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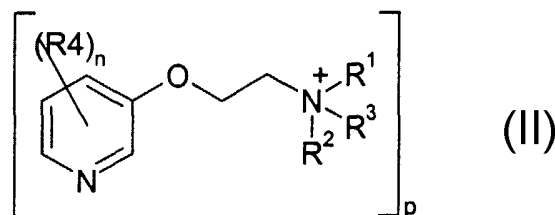
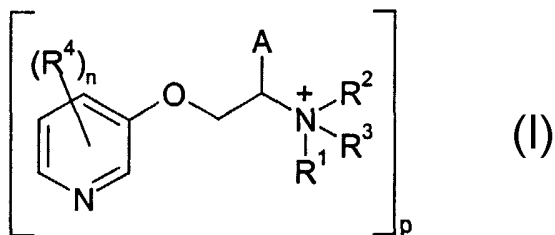
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(54) Title: NOVEL ANALGESICS



(57) Abstract: A salt of general formula I wherein R¹, R² and R³ are independently selected from the group consisting of C₁₋₆ alkyl groups or any two or three of R¹, R² and R³ may, together with the nitrogen to which they are attached, form a heterocyclic ring. R⁴ is a selected from the group of moieties which are effective to alter the solubility of the compound in physiological fluids and pharmaceutical carries, n is an integer of 0 to 5, A is selected from hydrogen or may, with the carbon to which it is attached and with any one of R¹, R² and R³ and the nitrogen to which they are attached, form a heterocyclic ring X is a negatively charged counterion and p is the number of negative charges thereon, the number of molecules of the positively charged tertiary amino ion being equal to the integer p in any given salt. Preferably the salt is of formula II below.

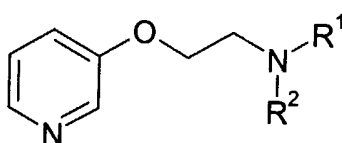


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NOVEL ANALGESICS

The present invention relates to novel compounds having activity at nicotinic acetylcholine receptors. The compounds have particular utility as peripheral analgesics, with advantage that they have relatively limited access to the central nervous system.

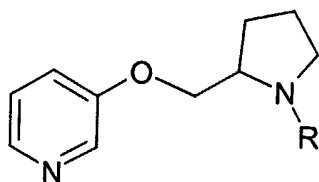
Compounds of general formula A



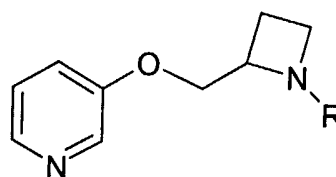
Formula A

Wherein R^1 and R^2 are lower alkyl, are known actives at the nicotinic acetylcholine receptor (nACh) (see Cheng et al (1999) J. Med. Chem 34 177-190 incorporated herein by reference) with potential in therapy of anxiety, appetite disorder, pain and impaired cognition. For example the compound N,N-dimethyl-AXP (formula A wherein R^1 and R^2 are both methyl) has been found by the present inventors to be active in the tail flick pain assay.

Holladay et al (1999) Neuronal Nicotinic Receptors, Arneric and Brioni eds Wiley-Liss, NY, pp253-270 report that compounds of the formula B and C also bind at nicotinic receptors.

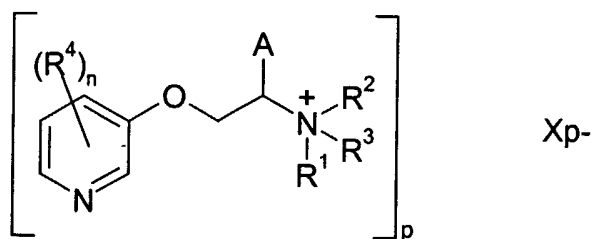


Formula B



Formula C

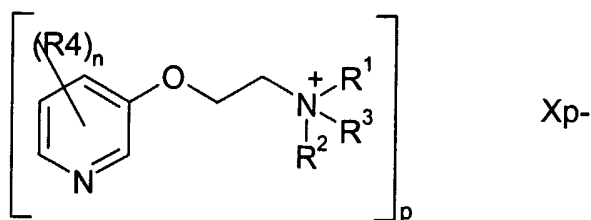
The present inventors have now provided salts of general formula I



Formula I

- wherein R^1 , R^2 and R^3 are independently selected from the group consisting of C_{1-6} alkyl groups or any two or three of R^1 , R^2 and R^3 may, together with the nitrogen to which they are attached, form a heterocyclic ring,
- R^4 is a selected from the group of moieties which are effective to alter the solubility of the compound in physiological fluids and pharmaceutical carriers,
- n is an integer of 0 to 5,
- 10 A is selected from hydrogen or may, with the carbon to which it is attached and with any one of R^1 , R^2 and R^3 and the nitrogen to which they are attached, form a heterocyclic ring
- X is a negatively charged counterion and
- p is the number of negative charges thereon, the number of molecules of the
- 15 positively charged tertiary amino ion being equal to the integer p in any given salt.

Preferably the salt of Formula I is of Formula II



Formula II

Preferably X is such that it is a pharmaceutically acceptable salt.

By pharmaceutically acceptable salt is particularly meant a salt with a pharmaceutically acceptable anion. Particularly preferred are halides, ie. chlorides, bromides, iodides, but also preferred are acetates, trifluoroacetates and other such salts.

The expression 'moieties which are effective to alter the solubility of the compound in physiological fluids or pharmaceutical carriers' particularly refers to alkyl, aryl, carboxyl, hydroxy, hydroxyalkyl, aralkyl, carboxylalkyl, haloalkyl, alkyloxy, aryloxy, acyloxy, alkoxyalkyl, amino, amido, nitro, nitrate and halo groups. Alkyl chains in such moieties are preferably of from 1 to 16 carbon atoms, more preferably 1 to 6 carbon atoms. Where alkyl is cycloalkyl this will be from 3 to 7 carbon atoms, more preferably 5 or 6 atoms in the ring.

Conveniently the substituent may be as simple as a methyl (relatively hydrophobic) or methoxy (relatively hydrophilic) group.

Where two or more of R^1 , R^2 , R^3 and A, together with the carbon and nitrogen to which they are attached form a heterocyclic ring this is most preferably a 4, 5, 6 or 7 membered ring comprising only carbon and nitrogen, although oxygen and sulphur may also be present as preferred ring members.

It will be realised that compounds of Formulae I and II may exist as optical isomers which may be prepared in forms other than the 50:50 racemate by selection of chirally pure starting materials or by resolution of racemic forms using, eg. column chromatography eg. using chiral columns.

In a second aspect of the present invention there is provided a method of treating a patient in need of therapy for pain comprising administering a therapeutically effect amount of a compound as described in the first aspect.

In a third aspect of the present invention there is provided a compound of the first aspect for use in therapy, and particularly to treat pain.

In a fourth aspect of the present invention there is provided the use of a compound of the first aspect in the manufacture of a medicament for the treatment of pain.

5 In a fifth aspect of the present invention there is provided an analgesic composition comprising a compound of the first aspect. Particularly such compositions are sterile and pyrogen free if for parenteral administration. Also for such parenteral administration, and further for non-parenteral administration, ie. via oral, buccal, rectal, topical or transdermal routes, the composition will preferably comprise a pharmaceutically acceptable carrier, excipient or diluent.

10 In a sixth aspect of the invention there is provided a method for synthesising a compound of the first aspect of formula II comprising reacting a 2-(3-pyridoxyl)-ethan-halide, preferably chloride, with a tertiary amine of formula $NR^1R^2R^3$, where R^1 , R^2 and R^3 are as defined above to yield the halide salt of a compound of the invention.

15 The compounds of the invention may be formulated into the compositions of the invention by associating them, eg. by mixing or enclosing them, with a physiologically acceptable diluent or carrier for use as pharmaceuticals for veterinary, for example in a mammalian context, and particularly for human use, by a variety of methods.

20 For instance, they may be applied as a composition incorporating a liquid diluent or carrier, for example an aqueous or oily solution, suspension or emulsion, which may often be employed in injectable form for parenteral administration and therefore may conveniently be sterile and pyrogen free. Oral administration is preferred for the preferred compounds of the invention. Although compositions for
25 this purpose may incorporate a liquid diluent or carrier, it is more usual to use a solid, for example a conventional solid carrier material such as starch, lactose, dextrin or magnesium stearate. Such solid compositions may conveniently be of a formed type, for example as tablets, capsules (including spansules), powders etc.

Other forms of administration than by injection or through the oral route may
30 also be considered in both human and veterinary contexts, for example the use of

suppositories or pessaries. Another form of pharmaceutical composition is one for buccal or nasal administration, for example lozenges, nose drops or an aerosol spray and as ointments or other creams for application topically. Compositions may be formulated in unit dosage form, i.e. in the form of discrete portions each comprising a unit dose, or a multiple or sub-multiple of a unit dose.

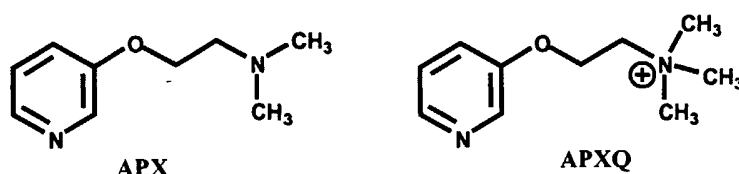
Typical dosages for use in human therapy will usually lie in the region of about 0.1 to 50g daily, preferably 0.5 g to 20 g daily, particularly from about 1 or 2 g to 10 or 15 g daily, for example about 5 g, veterinary doses being on a similar g/kg body weight ratio. However, it will be appreciated that it may be appropriate under certain circumstances to give daily dosages either below or above these levels. Where desired, more than one compound according to the present invention may be administered in the pharmaceutical composition, when the total dosage will usually correspond to those discussed.

Particular formulations may be devised by those skilled in the art by using principles well known in the art, eg by reference to Remington: Science and Practice of Pharmacy. Mack Publishing eg 19th Edition (1995) and any later Edition, incorporated herein by reference.

The present inventors have found that compounds of the present invention do not follow the structure-activity relationships of some of the other closely related nicotine analogs. For example APX, of Formula A, binds at nACh receptors with high affinity ($K_i = 21$ nM) and possesses antinociceptive activity (tail-flick assay; $ED_{50} = 1.5$ mg/kg). Like nicotine, the antinociceptive actions of APX are blocked by the nACh receptor antagonist mecamylamine.

Interestingly, and unexpectedly, quaternization of APX (of Formula A where R^1 and R^2 are methyl) to APX-Q (corresponding compound of Formula 1 where R^1 to R^3 are methyl and R^4 is hydrogen) results in 70-fold enhancement of affinity (APXQ, $K_i = 0.3$ nM). Even more interesting is that APX-Q retains antinociceptive activity ($ED_{50} = 1.4$ mg/kg). Its actions were blocked by intraperitoneal or subcutaneous administration of mecamylamine or the competitive nACh receptor antagonist dihydro- β -erythroidine, but not by the muscarinic antagonist atropine or the opioid

antagonist naloxone. This data suggest that the actions of APX-Q are mediated by nACh receptors.



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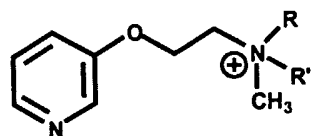
Formula II: Chemical structures of APX and APX-Q.

APX affects motor activity (mouse spontaneous activity assay; ED₅₀ = 15 mg/kg) at the same dose at which it produces its antinociceptive effects; these actions are also blocked by mecamylamine. This is somewhat interesting because nicotine (ED₅₀ = 0.8 mg/kg) is twice as potent in producing this “side effect” than it is in producing its antinociceptive effect. More interesting is that APX-Q (ED₅₀ = 2.3 mg/kg) is somewhat less potent in the locomotor assay than in the tailflick assay. Its actions in this assay were also blocked by mecamylamine.

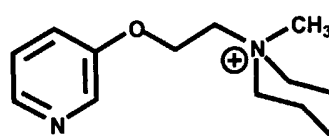
It is unclear why APX-Q is active in the tail-flick assay, or whether the effect is partially centrally-mediated or localized to spinal nACh receptors. Being a quaternary amine, APX-Q might not be expected to readily penetrate the blood brain barrier upon systemic administration. Consistent with this concept, the antinociceptive effects of APX-Q were blocked by hexamethonium (a nicotinic antagonist that does not readily penetrate the blood-brain barrier) at doses of 1 and 10 mg/kg. However, the locomotor effects of APX-Q were not blocked by hexamethonium.

If APX-Q does not readily penetrate the blood-brain barrier, it could represent a novel type of nicotinic agonist with reduced central activity relative to nicotine; that is, it might be a mechanistically novel “peripherally-acting” analgesic. The possibility also exists, as suggested by the locomotor assay results, that APXQ might possess fewer side effects than nicotine.

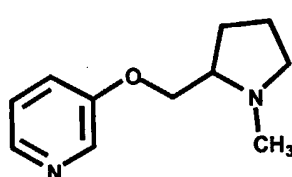
Thus preferred compounds of the invention may be compared with the existing prior art compounds as set out below.



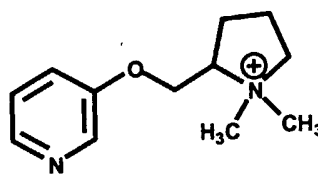
APXQ analogs



Cyclic APXQ analogs



A-84543



A-84543 Quaternary analog

Where APXQ and three analogues are related to prior art A-84543.

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The present invention will now be described further by way of illustration only by reference to the following non-limiting examples. Further embodiments of the invention will occur to those skilled in the art in the light of these.

10

EXAMPLES

Synthesis

Ethyl 3-pyridoxyacetate (APX-325). Ethyl bromoacetate (16.5 g, 0.1 mol) was added in a dropwise manner to a solution of 3-pyridinol sodium salt [prepared from 3-pyridinol (9.5 g, 0.1 mole) and 60% NaH (4.0 g, 0.1 mol) in DMSO (80 mL) at 0 °C] at 25 °C. The reaction was stirred at room temperature for 1 h. About 40 mL of DMSO was added and evaporated in vacuo. The residue was dissolved in H₂O (150 mL), extracted with CHCl₃ (3 x 150 mL). The combined CHCl₃ extracts were washed with 10% NaOH (10 mL), brine (20 mL), dried over Na₂SO₄, evaporated in vacuo to give black an oil (15.0 g). The oily residue was purified using Kugelrohr distillation apparatus to give **APX-325** (6.0 g, 33%), (100-150 °C; 0.1-0.05 mmHg). ¹H NMR (CDCl₃)δ: 8.23 (1H, d, J = 2.1 Hz), 8.15 (1H, s), 7.12 (2H, m), 4.56 (2H, s), 4.18 (2H,

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q, J = 7.1 Hz), 1.12 (3H, t, J = 7.1 Hz). [Reference: Mertes, M. P.; Borne, R. E.; Hare, L. E. J. Heterocyclic Chem. 1968, 5, 281-283.]

5 **2-(3-Pyridoxy)ethanol (APX-363).** The THF solution of 1M LiAlH₄ (15.0 mL, 15.00 mmol) was added to a solution of ethyl 3-pyridoxyacetate (2.5 g, 13.81 mmol) in anhydrous Et₂O (60 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight. Water (5 mL) was carefully added to destroy excess LiAlH₄ and stirring was continued until the solution was clear. The precipitate was filtered off and washed with Et₂O. The combined ethereal solution was dried over Na₂SO₄ and
10 evaporated in vacuo to give **APX-363** (1.50 g, 78%). The known compound was previously reported in the patent literature (US patent 5,025,031) by a different method of preparation).

15 **2-(3-Pyridoxy)ethyl]trimethylammonium chloride (APX-366; "APX-Q").** SOCl₂ (2 mL) was added to a solution of **APX-363** (0.93 g, 6.69 mmol) in CH₂Cl₂ (20 mL). The resultant solution was heated to reflux for 2 h. SOCl₂ and CH₂Cl₂ were evaporated to give a white solid which was dissolved in H₂O (10 mL). The aqueous solution was adjusted to pH = 8-9 and extracted with Et₂O (2 x 100 mL). The combined ethereal solution was washed with brine, dried over MgSO₄, evaporated in
20 vacuo to give a light yellow oil (0.94 g). The oil was dissolved in 45% Me₃N in H₂O (15 mL), and the resultant solution was heated to reflux for 6 h and additional 45% Me₃N (5 mL) was added after each one hour gap for 3 times. The reaction was allowed to cool to room temperature and extracted with Et₂O (30 mL). Then the aqueous solution was evaporated in vacuo to dryness and EtOH (50 mL) was added
25 and evaporated in vacuo to dryness. The yellow oil was triturated with acetone to give white solid (0.83 g, 57%). The product was recrystallized from acetone/2-PrOH, mp: 173-175 °C. ¹HNMR (DMSO-d₆)δ: 8.62 (1H, d, J = 2.7), 8.49 (1H, d, J = 4.7), 7.75 (1H, d, J = 5.7), 7.64 (1H, m), 4.83 (2H, br s), 4.13 (2H, br s), 3.18 (9H, s). CHN, C₁₀H₁₇ClN₂O: C, 55.43; H, 7.85; N, 12.93. Found: C, 55.33; H, 7.89; N, 12.84.

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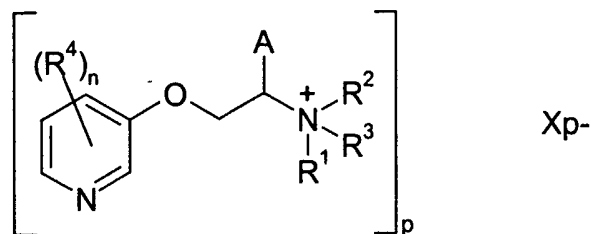
Biological studies.

Agent	NACH Receptor	Tail flick assay
	Affinity; Ki, nM	ED50)(mg/kg)[†]
AXP	21	15
AXP-Q	0.3	1.4
±Nicotine	1.8	1.6

[†] Effects effectively antagonised by nicotinic antagonist mecamylamine

CLAIMS.

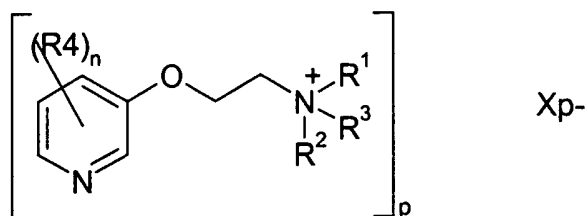
1. A salt of general formula I



Formula I

- 5 wherein R^1 , R^2 and R^3 are independently selected from the group consisting of C_{1-6} alkyl groups or any two or three of R^1 , R^2 and R^3 may, together with the nitrogen to which they are attached, form a heterocyclic ring,
 R^4 is selected from the group of moieties which are effective to alter the solubility of the compound in physiological fluids and pharmaceutical carriers,
 10 n is an integer of 0 to 5,
 A is selected from hydrogen or may, with the carbon to which it is attached and with any one of R^1 , R^2 and R^3 and the nitrogen to which they are attached, form a heterocyclic ring
 X is a negatively charged counterion and
 15 p is the number of negative charges thereon, the number of molecules of the positively charged tertiary amino ion being equal to the integer p in any given salt.

2. A salt of general Formula II



Formula II

3. A salt as claimed in Claim 1 or Claim 2 wherein X is such that the salt is a pharmaceutically acceptable salt.
- 5 4. A method of treating a patient in need of therapy for pain comprising administering a therapeutically effect amount of a salt as claimed in Claim 1 or Claim 2.
- 10 5. A salt as claimed in Claim 1 or Claim 2 for use in therapy, particularly to treat pain.
6. Use of a salt as claimed in Claim 1 or Claim 2 in the manufacture of a medicament for the treatment of pain.
- 15 7. An analgesic composition comprising a salt as claimed in Claim 1 or Claim 2.
8. An analgesic composition as claimed in Claim 7 wherein it is in sterile and pyrogen free form.
- 20 9. An analgesic composition as comprising a salt as claimed in Claim 1 or Claim 2 together with a pharmaceutically acceptable carrier, excipient or diluent.
- 25 10. A method for synthesising a compound of formula II comprising reacting a 2-(3-pyridoxyl)-ethan-halide, preferably chloride, with a tertiary amine of formula $\text{NR}^1\text{R}^2\text{R}^3$, where R^1 , R^2 and R^3 are as defined above to yield the halide of a compound of the invention.