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Piperidine-containing histamine H_3 receptor antagonists of the carbamate series: the alkyl derivatives

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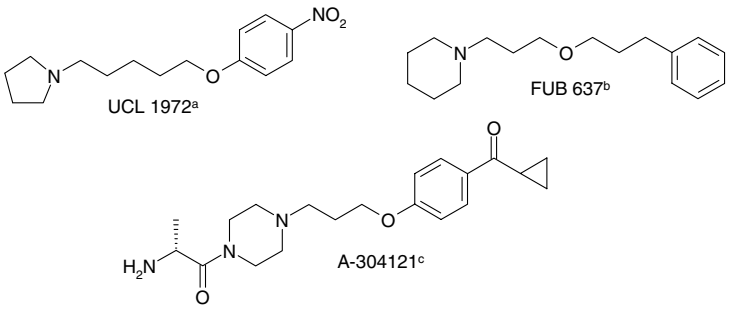
A series of *N*-alkyl urethanes, potential histamine H_3 receptor antagonists, was prepared. Carbamate derivatives were synthesized from appropriate isocyanates and *N*-piperidinoalkan-1-ols. The novel compounds were evaluated for histamine H_3 receptor activity *in vitro* on the guinea pig ileum. Some selected compounds were tested *in vivo* after p.o. application to mice and *in vitro* for selectivity towards other histamine receptors (H_1, H_2) in functional assays in the guinea pig. The most potent H_3 receptor antagonist *in vitro* was compound **14** ($pA_2 = 7.2$). Compound **14** was equipotent at M_3 receptors and lacked H_3 receptor activity *in vivo*. Predictions of octanol-water partition coefficient (Pallas) and metabolic fate (MetabolExpert, METEOR) were used to explore potential reasons for this absence of *in vivo* activity.

1. Introduction

The histamine H_3 receptor has been known since 1983 (Arrang et al. 1983). The first potent and highly selective ligands (agonists, partial agonists and antagonists) were described in 1987, establishing the pharmacological identity of the receptor (Arrang et al. 1987). Since that time a lot of potent histamine H_3 receptor antagonists have been prepared. Most of them are derived from histamine itself and contain a mono-substituted 4(5)-imidazole moiety. Recently, a new class of H_3 receptor antagonists was synthesized which lacks the formerly thought essential imidazole moiety. In 1998 Ganellin et al. described the first potent non-imidazole compounds. Their systematic structure-activ-



[a] Ganellin et al. (1998); [b] Meier et al. (2001); [c] Faghih et al. (2002a and 2002b)

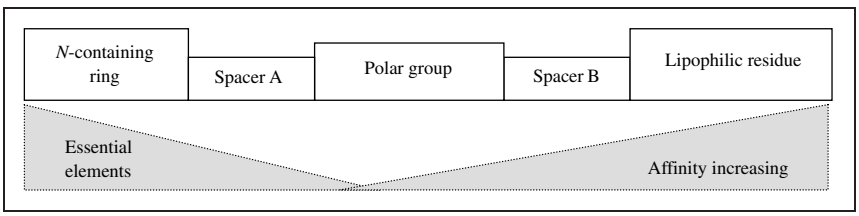
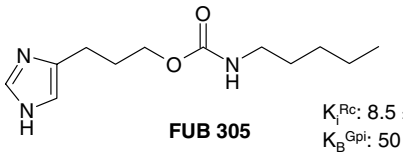


Fig. 1:
General construction pattern of many potent histamine H_3 receptor antagonists (Lipp et al. 1992)



FUB 305

K_i^{Rc}: 8.5 ± 1.7 (nM)
K_B^{Gpi}: 50 (nM)
ED_{50}^{Mbc}: 0.69 ± 0.37 (mg/kg)

[a] Sasse et al. (1999a); Rc = rat cortex; Gpi = guinea-pig ileum; Mbc = mice brain cortex

ity survey resulted in the discovery of UCL 1972, a pyrrolidine derivative. A piperidine ring instead of an imidazole ring seems also to be favourable (Ganellin et al. 1998; Meier et al. 2001). Recently, piperazine compounds were described as potent *in vitro* H_3 receptor antagonists, e.g. A-304121 (Faghih et al. 2002a, 2002b).

In our search for non-imidazole histamine H_3 receptor ligands, we synthesized compounds fitting to a general construction pattern suggested for H_3 receptor antagonists. A piperidine ring works as a nitrogen containing heterocycle – the essential part for receptor affinity (Lipp et al. 1992) (Fig. 1). In our previous studies we described *N*-aromatic and *N*-alkyl-aromatic urethanes, derivatives of piperidine (Łażewska et al. 2001, 2002).

The present work was focused on the synthesis and pharmacological *in vitro* evaluation of *N*-alkylcarbamates. Imidazole containing *N*-alkylurethanes were recently described as potent *in vitro* and *in vivo* H_3 receptor antagonists or partial agonists (Sasse et al. 1999a, 1999b). Compound FUB 305 was chosen as a lead structure for our studies. Sasse et al. (1999a) synthesized the series of compounds with the straight chain of which compound FUB 305 achieved one of the highest *in vivo* potencies. Many other alkyl derivatives were also potent, showing ED_{50} values of about 1 mg/kg p.o. Their *in vitro* potencies increased with elongation of the carbon skeleton reaching a maximum with a heptyl chain. (K_B^{Gpi}: 7.3 nM; K_i^{Rc}: 4.1 nM). Hence, these carbamates seem promising leads for further development. Branched *N*-alkylcarbamates (Sasse et al. 1999b) were even more interesting compounds as some of them showed partial to full agonist activity *in vivo* after p.o. application to mice.

Whilst our work was in progress, Meier et al. (2001) described a piperidine analogue of FUB 305. This compound turned out to be a moderate H_3 receptor antagonist *in vitro* in guinea pig ileum (pA_2: 6.3) but was not active *in vivo* ($ED_{50} > 10$ mg/kg). These results are in accordance with our observations.

A series of (branched) *N*-alkylcarbamates was synthesized. The compounds were tested *in vitro* on the guinea pig ileum for histamine H_3 receptor activity and some of them for *in vivo* potency. The selectivity for other receptors (histamine – H_1, H_2 and muscarinic M_3) was also evaluated. For final compounds **2**–**19** the octanol-water partition coefficient (log P) values were calculated using the Pallas program. We also predicted potential metabolites for compound **14** using the MetabolExpert and METEOR programs [MetabolExpert 2003, METEOR 2002].

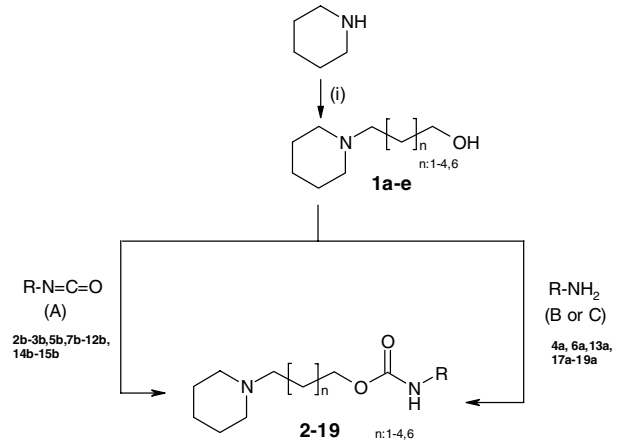
2. Investigations, results and discussion

2.1. Chemistry

Target molecules **2**–**19** were prepared as shown in Scheme 1 and Scheme 2. *N*-piperidinoalcan-1-ols **1a**–**1e** were obtained from piperidine and the corresponding halogenoalkanols by methods described previously (Łażewska et al. 2001). 2-Nonylamine (**17a**) was synthesized from 2-nonanol by a Mitsunobu-type reaction (Mitsunobu 1981). Carbamates **2**–**15**, **17**–**19** were synthesised by standard methods depending on the addition of the appropriate isocyanate to the alcohol. The non-commercially available isocyanates (**4b**, **6b**, **13b**, **17b**–**19b**) were obtained either by refluxing the corresponding amines **4a**, **6a**, **13a**, **17a**–**19a** with an excess of trichloromethyl chloroformate (diphosgene) (Katakai and Iizuka 1985) or using di-*tert*-butyl dicarbonate in the presence of 4-(dimethylamino)pyridine (DMAP) (Knölker and Braxmeier 1996). The ether **16** was prepared under solvent-free conditions using microwave irradiation (Bogdał et al. 1998). The reaction was carried out by mixing the alcohol **1a** with 50% excess of 1-bromooctane and a catalytic amount of tetrabutylammonium bromide (TBAB) (Scheme 2). The mixture was absorbed on a mixture of potassium carbonate and potassium hydroxide and then irradiated in an open vessel in a domestic microwave oven.

Compounds were purified by column chromatography and isolated as hydrogen oxalates. Their purity was checked by TLC and structures were confirmed by standard spectral techniques (^{1}H NMR, MS, IR) (Table 1) and elemental analysis. Structural and physicochemical data are given in Table 2.

Scheme 1



(i) $Cl-CH_2-(CH_2)_n-CH_2OH$, K_2CO_3, MeCN, reflux, n: 1–4, 6
(A) MeCN, reflux
(B) (**17a**–**19a**) diphosgene, AcOEt, 5h reflux; MeCN, alcohol (**1a**), reflux
(C) (**4a**, **6a**, **13a**) $(Boc)_2O$, DMAP, rt; alcohol (**1a**, **1c**), reflux

Scheme 2

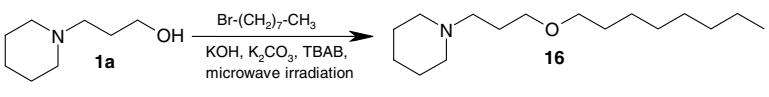


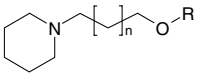
Table 1: MS, IR, ^{1}H NMR spectral data of compounds 2–19

Compd.	MS (70 eV) m/z (%)	IR (KBr) ν (cm^{-1})	^{1}H-NMR ([D_6]DMSO) δ (ppm)
2	242([M•]$^+$, 5), 142 ([Pip-CH_2)$_3$O$^+$], 7), 126 (4), 99 (10), 98([Pip-CH_2^+], 100), 84 ([Pip$^+$], 11), 57 (5), 55 (4), 46 (7), 45 (11), 42 (9), 41 (10);	1720s (ν [C=O])	6.86 (s, 1 H, CONH), 3.93 (t, J = 6.2 Hz, 2 H, CH_2O),), 3.16–2.97 (m, 6 H, Pip-2,6-H + Pip-CH_2), 1.92 (qu, J = 6.5 Hz, 2H, Pip-CH_2−CH_2), 1.80–1.63 (m, 4 H, Pip-3,5-H), 1.52 (br s, 2 H, pip-4-H), 1.21 (s, 9 H, C(CH_3)$_3$)
3	228 ([M•]$^+$, 3), 142 ([Pip-CH_2)$_3$O$^+$], 2), 99 (7), 98 ([Pip-CH_2^+], 100), 84 ([Pip$^+$], 6), 55 (5), 43 (5), 42 (8), 41 (11);	1728s (ν [C=O])	δ 7.13 (t, J = 5.3 Hz, 1 H, CONH*), 3.97 (t, J = 6.3 Hz, 2 H, CH_2O), 3.06 (br s, 2 H, CONH−CH_2), 3.01–2.95 (m, 4 H, Pip-2,6-H), 2.92 (t, J = 6.7 Hz, 2 H, Pip-CH_2), 1.97–1.85 (qu, J = 7.5 Hz, 2H, Pip-CH_2−CH_2), 1.73–1.70 (m, 4 H, Pip-3,5-H), 1.51 (br s, 2 H, Pip-4-H), 1.44–1.35 (sek, J = 7.2 Hz, 2 H, CH_2−CH_3), 0.83 (t, J = 7.4 Hz, 3 H, CH_3);
4	256([M•]$^+$, 4), 227 (5), 142([Pip-CH_2)$_3$O$^+$], 7), 126 (5), 99 (7), 98 ([Pip-CH_2^+], 100), 84 ([Pip$^+$], 9), 55 (4), 45 (6), 41 (7);	1720s (ν [C=O])	6,73 (s, 1 H, CONH), 3,93 (t, J = 6,3 Hz, 2 H, CH_2O),), 3,07 (br s, 2 H, Pip-CH_2), 3,01–2,97 (m, 4 H, Pip-2,6-H), 1,92 (qu, J = 6,5 Hz, 2H, Pip-CH_2−CH_2), 1,78–1,65 (m, 4 H, Pip-3,5-H), 1,60–1,55 (q, J = 7,5 Hz, 2 H, CH_2−CH_3), 1,52 (s, 2 H, Pip-4-H), 1,11 (s, 6 H, (CH_3)$_2$), 0,76 (t, J = 7,5 Hz, 3 H, CH_3);
5	242([M•]$^+$, 3), 142 ([Pip-CH_2)$_3$O$^+$], 3), 99 (7), 98 ([Pip-CH_2^+], 100), 84 ([Pip$^+$], 7), 55(4), 45 (6), 41 (8);	1731s (ν [C=O])	7.10* (s, 1 H, CONH*), 3.97 (t, J = 6.3 Hz, 2 H, CH_2O), 3.13–3.01 (br s, 2 H, CONH−CH_2), 3.01–2.86 (m, 6 H, Pip-2,6-H + Pip-CH_2), 1.92 (qu, J = 7.6 Hz, 2 H, PipCH$_2$-CH_2), 1.76–1.62 (m, 4 H, Pip-3,5-H), 1.51 (br s, 2 H, Pip-4-H), 1.37 (qu, J = 7.2 Hz, 2 H, CONH−CH_2−CH_2), 1.32–1.18 (sek, J = 7.6 Hz, 2 H, CH_2−CH_3), 0.86 (t, J = 7.2 Hz, 3 H, CH_3);
6	270([M•]$^+$, 3), 142 ([Pip-CH_2)$_3$O$^+$], 3), 126 (4), 99 (7), 98 ([Pip-CH_2^+], 100), 84 ([Pip$^+$], 8), 57 (3), 55 (4), 45 (3), 42 (5), 41 (9);	1712s (ν [C=O])	7.06 (s, 1 H, CONH*), 3.97 (t, J = 6,2 Hz, 2 H, CH_2O), 3.22–2.83 (m, 8 H, Pip-2,6-H + Pip-CH_2 + CONH−CH_2), 2.01–1.81 (m, 2 H, Pip-CH_2−CH_2), 1.81–1.61 (m, 4 H, Pip-3,5-H), 1.52 (br s, 2 H, Pip-4-H), 1.38–1.26 (m, 2 H, CH_2−C(CH_3)$_3$), 0.88 (s, 9 H, C(CH_3)$_3$);
7	298([M•]$^+$, 4), 227 (11), 142 ([Pip-CH_2)$_3$O$^+$], 8), 126 (8), 99 (7), 98 ([Pip-CH_2^+], 100), 84 ([Pip$^+$], 12), 57 (7), 55 (4), 45 (7), 42 (8), 41 (9);	1714s (ν [C=O])	6.78 (s, 1 H, CONH*), 3.94 (t, J = 6.2 Hz, 2 H, CH_2O), 3.27–2.82 (m, 6 H, Pip-2,6-H + Pip-CH_2), 1.91 (def qu, 2H, Pip-CH_2−CH_2), 1.80–1.65 (m, 4 H, Pip-3,5-H), 1.63 (s, 2 H, CH_2−C(CH_3)$_3$), 1.52 (br s, 2 H, Pip-4-H), 1.25 (s, 6 H, C(CH_3)$_2$), 0.94 (s, 9 H, C(CH_3)$_3$);
8	270([M•]$^+$, 2), 142 ([Pip-CH_2)$_3$O$^+$], 3), 99 (7), 98 ([Pip-CH_2^+], 100), 84 ([Pip$^+$], 8), 55(4), 45 (6), 41 (7);	1693s (ν [C=O])	7.11 (s, 1 H, CONH*), 3.97 (t, J = 6.1 Hz, 2 H, CH_2O), 3.05 (br s, 2 H, CONH−CH_2), 3.01–2.84 (m, 6 H, Pip-CH_2 + Pip-2,6-H), 1.93 (def qu, 2 H, Pip-CH_2−CH_2), 1.78–1.64 (m, 4 H, Pip-3,5-H), 1.51 (br s, 2 H, Pip-4-H), 1.44–1.31 (m, 2 H, CH_2−CH_3), 1.31–1.15 (m, 6 H, (CH_2)$_3$−CH_2CH_3), 0.86 (t, J = 7.0 Hz, 3 H, CH_3);
9	312([M•]$^+$, 2), 241 (3), 168 (3), 99 (7), 98 ([Pip-CH_2^+], 100), 85 (3), 84 ([Pip$^+$], 3), 55 (5), 43 (4), 41 (5);	1691s (ν [C=O])	10.2 (br s, 1 H, Pip-NH^+), 7.03 (s, 1 H, CONH), 3.94 (t, J = 6.6 Hz, 2 H, CH_2O), 3.36–3.13 (m, 4 H, Pip-2,6-H_e + CONH−CH_2), 3.12–2.88 (m, 4 H, Pip-2,6-H_a + Pip-CH_2), 2.83 (m, 2 H, CH_2−CH_2O), 1.99–1.78 (m, 3 H, Pip-CH_2−CH_2 + Pip-4-H_e), 1.72–1.62 (m, 2 H, Pip-3,5-H_e), 1.62–1.48 (m, 2 H, Pip-3,5-H_a), 1.47–1.36 (m, 3 H, Pip-4-H_a + $NHCH_2$−CH_2), 1.36–1.30 (m, 4 H, Pip(CH_2)$_2$−(CH_2)$_2$), 1.30–1.05 (m, 6 H, (CH_2)$_3$−CH_3), 0.88 (t, J = 7.0 Hz, 3 H, CH_3);
10	284([M•]$^+$, 2), 142 ([Pip-CH_2)$_3$O$^+$], 3), 99 (7), 98 ([Pip-CH_2^+], 100), 84 ([Pip$^+$], 8), 55(5), 45 (4), 41 (9);	1697s (ν [C=O])	7.10* (t, J = 5.4 Hz, 1 H, CONH*), 3.97 (t, J = 6.3 Hz, 2 H, CH_2O), 3.07 (br s, 2 H, CONH−CH_2), 3.02–2.89 (m, 6 H, Pip-CH_2 + Pip-2,6-H), 1.92 (qu, J = 7.1 Hz, 2 H, Pip-CH_2−CH_2), 1.79–1.59 (m, 4 H, Pip-3,5-H), 1.52 (br s, 2 H, Pip-4-H), 1.43–1.32 (m, 2 H, CH_2−CH_3), 1.32–1.16 (m, 8 H, (CH_2)$_4$−CH_2CH_3), 0.86 (t, J = 7.0 Hz, 3 H, CH_3);
11	298([M•]$^+$, 2), 142 ([Pip-CH_2)$_3$O$^+$], 3), 126 (2), 99 (8), 98 ([Pip-CH_2^+], 100), 84 ([Pip$^+$], 8), 55(5), 41 (9);	1694s (ν [C=O])	7.10* (t, J = 5.5 Hz, 1 H, CONH*), 3.97 (t, J = 6.3 Hz, 2 H, CH_2O), 3.05 (br s, 2 H, CONH−CH_2), 3.01–2.88 (m, 6 H, Pip-CH_2 + Pip-2,6-H), 1.94 (qu, J = 7.3 Hz, 2 H, Pip-CH_2−CH_2), 1.77–1.61 (m, 4 H, Pip-3,5-H), 1.51 (br s, 2 H, Pip-4-H), 1.43–1.31 (m, 2 H, CH_2−CH_3), 1.31–1.10 (m, 10 H, (CH_2)$_5$−CH_2CH_3), 0.86 (t, J = 7.0 Hz, 3 H, CH_3)
12	312([M•]$^+$, 2), 140 (5), 99 (7), 98 ([Pip-CH_2^+], 100), 84 ([Pip$^+$], 4), 55(5), 45 (3), 41 (6)	1697s (ν [C=O])	7.04* (def t, 1 H, CONH*), 3.94 (t, J = 6.2 Hz, 2 H, CH_2O), 3.29–2.96 (m, 8 H, CONH−CH_2 + Pip-CH_2 + Pip-2,6-H), 1.80–1.61 (m, 6 H, Pip-CH_2−(CH_2)$_2$ + CONH−CH_2−CH_2), 1.61–1.44 (m, 4 H, Pip-3,5-H), 1.44–1.31 (m, 2 H, Pip-4-H), 1.31–1.13 (m, 10 H, −(CH_2)$_5$−CH_3), 0.86 (t, J = 6.9 Hz, 3H, CH_3);
13	326([M•]$^+$, 2), 154 (7), 99 (7), 98 ([Pip-CH_2^+], 100), 84 ([Pip$^+$], 4), 55(4), 44 (5), 41 (7);	1691s (ν [C=O])	7,01* (def t, 1 H, CONH*), 3,92 (t, J = 6,5 Hz, 2H, CH_2O), 3,06 (br s, 2 H, CONH−CH_2), 2,98–2,88 (m, 6 H, Pip-CH_2 + Pip-2,6-H), 1,78–1,66 (m, 4 H, Pip-CH_2−CH_2 + CONH−CH_2−CH_2), 1,66–1,60 (m, 2 H, Pip-(CH_2)$_3$−CH_2), 1,60–1,43 (m, 4 H, Pip-3,5-H), 1,43–1,33 (m, 2 H, Pip-4-H), 1,33–1,27 (m, 2 H, CH_2−CH_3), 1,27–1,11 (m, 10 H, Pip-(CH_2)$_2$−CH_2 + −(CH_2)$_4$−CH_2CH_3), 0,86 (t, J = 7,0 Hz, 3H, CH_3);
14	340([M•]$^+$, 1), 241 (2), 168 (4), 99 (7), 98 ([Pip-CH_2^+], 100), 86 (3), 85 (4), 84 ([Pip$^+$], 2), 55 (4), 41 (4);	1693s (ν [C=O])	12.12 (br s, 1 H, Pip-NH^+), 4.85 (s, 1 H, CONH), 4.03 (t, J = 5.7 Hz, 2 H, CH_2O), 3.64–3.39 (m, 2 H, Pip-2,6-H_e), 3.27–3.05 (m, 2 H, CONH−CH_2), 2.97–2.80 (m, 2 H, Pip-CH_2), 2.68–2.50 (m, 2 H, Pip-2,6-H_a) 2.42–2.22 (m, 2 H, CH_2−CH_2O), 1.99–1.75 (m, 5 H, Pip-CH_2−CH_2 + CONH−CH_2−CH_2 + Pip-4-H_e), 1.75–1.52 (m, 4 H, Pip-3,5-H), 1.52–1.43 (m, 1 H, Pip-4-H_a), 1.43–1.35 (m, 4 H, Pip(CH_2)$_2$−(CH_2)$_2$), 1.34–1.12 (m, 10 H, (CH_2)$_5$−CH_3), 0.88 (t, J = 6.8 Hz, 3 H, CH_3);
15	368([M•]$^+$, 5), 269 ([M$^+$-pipCH_3], 3), 196 ([pip(CH_2)$_8^+$], 3), 99 (7), 98 ([pip-CH_2^+], 100), 85 (3), 55(5), 41 (4);	1696s (ν [C=O])	7,00* (t, J = 5,2 Hz, 1 H, CONH*), 3,91 (t, J = 6,6 Hz, 2 H, CH_2O), 3,38–2,80 (m, 8 H, CONH−CH_2 + Pip-CH_2 + Pip-2,6-H), 1,81–1,67 (m, 4 H, Pip-CH_2−CH_2 + CONH−CH_2−CH_2), 1,67–1,57 (m, 2 H, Pip-(CH_2)$_6$−CH_2), 1,57–1,42 (m, 4 H, Pip-3,5-H), 1,42–1,32 (m, 2 H, Pip-4-H), 1,32–1,19 (m, 18 H, Pip-(CH_2)$_2$−(CH_2)$_4$ + −(CH_2)$_5$−CH_3), 0,86 (t, J = 7,0 Hz, 3 H, CH_3);

Table 1 (continued)

Compd.	MS (70 eV) m/z (%)	IR (KBr) ν (cm^{-1})	^{1}H-NMR ([D_6]DMSO) δ (ppm)
16	255 ([M•]$^+$, 1), 142 ([Pip-CH_2)$_3$O$^+$], 20), 127 (3), 99 (9), 98 ([Pip-CH_2^+], 100), 84 ([Pip$^+$], 5), 55 (5), 45 (5), 41 (7);	1114s (ν [C−O−C])	3.39 (t, J = 6.0 Hz, 2 H, CH_2O), 3.34 (t, J = 6.6 Hz, 2 H, OCH_2), 3.28–3.02 (br, 4 H, Pip-2,6-H), 3.02–2.94 (m, 2 H, Pip-CH_2), 1.95–1.79 (m, 2 H, Pip-CH_2−CH_2), 1.79–1.59 (m, 4 H, Pip-3,5-H), 1.59–1.36 (m, 4 H, Pip-4-*H* + OCH_2CH_2), 1.36–1.14 (m, 10 H, $(CH_2)_5CH_3$), 0.86 (t, J = 7.0 Hz, 3 H, CH_3);
17	312([M•]$^+$, 2), 213 ([M$^+$-Pip-CH_3], 3), 142 ([Pip-CH_2)$_3$O$^+$], 4), 126 ([Pip$(CH_2)_3^+$], 3), 99 (7), 98 ([Pip-CH_2^+], 100), 84 ([Pip$^+$], 10), 55(4), 41 (6);	1701s (ν [C=O])	6,95* (d, J = 8,2 Hz, 1 H, CONH*), 3,97 (def t, 2 H, CH_2O), 3,45 (m, 1 H, NH−C*H*(CH_3)), 3,15–2,87 (m, 6 H, Pip-CH_2 + Pip-2,6-H), 1,92 (def qu, 2 H, Pip-CH_2−C*H*$_2$), 1,79–1,61 (m, 4 H, Pip-3,5-H), 1,52 (br s, 2 H, Pip-4-H), 1,45–1,30 (m, 2 H, CH_2−CH_3), 1,30–1,13 (m, 10 H, $(CH_2)_5$−CH_2CH_3), 1,01 (d, J = 6,5 Hz, 3 H, CH(CH_3)), 0,86 (t, J = 7,0 Hz, 3 H, CH_3);
18	312([M•]$^+$, 2), 142 ([Pip-CH_2)$_3$O$^+$], 3), 99 (8), 98 ([Pip-CH_2^+], 100), 84 ([Pip$^+$], 9), 55(4), 45 (6), 41 (6);	1693s (ν [C=O])	7,11* (t, J = 5,4 Hz, 1 H, CONH*), 3,98 (t, J = 6,2 Hz, 2 H, CH_2O), 3,34 (br s, 2 H, CONH−CH_2), 3,07–2,91 (m, 6 H, Pip-CH_2 + Pip-2,6-H), 1,97 (def qu, 2 H, Pip-CH_2−C*H*$_2$), 1,80–1,66 (m, 4 H, Pip-3,5-H), 1,59 (br s, 2 H, Pip-4-H), 1,44–1,31 (m, 2 H, C*H*$_2$−CH_3), 1,31–1,11 (m, 12 H, $(CH_2)_6$−CH_2CH_3), 0,86 (t, J = 7,0 Hz, 3 H, CH_3);
19	326([M•]$^+$, 2), 142 ([Pip-CH_2)$_3$O$^+$], 3), 99 (9), 98 ([Pip-CH_2^+], 100), 84 ([Pip$^+$], 10), 55(4), 45 (5), 41 (7);	1693s (ν [C=O])	7,10* (s, 1 H, CONH*), 3,98 (def t, 2 H, CH_2O), 3,23 (br s, 2 H, CONH−CH_2), 3,07–2,85 (m, 6 H, Pip-CH_2 + Pip-2,6-H), 1,95 (def qu, 2 H, PipCH$_2$-C*H*$_2$), 1,81–1,63 (m, 4 H, Pip-3,5-H), 1,53 (br s, 2 H, Pip-4-H), 1,44–1,31 (m, 2 H, C*H*$_2$−CH_3), 1,31–1,14 (m, 14 H, $(CH_2)_7$−CH_2CH_3), 0,86 (t, J = 6,9 Hz, 3 H, CH_3)

Table 2: Structure and physicochemical data of compounds 2–19



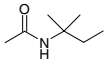
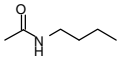
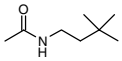
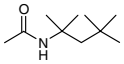
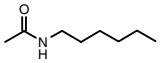
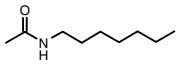
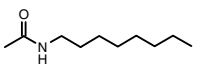
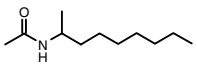
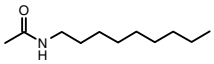
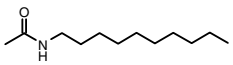
Compd.	n	R	Formula	Molecular Weight	M.p. (°C)	Yield (%)
2	1		$C_{13}H_{26}N_2O_2 \times C_2H_2O_4$	332.40	145–146	61
3	1		$C_{12}H_{24}N_2O_2 \times C_2H_2O_4$	318.38	121–123	40
4	1		$C_{14}H_{28}N_2O_2 \times C_2H_2O_4$	346.43	143–145	32
5	1		$C_{13}H_{26}N_2O_2 \times C_2H_2O_4$	332.40	138–139	34
6	1		$C_{15}H_{30}N_2O_2 \times C_2H_2O_4 \times 0{,}5\ H_2O$	369.47	115–117	8
7	1		$C_{17}H_{34}N_2O_2 \times C_2H_2O_4 \times 0{,}2\ H_2O$	392.12	126–128	51
8	1		$C_{15}H_{30}N_2O_2 \times C_2H_2O_4 \times 0{,}1\ H_2O$	362.26	82–86	37
9	4		$C_{18}H_{36}N_2O_2 \times HCl \times 0.5\ H_2O$	357.98	75–78	18
10	1		$C_{16}H_{32}N_2O_2 \times C_2H_2O_4 \times 0{,}25\ H_2O$	378.99	87–91	25
11	1		$C_{17}H_{34}N_2O_2 \times C_2H_2O_4$	388.51	88–91	64
12	2		$C_{18}H_{36}N_2O_2 \times C_2H_2O_4 \times 0{,}2\ H_2O$	406.14	74–80	26
13	3		$C_{19}H_{38}N_2O_2 \times C_2H_2O_4$	416.57	100–102	12
14	4		$C_{20}H_{40}N_2O_2 \times HCl \times 0.5\ H_2O$	386.02	88–92	25
15	6		$C_{22}H_{44}N_2O_2 \times C_2H_2O_4 \times 0{,}75\ H_2O$	472.17	76–82	14
16	1		$C_{16}H_{33}NO \times C_2H_2O_4 \times 0.2\ H_2O$	349.09	106–107	9
17	1		$C_{18}H_{36}N_2O_2 \times C_2H_2O_4$	402.54	92–95	20
18	1		$C_{18}H_{36}N_2O_2 \times C_2H_2O_4 \times 2\ H_2O$	438.58	91–94	30
19	1		$C_{19}H_{38}N_2O_2 \times C_2H_2O_4 \times 0{,}5\ H_2O$	425.58	90–93	19

Table 3: *In vitro* antagonist activities of compounds at histamine receptor subtypes (H_3, H_2, H_1) and muscarinic M_3 determined on functional models and *in vivo* H_3 potency

Compd.	H_3[a] pA_2 (95% conf. limit)	H_3[b] ED_{50} mg/kg p.o.	M_3[c] $pA_2 \pm$ SEM	H_1[d] $pA_2 \pm$ SEM	H_2[e] $pD_2' \pm$ range
2	5.27 (4.80–5.68)	nt	4.11 ± 0.12	4.51 ± 0.13	4.08 ± 0.12
3	5.42 (5.00–5.75)	nt	3.76 ± 0.04	4.34 ± 0.04	3.87 ± 0.24
4	5.28 (5.01–5.49)	nt	4.56 ± 0.06	4.30 ± 0.11	4.31 ± 0.11
5	5.67 (5.54–5.80)	nt	4.34 ± 0.08	4.45 ± 0.06	3.75 ± 0.08
6	6.29 (6.04–6.51)	nt	4.89 ± 0.04	4.87 ± 0.10	4.78 ± 0.15
7	5.63 (5.08–5.97)	nt	4.95 ± 0.05	4.85 ± 0.05	4.61 ± 0.02
8	6.28 (5.95–6.56)	>10	4.87 ± 0.03	4.91 ± 0.05	5.09 ± 0.19
9	6.54 (6.07–6.84)	>10	6.01 ± 0.06	5.63 ± 0.04	5.39 ± 0.02
10	6.28 (6.00–6.51)	nt	5.24 ± 0.07	5.27 ± 0.03	5.50 ± 0.15
11	6.41 (5.80–6.75)	nt	5.68 ± 0.04	5.55 ± 0.04	*5.61 ± 0.08
12	6.44 (5.97–6.71)	nt	6.35 ± 0.02	6.05 ± 0.06	5.95 ± 0.20
13	6.70 (6.24–6.96)	nt	6.81 ± 0.06	5.91 ± 0.27	5.97 ± 0.10
14	7.16 (6.52–7.49)	>10	7.02 ± 0.06	6.22 ± 0.04	5.63 ± 0.08
15	≤ 7.0	nt	7.11 ± 0.09	6.16 ± 0.04	5.30 ± 0.06
16	6.77 (6.59–6.92)	nt	6.10 ± 0.05	5.74 ± 0.03	5.12 ± 0.05
17	5.78 (5.24–6.08)	nt	5.53 ± 0.03	5.74 ± 0.07	5.75 ± 0.05
18	6.46 (6.04–6.79)	nt	5.85 ± 0.07	6.01 ± 0.06	$5.84 \pm 0,22$
19	6.69 (6.58–6.80)	nt	6.41 ± 0.05	6.17 ± 0.04	5.86 ± 0.25

[a] H_3 receptor assay on guinea-pig ileum; [b] Central H_3 receptor screening *in vivo* after p.o. administration to mice; [c] M_3 receptor assay on guinea-pig ileum; [d] H_1 receptor assay on guinea-pig ileum; [e] H_2 receptor assay on guinea pig atrium; nt = not tested
* pA_2 value

2.2. Pharmacological results and discussion

2.2.1. In vitro and in vivo potencies

Novel compounds were tested *in vitro* in the isolated guinea pig ileum. In order to avoid blocking of ileal M_3 receptors, compounds firstly needed to be screened for their potencies at muscarinic M_3 receptors (Table 3). Then they were tested in concentrations not blocking M_3 receptors. Compounds **8, 9, 14** were also screened for their modulating effect *in vivo* on mice brain cortex after p.o. administration, thereby measuring the level of the main metabolite of histamine in the CNS: N^{τ}-methylhistamine (N^{τ}-MeHA). Since the activation of the histamine H_3 autoreceptor inhibits the synthesis and release of histamine, antagonists increase the level of N^{τ}-MeHA. All compounds were evaluated for their antagonist activity at histamine H_1 and H_2 receptors in functional tests on isolated guinea pig tissues.

In the 3-piperidinopropan-1-ol series **2**–**8**, **10**–**11**, **17**–**19**, the short chain (propyl, butyl) and α,α-dibranched derivatives display weak antagonist potencies *in vitro*. Elongation of the carbon chain leads to a slight increase of H_3 antagonist potency from pA_2 – values of 5.27 (**2**) to 6.69 (**19**). This is accompanied by an increase in antagonist activity at other receptors especially muscarinic M_3 and histamine H_1 (e.g. compare results for **3** with **10** and **19**) (Table 3).

Branching in the α-position led to a decrease of H_3 receptor potency (**7** vs **6**, **17** vs **11**). *N*-octyl carbamate derivatives **11**–**15** showed moderate (**11**–**13**) to good (**14**, **15**) *in vitro* potencies. For compound **15** the exact measurement could not be performed due to the comparably high antimuscarinic activity ($pA_2 = 7.11$). In this series a gradual increase in *in vitro* potency was also observed as the length of the spacer between the piperidino and carbamate moieties (spacer A) increases. Based on the first series (**2**–**8**, **10**–**11**, **17**–**19**) and previous results (Łażewska et al. 2001), elongation of the spacer A was expected to increase antagonist potency at other tested receptors (mostly muscarinic M_3). The results are in agreement with expectations. The most active compound in this series (**14**) shows both good M_3 receptor and moderate histamine H_1 receptor antagonist activities.

Unfortunately, compounds tested *in vitro* (**8**, **9**, **14**) lacked *in vivo* potency. The introduction of the ether moiety instead of the carbamate one (**16** vs **11**) did not influence the *in vitro* potency; only a slightly positive effect was observed.

2.2.2. Physicochemical properties

2.2.2.1. Octanol-water partition coefficient

Calculated log P values from Pallas for the free-base analogues are presented in Table 4. (They were not verified with experimental data and are just theoretical considerations.) Values of log P are in the range 1.81–6.91. Lipophilicity was influenced by the elongation of the carbon chain both in the spacer A and the lipophilic residue

Table 4: Calculated octanol-water partition coefficients for compounds 2–19

Compd.	log P (Pallas 1.2)
2	2.09
3	1.81
4	2.60
5	2.32
6	2.94
7	3.72
8	3.34
9	4.87
10	3.85
11	4.36
12	4.87
13	5.38
14	5.89
15	6.91
16	4.87
17	4.90
18	4.87
19	5.38

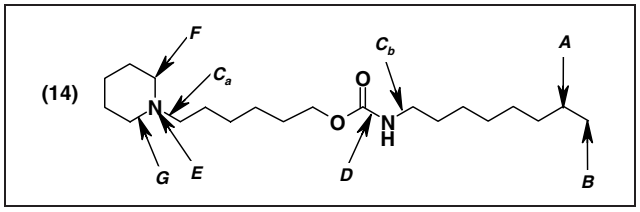


Fig. 2: The possible sites of metabolism of compound **14** predicted by the METEOR and MetabolExpert programs

(Fig. 1). An increased number of carbons led to increased lipophilicity. Identical values were predicted for carbamates **13** and **19** (log P: 5.38); **9**, **12** and **18** and the ether **16** (log P: 4.87). This program (Pallas with module PrologP 5.1) uses two data bases: CDR (26,7%) with Rekkers' coefficients (Rekker 1977) and ATOMIC5 (73,3%) based on Ghose's work (Ghose and Crippen 1986).

It is well known that compounds expected to act in the CNS tissues should possess a log P value of 2 to 2.5 (Hacksell et al. 1996). Compounds tested *in vivo* (**8**, **9** and **14**) have log P values much higher than the expected log P value of about 2. However, the log P values for these compounds may not provide the only explanation for their inactivity *in vivo*.

2.2.2.2. In silico metabolites

Phase I metabolites were predicted for compound **14** using the METEOR and MetabolExpert programs. The possible sites of metabolism identified by the two programs are presented in Fig. 2. They are products of: hydroxylation of the penultimate alkyl group (**A**), hydroxylation of the terminal group (ω-oxidation) (**B**) [further oxidation of the alcohol may occur yielding the corresponding acid], oxidative N-dealkylation ($\mathbf{C_a}$, $\mathbf{C_b}$), hydrolysis of the carbamate residue (**D**), N-oxidation (**E**), lactam formation (**F**) and ring-cleavage (**G**).

The occurrence of the predicted reactions is summarised in Table 5. The METEOR program limited to phase I biotransformations, but otherwise using default processing constraints, did not predict reactions **E**, **F** and **G**. Reaction **E** was discounted on the basis that the level of confidence in its occurrence was only "equivocal" (that is, below, the "plausible" level of confidence required by default for a biotransformation to be displayed). Whilst confidence in the biotransformations corresponding to pathways **F** and **G** were considered "plausible" and "probable" respectively, under default processing constraints these were also discounted on the basis that they were less likely to occur than **A** or **B** and $\mathbf{C_a}$ or $\mathbf{C_b}$ respectively. The MetabolExpert program did not predict carbamate hydrolysis (**D**) or oxidative deamination of the carbamate group (C_b). Hydrolysis of carbamates is likely to occur. An important example is loratidine, a potent H_1 receptor antagonist, which is metabolized to descarboxyethoxyloratadine (also a potent H_1 receptor antagonist). There is evidence that the formation of this metabolite, in human liver microsomes, is catalyzed by cytochrome P_{450}, primarily with the CYP3A4 and CYP2D6 isozymes (Yunibe et al. 1996).

The deactivation process caused by metabolism could be a contributory explanation to the lack of *in vivo* inactivity of compound **14**.

Table 5: Metabolites suggested by the METEOR and MetabolExpert programs

Type of reaction	METEOR Phase I	MetabolExpert Phase I
A	yes	yes
B	yes	yes
C_a	yes	yes
C_b	yes	no
D	yes	no
E	no[a]	yes
F	no[b]	yes
G	no[c]	yes

[a] Under default processing constraints, this pathway is not displayed as it is associated only with an "equivocal" level of confidence
[b] Under default processing constraints, this pathway is not displayed as it is considered less likely than A or B
[c] Under default processing constraints, this pathway is not displayed as it is considered less likely than C_a or C_b

3. Experimental

3.1. Chemistry

Melting points were determined on a Mel-Temp II apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DPX 400 Avance (400 MHz) spectrometer. Chemical shifts are expressed in ppm downfield from internal Me_4Si as reference. ^{1}H NMR Data are reported in the following order: multiplicity (br, broad; def, deformed; s, singlet; d, dublet; t, triplet; q, quartet; qu, quintet; sek, sekstet, m, multiplet); approximate coupling constants J in Hertz; number of protons; *, exchangeable by D_2O; Pip, piperidine. Mass spectra were obtained on an EI-MS Finnigan MAT CH7A (70 eV, 170°). Microwave irradiations are carried out with a domestic microwave oven Samsung M1618. IR spectra were recorded with a Perkin-Elmer 1420 Ratio-Recording or a Perkin-Elmer 297 spectral photometer from KBr discs (s, strong). Elemental analyses (C, H, N) were measured on a Perkin-Elmer 240 B or a Perkin-Elmer 240 C instrument and were within ±0.4% of theoretical values for all final compounds. Column chromatography (CC) was performed using silica gel 60 (0.063–0.20 mm; Merck). Thin layer chromatography (TLC) was carried out using silica gel F_{254} plates (Merck). The spots were visualized with Dragendorff's reagent.

3.1.1. Starting materials

3.1.1.1. Piperidinoalkan-1-ols (**1a**–**1e**)

The compounds were prepared as described before (Łażewska et al. 2001).

3.1.1.2. 2-Nonanamine (**17a**) (Thoms et al. 1903)

Compound **17a** was prepared from 2-nonanol by a Mitsunobu-protocol-adapted Gabriel synthesis (Mitsunobu 1981). The corresponding N-alkylphthalimide was transferred into the desired amine by hydrazinolysis as described by Sasse et al. 1999a. Compound **17a** was isolated as free base and used without further purification.

*3.1.2. Synthesis of carbamates **2**–**15**, **17**–**19***

Method A: General procedure (carbamates **2**–**3**, **5**, **7**–**12**, **14**): Isocyanate (2.5 mmol) was dissolved in 30 ml of dry MeCN, and the respective piperidinoalkanol **1a**–**1e** (2.5 mmol) in 15 ml of dry MeCN was added. The solution was refluxed for 4–12 h (controlled by TLC) and concentrated *in vacuo*. The residue was purified by CC. The pure fractions were concentrated *in vacuo*, dried and the carbamates were precipitated as hydrogen oxalates from EtOH/Et_2O.

Method B: General procedure (carbamates **17**–**19**)*:* A solution of trichloromethyl chloroformate (0.37 ml, 3 mmol) and a catalytic amount of charcoal in 20 ml of dry ethyl acetate were mixed at room temperature for 15 min. After heating up to 50 °C, the appropriate amine (**17a**–**19a**) (2.5 mmol) in 15 ml of dry ethyl acetate was added rapidly. The reaction mixture was heated to reflux for 5 h. Then the black solution was cooled, filtered, and the solvent was evaporated under reduced pressure. The freshly prepared isocyanate was redissolved in 30 ml of dry MeCN, and 3-piperidinopropan-1-ol (**1a**, 2.5 mmol) in 15 ml of dry MeCN was added. The solution was refluxed for 5–18 h (controlled by TLC) and concentrated *in vacuo*. The residue was purified by CC. The pure fractions were concentrated in vacuo, dried and the carbamates were precipitated as hydrogen oxalates from EtOH/Et_2O.

Method C: General procedure (carbamates **4**, **6**, **13**): To a solution of di-*tert*-butyl dicarbonate (1.53 g, 7.0 mmol) in 10 ml of freshly destilled MeCN was added dropwise 4-dimethylaminopyridine (0.61 g, 5 mmol) in 10 ml of dry MeCN and the appropriate amine (**4a**, **6a** or **13a**) (5 mmol). After stirring for 20–30 min at room temperature, the respective alcohol (**1a** or **1c**) (4.2 mmol) was added in 10 ml of dry MeCN. The reaction mixture was heated to reflux for 9–11 h. After removing of the solvent,

the residue was purified by CC. The pure fractions were concentrated in vacuo, dried and the carbamates were precipitated as hydrogen oxalates from EtOH/Et_2O.

3.1.1.3. Sythesis of ether **16**

A mixture of 3-piperidinopropan-1-ol (**1a**, 5 mmol, 0.72 g), 1-bromooctane (6 mmol, 1.16 g), tetrabutylammonium bromide (0.5 mmol, 0.17 g), potasium carbonate (20 mmol, 2.8 g) and potasium hydroxide (20 mmol, 1.1 g) was heated in a domestic microwave oven in an open Erlenmeyer flask for 60 s (M = 300 W). After cooling the mixture was extracted with CH_2Cl_2. The extracts were evaporated to dryness and purified by CC. The pure fractions were concentrated *in vacuo*, dried and the ether was precipitated as hydrogen oxalate from EtOH/Et_2O.

3.2. Pharmacology

3.2.1. Histamine H_3 receptor antagonist assay on guinea-pig ileum

Antagonist histamine H_3 receptor potency was measured by the concentration-dependent inhibition of electrically evoked twitches of longitudinal muscle strips of guinea-pig ileum induced by (*R*)-α-methylhistamine in the presence of antagonist by at least five experiments (Schlicker et al. 1994). Antagonist affinities were expressed as apparent pA_2 values (Furchgott 1972; van Rossum 1963). Full pA_2 values were calculated according to the Schild regression analysis (Arunlakshana et al. 1959). Experimental details were described by Łażewska et al. (2001).

3.2.2. Histamine H_3 receptor potency in vivo assay in mice

The test was performed after oral administration of the compound to Swiss mice as described by Garbarg et al. (1992). Brain histamine turnover was assessed by measuring the level of the main metabolite of histamine, N^{τ}-MeHA. Mice were fasted for 24 h before treatment. Animals were decapitated 90 min after treatment, and the cerebral cortex was isolated. The cortex was homogenized in 10 volumes of ice-cold perchloric acid (0.4 M). The N^{τ}-MeHa level was measured by radioimmunoassay (Garbarg et al. 1989). ED_{50} values were calculated as mg of free base/kg.

3.2.3. Histamine H_1, H_2, and muscarine M_3 receptors assays on isolated organs of guinea-pig

To investigate the receptor selectivity of the compounds functional *in vitro* assays were used: guinea-pig ileum assay for H_1 and M_3 receptor activities and the spontaneously beating right atrium for H_2 receptor activity, as described by Hirschfeld et al. (1992) and Ligneau et al. (1994). Results are expressed as mean ± standard error (*SEM*) unless otherwise indicated. The number of experiments was 4–12 for H_1 and M_3 and at least 2 for H_2 receptor assays.

3.3. Computer calculations

3.3.1. Pallas log P calculation method – (Prolog P) (Rekker et al. 1977; Ghose et al. 1986)

The Pallas program (version 1.2) predicts octanol-water partition coefficients using two databases: CDR and ATOMIC. The calculated log P (log P_{COM}) represents the summation of log $P_{ATOMIC5}$ and log P_{CDR} according to eq. (1):

$$\log P_{COM} = 0.733 \log P_{ATOMIC5} + 0.267 \log P_{CDR} \quad (1)$$

CDR database is based on Rekker's collection of hydrophobic fragmental constants (f_i) derived from an extended set of more than 1000 log P values in the n-octanol/water system. The fragmental constants (f_i) measure the absolute lipophilicity contribution of a given structural fragment i which occur a_i times in that structure. Interaction factors F correct intramolecular interactions (electronic, steric or hydrogen bond) between fragments according to eq. (2):

$$\log P = \Sigma a_i f_i + \Sigma F_i \quad (2)$$

In the ATOMIC5 system, log P is calculated using atomic fragments proposed by Ghose-Crippen. The "body" of these fragments is only one atom. The fragment is then described by what it is adjacent to it. Calculations are performed according to (eq) 3:

$$\log P = \Sigma a_i n_i \quad (3)$$

where n_i is the number of atoms of type i and a_i is the contribution of atom type i.

3.3.2. Prediction of metabolites

3.3.2.1. METEOR computer program (2002)

The METEOR program is developed by LHASA Limited and predicts the metabolic fate of chemical substances. In order to do this, it makes use of a dictionary of metabolic biotransformations and two reasoning models – one model dealing with absolute reasoning and the second with relative reasoning – to determine the more likely metabolites from all those which are possible (Button et al. 2003). The user is able to adjust the processing constraints within the program to determine, for example, the level of likelihood above which METEOR predicts metabolites and whether metabolites are generated from phase I and/or phase II biotransformations.
A description and bibliographic references are provided for each biotransformation in the knowledge base.
In this study, METEOR version 6.0 was used with default processing constraints except that metabolite prediction was restricted to the generation of phase I metabolites only. All possible species options were also explored but no differences were observed.

3.3.3.2. Computer program MetabolExpert 11.0 (2001)

MetabolExpert is a module of the Pallas system produced by Compudrug International Inc. This program predicts the metabolic pathways of compounds in mammals, plants or by photodegradation. Generated metabolites can be limited to phase I reaction or extended to phase II. The program knowledge base includes the most common transformation rules. Every rule in the database is composed of four elements: *active substructure* (in which bonds are changed during the metabolism), *replacing substructure* (where new bonds are formed), *positive conditions* (a list of substructures, at least one, which should be in the molecule for the transformation to occur), *negative conditions* (a list of substructures whose presence prevents the metabolic transformation from occurring). In this study the search was limited to: phase I and mammals.

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