (0.0044 mol) of (1) and 7 ml of thionyl chloride was stirred 1 h, the excess thionyl chloride was evaporated, and the residue was treated with ice-water. The solution was made basic with 5 N NaOH and the mixture extracted 3X with 25 ml of CH₂Cl₂. The solvent was evaporated from the dried extracts, the residue was dissolved in 10 ml of THF, and the solution was added to a suspension of sodium hexylthiolate in THF prepared from 0.18 g (0.0078 mol) NaH, 2 ml (0.016 mol) pentanethiol, and 30 ml of THF. The reaction was heated to reflux for 20 min followed by distillation of most of the THF from the reaction mix-

ture. The solvents were evaporated, the residue treated with water, and the mixture extracted 3X with 25 ml of CH_2Cl_2 . The solvent was evaporated from the dried extracts and the residue purified by radial chromatography eluting with 5% ethanol/ 0.5% NH_4OH / CHCl_3 . The hydrochloride salt (36), 0.26 g, 19% yield crystallized from ethyl acetate as colorless crystals, mp 123-124°C. NMR ppm (CDCl_3) 0.9 (3H, t), 1.38 (4H, m), 1.7 (2H, m), 2.58- 2.7 (1H, m), 3.0 (3H, d), 3.05-3.2 (4H, m), 3.5-3.6 (1H, m), 3.7-3.82 (1H, m), 4.4-4.47 (1H, d), 6.8 (1H, m), 8.15 (1H, d), 8.28 (1H, d). Anal. $\text{C}_{15}\text{H}_{23}\text{N}_3\text{S}\cdot\text{HCl}$ requires C: 57.40; H: 7.71; N: 13.37%. Found C: 57.43; H: 7.63; N: 13.45%.

15

EXAMPLE 2

3-(3-Chloropyrazinyl)-1-azabicyclo[2.2.2]octan-3-ol (7)

20

A solution of 7.2 ml 2,2,6,6-tetramethylpiperidine (0.034 mol) in 300 ml of dry THF was cooled to -8°C as 25 ml of 1.6 M butyllithium (0.04 mol) in hexane was added dropwise. The reaction was stirred 20 min then cooled to -77°C . A solution of 2.9 ml of 2-chloropyrazine (0.031 mol) in 5 ml of THF was added to the reaction dropwise. After 15 min, 4.4 g of 3-quinuclidinone (0.0352 mol) in 5 ml of THF was added dropwise and the reaction stirred another 1.5 h. A solution of 8 ml of concentrated HCl and 4 ml of ethanol was added and the cooling was removed. When the temperature reached -5°C , 20 ml of 5 N NaOH was added and the volatile organics were evaporated. The residue was suspended in 50 ml of ice-water and the mixture filtered. The aqueous filtrate was extracted 3X with 50 ml of CHCl_3 . The extracts were combined with the solid collected from the filtration and the volume of the mixture adjusted to 450 ml with additional CHCl_3 . The mixture was heated on a

steam bath until most of the solid had dissolved. The mixture was dried, filtered, and the solvent evaporated to give a dark brown solid that was recrystallized from isopropanol to give 6.3 g of (7), mp 215-216°C. NMR ppm

5 (CDCl₃) 1.25(1H, m), 1.5 (2H, m), 2.2 (1H, m), 2.65-3.1 (6H, m), 3.6 (1H, bs), 4.05 (1H, d), 8.3 (1H, d), 8.5 (1H, d). Anal. C₁₁H₁₄ClN₃O requires C: 55.12; H: 5.89; N: 17.53%. Found C: 55.21; H: 5.99; N: 17.30%.

10 3-(3-Methoxypyrazinyl)-1-azabicyclo[2.2.2]octan-3-ol (8)

To a solution of 40 ml of methanol that had reacted with 0.5 g of Na (0.022 mol) was added 0.5 g of (7) (0.0021
15 mol). The reaction was heated to reflux for 1 h followed by evaporation of the solvent. The residue was treated with ice-water and extracted 3X with 25 ml of CH₂Cl₂. The extracts were dried and evaporated to give a yellow solid that was recrystallized from ethyl acetate to give
20 (8), 0.12 g, mp 130-131°C. NMR ppm (CDCl₃) 1.15 (1H, m), 1.45 (2H, m), 2.25 (1H, m), 2.38 (1H, m), 2.7-3.15 (5H, m), 3.9 (1H, bs), 4.05 (3H, s), 4.3 (1H, d), 8.05 (1H, d), 8.15 (1H, d). Anal. C₁₂H₁₇N₃O₂ requires C: 61.26; H: 7.28; N: 17.86%. Found C: 61.02; H: 7.45; N: 17.95%.

5

Alternate synthesis of (8)

A solution of 5.4 ml of 2,2,6,6-tetramethylpiperidine, in 300 ml of dry THF was cooled to -8°C as 19 ml of 1.6
30 M butyllithium (0.03 mol) in hexane was added dropwise. The reaction was stirred 20 min then cooled to -77°C. A solution of 2.5 g of 2-methoxypyrazine (0.023 mol) in 5 ml of THF was added dropwise to the reaction. After 5h, 2.9 g of 3-quinuclidinone (0.023 mol) in 5 ml of THF was
35 added dropwise and the reaction stirred another h. A solution of 8 ml of concentrated HCl and 4 ml of ethanol was added, the cooling was removed, and when the

- temperature reached -10°C , 20 ml of 5 N NaOH was added. The volatile organics were evaporated and the residue extracted 3X with 10 ml of CHCl_3 . The extracts were washed with brine, dried, and the solvent evaporated to give a clear yellow liquid that solidified on further drying. Recrystallization from ether gave 3.53 g of (8) identical to the material produced in the previous reaction.
- 10 3-Chloro-3-(3-chloropyrazinyl)-1-azabicyclo[2.2.2]octane (9) and 3-(3-chloropyrazinyl)-1-azabicyclo[2.2.2]oct-2-ene (10)
-
- 15 A solution of 12 ml of thionyl chloride was cooled to 0°C as 1 g of (7) (0.0042 mol) was added. The cooling was removed and the reaction stirred overnight. The solvent was evaporated, the residue was treated with ice-water, and the mixture made basic with saturated aqueous K_2CO_3 .
- 20 The mixture was extracted 3X with 25 ml of CH_2Cl_2 , the extracts washed with brine, dried, and the solvent evaporated. The residue was purified by HPLC eluting with an 8 L gradient beginning with CH_2Cl_2 and going to 10% methanol-1% NH_4OH . Compound (9), 0.44 g, eluted first and was re-
- 25 crystallized from hexane to give yellow crystals, mp $120.5-122^{\circ}\text{C}$. NMR ppm (CDCl_3) 1.55 (1H, m), 1.7 (2H, m), 2.37 (1H, m), 2.7 (2H, m), 2.95-3.3 (3H, m), 3.9 (2H, m), 8.35 (1H, d), 8.5 (1H, d). Anal. $\text{C}_{11}\text{H}_{13}\text{Cl}_2\text{N}_3$ requires C: 51.18; H: 5.07; N: 16.27%. Found C: 51.18; H: 5.28; N: 16.20%.
- 30 The second component (10), 0.26 g, recrystallized from hexane to give yellow crystals, mp $66-67^{\circ}\text{C}$. NMR ppm (CDCl_3) 1.75 (4H, m), 2.75 (2H, m), 3.1 (2H, m), 3.4 (1H, bs), 7.35 (1H, d), 8.25 (1H, d), 8.5 (1H, d). Anal. $\text{C}_{11}\text{H}_{12}\text{ClN}_3$ requires C: 59.60; H: 5.46; N: 18.95%. Found C: 59.87; H: 5.47; N: 18.68%.
- 35

3-(3-Methoxypyrazinyl)-1-azabicyclo[2.2.2]oct-2-ene (11)

A solution of 12 ml of thionyl chloride was cooled to 0°C
5 as 1.2 g of (7) (0.005 mol) was added. The cooling was removed and the reaction stirred overnight. The solvent was evaporated, the residue treated with ice-water, and the mixture made basic with saturated aqueous K₂CO₃. The mixture was extracted 3X with 25 ml of CH₂Cl₂, the extracts
10 washed with brine, dried, and the solvent evaporated. The residue was dissolved in a small amount of methanol and added to a solution of 50 ml of methanol that had reacted with 1 g of Na (0.043 mol). The reaction was heated to reflux for 1 h, the solvent evaporated, the residue treated
15 with ice-water, and the mixture extracted 3X with 25 ml of CH₂Cl₂. The extracts were washed with brine, dried, and the solvent evaporated. The residue was purified by HPLC eluting with an 8 L gradient beginning with CH₂Cl₂ and going to 10% methanol-1% NH₄OH to give 0.14 g of (11)
20 after recrystallization from hexane, mp 95-96°C. NMR ppm (CDCl₃) 1.57 (2H, m), 1.8 (2H, m), 2.7 (2H, m), 3.05 (2H, m), 3.8 (1H, bs), 4.05 (3H, s), 7.6 (1H, s), 7.95 (1H, d), 8.15 (1H, d). Anal. C₁₂H₁₅N₃O requires C: 66.34; H: 6.96; N: 19.34%. Found C: 66.18; H: 7.09; N: 19.08%.

25

3-Chloro-3-(3-methoxypyrazinyl)-1-azabicyclo[2.2.2]
octane (12)

30 A solution of 2.4 g of (8) (0.010 mol) in 100 ml of CH₂Cl₂ was cooled to 0°C as 2 ml of thionyl chloride in 5 ml of CH₂Cl₂ was added dropwise. The cooling was removed, the reaction stirred for 1.5 h, then heated to reflux for 45
35 min. Upon cooling to ambient temperature, ice-water was added to the reaction, followed by enough saturated aqueous K₂CO₃ to make the reaction basic. The mixture was extracted 3X with 25 ml of CH₂Cl₂, the extracts washed

with brine, dried, and the solvent evaporated. The residue was purified by radial chromatography eluting with 2.5% ethanol-0.25% NH_4OH - CHCl_3 to give 1.74 g of (12). Recrystallization from hexane gave colorless crystals, mp 59-60°C. NMR ppm (CDCl_3) 1.5 (1H, bs), 1.65 (2H, m), 2.35 (1H, m), 2.7 (2H, m) 2.97 (1H, m), 3.15 (2H, m), 3.65 (1H, m), 4.03 (1H, bm), 4.07 (3H, s), 8.1 (2H, m). Anal. $\text{C}_{12}\text{H}_{16}\text{ClN}_3\text{O}$ requires C: 56.81; H: 6.36; N: 16.56%. Found C: 56.63; H: 6.41; N: 16.48%. Further elution with 5% ethanol-0.5% NH_4OH - CHCl_3 gave 0.13 g of (11), identical to the material produced previously.

3-(3-Methoxypyrazinyl)-1-azabicyclo[2.2.2]octane ethanedioate (13)

15

A mixture of 0.17 g of (11) (0.00078 mol) and 0.17 g PtO_2 in 50 ml of ethanol was hydrogenated overnight at 60 psi of H_2 . The catalyst was removed and the solvent evaporated to give 0.115 g of a clear liquid that crystallized from isopropanol as the oxalate salt (13), 0.07 g, mp 183-184°C. NMR ppm (D_2O) 1.7 (2H, m), 2.12 (2H, m), 2.5 (1H, m), 3.2-3.6 (5H, m), 4.8 (1H, t), 4.0 (3H, s), 4.05 (1H, m), 8.05 (1H, d), 8.1 (1H, d). Anal. $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}-\text{C}_2\text{H}_2\text{O}_4$ requires C: 54.36; H: 6.19; N: 13.58%. Found C: 54.12; H: 6.31; N: 13.36%.

3-(3-Hexyloxypyrazinyl)-1-azabicyclo[2.2.2]oct-2-ene ethandioate (14)

30

A solution of 15 ml of thionyl chloride was cooled to 0°C as 2 g of (7) (0.0088 mol) was added. The cooling was removed and the reaction stirred overnight. The solvent was evaporated, the residue treated with ice-water, and the mixture made basic with saturated aqueous K_2CO_3 . The mixture was extracted 3X with 25 ml

of CH_2Cl_2 , the extracts washed with brine, dried, and the solvent evaporated. The residue was dissolved in a small amount of hexanol and added to a solution of 100 ml of hexanol that had reacted with 1.5 g of Na (0.065 mol). The reaction was heated to 100°C for 2 h followed by evaporation of the solvent. The remaining hexanol was azeotroped off with water and the residue extracted 3X with 25 ml of CH_2Cl_2 . The extracts were washed with brine, dried, and the solvent evaporated to give a brown liquid. Purification by HPLC eluting with an 8 L gradient beginning with CH_2Cl_2 and going to 10% methanol gave 0.55 g of a yellow liquid. NMR ppm (CDCl_3) 0.9 (3H, t), 1.25-1.9 (12H, m), 2.7 (2H, m), 3.05 (2H, m), 3.75 (1H, bs), 4.4 (2H, t), 7.6 (1H, d), 8.15 (1H, d). The oxalate salt (14) crystallized from ethyl acetate, mp $127-128^\circ\text{C}$. Anal. $\text{C}_{17}\text{H}_{25}\text{N}_3\text{O}-\text{C}_2\text{H}_2\text{O}_4$ requires C: 60.46; H: 7.21; N: 11.13%. Found C: 60.21; H: 6.95; N: 11.36%.

3-(3-Hexyloxypyrazinyl)-1-azabicyclo[2.2.2]octane ethandioate (15)

A mixture of 0.29 g of the free base of (14) (0.001 mol) and 0.15 g PtO_2 in 50 ml of ethanol was hydrogenated overnight at 60 psi of H_2 . The catalyst was filtered off and the solvent evaporated to give 0.22 g of a clear liquid. The oxalate salt (15), 0.15 g, crystallized from ethyl acetate as a flocculant colorless solid, mp $137-138^\circ\text{C}$. NMR ppm (CDCl_3) 0.9 (3H, t), 1.3-1.55 (6H, m), 1.6-1.9 (4H, m), 2.1 (2H, m), 2.45 (1H, m), 3.25 (1H, m), 3.35-3.65 (4H, m), 3.72 (1H, t), 4.25 (1H, q), 4.35 (2H, t), 8.05 (1H, d), 8.1 (1H, d). Anal. $\text{C}_{17}\text{H}_{27}\text{N}_3\text{O}-\text{C}_2\text{H}_2\text{O}_4$ requires C: 60.14; H: 7.70; N: 11.07%. Found C: 60.29; H: 7.91; N: 10.85%.

3-(3-Heptyloxy-pyrazinyl)-1-azabicyclo[2.2.2]octane
hydrochloride (16)

- 5 A solution of 10 ml of thionyl chloride was cooled to 0°C as 1.5 g of (7) (0.0066 mol) was added. The cooling was removed and the reaction stirred overnight. The solvent was evaporated, the residue treated with ice-water, and the mixture made basic with saturated aqueous K₂CO₃.
- 10 The mixture was extracted 3X with 25 ml of CH₂Cl₂, the extracts washed with brine, dried, and the solvent evaporated. The residue was dissolved in a small amount of heptanol and added to a solution of 100 ml of heptanol that had reacted with 1.5 g of Na (0.065 mol). The reaction was heated to 100°C for 2 h followed by evaporation of the solvent. The remaining heptanol was azeotroped off with water and the residue extracted 3X with 25 ml of CH₂Cl₂. The extracts were washed with brine, dried, and the solvent evaporated to give a brown liquid. Purification by HPLC eluting with an 8 L gradient beginning with CH₂Cl₂ and going to 10% methanol gave 0.59 g of 3-(3-heptyloxy-pyrazinyl)-1-azabicyclo[2.2.2]oct-2-ene as a yellow liquid. NMR ppm (CDCl₃) 0.9 (3H, t), 1.25-2.0 (14H, m), 2.95 (2H, m), 3.3 (2H, m), 4.07 (1H, bs), 4.4 (2H, t), 7.65 (1H, s), 8.0 (1H, d), 8.15 (1H, d). A mixture of this material and 0.3 g of PtO₂ in 50 ml of ethanol was hydrogenated overnight at 60 psi of H₂. The catalyst was filtered off and the solvent evaporated. The clear residue was converted to the hydrochloride salt (16), 0.115 g, that crystallized from ethyl acetate, mp 147-148.5°C. NMR ppm (CDCl₃) 0.9 (3H, t), 1.25-2.9 (12H, m), 2.12 (2H, m), 2.45 (1H, m), 3.22 (1H, m), 3.37 (3H, m), 3.55 (1H, m), 3.72 (1H, m), 4.3 (1H, q), 4.35 (2H, t), 8.02 (1H, d), 8.1 (1H, d). Anal. C₁₈H₂₉N₃O·HCl requires C: 63.60; H: 8.90; N: 12.36%. Found C: 63.44; H: 8.96; N: 12.11%.
- 30
- 35

3-(3-Butyloxypyrazinyl)-1-azabicyclo[2.2.2]octan-3-ol
(18)

- 5 To a solution of 40 ml of butanol that had reacted with
0.5 g of Na (0.022 mol) was added 0.78 g of (7) (0.033
mol). The reaction was heated to 60°C for 1.5 h and the
cooled reaction treated with 6 ml of 5 N HCl. The butanol
was azeotroped off with water, the residue made basic
10 with saturated aqueous K₂CO₃, and the mixture extracted
3X with 25 ml of CH₂Cl₂. The extracts were washed with
brine, dried, and the solvent evaporated to give a yellow
solid that was purified by radial chromatography eluting
with 5% ethanol-0.5% NH₄OH-CHCl₃ to give 0.55 g of (18)
15 as a yellowish solid. Recrystallization from ether gave a
white solid, mp 107-108°C. NMR ppm (CDCl₃) 1.0 (3H, t),
1.15 (1H, m), 1.35-1.6 (4H, m), 1.85 (2H, m), 2.25 (1H,
m), 2.37 (1H, bs), 2.75 (1H, m), 2.82-3.0 (3H, m), 3.05
(1H, m), 3.95 (1H, s), 4.2 (1H, d), 4.45 (2H, q), 8.0 (1H,
20 d), 8.12 (1H, d). Anal. C₁₅H₂₃N₃O₂ requires C: 64.96; H:
8.36; N: 15.15%. Found C: 65.21; H: 8.11; N: 15.25%.

3-(3-Butyloxypyrazinyl)-3-chloro-1-azabicyclo[2.2.2]octane
hydrochloride (19) and 3-(3-butyloxypyrazinyl)-1-azabicyclo
25 [2.2.2]oct-2-ene hydrochloride (20)

A solution of 2.2 g of (18) in 100 ml of CH₂Cl₂ was cooled
to 0°C as 1.6 ml of thionyl chloride in 5 ml of CH₂Cl₂ was
30 added dropwise. The cooling was removed and after stirring
for 1.5 h the reaction was heated to reflux for 45 min.
After the reaction cooled to ambient temperature, ice-
water was added to the reaction followed by enough satu-
rated aqueous K₂CO₃ to make the mixture basic. The mixture
35 was extracted 3X with 25 ml of CH₂Cl₂, the extracts dried,
and the solvent evaporated to give a yellow liquid that
was purified by radial chromatography eluting with 2.5%

ethanol-0.25% $\text{NH}_4\text{OH}-\text{CHCl}_3$ to give 1.95 g of the free base of (19). NMR ppm (CDCl_3) 1.0 (3H, t), 1.5-1.9 (7H, m), 2.37 (1H, m), 2.6-2.82 (2H, m), 3.0 (1H, bt), 3.1-3.22 (2H, m), 3.6-4.05 (2H, m), 4.4 (2H, t), 8.05 (2H, m). The hydrochloride salt (19) crystallized from ethyl acetate to give white crystals, mp 140-141°C. Anal. $\text{C}_{15}\text{H}_{22}\text{ClN}_3\text{O}-\text{HCl}$ requires C: 54.22; H: 6.98; N: 12.65%. Found C: 54.49; H: 7.10; N: 12.90%. Further elution with 5% ethanol-0.5% $\text{NH}_4\text{OH}-\text{CHCl}_3$ gave 0.09 g of the free base of (20) that crystallized from ethyl acetate as the hydrochloride salt (20), mp 156-157°C. NMR of the free base ppm (CDCl_3) 1.0 (3H, t), 1.55 (4H, m), 2.7 (2H, m), 3.05 (2H, m), 3.8 (1H, bs), 4.42 (2H, t), 7.6 (1H, s), 7.95 (1H, d), 8.13 (1H, d). Anal. $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}-\text{HCl}$ requires C: 60.91; H: 7.50; N: 14.21%. Found C: 60.98; H: 7.51; N: 14.19%.

3-(3-Butyloxypyrazinyl)-1-azabicyclo[2.2.2]octane hydrochloride (21)

20

A mixture of 1.7 g of (19), (0.0057 mol) and 0.5 g of 10% Pd on carbon in 50 ml of ethanol was hydrogenated for 1 h at 60 psi of H_2 . The catalyst was filtered off and the solvent evaporated. The residue was treated with ethanolic HCl and the solvent evaporated. Recrystallization from ethyl acetate gave 1 g of (21), mp 138.5-139.5°C. NMR ppm (CDCl_3) 1.0 (3H, t), 1.45 (2H, m), 1.6-1.9 (5H, m), 2.1 (2H, m), 2.45 (1H, m), 3.15-3.8 (6H, m), 4.28 (1H, q), 4.35 (2H, t), 8.02 (1H, d), 8.1 (1H, d). Anal. $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}-\text{HCl}$ requires C: 60.49; H: 8.12; N: 14.11%. Found C: 60.35; H: 8.16; N: 13.85%.

3-(3-(3,3,4,4,5,5,6,6,6)Nonfluorohexyloxypyrazinyl)-1-azabicyclo[2.2.2]octan-3-ol hydrochloride (22)

35

To a solution of 30 ml of 3,3,4,4,5,5,6,6,6-nonafluoro-

hexan-1-ol that had reacted with 0.5 g of Na (0.022 mol) was added 1.63 g of (7) (0.0068 mol). The reaction was heated to 80°C for 2 h, the reaction cooled to ambient temperature, and 35 ml of 1 N HCl was added. The excess
5 hexanol was azeotroped from the reaction with water and the residue made basic with saturated aqueous K₂CO₃. The mixture was extracted 3X with 25 ml of CH₂Cl₂, the extracts washed with brine, and the solvent evaporated. The residue was purified by radial chromatography eluting with 5%
10 ethanol-0.5% NH₄OH-CHCl₃ and finally with 10% ethanol-1% NH₄OH-CHCl₃ to give 2.38 g of the free base of (22) as a tan solid. NMR ppm (CDCl₃) 1.15 (1H, m), 1.45 (2H, m), 2.22 (1H, m), 2.6-3.0 (6H, m), 3.07 (1H, m), 3.65 (1H, bs), 4.25 (1H, d), 4.8 (2H, m), 8.04 (1H, d), 8.20 (1H, d).
15 The hydrochloride salt (22) crystallized from ethyl acetate, mp 199-200.5°C. Anal. C₁₇H₁₈F₉N₃O₂-HCl requires C: 40.53; H: 8.80; N: 8.34%. Found C: 40.72; H: 3.72; N: 8.33%.

3-Chloro-3-(3-(3,3,4,4,5,5,6,6,6)nonafluorohexyloxy-
20 pyrazinyl)-1-azabicyclo[2.2.2]octane hydrochloride (23) and 3-(3-(3,3,4,4,5,5,6,6,6)nonafluorohexyloxy-pyrazinyl)-1-azabicyclo[2.2.2]oct-2-ene hydrochloride (24)

25 A solution of 2 g of the free base of (22) (0.0043 mol) in 100 ml of CH₂Cl₂ was cooled to 0°C as 1 ml of thionyl chloride in 5 ml of CH₂Cl₂ was added dropwise. The cooling was removed, the reaction stirred 1 h and then heated to reflux for 1 h. After cooling to ambient tem-
30 perature, the reaction was treated with ice-water and then made basic with saturated aqueous K₂CO₃. The mixture was extracted 3X with 25 ml of CH₂Cl₂, the extracts washed with brine, dried, and the solvent evaporated. The residue was purified by radial chromatography eluting with 2.5%
35 ethanol-0.25% NH₄OH-CHCl₃ to give 1.085 g of the free base of (23). NMR ppm (CDCl₃) 1.5 (1H, m), 1.65 (2H, m), 2.35 (1H, m), 2.55-2.82 (4H, m), 2.97 (1H, t), 3.1 (2H, m),

3.62 (1H, bd), 3.92 (1H, m), 4.73 (2H, t), 8.07 (1H, d), 8.15 (1H, d). The hydrochloride salt (23) crystallized from ethyl acetate, mp 160-161°C. Anal. $C_{17}H_{17}ClF_9N_3O \cdot HCl$ requires C: 39.10; H: 3.47; N: 8.04%. Found C: 39.16; H:

5 3.38; N: 7.86%. Further elution with 5% ethanol-0.5% NH_4OH - $CHCl_3$ gave the free base of (24) whose hydrochloride salt (24) crystallized from ethyl acetate, mp 89-90°C. Anal. $C_{17}H_{16}F_9N_3O \cdot HCl$ requires C: 42.03; H: 3.53; N: 8.65%. Found C: 41.80; H: 3.33; N: 8.42%.

10

3-(3-Pentyloxy-pyrazinyl)-1-azabicyclo[2.2.2]octane hydrochloride (25)

15 To a solution of 30 ml of pentanol that had reacted with 0.5 g of Na (0.022 mol) was added 1.7 g of (7) (0.0071 mol). The reaction was heated to 70°C for 2 h, the reaction cooled to ambient temperature, and 30 ml of 1 N HCl was added. The excess pentanol was azeotroped off with
20 water and the residue made basic with 5 N NaOH. The mixture was extracted 3X with 25 ml of CH_2Cl_2 , the extracts washed with brine, dried, and the solvent evaporated. The residue was purified by radial chromatography eluting with
25 5% ethanol-0.5% NH_4OH - $CHCl_3$ and then with 10% ethanol-1% NH_4OH - $CHCl_3$ to give 1.68 g of 3-(3-pentyloxy-pyrazinyl)-1-azabicyclo[2.2.2]octan-3-ol. NMR ppm ($CDCl_3$) 0.97 (3H, t), 1.2 (1H, m), 1.45 (6H, m), 1.87 (2H, m), 2.3 (1H, m), 2.4 (1H, t), 2.8 (1H, m), 2.93 (3H, m), 3.1 (1H, m), 3.98 (1H, s), 4.28 (1H, d), 4.42 (2H, m), 8.01 (1H, d), 8.11 (1H,
30 d). A solution of 1.48 g of this alcohol (0.0051 mol) in 50 ml of CH_2Cl_2 was cooled to 0°C as 1.1 ml of thionyl chloride in 5 ml of CH_2Cl_2 was added dropwise. The cooling was removed, the reaction stirred 1.5 h and then heated to reflux for 45 min. After cooling to ambient tem-
35 perature, ice-water was added to the reaction and the reaction made basic with saturated aqueous K_2CO_3 . The mixture was extracted 3X with 25 ml of CH_2Cl_2 , the ex-

tracts washed with brine, and the solvent evaporated. The residue was purified by radial chromatography eluting with 5% ethanol- 0.5% $\text{NH}_4\text{OH}-\text{CHCl}_3$ to give 1.27 g of 3-chloro-3-(3-pentyloxy-pyrazinyl)-1-azabicyclo[2.2.2]octane. NMR ppm (CDCl_3) 0.99 (3H, t), 1.35-1.8 (7H, m), 1.9 (2H, m), 2.37 (1H, m), 2.6-2.82 (2H, m), 3.0 (1H, t), 3.15 (2H, m), 3.6-4.1 (2H, m), 4.42 (2H, t), 8.06 (2H, m). A mixture of 1.05 g of this chloride (0.0034 mol) and 0.4 g of 10% Pd on carbon in 50 ml of ethanol was hydrogenated 1 h at 60 psi of H_2 . The catalyst was filtered off, 25 ml of isopropanolic HCl was added, and the solvent was evaporated. The residue was recrystallized from ethyl acetate to give 0.28 g of (25), mp 166-167°C. NMR ppm (CDCl_3) 0.95 (3H, t), 1.41 (4H, m), 1.57-1.9 (5H, m), 2.13 (2H, m), 2.45 (1H, m), 3.12 (1H, m), 3.3-4.46 (3H, m), 3.55 (1H, m), 3.7 (1H, m), 4.3 (1H, q), 4.37 (2H, t), 8.03 (1H, d), 8.1 (1H, d). Anal. $\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}-\text{HCl}$ requires C: 61.62; H: 8.40; N: 13.47%. Found C: 61.39; H: 8.07; N: 13.48%.

20 3-(3-Butylthiopyrazinyl)-1-azabicyclo[2.2.2]octane hydrochloride (29)

A 1 g sample of 60% NaH dispersion in oil was triturated twice with hexane then suspended in 300 ml of THF. The mixture was treated with 5 ml of butanethiol and after 30 min the mixture was heated to reflux for 45 min. After cooling to ambient temperature, 1.5 g of (7), (0.0063 mol) was added and the reaction was heated to reflux for 1 h. The mixture was diluted with 100 ml of butanethiol and the reaction was heated to reflux overnight. The solvent was removed by distillation, the residue suspended in 50 ml of H_2O , and the mixture extracted 3X with 25 ml of CHCl_3 , the extracts washed with brine, and the solvent evaporated. The brown solid residue was recrystallized from ether to give 1.25 g of 3-(3-butylthiopyrazinyl)-1-azabicyclo[2.2.2]octan-3-ol (29a). NMR ppm (CDCl_3) 0.97 (3H, t),

1.19 (1H, t), 1.19 (1H, m), 1.35-1.57 (4H, m), 1.7 (2H, m), 2.21 (1H, m), 2.5-3.02 (6H, m), 3.2 (2H, m), 4.1 (1H, d), 4.5 (1H, m), 8.17 (1H, d), 8.25 (1H, d). A solution of 1.2 g of (29a) (0.0041 mol) in 100 ml of CH_2Cl_2 was cooled to 0°C as 0.95 ml of thionyl chloride in 10 ml of CH_2Cl_2 was added dropwise. The cooling was removed and after 1 h the reaction was heated to reflux for 45 min. After cooling to ambient temperature, the reaction was treated with ice and the solution was made basic with 1 N NaOH. The mixture was extracted 3X with 25 ml of CH_2Cl_2 , the extracts washed with brine, dried, and the solvent evaporated to give a brown liquid. The liquid was purified by radial chromatography eluting with 5% ethanol-0.5% $\text{NH}_4\text{OH}-\text{CHCl}_3$ and then 10% ethanol-1% $\text{NH}_4\text{OH}-\text{CHCl}_3$ to give 1 g of 3-chloro-3-(3-butylthiopyrazinyl)-1-azabicyclo[2.2.2]octane (29b). NMR ppm (CDCl_3) 0.99 (3H, t), 1.5 (3H, m), 1.7 (4H, m), 2.38 (1H, m), 2.7 (2H, m), 2.98 (1H, m), 3.05-3.4 (4H, m), 3.76 (1H, d), 4.19 (1H, d), 8.18 (1H, d), 8.3 (1H, d). A mixture of 1 g of (29b) (0.0032 mol) and 0.4 g of 10% Pd on carbon in 50 ml of ethanol was hydrogenated for 1 h at 60 psi of H_2 . The catalyst was removed, the solvent was evaporated, the residue suspended in 5 ml of H_2O , and the mixture made basic with saturated aqueous K_2CO_3 . The mixture was extracted 3X with 25 ml of CH_2Cl_2 , the extracts dried, and the solvent evaporated. The residue was purified by radial chromatography eluting with 5% ethanol-0.5% $\text{NH}_4\text{OH}-\text{CHCl}_3$ and then 10% ethanol-1% $\text{NH}_4\text{OH}-\text{CHCl}_3$. The hydrochloride salt (29) crystallized from ethyl acetate to give 0.44 g of a flocculant white solid, mp $193-194^\circ\text{C}$. NMR ppm (CDCl_3) 0.99 (3H, t), 1.5 (2H, m), 1.7 (4H, m), 2.15 (2H, m), 2.5 (1H, m), 3.23 (3H, m), 3.4 (3H, m), 3.64 (2H, m), 4.38 (1H, t), 8.21 (1H, d), 8.31 (1H, d). Anal. $\text{C}_{15}\text{H}_{23}\text{N}_3\text{S}-\text{HCl}$ requires C: 57.40; H: 7.71; N: 13.37%. Found C: 57.14; H: 7.92; N: 13.12%.

3-(3-Chloropyrazinyl)-1-azabicyclo[2.2.2]octane
hydrochloride (31)

5

A mixture of 1.175 g of (9), (0.0046 mol), and 0.4 g of 10% Pd on carbon in 50 ml of ethanol was hydrogenated 1 h at 60 psi of H_2 . The catalyst was removed, the solvent was evaporated, the residue was suspended in 5 ml of H_2O , and the mixture made basic with saturated aqueous K_2CO_3 . The mixture was extracted 3X with CH_2Cl_2 , the extracts dried, and the solvent was evaporated. The residue was purified by radial chromatography eluting with 10% ethanol-1% $NH_4OH-CHCl_3$ and then with 12.5% ethanol-1.25% $NH_4OH-CHCl_3$. The less polar component crystallized from isopropanol as the hydrochloride salt (31), 0.12 g, that contained 0.25 mol of H_2O , mp $223^\circ C$ dec. NMR of (31) free base ppm ($CDCl_3$) 1.3 (1H, m), 1.55 (1H, m), 1.81 (2H, m), 2.13 (1H, m), 2.74-3.28 (5H, m), 3.55 (1H, t), 3.68 (1H, q), 8.22 (1H, d), 8.48 (1H, d). Anal. $C_{11}H_{14}ClN_3-HCl-0.25 H_2O$ requires C: 49.91; H: 15.88; N: 50.05%. Found C: 50.05; H: 5.69; N: 15.42%. ~~The more polar component crystallized from isopropanol as the hydrochloride salt (30), 0.23 g, that contained 0.25 mol of H_2O , mp $208-209^\circ C$ dec. NMR of (30) free base ppm ($CDCl_3$) 1.38 (1H, m), 1.57-1.88 (3H, m), 2.08 (1H, m), 2.77-3.3 (6H, m), 3.55 (1H, q), 8.42 (1H, d), 8.5 (1H, s), 8.56 (1H, d). Anal. $C_{11}H_{15}N_3-HCl-0.25H_2O$ requires: C: 57.38; H: 7.22; N: 18.25%. Found C: 57.36; H: 7.09; N: 17.84%.~~

30

3-(3-Ethoxypyrazinyl)-1-azabicyclo[2.2.2]octane hydrochloride (37)

35

To a solution of sodium ethoxide prepared from 0.75 g (0.0326 mol) of sodium and 75 ml of anhydrous ethanol was added 1.5 g (0.00625 mol) 3-(3-chloropyrazinyl)-1-



azabicyclo[2.2.2]octan-3-ol (7) and the mixture heated to reflux for 1.5 h. The solvent was evaporated, the residue was treated with ice-water, and the mixture extracted 3X with 25 ml of CH_2Cl_2 . The extracts were washed with brine, dried, and the solvent evaporated to give 1.48 g of yellowish solid. A solution of the solid in 100 ml of CH_2Cl_2 was cooled to 0°C as 1.15 ml of thionyl chloride in 10 ml of CH_2Cl_2 was added dropwise. The cooling was removed, the reaction stirred 45 min, and then heated to reflux for 45 min. After cooling to ambient temperature, ice-water was added to the reaction and the mixture made basic with 5N NaOH. The mixture was extracted 3X with 25 ml of CH_2Cl_2 and the extracts washed with brine, dried, and the solvent evaporated. The residue was purified by radial chromatography eluting with 5% ethanol/ 0.5% $\text{NH}_4\text{OH}/\text{CHCl}_3$ to give 0.68 g of straw-colored liquid. A mixture of 0.68 g of the liquid and 0.25 g of 10% Pd on carbon in 50 ml of ethanol was hydrogenated 1 h at 60 psi of H_2 . The catalyst was removed and the solvent was evaporated to give a white solid. The solid was dissolved in ice-water and treated with 3 ml of 1 N NaOH. The mixture was extracted 3X with 25 ml of CH_2Cl_2 , the extracts dried, and the solvent evaporated. The residue was purified by radial chromatography eluting with 10% ethanol/ 1% $\text{NH}_4\text{OH}/\text{CHCl}_3$ and the product converted to the hydrochloride salt (37), 0.23 g, 14% yield that crystallized from 2-propanol, mp 237°C dec. NMR ppm (CDCl_3) 1.39 (3H, t), 1.65 (2H, m), 2.0-2.23 (2H, m), 2.41 (1H, m), 3.16-3.58 (5H, m), 3.66-3.75 (1H, m), 4.18-4.28 (1H, m), 4.4 (2H, q), 8.0 (1H, d), 8.07 (1H, d). Anal. $\text{C}_{13}\text{H}_{19}\text{N}_3\text{O}\cdot\text{HCl}$ requires C: 57.88; H: 7.47; N: 15.58%. Found C: 57.96; H: 7.60; N: 15.75%.

3-(3-Propyloxypyrazinyl)-1-azabicyclo[2.2.2]octane hydrochloride (38)

To a solution of sodium propoxide prepared from 0.75 g (0.0326 mol) of sodium and 75 ml of 1-propanol was added 1.5 g (0.00625 mol) (7) and the mixture heated to reflux for 2 h. The solvent was evaporated, the residue was treated with ice-water, and the mixture extracted 3X with 25 ml of CH_2Cl_2 . The extracts were washed with brine, dried, and the solvent evaporated to give 1.67 g of white solid. A solution of the solid in 100 ml of CH_2Cl_2 was cooled to 0°C as 1.2 ml of thionyl chloride in 5 ml of CH_2Cl_2 was added dropwise. The cooling was removed, the reaction stirred 45 min, and then heated to reflux for 45 min. After cooling to ambient temperature, ice-water was added to the reaction and the mixture made basic with 5N NaOH. The mixture was extracted 3X with 25 ml of CH_2Cl_2 and the extracts washed with brine, dried, and the solvent evaporated. The residue was purified by radial chromatography eluting with 5% ethanol/ 0.5% NH_4OH / CHCl_3 to give 1.29 g of yellow liquid. A mixture of 1.29 g of the liquid and 0.45 g of 10% Pd on carbon in 50 ml of ethanol was hydrogenated 1h at 60 psi of H_2 . The catalyst was removed and the solvent was evaporated to give a white solid. The solid was dissolved in ice-water and treated with 5 ml of 1 N NaOH. The mixture was extracted 3X with 25 ml of CH_2Cl_2 , the extracts dried, and the solvent evaporated. The residue was purified by radial chromatography eluting with 10% ethanol/ 1% NH_4OH / CHCl_3 and the product converted to the hydrochloride salt (38), 0.57 g, 32% yield that crystallized from 2-propanol, mp $215-216^\circ\text{C}$ dec. NMR ppm (CDCl_3) 1.05 (3H, t), 1.59-1.7 (2H, m), 1.8 (2H, m), 2.0-2.23 (2H, m), 2.42 (1H, m), 3.1-3.59 (5H, m), 3.65-3.75 (1H, m), 4.2-4.35 (4H, m), 8.0 (1H, d), 8.06 (1H, d). Anal. $\text{C}_{14}\text{H}_{21}\text{N}_3\text{C-HCl}$ requires C: 59.46; H: 7.49; N: 14.86%. Found C: 59.49; H: 7.67; N: 14.83%.

SUBSTITUTE SHEET

3-(3-Pentylthiopyrazinyl)-1-azabicyclo[2.2.2]octane
hydrochloride (39)

- 5 A 1 g sample of 60% NaH dispersion in oil was tritu-
rated twice with hexane then suspended in 300 ml of
THF. The mixture was treated with 5 ml of 1-pentane-
thiol and after 30 min the mixture was heated to re-
flux for 30 min. After cooling to ambient temperature,
10 1.6 g (0.00625 mol) of (7) was added and the reaction
heated to reflux for 2 h. Most of the solvent was
distilled from the reaction mixture, the residue
cooled, and 30 ml of water added. After sitting under
vacuum over night, the residue was treated with water
15 and extracted 3X with 50 ml of CH_2Cl_2 . The extracts
were dried and the solvent was evaporated to give 1.99
g of slightly yellow solid. A solution of 1.5 g of the
solid in 100 ml of CH_2Cl_2 was cooled to 0°C as 1.15 ml
of thionyl chloride in 10 ml of CH_2Cl_2 was added drop-
20 wise. Cooling was removed and, after 1 h, the reaction
was heated to reflux for 1 h. The reaction was treated
with ice-water and the mixture made basic with 5N
NaOH. The mixture was extracted 3X with 50 ml of
 CH_2Cl_2 , the extracts washed with brine, dried, and the
25 solvent evaporated. The residue was purified by radial
chromatography eluting with 5% ethanol/ 0.5% NH_4OH /
 CHCl_3 to give 1.26 g of a slightly yellow liquid. A
mixture of 1.26 g of the liquid and 0.4 g of 10% Pd on
carbon in 50 ml of ethanol was hydrogenated 1 h at 60
30 psi of H_2 . The catalyst was removed, the solvent evap-
orated, and the residue dissolved in ice-water and
treated with 4 ml of 1 N NaOH. The mixture was ex-
tracted 3X with 25 ml of CH_2Cl_2 , the extracts dried,
and the solvent evaporated. The residue was purified
35 by radial chromatography eluting with 10% ethanol/ 1%
 NH_4OH / CHCl_3 and the product converted to the hydro-
chloride salt (39), 0.5 g, 30% yield that crystallized

from ethyl acetate, mp 219-220°C dec. NMR ppm (CDCl_3)
0.9 (3H, t), 1.4 (4H, m), 1.70 (4H, m), 2.05- 2.3 (2H,
m), 2.5 (1H, m), 3.1-3.3 (3H, m), 3.32-3.47 (3H, m),
3.75-3.9 (2H, m), 4.22-4.35 (1H, m), 8.19 (1H, d),
5 8.29 (1H, d). Anal. $\text{C}_{16}\text{H}_{25}\text{N}_3\text{S}\cdot\text{HCl}$ requires C: 58.11;
H: 7.99; N: 12.81%. Found C: 58.57; H: 8.24; N:
12.58%.

3-(3-Hexylthiopyrazinyl)-1-azabicyclo[2.2.2]octane
15 hydrochloride (40)

A 1 g sample of 60% NaH dispersion in oil was tritu-
rated twice with hexane then suspended in 300 ml of
15 THF. The mixture was treated with 5 ml of 1-hexane-
thiol and after 30 min the mixture was heated to re-
flux for 30 min. After cooling to ambient temperature,
1.5 g (0.0067 mol) of (7) was added and the reaction
heated to reflux for 2 h. Most of the solvent was
20 distilled from the reaction mixture, the residue cool-
ed, and 30 ml of water added. After sitting under
vacuum over night, the residue was treated with water
and extracted 3X with 50 ml of CH_2Cl_2 . The extracts
were dried and the solvent was evaporated to give 1.98
25 g of slightly yellow solid. A solution of 1.5 g of the
solid in 100 ml of CH_2Cl_2 was cooled to 0°C as 1.15 ml
of thionyl chloride in 10 ml of CH_2Cl_2 was added drop-
wise. Cooling was removed and, after 1 h, the reaction
was heated to reflux for 1 h. The reaction was treated
30 with ice-water and the mixture made basic with 5N
NaOH. The mixture was extracted 3X with 50 ml of
 CH_2Cl_2 , the extracts washed with brine, dried, and the
solvent evaporated. The residue was purified by radial
chromatography eluting with 5% ethanol/ 0.5% $\text{NH}_4\text{OH}/$
35 CHCl_3 to give 1.265 g of a slightly yellow liquid. A
mixture of 1.2 g of the liquid and 0.35 g of 10% Pd on
carbon in 50 ml of ethanol was hydrogenated 1h at 60

psi of H_2 . The catalyst was removed and the solvent was evaporated to give a gray solid. The solid was dissolved in ice-water and treated with 4 ml of 1 N NaOH. The mixture was extracted 3X with 25 ml of CH_2Cl_2 , the extracts dried, and the solvent evaporated. The residue was purified by radial chromatography eluting with 10% ethanol/ 1% NH_4OH / $CHCl_3$ and the product converted to the hydrochloride salt (40), 0.65 g, 40% yield that crystallized from ethyl acetate, mp 181-183°C dec. NMR ppm ($CDCl_3$) 0.9 (3H, t), 1.3 (4H, m), 1.45 (2H, m), 1.70 (4H, m) 2.05-2.25 (2H, m), 2.5 (1H, m), 3.1-3.3 (3H, m), 3.3-3.5 (3H, m), 3.55-3.7 (2H, m), 4.2-4.3 (1H, m), 8.19 (1H, d), 8.29 (1H, d). Anal. $C_{17}H_{27}N_3S \cdot HCl$ requires C: 59.71; .. 8.25; N: 12.29%. Found C: 59.43; H: 8.47; N: 12.18%.

EXAMPLE 3

20 3-(3-Chloropyrazinyl)-1-azabicyclo[2.2.1]heptan-3-ol (26)

A solution of 7.2 ml of 2,2,6,6-tetramethylpiperidine in 300 ml of THF was cooled to $-5^{\circ}C$ as 25 ml of 1.6 M butyllithium (0.04 mol) in hexane was added dropwise. The reaction was stirred 10 min then cooled to $-77^{\circ}C$ as 3 ml of 2-chloropyrazine in 7 ml of THF was added dropwise. After another 15 min, 4.4 g of 1-azabicyclo[2.2.1]heptan-3-one (0.0396 mol) in 10 ml of THF was added and the reaction stirred 1 h. A solution of 8 ml of conc. HCl in 4 ml of ethanol was added and the cooling was removed. When the temperature reached $-10^{\circ}C$, 100 ml of water was added, the organics were evaporated, and the residue treated with 11 ml of 5 N NaOH. The solvent was reduced to a small volume, ca. 50 ml, the mixture cooled in ice-water, and the solid collected by filtration. The aqueous fraction was extracted 3X with 50 ml of $CHCl_3$, the extracts added to the solid

filtrate, and the total volume of the mixture taken to 500 ml with more CHCl_3 . The mixture was heated to boiling, dried, filtered, and the solvent evaporated to give a brown solid. The solid was recrystallized from isopropanol to give 4.1 g of tan crystalline (26), mp 220°C dec. NMR ppm (CDCl_3) 1.55-1.9 (2H, m), 2.27 (1H, m), 2.42-2.58 (2H, m), 2.75 (2H, m), 2.95 (1H, m), 3.5 (1H, d) 3.6 (1H, d), 8.3 (1H, d) 8.42 (1H, d). Anal. $\text{C}_{10}\text{H}_{12}\text{ClN}_3\text{O}$ requires C: 53.22; H: 5.36; N: 18.62%. Found C: 53.10; H: 5.20; N: 18.41%.

Endo-3-(3-hexyloxy pyrazinyl)-1-azabicyclo[2.2.1]heptane hydrochloride hemihydrate (27)

15 A mixture of 4.8 g of (26) (0.021 mol) and 125 ml of hexanol that had reacted with 1.5 g of Na (0.065 mol) was heated to 80°C for 45 min. The reaction was cooled to ambient, 100 ml of 1 N HCl was added, and the hexanol was azeotroped off with water. The residue was made basic with 1 N NaOH and extracted 3X with 50 ml of CH_2Cl_2 . The extracts were washed with brine, dried, and the solvent evaporated to give a dark solid. Recrystallization of the solid from ether gave 3.83 g of 3-(3-hexyloxy pyrazinyl)-1-azabicyclo[2.2.1]heptan-3-ol (26a) as a flocculent yellow solid. NMR ppm (CDCl_3) 0.9 (3H, t), 1.25-1.65 (7H, m), 1.85 (2H, m), 2.25-3.07 (6H, m), 3.1 (1H, d), 3.75 (2H, d), 4.45 (2H, t), 8.01 (1H, d), 8.07 (1H, d). A solution of 1.5 g of (26a) (0.0052 mol) in 75 ml of CH_2Cl_2 was cooled to 0°C as 1.1 ml of thionyl chloride in 10 ml of CH_2Cl_2 was added dropwise. The cooling was removed and after 1.5 h the reaction was heated to reflux for 45 min. The reaction was cooled to ambient, water was added, and the reaction made basic with saturated aqueous K_2CO_3 . The mixture was extracted 3X with 25 ml of CH_2Cl_2 , the extracts washed with brine, dried, and the solvent evaporated to give a yellow oil. Radial chromatography eluting with 2.5%

- ethanol-0.25% $\text{NH}_4\text{OH}-\text{CHCl}_3$ gave 1.2 g 3-chloro-3-(3-hexyloxypyrazinyl)-1-azabicyclo[2.2.1]heptane (26b) as a pinkish liquid. NMR ppm (CDCl_3) 0.9 (3H, t), 1.25-1.95 (10H, m), 2.25-3.9 (7H, m), 4.4 (2H, t), 8.0-8.1 (2H, m).
- 5 A mixture of 1.2 g of (26b) (0.0039 mol) and 0.5 g of 10% Pd on carbon in 50 ml of ethanol was hydrogenated for 1 h at 60 psi H_2 . The catalyst was removed, the solvent evaporated, the residue suspended in water, and the mixture made basic with saturated aqueous K_2CO_3 . The mixture was
- 10 extracted 3X with 25 ml of CH_2Cl_2 , the extracts dried, and the solvent evaporated. Tlc shows two major spots, 10% ethanol-1% $\text{NH}_4\text{OH}-\text{CHCl}_3$. The less polar of the two component was not well separated. The more polar component was treated with HCl in isopropanol and thoroughly evaporated.
- 15 The residue was recrystallized from ether to give 0.15 g of (27) as slightly hygroscopic colorless crystals, mp 117-118°C. NMR ppm (CDCl_3) 0.9 (3H, t), 1.25-1.55 (8H, m), 1.85 (3H, m), 3.2-3.75 (6H, m), 4.05 (2H, m), 4.38 (2H, m), 8.05 (1H, d), 8.08 (1H, d). Anal. $\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}\cdot\text{HCl}\cdot 0.5\text{H}_2\text{O}$ requires C: 59.89; H: 8.48; N: 13.10%. Found C: 59.83; H: 8.31; N: 12.95%.

Exo-3-(3-hexyloxypyrazinyl)-1-azabicyclo[2.2.1]heptane hydrochloride (28)

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- A mixture of 0.35 g of the mixed components from the preparation of (27) (0.0013 mol) and 12 ml of hexanol that had reacted with 0.2 g of Na (0.0087 mol) was heated to
- 30 120°C overnight. The reaction was cooled to ambient temperature, 20 ml of 1 N HCl was added, and the hexanol was azeotroped off with water. The residue was made basic with 1 N NaOH and the mixture extracted 3X with 25 ml of CH_2Cl_2 . The extracts were dried and evaporated to give
- 35 0.33 g of yellow liquid. Tlc shows a two component mixture now highly enriched in the less polar component, 10% ethanol-1% $\text{NH}_4\text{OH}-\text{CHCl}_3$. Radial chromatography eluting

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with 5% ethanol- 0.5% $\text{NH}_4\text{OH}-\text{CHCl}_3$ gave 0.2 g of straw colored liquid. The hydrochloride salt (28), 0.15 g, crystallized from ethyl acetate, mp 153-154°C. NMR ppm (CDCl_3) 0.95 (3H, t), 1.25-1.55 (7H, m), 1.82 (2H, m), 1.98 (1H, m), 3.05 (1H, d), 3.15 (1H, d), 3.2-3.7 (7H, m), 4.22 (1H, m), 4.35 (2H, t), 8.05 (2H, m). Anal. $\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}-\text{HCl}$ requires C: 61.62; H: 8.40; N: 13.47%. Found C: 61.37; H: 8.31; N: 13.68%.

10

A reference to the method of generating the 2-chloro-3-lithiopyrazine used in the preparations of (1) and (7) is: Turck, A., Mojovic, L., Queguiner, G. Synthesis 1988,881.

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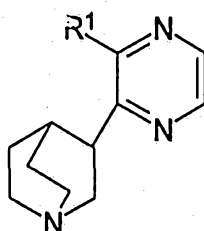
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COMPARATIVE EXAMPLE 1

Examples from the present application were compared with examples from Australian specification 28834/89. The results presented in Table 1 illustrate that the compounds of the present application unexpectedly bind more strongly to the muscarinic acetylcholine receptors, as can be seen by the concentration required for inhibition of ³H-Oxotremorine-M binding.

TABLE 1

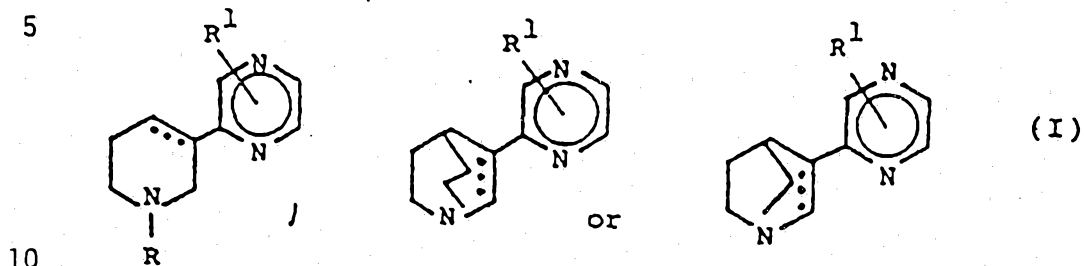


7	R ¹	Inhibition of ³ H-Oxotremorine-M binding (nM)
	-O-(CH ₂) ₂ CH ₃ , compound 38	9
	-O-(CH ₂) ₃ CH ₃ , compound 21	5
	-O-(CH ₂) ₄ CH ₃ , compound 25	6
	-CH ₃ , compound of example 23 of AU 28834/89	23
	-O-(CH ₂) ₃ CH ₃ , compound of example 54 of AU 28834/89	43



The claims defining the invention are as follows:

1. A compound of formula I, selected from:



wherein R is methyl and R¹ is in the 3-position of the pyrazinyl moiety and is halogen, S-R² or O-R² wherein R² is straight or branched C₁₋₁₅-alkyl unsubstituted or substituted with one or more
15 halogen atoms or R³-O-R⁴ wherein R³ and R⁴ independently are straight or branched C₁₋₁₅-alkyl, $\text{---}\text{---}\text{---}$ is HC-CH or $\text{C}=\text{C}$, or a salt thereof with a pharmaceutically-acceptable acid.

2. A compound according to claim 1 selected from the following:

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3-[2-(3-Methoxypyrazin)yl]-1,2,5,6-tetrahydro-1-methylpyridine;
3-[2-(3-Butyloxy pyrazin)yl]-1,2,5,6-tetrahydro-1-methylpyridine;
3-[2-(3-Hexyloxy pyrazin)yl]-1,2,5,6-tetrahydro-1-methylpyridine;
3-[2-(3-(2-Methoxyethoxy)pyrazin)yl]-1,2,5,6-tetrahydro-1-methyl-
pyridine;

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3-[2-(3-Chloropyrazin)yl]-1,2,5,6-tetrahydro-1-methylpyridine;
3-[2-(3-Chloropyrazin)yl]-1-azabicyclo[2.2.2]oct-2-ene;
3-[2-(3-Methoxypyrazin)yl]-1-azabicyclo[2.2.2]oct-2-ene;
3-[2-(3-Methoxypyrazin)yl]-1-azabicyclo[2.2.2]octane;
3-[2-(3-Hexyloxy pyrazin)yl]-1-azabicyclo[2.2.2]oct-2-ene;
3-[2-(3-Hexyloxy pyrazin)yl]-1-azabicyclo[2.2.2]octane;
3-[2-(3-Heptyloxy pyrazin)yl]-1-azabicyclo[2.2.2]octane;
3-[2-(3-Heptyloxy pyrazin)yl]-1,2,5,6-tetrahydro-1-methylpyridine;
3-[2-(3-Butyloxy pyrazin)yl]-1-azabicyclo[2.2.2]oct-2-ene;
3-[2-(3-Butyloxy pyrazin)yl]-1-azabicyclo[2.2.2]octane;
3-[2-(3-(3,3,4,4,5,5,6,6,6)nonafluorohexyloxy pyrazin)yl]-1-aza-
bicyclo[2.2.2]oct-2-ene;

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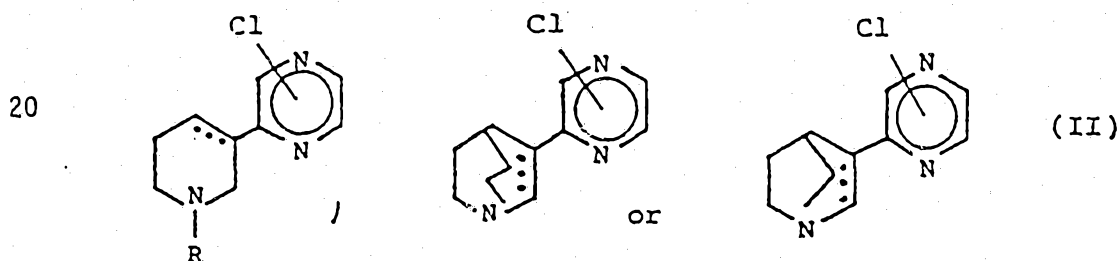
3-[2-(3-Pentyloxy pyrazin)yl]-1-azabicyclo[2.2.2]octane;
Endo-3-[2-(3-hexyloxy pyrazin)yl]-1-azabicyclo[2.2.1]heptane;
Exo-3-[2-(3-hexyloxy pyrazin)yl]-1-azabicyclo[2.2.1]heptane;

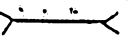


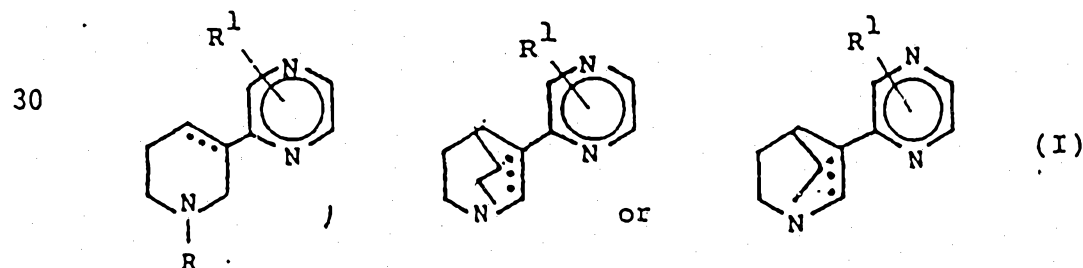
- 3-[2-(3-Butylthiopyrazin)yl]-1-azabicyclo[2.2.2]octane;
 3-[2-(3-Chloropyrazin)yl]-1-azabicyclo[2.2.2]octane;
 3-[2-(3-Ethoxythiopyrazin)yl]-1,2,5,6-tetrahydro-1-methylpyridine;
 3-[2-(3-Propyloxythiopyrazin)yl]-1,2,5,6-tetrahydro-1-methylpyridine;
 5 3-[2-(3-Pentyloxythiopyrazin)yl]-1,2,5,6-tetrahydro-1-methylpyridine;
 3-[2-(3-Hexylthiopyrazin)yl]-1,2,5,6-tetrahydro-1-methylpyridine;
 3-[2-(3-Pentylthiopyrazin)yl]-1,2,5,6-tetrahydro-1-methylpyridine;
 3-[2-(3-Ethoxythiopyrazin)yl]-1-azabicyclo[2.2.2]octane;
 3-[2-(3-Propyloxythiopyrazin)yl]-1-azabicyclo[2.2.2]octane;
 10 3-[2-(3-Pentylthiopyrazin)yl]-1-azabicyclo[2.2.2]octane;
 3-[2-(3-Hexylthiopyrazin)yl]-1-azabicyclo[2.2.2]octane;

or salts thereof with pharmaceutically-acceptable acids.

- 15 3. A method of preparing the compounds according to claims 1-2, including reacting a compound of formula II selected from the group consisting of



- wherein R and  have the meanings defined above, with NaOR¹ or NaSR¹ to form a compound of formula I selected from the group consisting of
- 25



- 35 wherein R, R¹ and  have the meanings defined above.

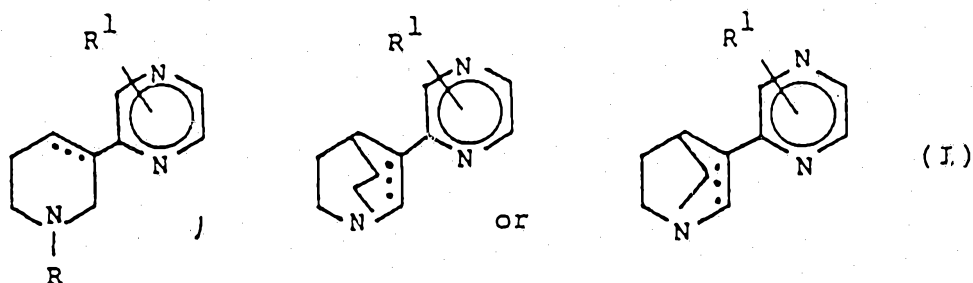
4. A pharmaceutical composition including a compound according to claim 1 or 2 or a salt thereof with a pharmaceutically-acceptable acid, together with a pharmaceutically-acceptable carrier or diluent.



5. A pharmaceutical composition according to claim 4 in the form of an oral dosage unit, or an parenteral dosage unit.

6. A pharmaceutical composition according to claim 5 wherein said dosage unit includes about 1 to about 100 mg of a compound of formula I or a salt thereof with a pharmaceutically-acceptable acid.

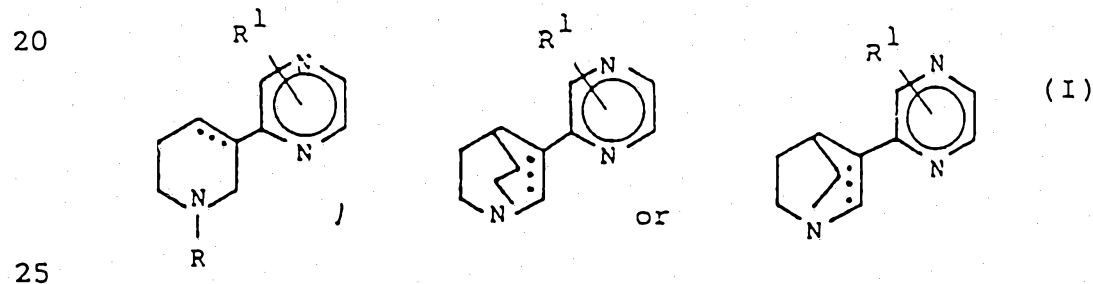
7. A method of stimulating the cognitive functions of the forebrain and hippocampus including providing to a subject in need of such stimulation an effective amount of a compound of formula I selected from the group consisting of



wherein R is H, C₁₋₃-alkyl, C₃₋₄-cycloalkyl, C₂₋₄-alkenyl or C₂₋₄-alkynyl and R¹ is straight or branched C₁₋₁₅-alkyl, straight or branched C₂₋₁₅-alkenyl, straight or branched

C₂₋₁₅-alkynyl, C₃₋₇-cycloalkyl, C₄₋₈-cycloalkylalkyl, halogen, amino, C₁₋₁₅-alkylamino, C₁₋₁₅-dialkylamino, C₁₋₁₅-alkoxyamino, S-R² or O-R² wherein R² is straight or branched C₁₋₁₅-alkyl unsubstituted or substituted with
 5 one or more halogen atoms, straight or branched C₂₋₁₅-alkenyl, straight or branched C₂₋₁₅-alkynyl, C₄₋₈-cycloalkylalkyl, R³-O-R⁴, R³-S-R⁴ wherein R³ and R⁴ independently are straight or branched C₁₋₁₅-alkyl, straight or branched C₁₋₁₅-alkenyl, straight or branched C₂₋₁₅-alkynyl,
 10 $\text{>}\cdots\text{<}$ is HC-CH or $\text{C}=\text{C}$, or a salt thereof with a pharmaceutically-acceptable acid together with a pharmaceutically-acceptable carrier or diluent.

8. A method of treating Alzheimer's disease in a subject in
 15 need of such treatment, including providing to said subject an effective amount of a compound of formula I selected from the group consisting of



wherein R is H, C₁₋₃-alkyl, C₃₋₄-cycloalkyl, C₂₋₄-alkenyl or C₂₋₄-alkynyl and R¹ is straight or branched C₁₋₁₅-alkyl,
 30 straight or branched C₂₋₁₅-alkenyl, straight or branched C₂₋₁₅-alkynyl, C₃₋₇-cycloalkyl, C₄₋₈-cycloalkylalkyl, halogen, amino, C₁₋₁₅-alkylamino, C₁₋₁₅-dialkylamino, C₁₋₁₅-alkoxyamino, S-R² or O-R² wherein R² is straight or branched C₁₋₁₅-alkyl unsubstituted or substituted with
 35 one or more halogen atoms, straight or branched C₂₋₁₅-alkenyl, straight or branched C₂₋₁₅-alkynyl, C₄₋₈-cycloalkylalkyl, R³-O-R⁴, R³-S-R⁴ wherein R³ and R⁴ indepen-



dently are straight or branched C₁₋₁₅-alkyl, straight or branched C₂₋₁₅-alkenyl, straight or branched C₂₋₁₅-alkynyl, $\text{>}\cdots\text{<}$ is HC-CH or $\text{C}=\text{C}$, or a salt thereof with a pharmaceutically-acceptable acid together with a pharmaceutically-acceptable carrier or diluent.

9. A method of claim 7 wherein said compound is administered in the form of a pharmaceutical composition together with a pharmaceutically-acceptable carrier or diluent.

10. A method of claim 8 wherein said compound is administered in the form of a pharmaceutical composition together with a pharmaceutically-acceptable carrier or diluent.

11. A method of claim 9 or 10 wherein said pharmaceutical composition is in the form of an oral dosage unit, or an parenteral dosage unit.

12. A compound according to claim 1, substantially as hereinbefore described with reference to any one of the examples, except comparative example 1.

DATED: 22 March 1995
PHILLIPS ORMONDE & FITZPATRICK
Attorneys for:
NOVO NORDISK A/S

David B Fitzpatrick



INTERNATIONAL SEARCH REPORT

International Application No PCT/DK 91/00087

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: C 07 D 453/02, 401/04, 471/08, A 61 K 31/495		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC5	C 07 D	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched ⁸		
SE,DK,FI,NO classes as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	EP, A2, 0327155 (MERCK SHARP & DOHME LTD) 9 August 1989, see the whole document --	1-6
P,X	EP, A2, 0416754 (MERCK SHARP & DOHME LTD) 13 March 1991, see the whole document -- -----	1-6
¹⁰ 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 "Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step with the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "Z" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
24th June 1991	1991-07-01	
International Searching Authority	Signature of Authorized Officer	
SWEDISH PATENT OFFICE	<i>Gunilla Claesson</i> Gunilla Claesson	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 7-11, because they relate to subject matter not required to be searched by this Authority, namely:
Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods [PCT Rule 39.1 (iv)].
2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.PCT/DK 91/00087**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on **91-05-29**.
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2- 0327155	89-08-09	AU-D- 2883489 JP-A- 2111768	89-08-03 90-04-24
EP-A2- 0416754	91-03-13	AU-D- 6083550	91-02-14