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2-(4-*R*-Phenoxy/phenylthio)alkanoic esters of l-lupinine

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Abstract

Considering the great pharmacological interest in phenoxy/phenylthioalkanoic esters of open-chain or cyclic aminoalcohols, a set of ten such esters of lupinine was prepared. Initially, their ability to displace [^{3}H]QNB from rat brain preparation was investigated. With the exception of two, all the prepared esters exhibited good affinity to muscarinic receptors (on a non-selective basis), with pK_i in the range 6.67–7.68. © 2001 Elsevier Science S.A. All rights reserved.

Keywords: Lupinine derivatives; Phenoxyalkanoic esters; Phenylthioalkanoic esters; Muscarinic receptor ligands

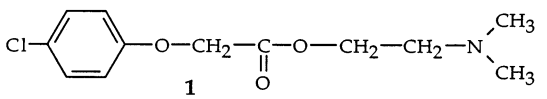
1. Introduction

4-Substituted phenoxyalkanoic esters of aminoalcohols have been the object of research for a long time.

Nootropic and CNS stimulating properties were described for meclofenoxate (**1**) in the late 1950s [1,2]. This compound enjoyed extensive clinical use as a resuscitating agent after cranial trauma and as a geriatric drug [3]. Several analogous 4-substituted phenoxyacetyl and propionyl derivatives of *tert*-aminoalcohols and *tert*-amino-alkylamines were prepared as potential psychostimulating agents and many of them were found to be endowed with anti-reserpine, local anesthetic, analgesic and antiinflammatory activities [4–11]. One of these compounds (mefexamide, **2**) was found to be clinically useful as an antidepressant agent.

Some aminoesters and aminoamides derived from 4-chlorophenoxyalkanoic acids exhibited cytostatic activity on neoplastic mast cells cultured in vitro [12].

Strong stimulating activity on the CNS was attributed to (4-chlorophenoxyacetyl)tropanol (**3**) [13],



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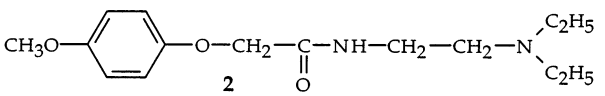

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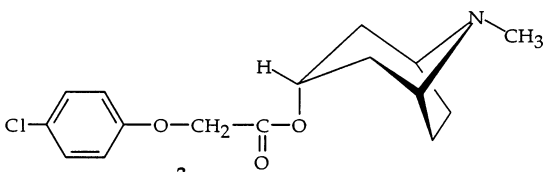

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though no detail for such an action was found in the available literature.

In 1969 Boido and Sparatore [14] prepared the 4-chlorophenoxyacetyl derivative of l-lupinine and aminolupinane (**4**, **5**), which in a preliminary screening failed to exhibit significant stimulating activity on the CNS after oral administration in mice and were not further investigated. On the other hand, the ester **4** and the amide **5** exhibited some local anesthetic activity, associated in the latter case with in vitro antithrombotic activity [15].

This last activity is reminiscent not only of the platelet antiaggregating and plasma fibrinogen reducing properties of clofibrate and other related phenoxyalka-

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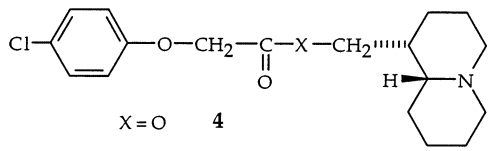
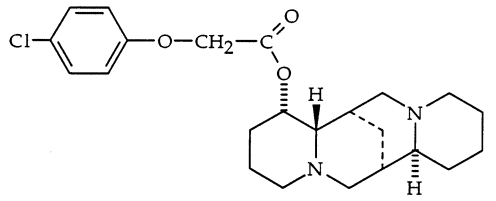


X = O 4

X = NH 5



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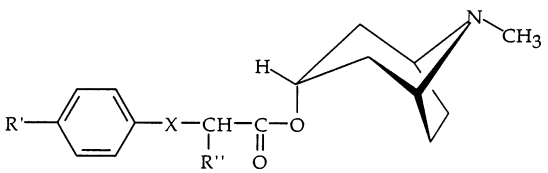
noic acids derivatives [16–18], but also that of some other structurally unrelated lupinyl derivatives [19,20].

A few years later Savelli and Sparatore [21] prepared the 4-chlorophenoxyacetic ester of retamine (**6**), which when administered p. os to mice induced weak sedative activity and hypothermia, followed, for sublethal doses (~ 800 mg/kg), by clonic convulsions. At the dose of 50 mg/kg p. os in mice, compound **6** was unable to modify the effects of pentylenetetrazole, reserpine and amphetamine. This in vivo pharmacological profile was quite similar to that of the starting alkaloid. However the ester **6** differed from retamine for the strong relaxant activity on isolated tissues contracted by acetylcholine, histamine (guinea pig ileum), barium chloride (rat ileum) and serotonin (rat stomach), with IC_{50} in the range 3–9 μg/ml.

Finally, very interesting analgesic and nootropic activities [22,23] were shown for tropic, 2-phenylpropionic and 2-phenoxy/phenylthioalkanoic esters of aminoalcohols, particularly of α-tropanol (**7**), as a consequence of their ability to increase central acetylcholine release through selective blockade of muscarinic autoreceptors.



7

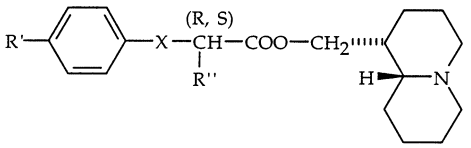
R' = H, Cl, Br, OCH_3

R'' = CH_3, C_2H_5

X = —, O, S

It is worth noting that one of the most active compounds (**7**; X = O; R′ = Cl; R″ = CH_3) is the homologue of compound **3** described by Zakharowa et al. in 1965 [13].

Based on the above observations, phenoxy/phenylthioalkanoic esters of open chain or cyclic aminoalcohols are of interest in several pharmacological areas (as CNS stimulating or sedative agents, analgetics, local anesthetic, smooth muscle relaxants, platelet antiaggregating and antihyperlipemic agents). Therefore, we were prompted to resume investigations on compound **4** and to prepare some new esters of l-lupinine corresponding to formulae **8**–**16**.



X = O ; R' = H ; R'' = H **8**

X = O ; R' = Cl ; R'' = H **4**

CH_3 **9**

C_2H_5 **10**

X = S ; R' = H ; R'' = H **11**

CH_3 **12**

C_2H_5 **13**

X = S ; R' = Cl ; R'' = H **14**

CH_3 **15**

C_2H_5 **16**

In this preliminary study, the prepared esters were assayed for their affinity to muscarinic receptors, on a non-selective basis. One single ester was assayed also for affinity to central nicotinic receptor and as acetylcholinesterase inhibitor. The last activity has been observed in a few naturally occurring *epi*-lupinine esters [24].

The results will be useful in subsequently planning more appropriately targeted in vitro and in vivo studies.

2. Chemistry

The required acids that were not commercially available were prepared according to the literature data [23,25–28], with only minor modifications.

In particular, thiophenol and 4-chlorothiophenol were reacted with iodoacetic, 2-bromopropionic and 2-bromobutyric acid in ethanolic sodium hydroxide solution to give the expected 2-(4-*R*-phenylthio)-alkanoic acids in high yields (90–98%). In the same experimental conditions 2-bromobutyric acid reacted poorly with 4-chlorophenol, affording only 35% of the expected 2-(4-chlorophenoxy)butyric acid, while 2-hydroxybutyric acid was formed mainly. Nevertheless, this method appears more convenient, for small preparations, than that reported in the literature [25], which involves the reaction of 4-chlorophenol, ethyl 2-bro-

mobutyrate and sodium ethoxide in absolute ethanol, followed by the hydrolysis of the ester formed, to give the required acid with an overall yield of 56%.

Acids were converted to the corresponding chlorides by refluxing with an excess of thionyl chloride. After removing the thionyl chloride, the crude products were reacted with lupinine in dichloromethane solution.

Chiral acids were used as racemic mixtures.

The esters obtained were characterized through elemental analyses, IR and ^{1}H NMR spectra that were in agreement with the proposed structures.

IR spectra (in KBr) of all prepared esters exhibited a sharp carbonyl band around 1735 cm^{-1}.

^{1}H NMR spectra did not exhibit any unusual features; thus only the spectrum of ester **10** is described as an example.

^{1}H NMR ($CDCl_3$): δ 7.26–7.16 and 6.84–6.74 (2m, 2H + 2H, paraphenylene); 4.514–4.509 (2 overlapping t, 1H, $-O-CH(CH_2-CH_3)-$, $J = 6.2$ Hz); 4.45–4.15 (m, 2H, $-O-CH_2-$quinolizidine); 2.72–2.74 (m, 2H, 2 equatorial H in α position to quinolizidine nitrogen); 2.20–1.00 [m, 14H, quinolizidine + quint (δ 1.97) 2H, CH_2-CH_3, $J = 6.9$ Hz + t (δ 1.06) 3H, CH_2-CH_3, $J =$ 7.4 Hz].

The prepared esters were commonly very viscous oils and their conversion to more convenient salts was attempted. Only compounds **9** and **10** gave well crystallized hydrogen fumarate in very high yields (86–90%), while the remaining esters gave crystalline salts (hydrogen fumarates, hydrochlorides or others) in only moderate or low yields. Since esters of l-lupinine with racemic acid must be considered as mixtures of diastereoisomers, it is possible that salts obtained in poor yields do not retain the original (likely 1:1) ratio of the two diastereoisomers, thus becoming unsuitable for biological assays.

Therefore for all assays the free bases were preferred (though less easy to handle); only compounds **9** and **10** were tested as hydrogen fumarates, since having been obtained in very high yields a significant variation in diastereoisomeric ratio should be excluded.

3. Experimental

Melting points were determined by the capillary method on a Büchi apparatus and are uncorrected.

The elemental analyses were performed at the Microanalytical Laboratory of the Dipartimento di Scienze Farmaceutiche of Genoa University with a CE EA 1110 CHNS-O instrument and the analytical results for C, H, N or C, H, N, S were within $\pm 0.4\%$ of the calculated values.

IR spectra were recorded with a Perkin–Elmer Paragon 1000 PC spectrophotometer.

^{1}H NMR spectra were taken on a Bruker AC 200 or Varian Gemini 200 spectrometers using $CDCl_3$ as solvent for free bases and DMSO-d_6 for salts, with Me_4Si as internal standard.

3.1. 2-(4-R-Phenoxy)alkanoic acids

Phenoxyacetic, 4-chlorophenoxyacetic and 2-(4-chlorophenoxy)propionic acids were commercially available. 2-(4-Chlorophenoxy)butyric acid was prepared as follows.

To a solution of 0.8 g (20 mmol) of NaOH in 45 ml of ethanol, 1.28 g (10 mmol) of 4-chlorophenol and 1.67 g (10 mmol) of 2-bromobutyric acid were added and the mixture was refluxed under nitrogen for 4 h. The solvent was removed under reduced pressure and the residue taken up with water; the solution was adjusted to pH 9–10 and extracted with ether to remove the unreacted phenol. The solution was acidified to pH 6–7 with acetic acid and extracted with ether, obtaining 750 mg (35% yield) of 2-(4-chlorophenoxy)butyric acid. The aqueous solution was further acidified with HCl and extracted again with ether to obtain a bromine free acid, whose NMR spectrum showed it to be 2-hydroxybutyric acid.

3.2. 2-(4-R-Phenylthio)alkanoic acids

Only phenylthioacetic acid was commercially available; the remaining were obtained as described in the literature [23,26–28] with minor modification.

To a solution of 1.2 g (30 mmol) of NaOH in 85 ml of ethanol, 15 mmol of thiophenol or 4-chlorothiophenol and 15 mmol of 2-haloacid (iodoacetic, 2-bromopropionic, 2-bromobutyric) were added and the mixture was refluxed for 4 h under a stream of nitrogen. The reaction was monitored by TLC on silica with dichloromethane–ethyl acetate–acetic acid (10:10:0.5 v/v) as eluent.

The solvent was removed under reduced pressure; the residue taken up with water, adjusted to pH 9–10 and extracted with ether to remove a little of unreacted thiophenol. The solution was acidified to pH 2 and extracted with ether to give the 2-(4-*R*-phenylthio)-alkanoic acids with yields from 90 to 98%.

3.3. l-Lupinine 2-(4-R-phenoxy/phenylthio)alkanoic esters

The suitable acid (6.5 mmol) was dissolved in 15 ml of thionyl chloride and refluxed for 1.5 h. Thionyl chloride was evaporated under reduced pressure and the residue was dissolved three times in cyclohexane (3 × 3.5 ml) and evaporated to dryness each time.

A solution of l-lupinine (1.1 g = 6.5 mmol) in 30 ml of dichloromethane (freed from ethanol by running through basic alumina) was added to the acyl chloride

and the solution was refluxed for 1.5–2.5 h under nitrogen. The reaction progression was monitored through TLC on silica (eluent: dichloromethane–methanol–conc. aqueous ammonia, 20:3:0.1 v/v).

The solvent was removed at reduced pressure; the residue was taken up with iced water, made alkaline with cold 2 N NaOH and rapidly extracted with ether. The joined ether extracts were dried with sodium sulfate and evaporated to yield the crude esters as yellow oils (only compound **4** is solid) that were chromatographed on a silica column. Initially, dichloro methane was used as the eluent, to which was added an increasing amount of methanol up to 3% v/v. Esters were eluted with mixtures containing 1–3% methanol. Yields and other characteristics of lupinine esters are given in Table 1.

To a solution of lupinine esters **9** and **10** (2 mmol) in absolute ethanol, a solution of fumaric acid (2 mmol) in absolute ethanol was added. The solution was evaporated to dryness at reduced pressure, a drop of absolute ethanol was added and, after standing a long time in the freezer, the crystals were rinsed with dry ether or dry ether–absolute ethanol (4:1, v/v).

4. Biological assays

Binding and enzyme inhibition assays were performed by MDS Panlabs Inc. of Bothell, WA.

(a) All the prepared lupinine esters were tested for affinity to central muscarinic receptors through the displacement of [^{3}H]QNB from rat brain preparations [29].

Brain cortices were obtained from male Wistar rats, and a membrane fraction was prepared by standard technique.

Membrane preparation (1 mg) was incubated with 0.15 nM [^{3}H]QNB for 60 min at 25°C. Non specific binding is estimated in the presence of 100 nM atropine sulphate. Membranes were filtered and washed three times and the filters were counted to determine [^{3}H]QNB bound. Compounds were initially screened at 10 μM concentration. Radioligand $K_D = 0.074$ nM.

(b) Lupinine ester **13** was tested for affinity to central nicotinic acetylcholine receptor through displacement of [^{3}H]cytisine from rat brain preparation [30]. Brain cortices were removed from Wistar rats and a membrane fraction was prepared as usual. Membrane preparation (600 μg) was incubated with [^{3}H]cytisine at a concentration of 2 nM for 75 min at 0°C. Non specific binding was estimated in the presence of 100 μM nicotine. Further work-up as above. Radioligand $K_D = 3.2$ nM.

(c) Lupinine ester **13** was tested as acetylcholinesterase inhibitor [31]. Human recombinant acetylcholinesterase (Sigma, C-1682) is used.

Test compound and/or vehicle is incubated with acetylthiocholine iodide and 5,5-dithio bis-2-nitrobenzoic acid in sodium phosphate buffer (pH 7.4) at 25°C. The reaction is initiated by addition of 2 ng acetylcholinesterase and the thiocholine generated reacts continuously with dithio-bis(nitrobenzoic) acid to produce a yellow anion (5-thio-2-nitrobenzoic acid) proportional to enzymatic activity which is determined after 20 min by spectrophotometry at 405 nm. Compounds are initially screened at 10 μM. Physostigmine is used as reference compound, with $IC_{50} = 0.12$ nM.

Table 1
Characteristics of l-lupinine 2-(4-*R*-phenoxy/phenylthio)alkanoic esters and their effect on [^{3}H]QNB binding to rat central muscarinic receptors

Comp.	Formula [a]	M.p. (°C)	Solvent [b]	Yield (%) [c]	pK_i [d]
8	$C_{18}H_{25}NO_3$ [e]	oil		75.5	6.10
4	$C_{18}H_{24}ClNO_3$ [f]	62.3–63.5	A	68.3	6.23
9	$C_{19}H_{26}ClNO_3$	oil		89.3	
9a	$C_{19}H_{26}ClNO_3 + C_4H_4O_4$ [g]	140–141	B/C	90.1	6.97
10	$C_{20}H_{28}ClNO_3$	oil		94.3	
10a	$C_{20}H_{28}ClNO_3 + C_4H_4O_4$ [g]	132–136	B/D	86.4	6.67
11	$C_{18}H_{25}NO_2S$	oil		72.4	7.04
12	$C_{19}H_{27}NO_2S$	oil		60.9	7.44
13	$C_{20}H_{29}NO_2S$	oil		57	7.68
14	$C_{18}H_{24}ClNO_2S$	oil		72	6.76
15	$C_{19}H_{26}ClNO_2S$	oil		85.3	7.19
16	$C_{20}H_{28}ClNO_2S$	oil		86.7	7.07

[a] Analytical results for C, H, N (**4**, **8**–**10a**) or C, H, N, S (**11**–**16**) were within ± 0.4% (generally ± 0.1%) of calculated values.
[b] Solvent used for crystallization and/or washing of crystals: A, petroleum ether; B, absolute ethanol; C, dry ether/abs. ethanol 4:1; D, dry ether.
[c] Yields of bases and salts are referred, respectively, to pure oils resulting from chromatography and to the crystallized salts.
[d] Mean of duplicate experiments: each value differed from the mean by less than 10%.
[e] Known [32].
[f] Known [14].
[g] Hydrogen fumarate.

5. Results and discussion

Results of binding assays on central muscarinic receptors (on a non selective basis) are presented in Table 1.

With the exception of compounds **4** and **8** (only moderately active), the prepared esters exhibited good affinity for central muscarinic receptors ([^{3}H]QNB displacement assay) with pK_i in the range 6.67–7.68.

The comparison of data relative to aryloxyalkanoic esters and the corresponding arylthioalkanoic esters clearly indicate the affinity enhancing effect of the sulphur bridge, which is particularly strong in the case of unsubstituted unbranched esters **8** and **11**.

Aryloxy- and arylthiopropionic esters were always more active than the corresponding acetic derivatives, while the further chain elongation produced a further increase of affinity only in the set of phenylthioalkanoic esters **11**–**13**. Thus lupinine 2-(phenylthio)butyric ester (**13**) exhibited the highest affinity (p$K_i = 7.68$) which is comparable with that of tropanol 2-(phenylthio)-butyrate [23].

In the set of arylthioalkanoic esters the *p*-chloro substitution produces a general decrease of affinity, however a slight increase of affinity was observed when comparing phenoxyacetic esters **8** and **4**; thus more data are necessary to soundly assert the effect of *para* chloro substitution in these kinds of compounds.

The ester **13,** which exhibited the highest affinity to muscarinic receptors, was assayed for affinity to central nicotinic receptor and for inhibitory activity on acetylcholinesterase. At a concentration 10 μM this compound failed completely in displacing [^{3}H]cytisine from nicotinic receptor and also in the inhibition of acetylthiocholine hydrolysis by means of the human erythrocytes enzyme.

Concluding, the prepared esters display a generally good affinity for muscarinic receptors, however, in order to plan appropriately targeted in vivo studies, further assays are needed to define their affinities for M_1, M_2 and M_3 receptor subtypes.

Acknowledgements

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