Synthesis of Potent Non-imidazole Histamine H_3-Receptor Antagonists

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Summary

Histamine has been converted into a non-imidazole H_3-receptor histamine antagonist by addition of a 4-phenylbutyl group at the N^{α}-position followed by removal of the imidazole ring. The resulting compound, *N*-ethyl-*N*-(4-phenylbutyl)amine, remarkably has a K_i = 1.3 µM as an H_3 antagonist. Using this as a lead compound, a novel series of homologous O and S isosteric tertiary amines was synthesised and structure-activity studies furnished *N*-(5-phenoxypentyl)pyrrolidine (K_i = 0.18 ± 0.10 µM, for [^{3}H]histamine release from rat cerebral cortex synaptosomes) which, more importantly, was active *in vivo*. Substitution of NO_2 into the *para* position of the phenoxy group gave *N*-(5-*p*-nitrophenoxypentyl)pyrrolidine, UCL 1972 (K_i = 39 ± 11 nM), ED_{50} = 1.1 ± 0.6 mg/kg *per os* in mice on brain *tele*-methylhistamine levels.

Introduction

Histamine H_3 receptors have been shown to be inhibitory presynaptic autoreceptors which modulate the synthesis [1] and release [2] of histamine at histaminergic neurones in the central nervous system (CNS). Inhibition of the action of histamine at the H_3 receptor therefore increases the concentration released of the histamine neurotransmitter. The H_3 receptors also occur as heteroreceptors [3] on non-histaminergic neurones modulating the release of other neurotransmitters in the brain and periphery.

An H_3-receptor histamine antagonist entering the brain would lead to an increase in histamine transmission through histaminergic pathways and thereby potentiate the role of histamine in the CNS. Possible therapeutic applications of such compounds which have been proposed [4,5] include various CNS disorders such as memory and learning deficits, Alzheimer's disease, epilepsy, schizophrenia, sleep disturbance, and obesity.

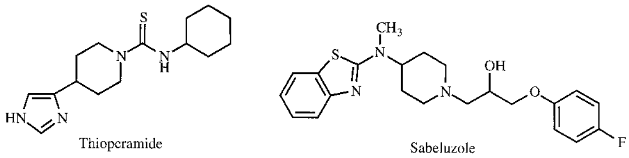

Chart 1

The prototype H_3 antagonist is thioperamide (Chart 1) which is very potent *in vitro* (K_i = 4.3 nM) but relatively high doses are required *in vivo* to enhance histamine release in the brain [6]. This suggests that thioperamide has a limited brain penetration, but the direct determination of penetrability which has been reported is somewhat conflicting. Thus, when given intravenously to rats, thioperamide was rather rapidly eliminated and had low brain levels [7] but at higher doses, given intraperitoneally, the results were more complex to interpret [8].

Brain penetration is greatly reduced by the presence of polar acceptor or donor hydrogen-bonding groups [9,10]. Since thioperamide contains an imidazole ring (strong H-bond acceptor and donor) and a thiourea moiety (two strongly H-bond donating groups and one mild H-bond acceptor) it is likely that these act to markedly reduce the penetrability of thioperamide. Although brain penetration is assisted when compounds are lipophilic this is not a sufficient criterion if the compounds are also strong hydrogen bonders. Previous studies in designing brain-penetrating H_2-receptor histamine antagonists have served to emphasise these conclusions [11]. We therefore sought to devise non-imidazole containing compounds as H_3 antagonists which should have improved brain penetration, aiming also to avoid thiourea and urea-type polar groups.

All potent and selective H_3-receptor ligands possess a 4(5)-substituted imidazole ring. A few weakly active non-imidazole compounds have been described as H_3 antagonists, e.g. betahistine [12] (K_i = 7 µM), phencyclidine [13] (K_i = 13 µM), dimaprit [14] (K_i = 3 µM), the pyridine analogue of thioperamide [15] (K_i = 13 µM), and clozapine [16] (K_i = 0.7 µM). Generally, however, replacement of the imidazole ring in H_3 antagonists by other heterocycles is accompanied by a loss of activity [17,18]. It should be possible to obtain non-imidazole antagonists using one of the foregoing compounds as a lead even though they are only weakly active and, indeed, this approach has very recently been reported in posters [19] starting from the compound sabeluzole [20] (Chart 1), which is a benzothiazole derivative. However, it was attractive to take a more fundamental line of reasoning, as follows.

It is possible to convert an agonist into an antagonist by introducing additional groups into the molecule which can locate binding sites in the vicinity of the receptor [21]. Whether the resulting molecule will be a partial agonist, or a pure antagonist, probably depends upon whether the agonist

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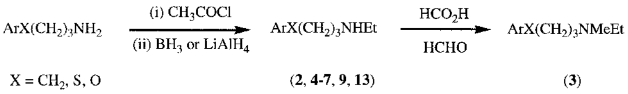
moieties continue to engage the receptor in the critical manner required to elicit the receptor response [21]. If they do not, then the molecule will be an antagonist (see for example the structure-activity relationships for H_2-receptor ligands [22]) and one may question whether the agonist moieties actually make any useful contribution to the affinity. If the additional groups are correctly positioned and interact appropriately with the receptor, the resultant molecule should achieve a considerable increase in affinity.

For histamine, the thought arose that it might be possible to convert histamine into an antagonist by addition of appropriate groups, and then to remove the imidazole ring to yield a non-imidazole antagonist molecule. It therefore seemed to be worthwhile applying this analysis to the interaction of histamine at the H_3 receptor. The difficulty of the approach resides in finding out what may be appropriate groups to incorporate into the histamine molecule and in which positions they should be introduced to achieve a sufficient increase in affinity.

Of various attempts made, the one that appeared to hold promise was the finding that N^{α}-(4-phenylbutyl)histamine (**1**) was a pure antagonist of histamine at the H_3 receptor with a K_i = 0.63 μM [23]. Removal of the imidazole ring from this structure led to the synthesis and testing of *N*-ethyl-*N*-(4-phenylbutyl)amine (**2**) which, remarkably, was found to have a K_i = 1.3 μM as an H_3-receptor histamine antagonist [24]. Thus removal of the imidazole ring had led merely to a twofold drop in affinity and had successfully produced the necessary lead to generate a non-imidazole H_3-receptor histamine antagonist.

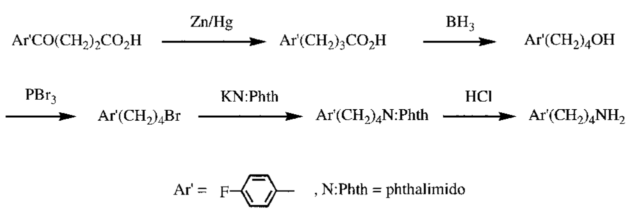
Chemical Synthesis

The ethylamines **2**, **4** to **7**, **9,** and **13** were prepared from the primary amine by acetylation followed by reduction of the amide with borane or lithium aluminium hydride (Scheme 1).



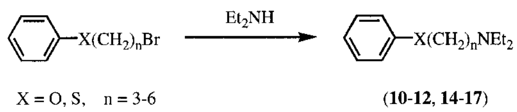
Scheme 1

The requisite primary amines were obtained as follows. 4-(4-Methoxyphenyl)butylamine was prepared in 3 steps from 4-(4-methoxyphenyl)butyric acid by conversion of the acid to the acid chloride, reaction with ammonia and reduction of the amide with lithium aluminium hydride. 4-(4-Nitrophenyl)butylamine [25] and 4-(4-chlorophenyl)butylamine [26] were prepared according to published procedures.



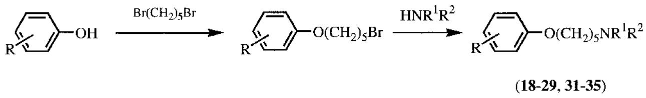
Scheme 2

4-(4-Fluorophenyl)butylamine was prepared in 5 steps from the commercially available 3-(4-fluorobenzoyl)propanoic acid by reduction of the ketone followed by reduction of the acid, bromination of the resulting primary alcohol and a Gabriel synthesis to give the primary amine (Scheme 2). 3-Phenylthiopropylamine [27] and 3-phenoxypropylamine [28] were prepared according to published procedures. The tertiary amine **3** was made from **2** by alkylation using the Eschweiler-Clarke procedure.



Scheme 3

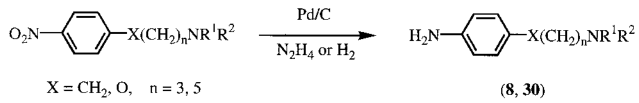
The diethylamine derivatives **10** to **12** and **14** to **17** (Scheme 3) derive from the corresponding bromides: 1-bromo-3-phenoxypropane and 1-bromo-4-phenoxybutane were commercially available; 1-bromo-3-phenylthiopropane [29], 1-bromo-4-phenylthiobutane [29], 1-bromo-5-phenoxypentane [30], 1-bromo-6-phenoxyhexane [31] were synthesised according to the published methods. 1-Bromo-5-phenylthiopentane was prepared in a similar way to its lower homologues rather than as published [32]. The tertiary amines **18** to **26** were also made from 1-bromo-5-phenoxypentane (Scheme 4) but under somewhat different conditions.



Scheme 4

The substituted phenoxypentylpyrrolidines **27** to **29** and **31** to **35** were made from the appropriate substituted 1-bromo-5-phenoxypentanes which had been synthesised from the corresponding phenols by alkylation with 1,5-dibromopentane (Scheme 4).

The anilines **8** and **30** were obtained from the aromatic nitro compounds **5** and **32** respectively by reduction with hydrazine hydrate or hydrogen in the presence of palladium on carbon catalyst (Scheme 5).

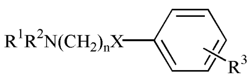


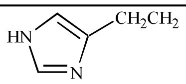
Scheme 5

Pharmacological Results and Discussion

The compounds were tested for histamine antagonism at the H_3-receptor in an *in vitro* functional assay on synaptosomes of rat cerebral cortex [33] and, *in vivo*, given orally to mice for their effect on brain *tele*-methylhistamine levels [33]. The structures and activities of the compounds are given in Table 1. *N*-Methylation to give the tertiary amine did not appear to change affinity. Substituents were introduced into the *para* position of the phenyl ring to probe for electronic effects and were found to have some influence: OMe and NO_2 groups (compounds **4** and **5** respectively) did not alter the potency, whereas F, Cl, or NH_2 markedly decreased potency (**6–8**) [34].

Table 1. Structures and potencies of compounds as H_3-receptor histamine antagonists.



No.	R^1	R^2	n	X	R^3	*In Vitro* [a] $K_i \pm$ SEM (µM)	*In Vivo* [b] $ED_{50} \pm$ SEM (mg/kg/po)
1		H	3	CH_2	H	0.70 ± 0.34	
2	C_2H_5	H	3	CH_2	H	1.3 ± 0.5[c]	n.d.[d]
3	C_2H_5	CH_3	3	CH_2	H	1.1 ± 0.1[c]	n.d.[d]
4	C_2H_5	H	3	CH_2	4-OCH_3	1.2 ± 0.3	> 10
5	C_2H_5	H	3	CH_2	4-NO_2	0.8 ± 0.1	> 10
6	C_2H_5	H	3	CH_2	4-F	ca 5	> 10
7	C_2H_5	H	3	CH_2	4-Cl	ca 5	> 10
8	C_2H_5	H	3	CH_2	4-NH_2	> 5	> 10
9	C_2H_5	H	3	S	H	> 5	n.d.[d]
10	C_2H_5	C_2H_5	3	S	H	0.18 ± 0.04	> 10
11	C_2H_5	C_2H_5	4	S	H	0.19 ± 0.03	> 10
12	C_2H_5	C_2H_5	5	S	H	0.34 ± 0.08	ca 15
13	C_2H_5	H	3	O	H	ca 5	n.d.[d]
14	C_2H_5	C_2H_5	3	O	H	0.15 ± 0.01	> 10
15	C_2H_5	C_2H_5	4	O	H	0.11 ± 0.02	> 10
16	C_2H_5	C_2H_5	5	O	H	0.23 ± 0.06	17 ± 4
17	C_2H_5	C_2H_5	6	O	H	ca 0.2	> 10
18	CH_3	CH_3	5	O	H	0.31 ± 0.10	> 10
19	C_2H_5	CH_3	5	O	H	0.36 ± 0.15	ca 10
20	C_3H_7	C_2H_5	5	O	H	0.46 ± 0.11	> 10
21	C_3H_7	C_3H_7	5	O	H	ca 1.5	> 10
22	CH_2-$(CH_2)_2$-CH_2		5	O	H	0.18 ± 0.10	3.4 ± 1.7
23	CH_2-$(CH_2)_3$-CH_2		5	O	H	0.14 ± 0.07	6.9 ± 3.1
24	CH_2-$(CH_2)_4$-CH_2		5	O	H	0.12 ± 0.05	> 10
25	$(CH_2)_2$-O-$(CH_2)_2$		5	O	H	0.64 ± 0.28	> 10
26	$(CH_2)_2$-N(CH_3)-$(CH_2)_2$		5	O	H	2.8 ± 0.7	> 10
27	CH_2-$(CH_2)_2$-CH_2		5	O	4-F	0.11 ± 0.03	5.1 ± 1.8
28	CH_2-$(CH_2)_2$-CH_2		5	O	4-Cl	0.13 ± 0.05	7.3 ± 3.4
29	CH_2-$(CH_2)_2$-CH_2		5	O	3-Cl	0.21 ± 0.06	ca 10
30	CH_2-$(CH_2)_2$-CH_2		5	O	4-NH_2	0.10 ± 0.05	2.6 ± 0.9
31	CH_2-$(CH_2)_2$-CH_2		5	O	4-CH_3	0.11 ± 0.05	ca 20
32	CH_2-$(CH_2)_2$-CH_2		5	O	4-NO_2	0.039 ± 0.011	1.1 ± 0.6
33	CH_2-$(CH_2)_2$-CH_2		5	O	3-NO_2	0.10 ± 0.04	ca 10
34	CH_2-$(CH_2)_2$-CH_2		5	O	4-CN	0.019 ± 0.007	1.9 ± 1.2
35	CH_2-$(CH_2)_2$-CH_2		5	O	3-CN	0.073 ± 0.020	ca 10

[a] functional assay *in vitro* for [^{3}H]histamine release from rat cerebral cortex synaptosomes; [b] *in vivo* assay in mice for effect on brain *tele*-methylhistamine levels, ED_{50} values calculated as mg free base per kg; [c] measured on rat cerebral cortex slices; [d] n.d. = not determined.

In retrospect it is of interest to note that compound **6** is a partial structure of sabeluzole.

In order to improve the accessibility of compounds and facilitate the structure-activity exploration, ether isosteres were examined. The sulfur isostere (**9**) of **2** was not active but, surprisingly, *N*-ethylation to give the tertiary amine **10** increased affinity by nearly an order of magnitude (K_i = 0.18 μM). Homologues (n = 4–5) were also examined (compounds **11**–**12**) and found to be similarly active *in vitro* and, interestingly, compound **12** (n = 5) was active *in vivo* ($ED_{50} \approx$ 15 mg/kg *per os*) [34].

Similar results were obtained with the oxygen ether series. The oxygen isostere (**13**) of **2** had some activity, and the *N*-ethyl derivative (**14**) was approximately 30 fold more potent (K_i = 0.15 μM). Homologues (n = 4–6) (**15**–**17**) were similarly active *in vitro* (K_i = 0.11–0.23 μM) and **16** was active *in vivo* ($ED_{50} \approx$ 17 mg/kg *per os*) [34].

The phenoxypentylamine structure was then optimised for activity with respect to the tertiary amino group. The amine series NMe_2 (**18**), NMeEt (**19**), NEt_2 (**16**), NEtPr (**20**) showed little variation in activity *in vitro* (K_i = 0.23–0.46 μM), but NPr_2 (**21**) was less active; **19**, however, was also active *in vivo* ($ED_{50} \approx$ 10 mg/kg *per os*). The compounds with pyrrolidino (**22**), piperidino (**23**), and homopiperidino (**24**) groups were all of similar potencies *in vitro* (K_i = 0.12–0.18), but the morpholino (**25**) and *N*-methylpiperazino (**26**) compounds were distinctly less active. Most important, however, was the finding that the pyrrolidino and piperidino compounds were active orally *in vivo*, with the former being of special interest, having an ED_{50} value of 3.4 mg/kg. It is apparent that the amino group is a determinant of *in vivo* activity; potency decreases in the order $N(CH_2)_4 > N(CH_2)_5 > N(CH_3)C_2H_5 > N(C_2H_5)C_2H_5 > N(C_3H_7)C_2H_5$ but there is no obvious overall correlation, either with carbon content or size.

Substituents were then introduced into the phenoxy group of the pyrrolidine derivative **22** and the compounds **27**–**35** were tested *in vivo*. Activity was found to be in the potency order: p-NO_2 > p-CN > p-NH_2 > p-F > p-Cl > m-Cl ~ m-NO_2 ~ m-CN > p-Me. The p-NO_2 and p-CN compounds **32** and **34** being the most potent (ED_{50} = 1.1 and 1.9 mg/kg *per os* respectively). This represents a very important finding since the potency is similar to that of the standard reference H_3 antagonist, thioperamide ($ED_{50} = 1.0 \pm 0.5$ mg/kg *per os*) [33]. Since these structures are generically phenylalkylamines or phenoxy(thio)alkylamines, and various alkylamines are known to act at biogenic amine receptors, it will be very important to establish that the compounds have selectivity towards histamine H_3 receptors. Studies to determine selectivity will certainly have to be undertaken before any of these compounds or related structures can be considered as potential clinical candidates.

The p-NO_2 and p-CN compounds **32** and **34** were also examined *in vitro* and found to have approximately only one fifth to one tenth (K_i = 19–39 nM) of the potency of thioperamide in this test. Presumably, therefore, **32** and **34** are inherently less active at the receptor than is thioperamide but, since they are similarly active *in vivo*, it suggests that they, indeed, have a better brain penetrability.

Conclusion

In the above structure-activity investigation, which successfully led to the design of a non-imidazole H_3 antagonist, one can see that the histamine substructure of compound **1** locates the receptor and the additional group [$Ph(CH_2)_4$] contributes to affinity. Since **1** is not a partial agonist, it appears that the histamine substructure is no longer able to engage the receptor in the productive manner required for stimulating it to respond.

The imidazole group in **1** can be removed without substantial loss of affinity and molecular manipulation has furnished suitable affinity groups. Hence it now appears that the imidazole group in the antagonist is not even required for locating the receptor so long as appropriate affinity groups have been identified. In such antagonist structures it is therefore apparent that one is no longer building on the affinity of the agonist. The agonist structure merely served as a tool to probe for the necessary binding sites at the receptor.

Acknowledgements

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Experimental

Chemistry

Melting points (open capillaries) were determined using an Electrothermal® electrically heated Cu block apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian XL-200 (200 MHz) or a Varian VXR-400 (400 MHz) spectrometer on the δ scale relative to TMS as internal reference. Elemental analyses, C, H, N and Cl (all within ± 0.4% of the calculated values unless indicated) were determined by A.A.T. Stones and G.A. Maxwell in the Department of Chemistry, University College London. Column chromatography was performed on Merk silica gel 60 (70–230 mesh). Analytical and preparative HPLC were performed on a Gilson HPLC apparatus fitted with a Kromasil C_{18} 5 μm reverse phase column 250 × 4.6 mm (analytical) or 250 × 22 mm (preparative) with a flow rate of 1 mL min^{-1} (analytical) or 18 mL min^{-1} (preparative) and a detector at 215 nm. Fast atom bombardment mass spectrometry was performed on a VG ZAB-SE double focussing mass spectrometer by the Mass Spectrometry Service in the Department of Chemistry, University College London. All compounds were at least 98% pure by analytical HPLC and their mass spectra were consistent with their attributed structures. A few compounds retained an excess of oxalic acid (see Table 2).

General Method A

A solution of the appropriately substituted alkylamine (40 mmol) and triethylamine (2 equiv.) in dry dichloromethane (60 mL) was stirred under nitrogen and cooled to 0 °C. Acetyl chloride (1.5 equiv.) was added dropwise and the resulting mixture was stirred at room temperature for 3 h. Water (50 mL) was added and the organic layer was separated, washed with aqueous HCl (4N), then with saturated NaCl, dried over magnesium sulfate and concentrated under reduced pressure to give the crude amide. A solution of the amide (23 mmol) in dry dichloromethane (50 mL) was added to a molar solution of borane in THF (60 mL, 60 mmol) stirred at 0 °C under nitrogen. The mixture was then heated under reflux for 16 h with stirring under nitrogen. After cooling to 0 °C, an aqueous HCl solution (6N, 20 mL) was slowly added and the resulting mixture was evaporated to dryness. The crude hydrochloride salt was dissolved in water and the solution was basified with an aqueous NaOH solution (10N). The free base was extracted with

Table 2. Chemical and physical data on tested compounds.

No.	Formula[a]	Anal.	Yield (%)	M.p. (°C)	Cryst. solvent[b]	Synth. scheme
2	$C_{12}H_{19}N$; HCl	C,H,N,Cl	56	152–154	A	1
3	$C_{13}H_{21}N$; $C_2H_2O_4$	C,H,N	44	110–112	A	1
4	$C_{13}H_{21}NO$; $C_2H_2O_4$	C,H,N	18	178–180	A	1
5	$C_{12}H_{18}N_2O_2$; $C_2H_2O_4$	C,H,N	26	183–185	B	1
6	$C_{12}H_{18}FN$; $C_2H_2O_4$	C,H,N	21	203–205	C	1
7	$C_{12}H_{18}ClN$; $C_2H_2O_4$	C,H,N	23	203–205	B	1
8	$C_{12}H_{20}N_2$; 2.6 $C_2F_3O_2H$	C,H,N	15	[c]	D	5
9	$C_{11}H_{17}NS$; $C_2H_2O_4$	C,H,N	5	210–212	C	1
10	$C_{13}H_{21}NS$; $C_2H_2O_4$	C,H,N	42	109–111	C	3
11	$C_{14}H_{23}NS$; $C_2H_2O_4$	C,H,N	33	95–97	C	3
12	$C_{15}H_{25}NS$; 1.1 $C_2H_2O_4$	C,H,N	30	83–85	C	3
13	$C_{11}H_{17}NO$; $C_2H_2O_4$	C,H,N	30	191–193	C	1
14	$C_{13}H_{21}NO$; 1.6 $C_2H_2O_4$	C,H,N	51	91–92	C	3
15	$C_{14}H_{23}NO$; 1.05 $C_2H_2O_4$	C,H,N	60	111–113	C	3
16	$C_{15}H_{25}NO$; $C_2H_2O_4$	C,H,N	47	107–109	C	3
17	$C_{16}H_{27}NO$; $C_2H_2O_4$	C,H,N	57	88–91	C	3
18	$C_{13}H_{21}NO$; 2 $C_2H_2O_4$; 2 H_2O	C,H,N[d]	52	129–130	D	4
19	$C_{14}H_{23}NO$; $C_2H_2O_4$	C,H,N	58	122–124	C	4
20	$C_{16}H_{27}NO$; $C_2H_2O_4$	C,H,N	11	90–91	D	4
21	$C_{17}H_{29}NO$; $C_2H_2O_4$	C,H,N	62	112–114	C	4
22	$C_{15}H_{23}NO$; $C_2H_2O_4$	C,H,N	56	153–155	C	4
23	$C_{16}H_{25}NO$; $C_2H_2O_4$	C,H,N	36	143–145	C	4
24	$C_{17}H_{27}NO$; $C_2H_2O_4$	C,H,N	33	132–134	C	4
25	$C_{15}H_{23}NO_2$; $C_2H_2O_4$	C,H,N	48	166–168	C	4
26	$C_{16}H_{26}N_2O$; 2 HCl	C,H,N	56	208–210	C	4
27	$C_{15}H_{22}FNO$; $C_2H_2O_4$	C,H,N	66	149–150	C	4
28	$C_{15}H_{22}ClNO$; $C_2H_2O_4$	C,H,N,Cl	52	139–141	C	4
29	$C_{15}H_{22}ClNO$; $C_2H_2O_4$	C,H,N,Cl	77	131–132	C	4
30	$C_{15}H_{24}N_2O$; 2.1 $C_2H_2O_4$	C,H,N	63	120–122	C	5
31	$C_{16}H_{25}NO$; $C_2H_2O_4$	C,H,N	47	138–140	C	4
32	$C_{15}H_{22}N_2O_3$; $C_2H_2O_4$; 0.2 H_2O	C,H,N	32	145–147	C	4
33	$C_{15}H_{22}N_2O_3$; $C_2H_2O_4$	C,H,N	69	130–131	C	4
34	$C_{16}H_{22}N_2O$; 1.1 $C_2H_2O_4$	C,H,N	41	129–130	C	4
35	$C_{16}H_{22}N_2O$; $C_2H_2O_4$	C,H,N	38	119–120	C	4

[a)] $C_2H_2O_4$ = oxalate; $C_2F_3O_2H$ = trifluoroacetate; [b)] A = ethanol:methanol (9:1); B = ethanol:methanol (1:1); C = ethanol; D = isopropanol; [c)] hygroscopic glassy solid; [d)] N: calcd, 3.31; found, 3.87.

diethyl ether (3×100 mL) and the combined extracts were dried over magnesium sulfate and concentrated to give the crude base as an oil. The base was purified by column chromatography on silica gel eluting with a 9:1 mixture of chloroform and methanol and the pure product was converted into the oxalate salt by adding an ethanolic solution of oxalic acid (1.5 equiv.), and the resulting oxalate was crystallised from the solvent indicated in Table 2.

General Method B

A solution of the suitable bromoalkyl derivative (9 mmol) in a large excess of diethylamine was heated at 50 °C for 48 h. The excess amine was removed under reduced pressure and the residue dissolved in water (100 mL), the solution basified with sodium hydroxide and the free base extracted into diethyl ether (3×100 mL). The combined extracts were dried over magnesium sulfate and concentrated to give the crude base as an oil. The base was purified by column chromatography on silica gel eluting with a 9:1 mixture of chloroform and methanol and the pure product was converted into the oxalate salt by adding an ethanolic solution of oxalic acid (1.5 equiv.).

General Method C

A solution of the suitable bromoalkyl derivative (1 mmol) and pyrrolidine (10 equiv.) in absolute ethanol (10 mL) was stirred and heated under reflux for 24 h. The solvent and excess amine were removed under reduced pressure, the residue dissolved in water (40 mL) and sodium hydroxide was added to reach a basic pH. The free base was extracted into diethyl ether (3×40 mL) and the combined extracts were washed with water, dried over magnesium sulfate and concentrated to give the crude base as a brown oil. The base was converted into the oxalate salt by adding an ethanolic solution of oxalic acid (1.5 equiv.).

General Method D

A suspension of the appropriately substituted phenol (15 mmol), 1,5-dibromopentane (2 equiv.), and water (30 mL) was vigorously stirred and heated under reflux. A solution of sodium hydroxide (1.5 equiv.) in water (20 mL) was added dropwise and the mixture was then stirred and heated under reflux for 4 h. After cooling, the organic layer was extracted into chloroform (3 × 40 mL) and the combined extracts washed with water (40 mL) and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the residue was distilled *in vacuo* (oil pump) to yield first the excess of 1,5-dibromopentane and then the product as an oil.

*N-Ethyl(4-phenylbutyl)amine hydrochloride (**2**)*

4-Phenylbutyl acetamide [35] (7.12 g, 37 mmol) was added dropwise to a stirred suspension of lithium aluminium hydride (4.10 g, 110 mmol) in 25 mL dry THF kept at 0 °C under nitrogen. The mixture was subsequently heated under reflux overnight with stirring under nitrogen. The reaction vessel was then cooled in an ice and water bath and sodium sulfate decahydrate was added portionwise followed by 5 mL THF. After 2.5 h, the resulting white suspension was filtered, dried over magnesium sulfate and the crude product obtained after removal of the solvent was distilled *in vacuo* to yield a colourless liquid (3.67 g, 56%, bp = 90–94 °C/ 0.3 Torr). *N*-(4-Phenylbutyl)ethylamine (1.08 g, 61 mmol) was converted into the hydrochloride salt by adding a cooled ethanolic solution of HCl.– ^{1}H NMR (DMSO d_6/TMS) δ = 9.10 (m, 2H), 7.25 (m, 5H), 2.86 (m, 2×2H), 2.61 (m, 2H), 1.67 (m, 2H), 1.22 (t, 8 Hz, 3H).

*N-Ethyl-N-methyl(4-phenylbutyl)amine oxalate (**3**)*

To *N*-ethyl(4-phenylbutyl)amine (see compound **2**, 2.03 g, 11 mmol) was added formic acid (2.75 g, 60 mmol), and formaldehyde (37% aqueous solution, 1.1 g, 40 mmol). The mixture was heated to 65–70 °C in a water bath with stirring for 4.5 h. After cooling, the mixture was poured into an ice and water mixture and made strongly basic by adding sodium hydroxide pellets. The base was extracted into diethyl ether and the crude product obtained after concentration was distilled *in vacuo* (1.23 g, 56%, bp = 90–94 °C/0.8 Torr). *N*-Methyl-*N*-4-phenylbutyl)ethylamine (1.00 g, 4.4 mmol) was converted into the oxalate salt by adding an ethanolic solution of oxalic acid (432 mg, 4.8 mmol).– ^{1}H NMR (DMSO d_6/TMS) δ = 7.27 (m, 5H), 3.02 (m, 2 × 2H), 2.67 (m, 2H+3H), 1.60 (m, 2×2H), 1.18 (t, 8 Hz, 3H).

4-(4-Methoxyphenyl)butanamide

A solution of 4-(4-methoxyphenyl)butanoic acid (24 g, 124 mmol) in freshly distilled thionyl chloride (60 mL, 820 mmol) was stirred and heated under reflux for 3 h. The excess thionyl chloride was distilled off to give the crude acid chloride (26.28 g, 100%).– A solution of aqueous ammonia (δ = 0.88, 20 mL) was stirred and cooled to 0 °C and the acid chloride (18.43 g, 86.65 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 min and the crude amide collected by filtration (16.74 g, 100%).– ^{1}H NMR ($CDCl_3$) δ = 7.26 (m, 2H), 6.83 (m, 2H), 3.70 (s, 3H), 3.34 (br, 2H), 2.48 (m, 2H), 2.02 (t, 7.5 Hz, 2H), 1.73 (m, 2H).

4-(4-Methoxyphenyl)butylamine

A solution of 4-(4-methoxyphenyl)butanamide (16.7 g, 86.73 mmol) in dry dichloromethane (10 mL) was added dropwise to an ice-cold solution of lithium aluminium hydride (10 g, 260 mmol) in dry THF (50 mL) under nitrogen. The resulting mixture was heated under reflux for 96 h. After cooling to 0 °C, a saturated solution of sodium sulfate was cautiously added. The resulting mixture was heated under reflux and the solution filtered hot. The residue was extracted with boiling THF and filtered. The combined filtrates were dried over magnesium sulfate and concentrated under reduced pressure. The crude amine was purified by column chromatography on silica gel eluting with 9/1 chloroform/methanol to give a yellow oil (2.2 g, 14%).– ^{1}H NMR (DMSO d_6) δ = 7.10 (m, 2H), 6.82 (m, 2H), 3.69 (s, 3H), 2.71 (t, 7.0 Hz, 2H), 2.49 (m, 2H), 1.52 (m, 2H).

*N-Ethyl[4-(4-methoxyphenyl)butyl]amine oxalate (**4**)*

Prepared according to general method A from 4-(4-methoxyphenyl)butylamine.– ^{1}H NMR (DMSO d_6) δ = 7.11 (m, 2H), 6.84 (m, 2H), 3.71 (s, 3H), 2.89 (m, 2×2H), 2.52 (t, 2H), 1.57 (m, 2×2H), 1.16 (t, 7.3 Hz, 3H).

*N-Ethyl[4-(4-nitrophenyl)butyl]amine oxalate (**5**)*

Prepared according to general method A from 4-(4-nitrophenyl)butylamine [25].– ^{1}H NMR (DMSO d_6) δ = 8.15 (m, 2H), 7.51 (m, 2H), 2.90 (m, 2×2H), 2.74 (t, 7.6 Hz, 2H), 1.63 (m, 2×2H), 1.15 (t, 7.3 Hz, 3H).

4-(4-Fluorophenyl)butanoic acid

A mixture of zinc wool (162 g, 2.48 mol), mercury(II) chloride (12.8 g, 47 mmol) and concentrated hydrochloric acid (10 mL) in water (220 mL) was stirred for 5 min. The liquid was then decanted and to the amalgam was added water (70 mL), concentrated hydrochloric acid (150 mL), toluene (90 mL) and 3-(4-fluorobenzoyl)propanoic acid (50 g, 255 mmol). The reaction mixture was stirred and heated under reflux for 48 h with regular additions of concentrated hydrochloric acid (50 mL) every 6 h. After cooling, two layers separated. The aqueous layer was diluted with water (200 mL) and extracted into diethyl ether (3 × 100 mL). The combined organic phases were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was distilled *in vacuo* to give an orange oil (39.57 g, 85%).– ^{1}H NMR ($CDCl_3$) δ = 7.16 (m, 2H), 6.95 (m, 2H), 2.64 (t, 2H), 2.35 (t, 2H), 1.92 (m, 2H).

4-(4-Fluorophenyl)butan-1-ol

To a solution of borane (1 M) in THF (180 mL, 180 mmol) stirred at 0 °C under nitrogen was slowly added a solution of 4-(4-fluorophenyl)butanoic acid (25 g, 137 mmol) in dry dichloromethane (150 mL). The resulting solution was then heated under reflux for 16 h. After cooling to 0 °C, a 1:1 mixture of water and THF (75 mL) was cautiously added, the aqueous phase was saturated with potassium carbonate, the organic layer separated and the product extracted into diethyl ether (6 × 100 mL). The combined organic phases were dried over magnesium sulfate and the solvent removed under reduced pressure to leave an oil that was purified by column chromatography on silica gel eluting with chloroform to give a colourless oil (10.19 g, 44%).– ^{1}H NMR ($CDCl_3$) δ = 7.16 (m, 2H), 6.94 (m, 2H), 3.63 (t, 2H), 2.59 (t, 7.4 Hz, 2H), 1.62 (m, 2×2H).

1-Bromo-4-(4-fluorophenyl)butane

To a solution of 4-(4-fluorophenyl)butan-1-ol (4.98 g, 29.6 mmol) in dry dichloromethane (200 mL) stirred at 0 °C under nitrogen was added dropwise a solution of phosphorus tribromide (6 mL, 17.1 g, 63.2 mmol). The reaction mixture was then heated at 60 °C for 14 h. After cooling to 0 °C, water was cautiously added and the organic phase separated. The product was extracted into dichloromethane (3 × 50 mL) and the combined organic solutions were dried over magnesium sulfate. The solvent was removed under reduced pressure to leave an oil that was purified by column chromatography on silica gel eluting with chloroform to give a yellow oil (3.62 g, 53%).– ^{1}H NMR ($CDCl_3$) δ = 7.10 (m, 2H), 6.95 (m, 2H), 3.40 (t, 2H), 2.60 (t, 7.4 Hz, 2H), 1.62 (m, 2×2H).

N-[4-(4-Fluorophenyl)butyl]phthalimide

Potassium phthalimide (8 g, 43.2 mmol) was added to a solution of 1-bromo-4-(4-fluorophenyl)butane (6.64 g, 28.74 mmol) in anhydrous DMF (200 mL) under nitrogen. The reaction mixture was then heated at 90 °C for 16 h. After cooling to room temperature, chloroform (200 mL) was added, followed by water (200 mL). The two layers separated and the product was extracted into chloroform (3 × 100 mL), the combined organic solutions were dried over magnesium sulfate and the solvent was removed under reduced pressure to leave a white solid. The crude product was purified by column chromatography on silica gel eluting with chloroform to give the pure product as a white solid (5.55 g, 65%).– ^{1}H NMR ($CDCl_3$) δ = 7.82 (m, 4H), 7.20 (m, 2H), 7.05 (m, 2H), 3.58 (t, 2H), 2.57 (t, 2H), 1.52 (m, 2×2H).

4-(4-Fluorophenyl)butylamine

A mixture of *N*-[4-(4-fluorophenyl)butyl]phthalimide (5.03 g, 17 mmol), glacial acetic acid (150 mL) and concentrated hydrochloric acid (150 mL) was stirred and heated under reflux for 36 h. The mixture was evaporated to dryness, the white residue was dissolved in water, anhydrous potassium carbonate was added and the free base extracted into chloroform (3 × 100 mL). The combined extracts were dried over magnesium sulfate and the solvent removed under reduced pressure to leave the product as a yellow oil (1.17 g, 7 mmol).– ^{1}H NMR (DMSO d_6) δ = 7.17 (m, 4H), 3.58 (t, 2H), 2.50 (m, 2H), 1.52 (m, 2×2H).

*N-Ethyl[4-(4-fluorophenyl)butyl]amine oxalate **(6)***

Prepared according to general method A from 4-(4-fluorophenyl)butylamine.– ^{1}H NMR (DMSO d_6) δ = 7.23 (m, 2H), 7.09 (m, 2H), 2.88 (m, 2×2H), 2.57 (t, 2H), 1.56 (m, 2×2H), 1.14 (t, 7.3 Hz, 3H).

*N-Ethyl[4-(4-chlorophenyl)butyl]amine oxalate **(7)***

Prepared according to general method A from 4-(4-chlorophenyl)butylamine [26]**.–** ^{1}H NMR (DMSO d_6) δ = 7.32 (m, 2H), 7.24 (m, 2H), 2.89 (m, 2×2H), 2.59 (t, 2H), 1.58 (m, 2×2H), 1.16 (t, 7.3 Hz, 3H).

*N-Ethyl[4-(4-aminophenyl)butyl]amine trifluoroacetate **(8)***

N-Ethyl[4-(4-nitrophenyl)butyl]amine (770 mg, 3.47 mmol) was dissolved in absolute ethanol (30 mL) and the solution heated to 50 °C. Palladium (5%) on carbon (100 mg) was added followed by hydrazine hydrate (4.12 g, 82.3 mmol) in 0.5 mL portions over 10 minutes. Additional palladium (5%) on carbon (100 mg) was added and the mixture was stirred at 50 °C for 72 h. After cooling, the catalyst was filtered off and the solution concentrated to dryness. The base was purified by preparative HPLC eluting with 90% water and 10% methanol, both containing 0.1% TFA. After concentration, the product was dissolved in isopropanol, filtered and concentrated to give the product as a hygroscopic brown glassy solid.– ^{1}H NMR (DMSO d_6) δ = 8.37 (br, 2H), 7.16 (m, 2H), 7.00 (m, 2H), 2.90 (m, 2×2H), 2.54 (t, 6.7 Hz, 2H), 1.54 (m, 2×2H), 1.14 (t, 7.3 Hz, 3H).

*N-Ethyl(3-phenylthiopropyl)amine oxalate **(9)***

Prepared according to general method A from 3-phenylthiopropylamine [27].– ^{1}H NMR (DMSO d_6) δ = 7.27 (m, 5H), 2.97 (m, 3×2H), 1.85 (m, 2H), 1.14 (t, 7.3 Hz, 3H).

*N,N-Diethyl(3-phenylthiopropyl)amine oxalate **(10)***

Prepared according to general method B from 1-bromo-3-phenylthiopropane [29].– ^{1}H NMR (D_2O) δ = 7.29 (m, 5H), 2.99 (m, 4×2H), 1.79 (m, 2H), 1.08 (t, 7.3 Hz, 2×3H).

*N,N-Diethyl(4-phenylthiobutyl)amine oxalate **(11)***

Prepared according to general method B from 1-bromo-4-phenylthiobutane [29]**.–** ^{1}H NMR (D_2O) δ = 7.27 (m, 5H), 3.01 (t, 7.3 Hz, 2H), 2.91 (m, 3×2H), 1.59 (m, 2×2H), 1.04 (t, 7.3 Hz, 2×3H).

1-Bromo-5-phenylthiopentane [32]

A mixture of thiophenol (1.82 g, 16.6 mmol), 1,5-dibromopentane (9.28 g, 40.4 mmol), sodium hydroxide (1.05 g, 26.3 mmol), water (50 mL), toluene (50 mL) and a 40% aqueous solution of tetrabutylammonium hydroxide (1 mL) was stirred at room temperature under nitrogen for 25 min. The organic layer was separated, washed with 10% aqueous sodium hydroxide, water and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the oil was distilled *in vacuo* (2.28 g, 53%).– ^{1}H NMR ($CDCl_3$) δ = 7.23 (m, 5H), 3.39 (t, 2H), 2.90 (t, 2H), 1.72 (m, 3×2H).

*N,N-Diethyl(5-phenylthiopentyl)amine oxalate **(12)***

Prepared according to general method B from 1-bromo-5-phenylthiopentane.– ^{1}H NMR (DMSO d_6) δ = 7.24 (m, 5H), 3.00 (m, 4×2H), 1.50 (m, 3×2H), 1.15 (t, 7.3 Hz, 2×3H).

*N-Ethyl(3-phenoxypropyl)amine oxalate **(13)***

Prepared according to general method A from 3-phenoxypropylamine [28]**.–** ^{1}H NMR (DMSO d_6) δ = 7.28 (m, 2H), 6.93 (m, 3H), 4.03 (t, 6.1 Hz, 2H), 2.98 (m, 4H), 2.04 (m, 2H), 1.17 (t, 7.2 Hz, 3H).

*N,N-Diethyl(3-phenoxypropyl)amine oxalate **(14)***

Prepared according to general method B from 1-bromo-3-phenoxypropane.– ^{1}H NMR (D_2O) δ = 7.25 (m, 2H), 6.90 (m, 3H), 4.03 (t, 2H), 3.12 (m, 3×2H), 2.04 (m, 2H), 1.15 (t, 7.3 Hz, 2×3H).

*N,N-Diethyl(4-phenoxybutyl)amine oxalate **(15)***

Prepared according to general method B from 1-bromo-4-phenoxybutane.– ^{1}H NMR (D_2O) δ = 7.24 (m, 2H), 6.90 (m, 3H), 3.98 (t, 5.9 Hz, 2H), 3.07 (m, 3×2H), 1.71 (m, 2×2H), 1.13 (t, 7.3 Hz, 2×3H).

*N,N-Diethyl(5-phenoxypentyl)amine oxalate **(16)***

Prepared according to general method B from 1-bromo-5-phenoxypentane [30].– ^{1}H NMR (D_2O) δ = 7.24 (m, 2H), 6.93 (m, 3H), 3.95 (t, 6.3 Hz, 2H), 3.00 (m, 3×2H), 1.62 (m, 2×2H), 1.36 (m, 2H), 1.12 (t, 7.3 Hz, 2×3H).

*N,N-Diethyl(6-phenoxyhexyl)amine oxalate **(17)***

Prepared according to general method B from 1-bromo-6-phenoxyhexane [31].– ^{1}H NMR (D_2O) δ = 7.23 (m, 2H), 6.89 (m, 3H), 3.93 (t, 6.4 Hz, 2H), 2.99 (m, 3×2H), 1.58 (m, 2×2H), 1.31 (m, 2×2H), 1.11 (t, 7.3 Hz, 2×3H).

*N,N-Dimethyl(5-phenoxypentyl)amine oxalate **(18)***

1-Bromo-5-phenoxypentane (200 mg, 0.82 mmol) was added to a solution of dimethylamine (2M) in THF (20 mL, 40 mmol) and the mixture was heated at 55 °C for 48 h. After cooling, the solvent and excess amine were removed under reduced pressure and the residue dissolved in water (100 mL), the solution basified with sodium hydroxide and the free base extracted into diethyl ether (3×100 mL). The combined extracts were dried over magnesium sulfate and concentrated to give the crude base as a yellow oil (151 mg, 94%). The base was purified by column chromatography on silica gel eluting with a 3:2 mixture of chloroform and methanol and the pure product (147 mg, 0.71 mmol) was converted into the oxalate salt by adding an ethanolic solution of oxalic acid (126 mg, 1.4 mmol).– ^{1}H NMR (D_2O) δ = 7.23 (m, 2H), 6.88 (m, 3H), 3.95 (t, 6.3 Hz, 2H), 2.99 (t, 2H), 2.71 (s 2×3H), 1.65 (m, 2×2H), 1.37 (m, 2H).

*N-Ethyl-N-methyl(5-phenoxypentyl)amine oxalate (**19**)*

A solution of 1-bromo-5-phenoxypentane (511 mg, 2.1 mmol) in *N*-methylethylamine (1.24 g, 21 mmol) was stirred at room temperature for 48 h. The excess amine was removed under reduced pressure, the residue dissolved in water (40 mL) and sodium hydroxide was added to reach a basic pH. The free base was extracted into diethyl ether (3×40 mL) and the combined extracts were washed with water, dried over magnesium sulfate and concentrated to give the crude base as a yellow oil. The base was converted into the oxalate salt by adding an ethanolic solution of oxalic acid (180 mg, 2 mmol).– ^{1}H NMR (DMSO d_6) δ = 7.28 (m, 2H), 6.92 (m, 3H), 3.95 (t, 6.3 Hz, 2H), 3.05 (q, 7.2 Hz, 2H), 2.98 (m, 2H), 2.66 (s, 3H), 1.70 (m, 2×2H), 1.44 (m, 2H), 1.18 (t, 7.2 Hz, 3H).

*N-Ethyl-N-propyl(5-phenoxypentyl)amine oxalate (**20**)*

A solution of 1-bromo-5-phenoxypentane (360 mg, 1.5 mmol) and *N*-ethylpropylamine (1 g, 11 mmol) in absolute ethanol (10 mL) was stirred and heated under reflux for 48 h. The excess amine and the solvent were removed under reduced pressure, the residue diluted with aqueous sodium hydroxide (40 mL) and the free base was extracted into diethyl ether (3×40 mL). The combined extracts were washed with water, dried over magnesium sulfate and concentrated to give the crude base as a brown oil. The base was converted into the oxalate salt by adding an ethanolic solution of oxalic acid (150 mg, 1.7 mmol).– ^{1}H NMR (DMSO d_6) δ = 7.27 (m, 2H), 6.92 (m, 3H), 3.95 (t, 6.2 Hz, 2H), 3.06 (m, 2H), 2.96 (m, 2×2H), 1.68 (m, 3×2H), 1.44 (m, 2H), 1.16 (t, 7.1 Hz, 3H), 0.89 (t, 7.3 Hz, 3H).

*N,N-Dipropyl(5-phenoxypentyl)amine oxalate (**21**)*

Prepared according to general method B from 1-bromo-5-phenoxypentane, using dipropylamine and heating at 110 °C for 48 h.– ^{1}H NMR (D_2O) δ = 7.24 (m, 2H), 6.89 (m, 3H), 3.96 (t, 6.3 Hz, 2H), 2.96 (m, 3×2H), 1.53 (m, 5×2H), 1.31 (m, 2×2H), 0.80 (t, 7.4 Hz, 2×3H).

*1-(5-Phenoxypentyl)pyrrolidine oxalate (**22**)*

A solution of 1-bromo-5-phenoxypentane (788 mg, 3.24 mmol) in pyrrolidine (2.56 g, 36 mmol) was stirred and heated under reflux for 24 h. The excess amine was removed under reduced pressure, the residue dissolved in water (40 mL) and sodium hydroxide was added to reach a basic pH. The free base was extracted into diethyl ether (3×40 mL) and the combined extracts were washed with water, dried over magnesium sulfate and concentrated to give the crude base as a yellow oil. The base was converted into the oxalate salt by adding an ethanolic solution of oxalic acid (303 mg, 3.4 mmol).– ^{1}H NMR (DMSO d_6) δ = 7.27 (m, 2H), 6.92 (m, 3H), 3.95 (t, 6.3 Hz, 2H), 3.21 (br, 2×2H), 3.07 (m, 2H), 1.91 (m, 2×2H), 1.70 (m, 2×2H), 1.42 (m, 2H).

*1-(5-Phenoxypentyl)piperidine oxalate (**23**)*

A solution of 1-bromo-5-phenoxypentane (780 mg, 3.2 mmol) in piperidine (2.93 g, 34 mmol) was stirred and heated under reflux for 48 h. The excess amine was removed under reduced pressure, the residue dissolved in water (40 mL) and sodium hydroxide was added to reach a basic pH. The free base was extracted into diethyl ether (3×40 mL) and the combined extracts were washed with water, dried over magnesium sulfate and concentrated to give the crude base as a yellow oil. The base was converted into the oxalate salt by adding an ethanolic solution of oxalic acid (288 mg, 3.2 mmol).– ^{1}H NMR (DMSO d_6) δ = 7.26 (m, 2H), 6.90 (m, 3H), 3.94 (t, 6.3 Hz, 2H), 3.06 (br, 2×2H), 2.95 (m, 2H), 1.70 (m, 4×2H), 1.52 (br, 2H), 1.42 (m, 2H).

*1-(5-Phenoxypentyl)homopiperidine oxalate (**24**)*

A solution of 1-bromo-5-phenoxypentane (520 mg, 2.1 mmol) in homopiperidine (2.64 g, 26.6 mmol) was stirred and heated under reflux for 4 h. The mixture was diluted with aqueous sodium hydroxide (40 mL), the free base was extracted into diethyl ether (3×40 mL) and the combined extracts were washed with water, dried over magnesium sulfate and concentrated to give the crude base as an oil. The base was converted into the oxalate salt by adding an ethanolic solution of oxalic acid (400 mg, 4.4 mmol).– ^{1}H NMR (DMSO d_6) δ = 7.27 (m, 2H), 6.93 (m, 3H), 3.96 (t, 6.3 Hz, 2H), 3.20 (br, 2×2H), 3.04 (m, 2H), 1.77 (m, 2×2H), 1.72 (m, 2×2H), 1.59 (br, 2×2H), 1.42 (m, 2H).

*4-(5-Phenoxypentyl)morpholine oxalate (**25**)*

A solution of 1-bromo-5-phenoxypentane (785 mg, 3.2 mmol) in morpholine (3.06 g, 35 mmol) was stirred and heated under reflux for 48 h. The excess amine was removed under reduced pressure, the residue dissolved in water (40 mL) and sodium hydroxide was added to reach a basic pH. The free base was extracted into diethyl ether (3×40 mL) and the combined extracts were washed with water, dried over magnesium sulfate and concentrated to give the crude base as a brown oil. The base was purified by column chromatography on silica gel eluting with a 1:1 mixture of chloroform and methanol. After removal of the solvents, the pure product was converted into the oxalate salt by adding an ethanolic solution of oxalic acid (225 mg, 2.5 mmol).– ^{1}H NMR (DMSO d_6) δ = 7.26 (m, 2H), 6.90 (m, 3H), 3.95 (t, 6.3 Hz, 2H), 3.75 (br, 2×2H), 3.02 (br, 2×2H), 2.90 (m, 2H), 1.70 (m, 2×2H), 1.42 (m, 2H).

*4-Methyl-1-(5-phenoxypentyl)piperazine dihydrochloride (**26**)*

A solution of 1-bromo-5-phenoxypentane (510 mg, 2.1 mmol) in *N*-methylpiperazine (2.2 g, 22 mmol) was stirred and heated under reflux for 48 h. The mixture was diluted with aqueous sodium hydroxide (40 mL), the free base was extracted into diethyl ether (3×40 mL) and the combined extracts were washed with water, dried over magnesium sulfate and concentrated to give the crude base as a brown oil. The base was converted into the hydrochloride salt by adding aqueous 4N HCl (5 mL).– ^{1}H NMR (DMSO d_6) δ = 7.28 (m, 2H), 6.93 (m, 3H), 3.96 (t, 6.3 Hz, 2H), 3.44 (br, 4×2H), 3.12 (br, 2H), 2.81 (br, 3H), 1.76 (m, 2×2H), 1.45 (m, 2H).

1-Bromo-5-(4-fluorophenoxy)pentane

Prepared according to general method D from 4-fluorophenol.– bp: ~140 °C/1 Torr.– ^{1}H NMR ($CDCl_3$) δ = 6.94 (m, 2H), 6.81 (m, 2H), 3.90 (t, 6.3 Hz, 2H), 3.42 (t, 6.7 Hz, 2H), 1.92 (m, 2H), 1.78 (m, 2H), 1.60 (m, 2H).

*1-[5-(4-Fluorophenoxy)pentyl]pyrrolidine oxalate (**27**)*

Prepared according to general method C from 1-bromo-5-(4-fluorophenoxy)pentane.– ^{1}H NMR (DMSO d_6) δ = 7.11 (m, 2H), 6.94 (m, 2H), 3.94 (t, 6.3 Hz, 2H), 3.23 (br, 2×2H), 3.09 (m, 2H), 1.92 (br, 2×2H), 1.71 (m, 2×2H), 1.44 (m, 2H).

1-Bromo-5-(4-chlorophenoxy)pentane [36]

Prepared according to general method D from 4-chlorophenol.– ^{1}H NMR ($CDCl_3$) δ = 7.23 (m, 2H), 6.82 (m, 2H), 3.93 (t, 6.3 Hz, 2H), 3.44 (t, 6.7 Hz, 2H), 1.94 (m, 2H), 1.80 (m, 2H), 1.62 (m, 2H).

*1-[5-(4-Chlorophenoxy)pentyl]pyrrolidine oxalate (**28**)*

Prepared according to general method C from 1-bromo-5-(4-chlorophenoxy)pentane.– ^{1}H NMR (DMSO d_6) δ = 7.30 (m, 2H), 6.94 (m, 2H), 3.95 (t, 6.3 Hz, 2H), 3.20 (br, 2×2H), 3.06 (m, 2H), 1.90 (br, 2×2H), 1.70 (m, 2×2H), 1.42 (m, 2H).

1-Bromo-5-(3-chlorophenoxy)pentane

Prepared according to general method D from 3-chlorophenol.– bp: 145-150 °C/1 Torr.–^{1}H NMR ($CDCl_3$) δ = 7.19 (t, 8.1 Hz, 1H), 6.92 (dd, 0.8 and 8.9 Hz, 1H), 6.89 (dd, 2.1 and 2.4 Hz, 1H), 6.78 (ddd, 0.8 and 2.4 and 8.4 Hz, 1H), 3.96 (t, 6.3 Hz, 2H), 3.45 (t, 6.8 Hz, 2H), 1.94 (m, 2H), 1.82 (m, 2H), 1.63 (m, 2H).

*1-[5-(3-Chlorophenoxy)pentyl]pyrrolidine oxalate (**29**)*

Prepared according to general method C from 1-bromo-5-(3-chlorophenoxy)pentane.– ^{1}H NMR (DMSO d_6) δ = 7.28 (t, 8.1 Hz, 1H), 6.98 (m, 2H), 6.89 (dd, 2.3 and 8.4 Hz, 1H), 3.98 (t, 6.3 Hz, 2H), 3.21 (br, 2×2H), 3.07 (m, 2H), 1.90 (br, 2×2H), 1.70 (m, 2×2H), 1.42 (m, 2H).

*1-[5-(4-Aminophenoxy)pentyl]pyrrolidine dioxalate (**30**)*

A solution of 1-[5-(4-nitrophenoxy)pentyl]pyrrolidine oxalate (see compound 32, 210 mg, 0.57 mmol) in a mixture of methanol (10 mL) and absolute ethanol (10 mL) was vigorously stirred at room temperature under hydrogen in the presence of palladium (5%) on carbon (100 mg) for 3 h. The catalyst was filtered off and the solvents removed under reduced pressure. The residue was dissolved in methanol and oxalic acid was added (100 mg, 1.1 mmol).– ^{1}H NMR (DMSO d_6) δ = 6.70 (m, 4H), 6.50 (br, 2H), 3.85 (t, 6.3 Hz, 2H), 3.27 (br, 2×2H), 3.10 (m, 2H), 1.92 (br, 2×2H), 1.60 (m, 2×2H), 1.42 (m, 2H).

1-Bromo-5-(4-methylphenoxy)pentane

Prepared according to general method D from *para* cresol.– ^{1}H NMR ($CDCl_3$) δ = 7.09 (m, 2H), 6.81 (m, 2H), 3.96 (t, 6.3 Hz, 2H), 3.45 (t, 6.8 Hz, 2H), 2.30 (s, 3H), 1.95 (m, 2H), 1.81 (m, 2H), 1.63 (m, 2H).

*1-[5-(4-Methylphenoxy)pentyl]pyrrolidine oxalate (**31**)*

Prepared according to general method C from 1-bromo-5-(4-methylphenoxy)pentane.– ^{1}H NMR (DMSO d_6) δ = 7.05 (m, 2H), 6.79 (m, 2H), 3.90 (t, 6.3 Hz, 2H), 3.20 (br, 2×2H), 3.06 (m, 2H), 1.90 (br, 2×2H), 1.68 (m, 2×2H), 1.42 (m, 2H).

1-Bromo-5-(4-nitrophenoxy)pentane [36]

Prepared according to general method D from 4-nitrophenol.– bp: 196–198 °C/2 Torr.– ^{1}H NMR ($CDCl_3$) δ = 8.21 (m, 2H), 6.95 (m, 2H), 4.07 (t, 6.3 Hz, 2H), 3.46 (m, 2H), 1.92 (m, 2×2H), 1.62 (m, 2H).

*1-[5-(4-Nitrophenoxy)pentyl]pyrrolidine oxalate (**32**)*

Prepared according to general method C from 1-bromo-5-(4-nitrophenoxy)pentane.– ^{1}H NMR (DMSO d_6) δ = 8.19 (m, 2H), 7.13 (m, 2H), 4.12 (t, 6.3 Hz, 2H), 3.19 (br, 2×2H), 3.07 (m, 2H), 1.90 (br, 2×2H), 1.76 (m, 2×2H), 1.44 (m, 2H).

1-Bromo-5-(3-nitrophenoxy)pentane

Prepared according to general method D from 3-nitrophenol. Heated under reflux for 6 h.– bp: 190–196 °C/1 Torr.– ^{1}H NMR ($CDCl_3$) δ = 7.76 (ddd, 8.1 and 1.3 and 0.8 Hz, 1H), 7.67 (dd, 2.3 and 2.3 Hz, 1H), 7.38 (dd, 8.2 and 8.2 Hz, 1H), 7.18 (ddd, 8.2 and 3.3 and 2.5 Hz, 1H), 4.01 (t, 6.3 Hz, 2H), 3.42 (t, 6.7 Hz, 2H), 1.93 to 1.78 (m, 4H), 1.62 (m, 2H).

*1-[5-(3-Nitrophenoxy)pentyl]pyrrolidine oxalate (**33**)*

Prepared according to general method C from 1-bromo-5-(3-nitrophenoxy)pentane.– ^{1}H NMR (DMSO d_6) δ = 7.81 (dd, 2.2 and 8.1 Hz, 1H), 7.70 (dd, 2.3 and 2.3 Hz, 1H), 7.58 (dd, 8.2 and 8.2 Hz, 1H), 7.42 (dd, 2.4 and 8.3 Hz, 1H), 4.11 (t, 6.4 Hz, 2H), 3.23 (br, 2×2H), 3.10 (m, 2H), 1.92 (br, 2×2H), 1.78 (m, 2H), 1.71 (m, 2H), 1.47 (m, 2H).

1-Bromo-5-(4-cyanophenoxy)pentane [36]

Prepared according to general method D from 4-hydroxybenzonitrile.– ^{1}H NMR ($CDCl_3$) δ = 7.58 (m, 2H), 6.93 (m, 2H), 4.02 (t, 6.3 Hz, 2H), 3.45 (t, 6.7 Hz, 2H), 1.93 (m, 2H), 1.84 (m, 2H), 1.64 (m, 2H).

*1-[5-(4-Cyanophenoxy)pentyl]pyrrolidine oxalate (**34**)*

Prepared according to general method C from 1-bromo-5-(4-cyanophenoxy)pentane.– ^{1}H NMR (DMSO d_6) δ = 7.50 (m, 2H), 7.09 (m, 2H), 4.06 (t, 6.3 Hz, 2H), 3.20 (br, 2×2H), 3.07 (m, 2H), 1.90 (br, 2×2H), 1.75 (m, 2H), 1.66 (m, 2H), 1.43 (m, 2H).

1-Bromo-5-(3-cyanophenoxy)pentane

Prepared according to general method D from 3-hydroxybenzonitrile.– ^{1}H NMR ($CDCl_3$) δ = 7.36 (dd, 7.5 and 7.2 Hz, 1H), 7.23 (ddd, 7.6 and 1.2 and 1.2 Hz, 1H), 7.13 (m, 2H), 3.98 (t, 6.3 Hz, 2H), 3.45 (t, 6.7 Hz, 2H), 1.92 (m, 2H), 1.84 (m, 2H), 1.64 (m, 2H).

*1-[5-(3-Cyanophenoxy)pentyl]pyrrolidine oxalate (**35**)*

Prepared according to general method C from 1-bromo-5-(3-cyanophenoxy)pentane.– ^{1}H NMR (DMSO d_6) δ = 7.49 (dd, 7.8 and 7.9 Hz, 1H), 7.40 (m, 2H), 7.28 (m, 1H), 4.05 (t, 6.4 Hz, 2H), 3.23 (br, 2×2H), 3.10 (m, 2H), 1.92 (br, 2×2H), 1.77 (m, 2H), 1.69 (m, 2H), 1.45 (m, 2H).

Pharmacology. General Procedures

In vitro

Compounds were tested for their potencies as histamine H_3-receptor antagonists in an assay using K^+-evoked depolarization-induced release of [^{3}H] histamine from synaptosomes of rat cerebral cortex as described [33].

In vivo

The compounds were tested *in vivo* by administration as the salt form indicated in Table 2 as a suspension in 1% methylcellulose *per os* to groups of at least six male Swiss mice (weighing 18–22g) as described [33].

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