Structure−Activity Relationships of Dimethindene Derivatives as New M$_2$-Selective Muscarinic Receptor Antagonists

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A series of 2,3-disubstituted indenes, which are analogues of the widely used histamine H$_1$ receptor antagonist dimethindene, have been synthesized and studied as muscarinic and histamine receptor antagonists. The affinities of these compounds for the five human muscarinic receptor subtypes (M$_1$−M$_5$) and for human histamine H$_1$ receptors were determined in radioligand binding studies using membranes from transfected Chinese hamster ovary (CHO) cells and [^{3}H]N-methylscopolamine ([^{3}H]NMS). The results demonstrate that the diisopropyl analogue **19** has a similar high affinity as (S)-dimethindene at M$_2$ receptors ((S)-dimethindene: pK_i = 7.52; (−)-**19**: pK_i = 7.37) with an improved selectivity pattern ((S)-dimethindene: M$_2$/M$_1$ = 6-fold, M$_2$/M$_3$ = 5-fold, M$_2$/M$_4$ = 10-fold, M$_2$/M$_5$ = 25-fold; (−)-**19**: M$_2$/M$_1$ = 36-fold, M$_2$/M$_3$ = 96-fold, M$_2$/M$_4$ = 42-fold, M$_2$/M$_5$ = 275-fold). In addition, compound (−)-**19** showed 35-fold lower affinity at histamine H$_1$ receptors (pK_i = 5.61) than (S)-dimethindene (pK_i = 7.16). Another interesting compound is the fluoroethyl derivative **20** (pK_i/M$_2$ = 7.49), which also exhibits a higher M$_2$ selectivity (M$_2$/M$_1$ = 19-fold; M$_2$/M$_3$ = 22-fold; M$_2$/M$_4$ = 13-fold; M$_2$/M$_5$ = 62-fold) than (S)-dimethindene. Unfortunately, compound **20** also shows a high affinity for histamine H$_1$ receptors (pK_i = 8.14). The compound with the highest affinity for M$_2$ receptors (pK_i = 7.91), the dimethylaminomethylene analogue **31**, displayed only a small preference for M$_2$ receptors. In conclusion, compound (−)-**19** might be useful to test the hypothesis that blockade of muscarinic M$_2$ receptors in the brain is a viable mechanism by which to produce improved cognition. This second-generation dimethindene analogue might also be the starting point for the development of M$_2$-selective muscarinic antagonists useful for quantifying M$_2$ receptors in the central nervous system with positron emission tomography imaging.

Introduction

Muscarinic receptors are present in the central and peripheral nervous system as well as in organs innervated by the autonomic nervous system. These receptors play an important role in a wide range of different functions such as central control of movement and cognition as well as in the peripheral control of smooth muscle tone and glandular secretion. Due to their wide distribution, the use of nonselective antagonists as therapeutics involves potential side effects, which could be avoided with subtype-selective compounds.

The interest in muscarinic receptors arose with the discovery of the pharmacological profile of pirenzepine, which shows M$_1$ receptor subtype selectivity. Four muscarinic receptor subtypes (M$_1$, M$_2$, M$_3$, and M$_4$) were subsequently characterized pharmacologically by the use of selective antagonists,[1,2] and five distinct subtypes (M$_1$−M$_5$) were cloned.[3] These developments have made it possible to specifically target the blockade of one

muscarinic receptor subtype. Currently, pirenzepine is used for the inhibition of gastric acid secretion in the treatment of peptic ulcers.[4] An M$_2$ antagonist might be useful in the treatment of bradycardia,[5] and an M$_3$ selective compound in the treatment of obstructive airways diseases.[6] Another possible indication for an M$_2$ and/or M$_3$ antagonist could be urinary incontinence,[7] and an M$_4$ antagonist may be useful to treat tremor in patients with Parkinson's disease.[8]

Alzheimer's disease (AD) is a chronic cognitive disorder, characterized by the progressive degeneration of cholinergic neurons that project from the basal forebrain to the cerebral cortex and hippocampus.[9] AD is currently treated with inhibitors of acetylcholinesterase, such as donepezil, which enhance the acetylcholine concentration in the synaptic cleft by impeding its enzymatic breakdown.[10] Another possible mechanism for augmenting central cholinergic activity is to increase acetylcholine release by blockade of inhibitory presynaptic M$_2$ autoreceptors in the CNS,[11] making a selective M$_2$ receptor antagonist useful in the treatment of AD.[12] Such centrally acting M$_2$ antagonists may improve cognition without the side effects associated with other cholinergic approaches provided there is sufficient selectivity for the M$_2$ subtype. Nonselective muscarinic antagonists such as scopolamine are known to produce cognitive deficits. Very few compounds with the requi-

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Dimethindene

19
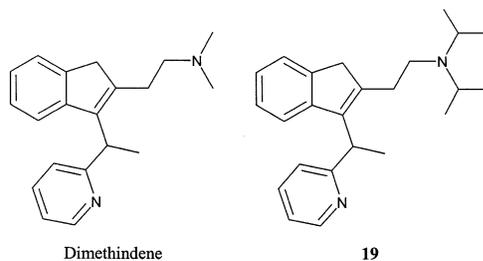
Figure 1.

site selectivities are known, and many of these do not penetrate into the brain to an appreciable extent.[12] Particularly, M_2/M_1 selectivity is crucial since the drug of interest should not functionally counteract its own presynaptic action by blocking postsynaptic M_1 receptors, which mediate the acetylcholine effect.

Brains from AD patients show a number of typical histopathologic alterations, e.g. axonal loss in the hippocampus and cortex. Due to their presynaptic location the density of M_2 receptors might therefore be reduced in these regions.[13] A labeled M_2-selective muscarinic antagonist suitable for positron emission tomography (PET) might therefore also be used as a diagnostic tool to provide information about the density of M_2 receptors in the brain.[14−16]

Racemic dimethindene maleate (Figure 1) is a histaminic H_1 receptor antagonist, which penetrates readily into the brain.[17−19] It was also shown to possess antimuscarinic activities by inhibiting the contractile responses to carbachol in guinea-pig ileum.[20] In an effort to explore its affinity for muscarinic receptor subtypes, the enantiomers of dimethindene, including the racemate, were examined in functional as well as in binding studies at native muscarinic receptor subtypes $M_1−M_4$.[15] The results of these studies demonstrated that (S)-dimethindene is a potent M_2-selective muscarinic receptor antagonist (guinea-pig atrium and rabbit vas deferens: $pA_2 = 7.86/7.74$; rat heart: $pK_i = 7.78$) with lower affinities for the muscarinic M_1 (rabbit vas deferens/rat duodenum: $pA_2 = 6.83/6.36$; NB−OK1-cells: $pK_i = 7.08$), M_3 (guinea-pig ileum/guinea pig trachea: $pA_2 = 6.92/6.96$; rat pancreas: $pK_i = 6.70$) and M_4 receptors (rat striatum: $pK_i = 7.00$). The (S)-enantiomer of dimethindene was more potent (up to 41-fold) than the (R)-isomer in all muscarinic assays. On the other hand, the (S)-isomer showed a lower affinity for histamine H_1 receptors in guinea-pig ileum ($pA_2 = 7.48$) than the (R)-enantiomer ($pA_2 = 9.42$).

The aim of the present study was to synthesize analogues of dimethindene in order to increase affinity and selectivity at muscarinic M_2 receptors as well as to diminish the binding toward histamine H_1 receptors. Structural modifications were made through functional group substitution on the indene phenyl ring and at the chiral center of the dimethindene molecule. Derivatives with different basic side chains were also evaluated. The new derivatives were examined for their affinities to human recombinant muscarinic $M_1–M_5$ and histamine H_1 receptors in radioligand binding studies. All chiral compounds, except dimethindene and **19**, were tested as racemates. (R)- and (S)-dimethindene were used as reference drugs.[15]

Chemistry

The compounds **6−37** shown in Table 1 were prepared by the synthetic routes illustrated in Scheme 1−3.

In Scheme 1, diethyl malonate was reacted with commercially available benzyl chlorides **1a−h**. 4-Methylthiobenzyl chloride **1i** was prepared following the procedure of Pines et al.[21] The benzyl malonic diethyl esters **2a−i** were alkylated with commercially available (2-chloroethyl)dialkylamines to give the tertiary amines **3a−p**. The (2-chloroethyl)dialkylamines **41a** and **41b** were prepared from the corresponding alcohol, which were treated with thionyl chloride.

Saponification of the corresponding malonic esters yielded the amino acids **4a−p**. The ring closure reaction was carried out in polyphosphoric acid (PPA) to give the indanone-1 derivatives **5a−p**. Treatment of **5a−p** with the lithium salts of different commercially available picolines, 2-ethyl-pyridine and 2-benzyl-pyridine formed tertiary alcohols, which were refluxed in HCl (20%) and yielded the indenes **6−19**, **22−25**, **27**, **28**, and **39**. 2-Isopropylpyridine (**45**) was synthesized from 2-ethylpyridine by deprotonation and subsequent alkylation with methyl iodide. Compound **45** was used to synthesize compound **26** by addition to compound **5a** and elimination of water. Treatment of commercially available 1-(bromoethyl)benzene with lithium gave the corresponding lithium compound, to which compound **5a** was added to give the phenyl-substituted compound **30**.

Reduction of compound **5a** with sodium borohydride and dehydration with hydrochloric acid gave compound **38**, which in turn gave compound **29** by alkylation of the lithium salt with 3-chloromethylpyridine. Compound **39** was debenzylated by hydrogenation in the presence of formic acid to yield the secondary amine **40**, which was converted by alkylation to the tertiary amines **20** and **21**.

The indanone intermediates **43** and **44** (Scheme 2) were synthesized under standard Mannich reaction conditions.[22−24] Treatment of **43** and **44** with the lithium salt of 2-ethylpyridine and subsequent reflux in HCl (20%) gave **31** and **32**, respectively, as illustrated in Scheme 2.

The compounds **33−37** were prepared via the general synthesis outlined in Scheme 3. To synthesize compounds **33−37**, treatment of commercially available indene with commercially available oxalylbromide neat, followed by addition of commercially available dimethylaminoethylamine or dimethylaminoethanol, gave the corresponding amides and esters **42a** and **42b**, respectively. Treatment of **42a,b** with butyllithium formed the anion, which was alkylated with different chloromethyl pyridines to give the compounds **33−37**.

Results and Discussion

New dimethindene analogues were synthesized in order to identify derivatives with improved M_2 selectivity and affinity as compared with the parent compound. The affinities of the new derivatives for the five human muscarinic receptor subtypes ($M_1−M_5$) and for histamine H_1 receptors were determined in radioligand binding studies using membranes from transfected Chinese hamster ovary (CHO) cells and [³H]NMS and [³H]mepyramine, respectively, as radioligands.[25] All chiral compounds, except dimethindene and **19**, were

Table 1. Structure and Binding Affinities of 2,3-Disubstituted Indenes[a] at Muscarinic Receptors
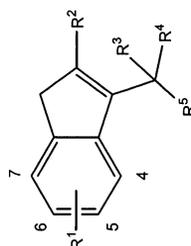
compd[b]	R[1]	R[2 c]	R[3]	R[4]	R[5 d]	pK_i M_1	M_2	M_3	M_4	M_5	formula[e]
(R)-(−)-Dim[k]	H	(CH$_2$)$_2$N(CH$_3$)$_2$	CH$_3$	H	2-pyridyl	5.73 ± 0.03	5.91 ± 0.05	5.47 ± 0.04	5.41 ± 0.01	5.57 ± 0.03	C$_{20}$H$_{24}$N$_2$·C$_4$H$_4$O$_4$
(S)-(+)-Dim[j]	H	(CH$_2$)$_2$N(CH$_3$)$_2$	CH$_3$	H	2-pyridyl	6.72 ± 0.05	7.52 ± 0.05	6.86 ± 0.01	6.53 ± 0.05	6.12 ± 0.03	C$_{20}$H$_{24}$N$_2$·C$_4$H$_4$O$_4$
6	5-CH$_3$	(CH$_2$)$_2$N(CH$_3$)$_2$	CH$_3$	H	2-pyridyl	5.79 ± 0.14	5.71 ± 0.14	5.60 ± 0.22	5.49 ± 0.22	5.23 ± 0.16	C$_{21}$H$_{26}$N$_2$·C$_4$H$_4$O$_4$·0.1H$_2$O
7	5-OMe	(CH$_2$)$_2$N(CH$_3$)$_2$	CH$_3$	H	2-pyridyl	5.43 ± 0.22[h]	5.99 ± 0.16[h]	5.50 ± 0.19	5.07 ± 0.35[h]	5.05 ± 0.16	C$_{21}$H$_{26}$N$_2$O·C$_4$H$_4$O$_4$
8	5-Cl	(CH$_2$)$_2$N(CH$_3$)$_2$	CH$_3$	H	2-pyridyl	6.46 ± 0.04	6.44 ± 0.02	6.30 ± 0.05	6.13 ± 0.03	6.04 ± 0.02	C$_{20}$H$_{23}$ClN$_2$·C$_4$H$_4$O$_4$
9	5-SMe	(CH$_2$)$_2$N(CH$_3$)$_2$	CH$_3$	H	2-pyridyl	6.06 ± 0.06	6.04 ± 0.03[h]	5.98 ± 0.04	5.70 ± 0.03	5.49 ± 0.03	C$_{21}$H$_{26}$N$_2$S·C$_4$H$_4$O$_4$·0.02H$_2$O
10	5-F	(CH$_2$)$_2$N(CH$_3$)$_2$	CH$_3$	H	2-pyridyl	6.48 ± 0.05	6.95 ± 0.15	6.58 ± 0.03	6.19 ± 0.05	5.98 ± 0.04	C$_{20}$H$_{23}$FN$_2$·C$_4$H$_4$O$_4$
11	6-CH$_3$	(CH$_2$)$_2$N(CH$_3$)$_2$	CH$_3$	H	2-pyridyl	6.25 ± 0.02	6.23 ± 0.06	6.30 ± 0.03	5.85 ± 0.03	5.84 ± 0.05	C$_{21}$H$_{26}$N$_2$·C$_4$H$_4$O$_4$·0.05H$_2$O[f]
12	6-OMe	(CH$_2$)$_2$N(CH$_3$)$_2$	CH$_3$	H	2-pyridyl	5.81 ± 0.01	5.97 ± 0.10	5.93 ± 0.04	5.38 ± 0.02	5.22 ± 0.01	C$_{21}$H$_{26}$N$_2$O·C$_4$H$_4$O$_4$
13	6-Cl	(CH$_2$)$_2$N(CH$_3$)$_2$	CH$_3$	H	2-pyridyl	6.82 ± 0.04	7.48 ± 0.05	7.02 ± 0.02	6.48 ± 0.04	6.11 ± 0.06	C$_{20}$H$_{23}$ClN$_2$·C$_4$H$_4$O$_4$
14	6-Cl	(CH$_2$)$_2$N(CH$_3$)$_2$	CH$_2$CH$_3$	H	2-pyridyl	6.65 ± 0.11	6.97 ± 0.07	6.55 ± 0.05	6.08 ± 0.10	6.11 ± 0.03	C$_{21}$H$_{25}$ClN$_2$·C$_4$H$_4$O$_4$
15	H	(CH$_2$)$_2$piperidino	CH$_3$	H	2-pyridyl	5.72 ± 0.10	6.07 ± 0.09	5.75 ± 0.07	5.72 ± 0.15	5.63 ± 0.05	C$_{23}$H$_{28}$N$_2$·C$_4$H$_4$O$_4$·0.16H$_2$O
16	H	(CH$_2$)$_2$morpholino	CH$_3$	H	2-pyridyl	5.36 ± 0.10	5.84 ± 0.13	5.56 ± 0.09	5.38 ± 0.12	5.57 ± 0.05	C$_{22}$H$_{26}$N$_2$O·C$_4$H$_4$O$_4$
17	H	(CH$_2$)$_2$pyrrolidino	CH$_3$	H	2-pyridyl	5.98 ± 0.04	6.40 ± 0.09	5.72 ± 0.02	5.91 ± 0.03	5.70 ± 0.03	C$_{22}$H$_{26}$N$_2$·C$_4$H$_4$O$_4$·0.66 H$_2$O
18	H	(CH$_2$)$_2$N(C$_2$H$_5$)$_2$	CH$_3$	H	2-pyridyl	6.35 ± 0.06	7.35 ± 0.04	6.02 ± 0.06	6.34 ± 0.07	5.68 ± 0.03	C$_{22}$H$_{28}$N$_2$·C$_4$H$_4$O$_4$
19	H	(CH$_2$)$_2$NCH(CH$_3$)$_2$)$_2$	CH$_3$	H	2-pyridyl	6.13 ± 0.03	7.60 ± 0.11	5.65 ± 0.04	6.13 ± 0.07	5.66 ± 0.04	C$_{24}$H$_{32}$N$_2$·C$_7$H$_8$SO$_3$
(+)-**19**	H	(CH$_2$)$_2$NCH(CH$_3$)$_2$)$_2$	CH$_3$	H	2-pyridyl	5.23 ± 0.11	6.24 ± 0.21	4.68 ± 0.05	5.26 ± 0.10	5.29 ± 0.06	C$_{24}$H$_{32}$N$_2$
(−)-**19**	H	(CH$_2$)$_2$NCH(CH$_3$)$_2$)$_2$	CH$_3$	H	2-pyridyl	5.81 ± 0.04	7.37 ± 0.18	5.39 ± 0.05	5.75 ± 0.03	4.93 ± 0.04	C$_{24}$H$_{32}$N$_2$
20	H	(CH$_2$)$_2$NCH$_3$(CH$_2$)$_2$F	CH$_3$	H	2-pyridyl	6.22 ± 0.06	7.49 ± 0.06	6.15 ± 0.04	6.36 ± 0.04	5.70 ± 0.02	C$_{21}$H$_{25}$FN$_2$·C$_4$H$_4$O$_4$
21	H	(CH$_2$)$_2$NCH$_3$CH$_2$CH(CH$_3$)$_2$	CH$_3$	H	2-pyridyl	6.06 ± 0.03	6.84 ± 0.05	5.74 ± 0.02	6.00 ± 0.08	5.66 ± 0.04	C$_{22}$H$_{28}$N$_2$·C$_4$H$_4$O$_4$
22	H	(CH$_2$)$_3$N(CH$_3$)$_2$	CH$_3$	H	2-pyridyl	6.05 ± 0.08	6.58 ± 0.10	6.24 ± 0.05	5.77 ± 0.06	5.49 ± 0.05	C$_{21}$H$_{26}$N$_2$·C$_4$H$_4$O$_4$
23	H	(CH$_2$)$_2$N(CH$_3$)$_2$	CH$_2$CH$_3$	H	2-pyridyl	6.62 ± 0.06	7.01 ± 0.10	6.51 ± 0.00	6.18 ± 0.08	6.17 ± 0.04	C$_{21}$H$_{26}$N$_2$·C$_4$H$_4$O$_4$
24	H	(CH$_2$)$_2$N(CH$_3$)$_2$	(CH$_2$)$_2$CH$_3$	H	2-pyridyl	6.61 ± 0.07	6.17 ± 0.10	6.20 ± 0.06	6.21 ± 0.09	6.52 ± 0.06	C$_{22}$H$_{28}$N$_2$·C$_4$H$_4$O$_4$
25	H	(CH$_2$)$_2$N(CH$_3$)$_2$	phenyl	H	2-pyridyl	7.36 ± 0.07	6.64 ± 0.03	7.17 ± 0.07	6.89 ± 0.07	7.18 ± 0.09	C$_{25}$H$_{31}$N$_2$·C$_4$H$_4$O$_4$·H$_2$O
26	H	(CH$_2$)$_2$N(CH$_3$)$_2$	CH$_3$	CH$_3$	2-pyridyl	7.28 ± 0.06	7.81 ± 0.03	7.59 ± 0.07	7.09 ± 0.05	6.43 ± 0.07	C$_{21}$H$_{26}$N$_2$·C$_4$H$_4$O$_4$
27	H	(CH$_2$)$_2$N(CH$_3$)$_2$	H	H	2-pyridyl	5.80 ± 0.04	6.63 ± 0.07	5.81 ± 0.06	5.62 ± 0.11	5.44 ± 0.05	C$_{19}$H$_{22}$N$_2$·C$_4$H$_4$O$_4$
28	H	(CH$_2$)$_2$N(CH$_3$)$_2$	H	H	4-pyridyl	5.37 ± 0.07	5.17 ± 0.05	4.93 ± 0.09	5.08 ± 0.13	4.99 ± 0.05	C$_{19}$H$_{22}$N$_2$·C$_4$H$_4$O$_4$·0.07H$_2$O
29	H	(CH$_2$)$_2$N(CH$_3$)$_2$	H	H	3-pyridyl	5.43 ± 0.08	5.27 ± 0.12	5.09 ± 0.10	5.13 ± 0.09	5.10 ± 0.06	C$_{19}$H$_{22}$N$_2$·C$_4$H$_4$O$_4$
30	H	(CH$_2$)$_2$N(CH$_3$)$_2$	CH$_3$	H	phenyl	6.80 ± 0.12	6.59 ± 0.12	6.54 ± 0.18	6.43 ± 0.17	6.51 ± 0.13	C$_{21}$H$_{25}$N·C$_4$H$_4$O$_4$
31	H	CH$_2$N(CH$_3$)$_2$	CH$_3$	H	2-pyridyl	7.46 ± 0.03	7.91 ± 0.07	7.50 ± 0.05	7.01 ± 0.03	7.06 ± 0.04	C$_{19}$H$_{22}$N$_2$·C$_4$H$_4$O$_4$
32	H	CH$_2$NCH$_3$CH(CH$_3$)$_2$	CH$_3$	H	2-pyridyl	6.64 ± 0.04	7.29 ± 0.02	6.13 ± 0.06	6.22 ± 0.02	5.95 ± 0.05	C$_{21}$H$_{24}$N$_2$[g]
33	H	CO$_2$(CH$_2$)$_2$N(CH$_3$)$_2$	H	H	2-pyridyl	5.27 ± 0.05[h]	5.31 ± 0.07	5.05 ± 0.04	4.83 ± 0.06	4.76 ± 0.03	C$_{20}$H$_{22}$N$_2$O$_2$·2C$_4$H$_4$O$_4$·0.42H$_2$O
34	H	CO$_2$(CH$_2$)$_2$N(CH$_3$)$_2$	H	H	3-pyridyl	5.45 ± 0.06[h]	5.22 ± 0.02	5.09 ± 0.05	4.88 ± 0.02	4.95 ± 0.04	C$_{20}$H$_{22}$N$_2$O$_2$·2C$_4$H$_4$O$_4$·0.16H$_2$O
35	H	CONH(CH$_2$)$_2$N(CH$_3$)$_2$	H	H	2-pyridyl	4.79 ± 0.19	4.83 ± 0.19	4.62 ± 0.20	4.57 ± 0.30	4.34 ± 0.27	C$_{20}$H$_{23}$N$_3$O·C$_4$H$_4$O$_4$·0.13H$_2$O
36	H	CONH(CH$_2$)$_2$N(CH$_3$)$_2$	H	H	3-pyridyl	4.31 ± 0.04	4.40 ± 0.25[i]	4.31 ± 0.10	4.33 ± 0.03	4.18 ± 0.05	C$_{20}$H$_{23}$N$_3$O·2C$_4$H$_4$O$_4$
37	H	CONH(CH$_2$)$_2$N(CH$_3$)$_2$	H	H	4-pyridyl	4.27 ± 0.09	4.03 ± 0.25[i]	3.87 ± 0.08	4.06 ± 0.06[i]	4.38 ± 0.02[h]	C$_{20}$H$_{23}$N$_3$O·2C$_4$H$_4$O$_4$

[a] Data are given as means ± SD of at least three experiments performed in duplicate. [b] All chiral compounds were used as racemates except dimethindene and **19**. [c] Morpholino = N-substituted morpholine; piperidino = N-substituted piperidine; pyrolidine = N-substituted pyrrolidine. [d] 2-, 3-, 4-pyridyl = 2-, 3- or 4-substituted pyridine. [e] Compounds were analyzed for C, H, N; the results agreed to within ±0.4% of the theoretical values. [f] Mixture of isomers, 6-methyldimethindene (80%) and 4-methyldimethindene (20%). [g] Compound was purified by flash chromatography. [h] Hill coefficients significantly different from unity. [j] (+)-Dim = (+)-dimethindene. [k] (−)-Dim = (−)-dimethindene.

Scheme 1[a]
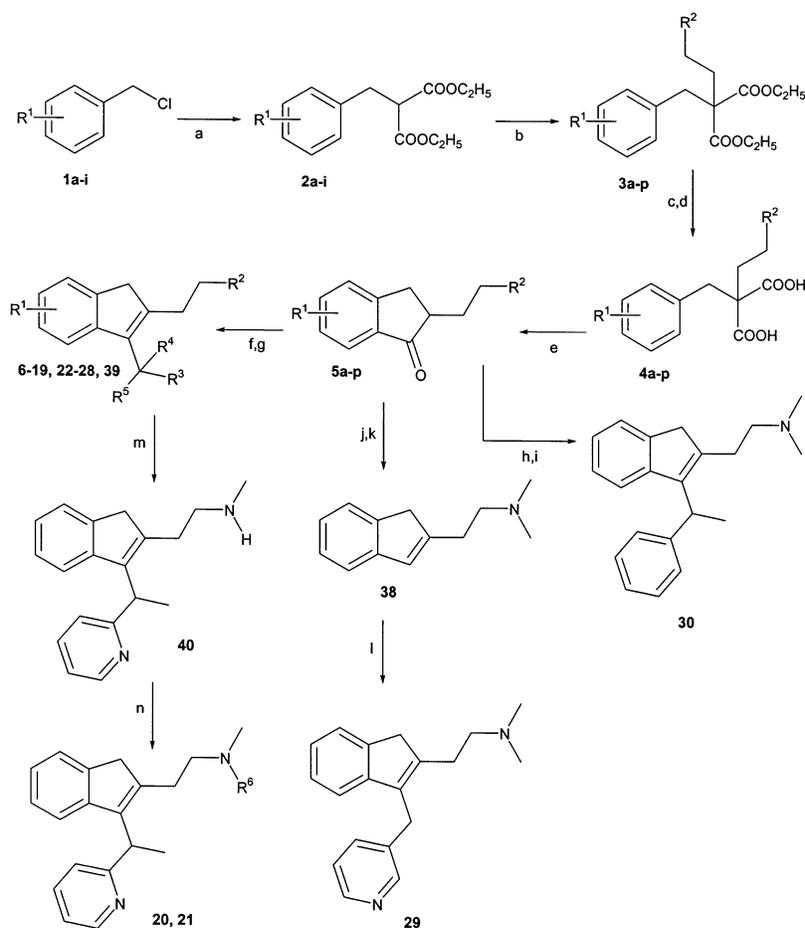
[a] (a) Diethyl malonate, Na, EtOH, Δ; (b) NaH, R²-(CH₂)$_x$-Cl, toluene, Δ; (c) NaOH, Δ; (d) CH₃COOH, 0 °C; (e) PPA, Δ; (f) 2-picolyl-R³,R,⁴ BuLi, ether, −78 °C; (g) HCl (20%), Δ; (h) (1-bromoethyl)benzene, Li, ether, 25 °C; (i) HCl (20%), Δ; (j) NaBH₄, EtOH, Δ; (k) HCl concentrated, acetic acid, Δ; (l) BuLi, ether, 3-chloromethylpyridine, −78 °C; (m) Pd/H₂, HCOOH, methanol; (n) K₂CO₃, Hal-alkyl, acetone.

Scheme 2[a]
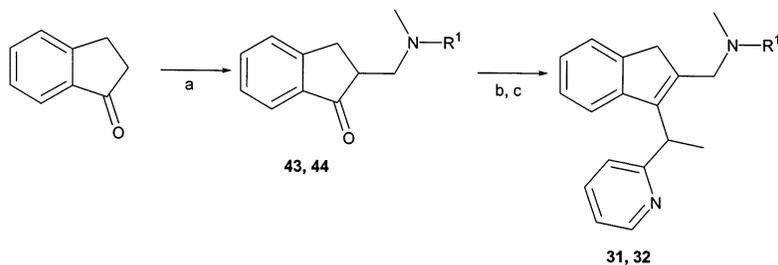
[a] (a) Paraformaldehyde, N(CH₃)R¹, ethanol, Δ; (b) 2-ethylpyridine; BuLi, THF, −78 °C; (c) HCl (20%), Δ.

Scheme 3[a]
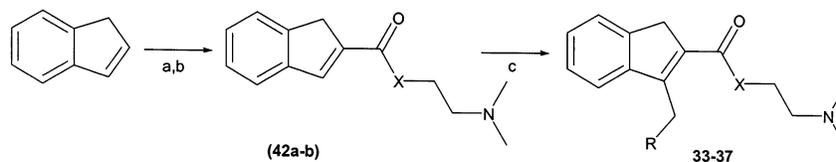
[a] (a) Oxalyl bromide, Δ; (b) 2-dimethylaminoethanol, *N,N*-dimethylethane-1,2-diamine resp., THF, Δ; (c) BuLi, THF, chloromethylpyridine, −78 °C.

investigated as racemates. The respective pK_i values are listed in Tables 1 and 2. Unless stated otherwise, all tested compounds behaved as competitive inhibitors of radioligand binding with competition curves indicating the existence of one single binding site, the Hill coefficients being not significantly different from unity.

Our initial studies explored the effects of substituting the indene moiety of dimethindene at position 5 and 6

Table 2. Binding Affinities[a] of Dimethindene (Dim), **13**, (−)-**19**, (+)-**19**, **20**, and **31** at Histamine H_1 Receptors
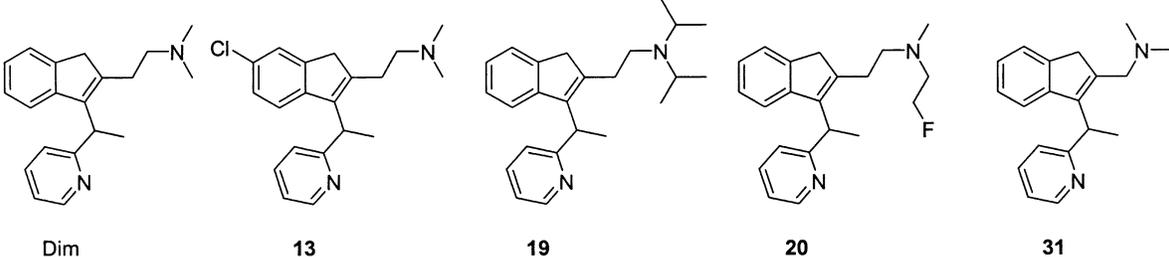
	Dim	R-(−)-Dim	S-(+)-Dim	**13**	(+)−**19**	(−)-**19**	**20**	**31**
pK_i value[a]	9.16 ± 0.12	9.36 ± 0.14	7.16 ± 0.06	9.09 ± 0.14	6.66 ± 0.10	5.61 ± 0.05	8.14 ± 0.06	7.54 ± 0.03

[a] Values are means + SD of at least three independent experiments performed in duplicate.

with electron-withdrawing and electron-donating groups (**6**−**14**). All compounds, except **13**, synthesized with a substituent at positions 5 or 6 showed lower affinity and selectivity toward M_2 receptors (pK_i = 5.71−6.97) than (*S*)-dimethindene. Analogue **10**, which contains a fluorine atom, produced the smallest decrease in affinity among the 5-substituted derivatives. Comparing the fluoro-analogue **10** with compounds **6**−**9** suggests that the bulk of the substituent has the highest impact on receptor binding. Compound **13**, which is substituted with chlorine, demonstrates that this lipophilic electron-withdrawing atom at position 6, in contrast to position 5 (compound **8**), did not significantly affect the affinity for M_1−M_5 receptors. Taken together, the functional group variation at positions 5 and 6 of the indene moiety of dimethindene was found to decrease the affinity and selectivity at muscarinic receptors (**6**−**12**, **14**). Only compound **13** with a chloro-substituent in position 6 maintained affinity for muscarinic receptors.

On the basis of the assumption that the basic tertiary amine moiety in muscarinic antagonists is important for binding to muscarinic receptors,[26] cyclic (**15**−**17**) as well as acyclic (**18**−**21**) tertiary amine derivatives of dimethindene were synthesized. Compounds **15**−**17** had affinities for M_{1-5} receptors lower than those of the acyclic analogues **18**−**21** (up to 45-fold). In comparison to (*S*)-dimethindene, compound **20** showed a significant improvement in M_2-selectivity maintaining high affinity for M_2 receptors (**20**: pK_i − M_2 = 7.49, M_2/M_1 = 19-fold, M_2/M_3 = 22-fold, M_2/M_4 = 13-fold, M_2/M_5 = 62-fold). In general, (*S*)-dimethindene displayed a higher affinity than the (*R*)-enantiomer in all muscarinic assays. However, their stereoselectivity ratios were found to be different at the five recombinant muscarinic receptor subtypes, being greatest at M_2 receptors (40-fold). The same holds true for compound **19** (stereoselectivity ratio at M_2 = 14), the (−)-enantiomer being the eutomer at M_{1-4} receptors, but the distomer at M_5 receptors. However, the affinity of (+)- and (−)-**19** for M_5 receptors and the stereoselectivity ratio (2.3-fold) are low and should therefore not be considered as an unusual finding of reverse stereoselectivity between receptor subtypes. Thus, it is tempting to speculate that the compound (−)-**19** has the (*S*)-configuration. However, further experiments are needed to clarify this issue. Compound (−)-**19** exhibited a similar high affinity for the M_2 receptor (pK_i = 7.37) as (*S*)-dimethindene (pK_i = 7.52), but an improved selectivity profile [(*S*)-dimethindene = M_2/M_1: 6-fold, M_2/M_3: 5-fold, M_2/M_4:

10-fold, M_2/M_5: 25-fold; (−)-**19** = M_2/M_1: 36-fold, M_2/M_3: 96-fold, M_2/M_4: 42-fold, M_2/M_5: 275-fold]. Whereas (*R*)-dimethindene had similar affinities for the five muscarinic receptor subtypes, (+)-**19** (the distomer) is still an M_2-selective muscarinic antagonist.

The pK_i values of racemic **19** (Table 1) should be lower by at most 0.3 log unit than the pK_i values of the high affinity enantiomer of **19** at M_1−M_5 receptors, due to the presence of 50% of the low affinity enantiomer in the racemic mixture. Unfortunately, this was not found. In fact, the affinity of (±)-**19** for M_1−M_5 receptors is on average 4-fold higher than expected (Table 1). However, this discrepancy is not due to chemical impurities of the compounds under study (see Experimental Section), and further experiments are needed to clarify this issue.

The length of the tertiary amine side chain was varied in compounds **22**, **31**, and **32**. While the analogue **22** with an aminopropyl side chain showed a 6-fold decreased M_2-affinity along with a lower selectivity compared to (*S*)-dimethindene, compound **31** with an amino-methyl chain displayed the highest affinity toward the M_2 receptor among all derivatives examined. Unfortunately, the M_2-selectivity of **31** is lower than that of the parent compound. To restore the selectivity while maintaining the affinity, analogue **32**, bearing a methyl-isopropylaminomethyl moiety, was synthesized. This compound showed indeed a similar affinity profile as (*S*)-dimethindene.

In comparison to (*S*)-dimethindene, compounds **33**−**37** showed a decrease in affinity at the muscarinic receptors up to 3090-fold. Each of these derivatives has either an ester or an amide group introduced into the molecule. The lengthening of these compounds by two atoms in comparison to dimethindene might be responsible for the substantial loss in affinity. However, the introduction of a polar group can drastically alter the physical properties of a compound and might also have a dramatic impact on binding to muscarinic receptors.

The impact on affinity of an altered heteroaromatic system was investigated by testing the phenyl analogue (**30**) and the achiral 3- and 4-pyridyl derivatives **28** and **29**. The phenyl derivative **30** showed similar M_1 and M_{3-5} affinities as (*S*)-dimethindene while the M_2-affinity decreased 9-fold, resulting in a nonselective muscarinic antagonist. The affinity of the compounds **28** and **29** for M_2 receptors was 23- and 29-fold, respectively, lower than that of their achiral parent compound **27**. As a result, the M_2-selectivity was completely lost. Taken

together, the pyridyl nitrogen seems to specifically interact with the M_2 receptor protein, since the presence as well as the position of the heteroaryl nitrogen has a major impact on affinity and selectivity.

To examine the effect of the substitution of the chiral center of dimethindene on selectivity and affinity, analogues **23**−**26** were synthesized. The chiral compound **23,** which contains an ethyl substituent instead of methyl, showed lower affinity (2-fold) and selectivity at the M_2 receptors. The derivatives with a propyl substituent (**24**) or a phenyl group (**25**) were found to be M_1-selective compounds. The achiral analogue **26** had a 2-fold higher affinity at M_2 receptors than (*S*)-dimethindene but showed less subtype selectivity.

The pharmacologically most interesting derivatives, **13**, (+)-**19**, (−)-**19**, **20**, and **31**, were investigated for their affinities at recombinant histamine H_1 receptors and compared with the results that were obtained for (*R*)- and (*S*)-dimethindene (Table 2).

The affinity estimates of (*R*)- and (*S*)-dimethindene at recombinant human histamine H1 receptors (Table 2; $pK_i/(R) = 9.36$; $pK_i/(S) = 7.16$) were found to be very similar to that reported by Pfaff et al.,[15] using a functional guinea-pig ileum assay. In contrast with muscarinic receptors (Table 1) the (*R*)-enantiomer proved to be the eutomer at histamine H_1 receptors, being 158-fold more potent than the (*S*)-configured stereoisomer. Accordingly, these results demonstrate an inverse stereoselectivity and imply that the stereochemical requirements of the muscarinic receptors and histamine H_1 receptors, respectively, are different for the enantiomers of dimethindene, being most stringent at H_1 receptors. Such an inverse stereoselectivity for recognition of histamine H_1 and muscarinic M_1−M_4 receptors has also been found for the enantiomers of compound **19** (Table 2). As a result, (−)-**19** has a 14-fold higher affinity for muscarinic M_2 receptors than (+)-**19**, but (+)-**19** is the eutomer at histamine H_1 receptors. As far as M_2 receptor specificity is concerned, the data show that (−)-**19** is an M_2-selective muscarinic antagonist possessing a 58-fold lower affinity for histamine H_1 receptors. It is noteworthy, that the M_2 versus H_1 receptor specificity of (*S*)-dimethindene is much lower than that of (−)-**19** (only 2-fold). This is due to the fact that the affinity for muscarinic M_2 receptors did not change significantly by replacing the two *N*-methyl groups of (*S*)-dimethindene by two isopropyl substituents [(−)-**19**], whereas the affinity for histamine H_1 receptors decreased significantly by a factor of 35. Taken together, the analysis of the individual enantiomers of compound **19** resulted in (−)-**19** with improved M_2 subtype selectivity and M_2 receptor specificity.

The chloro-substituted dimethindene analogue **13** showed about the same high affinity for histamine H_1 receptors as the (*R*)-enantiomer of the parent compound, whereas introduction of a fluoroethyl moiety (**20**) or shortening the aminoethylene chain to one methylene group (**31**) reduced affinity for H_1 receptors 17- and 66-fold, respectively.

In conclusion, this study has generated the diisopropyl derivative (−)-**19**, which has the same high affinity for muscarinic M_2 receptors as the parent compound, (*S*)-dimethindene. However, compound (−)-**19** exhibits an improved M_2 receptor selectivity (at least

36-fold) and M_2/H_1 receptor specificity (58-fold). It is also noteworthy that (−)-**19** is more selective for M_2 versus M_1 and M_{3-5} receptors than any so-called M_2-selective antagonists recommended by the muscarinic receptor Committee on Receptor Nomenclature and Drug Classifications of the International Union of Pharmacology.[25] The antagonists recommended include methoctramine, himbacine and tripitramine. The second generation dimethindene analogue (−)-**19** might become the starting point for the development of M_2-selective muscarinic receptor antagonists useful as diagnostic tools for quantifying M_2 receptors in the central nervous system with positron emission tomography imaging, and to test the hypothesis that muscarinic M_2 receptor antagonists show beneficial effects in the treatment of cognitive disorders. Due to the abundant presence of muscarinic M_1 and histamine H_1 receptors in the brain, the high M_2 versus M_1 (H_1) selectivity (specificity) of compound (−)-**19** is of special importance. In particular, the M_2 versus M_1 receptor selectivity may guarantee that such a compound does not counteract its acetylcholine releasing action via blockade of presynaptic autoreceptors by inhibition of postsynaptic M_1 receptors.[27]

It is significant that dimethindene is a lipophilic compound, both enantiomers of which were able to penetrate into the brains of healthy human volunteers.[17−19] In addition, it has been shown by Radler and Blaschke that differences in metabolism of the (*R*)- and (*S*)-enantiomers do not influence the ease with which they cross the blood brain barrier.[28] Although the same type of investigation has not been carried out with (+)- or (−)-**19**, it seems likely that the enantiomers of **19** behave similarly due to their close chemical relationship to dimethindene. Further experiments are needed to address this point.

Experimental Section

High-field nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Unity 200 MHz Spectrometer or Bruker Unity 400 MHz Spectrometer. All chemical shifts are reported in ppm downfield relative to the residual signal of the deuterated solvent ($CHCl_3$, δ 7.26). All spectra were obtained in $CDCl_3$. Infrared spectra were determined on a Perkin-Elmer 299 IR spectrophotometer. Elemental analysis for carbon, hydrogen, and nitrogen were determined on a Carlo Erba Strumentazione, model 1106 elemental analyzer and are within 0.4% of theory unless noted otherwise. Mass spectra were obtained by using a Varian CH 7a or MAT 311 A mass spectrometer. Melting points were determined on a Dr. Tottoli (Buechi) melting point apparatus and are uncorrected. All target compounds were crystallized as salts of maleic acid ($C_4H_4O_4$) or toluenesulfonic acid except compounds (−)-**19**, (+)-**19**, and **32**.

Resolution of the Racemate 19 and Purity. Separation of the enantiomers (−)-**19** and (+)-**19** was performed on a GILSON/ABIMED HPLC (Sampling Injector 231 XL, UV/Vis-Detector 119, Fraction Collector 202). The column was MERCK Chiralpak ADH33, 250 mm × 4.6 mm. The eluent was acetonitrile: 2-propanol:heptane 50:3:4 + 0.1 diethylamine. The flow rate was: 1 mL/min. The retension times were 3.76 min for (−)-**19** and 4.20 for (+)**19**. (−)-**19** and (+)-**19** showed no impurities.

Determination of Optical Rotation of (−)-19 and (+)-19. The optical rotation of the enantiomers was determined on a PerkinElmer Polarimeter Model 343 in chloroform solution ($c = 0.0023$ mol/L, 20 °C), result: ±90.1°.

General Procedure for the Preparation of Maleic Acid Salts. To a solution of tertiary amine (1 mmol) in absol ethanol (1 mL) was added maleic acid (1 mmol) in absol ethanol (1

mL). The clear solution was kept at 5 °C overnight. The white precipitate was filtered and washed with a mixture of cold absol ethanol and ether (1:1).

Procedure for the Preparation of Toluenesulfonic Acid Salt of 19. To a solution of **19** (1 mmol) in absol ethanol (1 mL) was added toluenesulfonic acid (1 mmol) in absol ethanol (1 mL). The clear solution was kept at 5 °C for 1 month. The white precipitate was filtered and washed with a mixture of cold absol ethanol and ether (1:1).

(4-Chloromethylphenyl) Methyl Sulfide (1i).[21] To a stirred suspension of AlCl$_3$ (61.4 g, 0.46 mol) in 1,2-dichloromethane (200 mL) was added dropwise dimethoxymethane (18.2 g, 0.24 mol) over 30 min at 5 °C. Then, methyl phenyl sulfide (24.8 g, 0.2 mol) was added under the same conditions. The reaction mixture was stirred for 6 h at RT while crystals precipitated. The suspension was kept below 25 °C with an ice bath and stirred vigorously while adding ice chips (250 g). The organic layer was separated and the water layer extracted with 1,2-dichloroethane (2 × 100 mL). The combined organic layers were washed with cold water (30 mL), dried (Na$_2$SO$_4$), and evaporated to give a dark oil. The oil was used without further purification.

2-(4-Methylbenzyl)malonic Acid Diethyl Ester (2a). Sodium (0.1 mol, 2.3 g) was dissolved in 100 mL of dry ethanol, and diethyl malonic acid ester (8 g, 0.1 mol) was added dropwise at 50 °C to give a clear solution. To this solution was added dropwise 4-methylbenzyl chloride (0.1 mol, 26.4 g), and the reaction mixture was refluxed for 1 h. The precipitated sodium chloride was filtered, the ethanol was evaporated, and the residue was purified by distillation to give a colorless oil (11.8 g, 45%). ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.18 (t, $J = 7$ Hz, 6H), 2.28 (s, 3H), 3.12 (t, $J = 7.3$ Hz, 2H), 3.60 (t, $J = 7.3$ Hz, 1H), 4.12 (q, $J = 7$ Hz, 4H), 7.02 (m, 4H). MS: 264.1 (40%, [M$^{•+}$]).

The following analogues were prepared using the procedure outlined for **2a** above.

2-(4-Methoxybenzyl)malonic acid diethyl ester (2b): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.20 (t, $J = 7.2$ Hz, 6H), 3.11 (d, $J = 7.8$ Hz, 2H), 3.58 (t, $J = 7.8$ Hz, 1H), 3.76 (s, 3H), 4.14 (q, $J = 7.2$ Hz, 4H), 6.80 (A,A′, 2H), 7.11 (B,B′, 2H).

2-(4-Chlorobenzyl)malonic acid diethyl ester (2c): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.16 (t, $J = 7.3$ Hz, 6H), 3.12 (d, $J = 7.6$ Hz, 2H), 3.57 (t, $J = 7.6$ Hz, 1H), 4.12 (q, $J = 7.3$ Hz, 4H), 7.06 (A,A′, 2H), 7.16 (B,B′, 2H). MS: 284.2 (37%, [M$^{•+}$]).

2-(4-Methylsulfanylbenzyl)malonic acid diethyl ester (2d): ^{1}H NMR (CDCl$_3$, 200 MHz, $\delta\delta$ [ppm]) = 1.19 (t, $J = 7.3$ Hz, 6H), 2.44 (s, 3H), 3.15 (d, $J = 7.8$ Hz, 2H), 3.58 (t, $J = 7.8$ Hz, 1H), 4.14 (q, $J = 7.3$ Hz, 4H), 7.08−7.22 (m, 4H).

2-(4-Fluoro-benzyl)-malonic acid diethyl ester (2e): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.20 (t, $J = 7.2$ Hz, 6H), 3.14 (d, $J = 7.6$ Hz, 2H), 3.58 (t, $J = 7.6$ Hz, 1H), 4.13 (q, $J = 7.2$ Hz, 4H), 6.90−7.17 (m, 4H).

2-(3-Methylbenzyl)malonic acid diethyl ester (2f): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.21 (t, $J = 7.3$ Hz, 6H), 2.3 (s, 3H), 3.17 (d, $J = 7.6$ Hz, 2H), 3.62 (t, $J = 7.6$ Hz, 1H), 4.15 (q, $J = 7.3$ Hz, 4H), 7.0−7.19 (m, 4H). MS: 264.1 (41%, [M$^{•+}$]).

2-(3-Methoxybenzyl)malonic acid diethyl ester (2 g): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.20 (t, $J = 7.3$ Hz, 6H), 3.16 (d, $J = 7.8$ Hz, 2H), 3.63 (t, $J = 7.8$ Hz, 1H), 3.76 (s, 3H), 419 (q, $J = 7.3$ Hz, 4H), 6.70−6.80 (m, 3H), 7.10−7.25 (m, 1H). MS: 280.1 (68%, [M$^{•+}$]).

2-(3-Chlorobenzyl)malonic acid diethyl ester (2h): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.20 (t, $J = 7.3$ Hz, 6H), 3.16 (d, $J = 7.6$ Hz, 2H), 3.60 (t, $J = 7.6$ Hz, 1H), 4.15 (q, $J = 7.3$ Hz, 4H), 7.00−7.23 (m, 4H). MS: 284 (58%, [M$^{•+}$]).

2-Benzyl-2-[2-(dimethylamino)ethyl]malonic acid diethyl ester (3a). To a refluxing suspension of sodiumhydride (1.2 g, 50 mmol) in toluene (500 mL) was added dropwise 2-benzylmalonic acid diethyl ester (12.6 g, 50 mmol). The reaction mixture was refluxed for 1 h to give a clear yellow solution. (2-Chloroethyl)dimethylamine (5.4 g, 50 mmol) was added dropwise, and the reaction mixture was refluxed for 6 h. The resulting suspension was extracted with HCl (5%) (3 × 50 mL). The aqueous layers were combined, basified with NH$_4$OH (pH > 10), and extracted with ether (3 × 50 mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated to yield a yellow oil (9.2 g, 85%) ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.24 (t, $J = 7.3$ Hz, 6H), 1.91−1.97 (m, 2H), 2.20 (s, 6H), 2.27−2.34 (m, 2H), 3.18 (s, 2H), 4.18 (q, $J = 7.3$ Hz, 1H), 7.05−7.23 (m, 5H).

The following analogues were prepared using the procedure outlined for **3a** above.

2-[2-(Dimethylamino)ethyl]-2-(4-methylbenzyl)malonic acid diethyl ester (3b): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.25 (t, $J = 7.3$ Hz, 6H), 1.94 (t, $J = 7.5$ Hz, 2H), 2.18 (s, 6H), 2.3 (s, 3H), 2.31 (t, $J = 7.5$ Hz, 2H), 3.18 (s, 2H), 4.18 (q, $J = 7.3$ Hz, 1H), 6.92−7.10 (A,A′, B,B′, 4H). MS: 335.1 (3%, [M$^{•+}$]).

2-[2-(Dimethylamino)ethyl]-2-(4-methoxybenzyl)malonic acid diethyl ester (3c): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.22 (t, $J = 7.3$ Hz, 6H), 1.94 (t, $J = 7.2$ Hz, 2H), 2.18 (s, 6H), 2.28 (t, $J = 7.2$ Hz, 2H), 3.16 (s, 2H), 3.75 (s, 3H), 4.18 (q, $J = 7.3$ Hz, 4H), 6.74 (A,A′, 2H), 6.97 (B,B′, 2H).

2-(4-Chloro-benzyl-2-[2-(dimethylamino)ethyl]malonic acid diethyl ester (3d): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.24 (t, $J = 7.3$ Hz, 6H), 1.95 (t, $J = 8$ Hz, 2H), 2.18 (s, 6H), 2.28 (t, $J = 8$ Hz, 2H), 3.21 (s, 2H), 4.15 (q, $J = 7.3$ Hz, 4H), 7.04 (A,A′, 2H), 7.19 (B,B′, 2H). MS: 355.2 (4%, [M$^{•+}$]).

2-[2-(Dimethylamino)ethyl]-2-(4-methylsulfanylbenzyl)malonic acid diethyl ester (3e): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.23 (t, $J = 7.3$ Hz, 6H), 1.92−1.99 (m, 2H), 2.22 (s, 6H), 2.33 (m, 2H), 2.43 (s, 3H), 3.18 (s, 2H), 4.16 (q, $J = 7.3$ Hz, 4H), 7.04−7.36 (m, 4H).

2-[2-(Dimethylamino)ethyl]-2-(4-fluorobenzyl)malonic acid diethyl ester (3f): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.21 (t, $J = 7.3$ Hz, 6H), 1.88−1.97 (m, 2H), 2.21 (s, 6H), 2.25−2.33 (m, 2H), 3.20 (s, 2H), 4.13 (q, $J = 7.3$ Hz, 4H), 6.87−7.10 (m, 4H).

2-[2-(Dimethylamino)ethyl]-2-(3-methylbenzyl)malonic acid diethyl ester (3 g): IR (NaCl, ν [cm^{-1}]) = 1730 (C=O).

2-[2-(Dimethylamino)ethyl]-2-(3-methoxybenzyl)malonic acid diethyl ester (3h): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.20 (t, $J = 7.3$ Hz, 6H), 1.88−1.95 (m, 2H), 2.16 (s, 6H), 2.24−2.31 (m, 2H), 3.16 (s, 2H), 3.72 (s, 3H), 4.11 (q, $J = 7.3$ Hz, 4H), 6.60−6.72 (m, 3H), 7.06−7.14 (m, 1H).

2-(3-Chloro-benzyl)-2-[2-(dimethylamino)ethyl]malonic acid diethyl ester (3i): IR (NaCl, ν [cm^{-1}]) = 1725 (C=O).

2-Benzyl-2-[2-(*N*-benzyl-*N*-methylamino)ethyl]malonic acid diethyl ester (3j): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.19 (t, $J = 7.3$ Hz, 6H), 2.00 (m, 2H), 2.20 (s, 3H), 2.41 (m, 2H), 3.16 (s, 2H), 3.48 (s, 2H), 4.12 (q, $J = 7.3$ Hz, 4H), 6.95−7.21 (m, 10H).

2-Benzyl-2-[2-(diisopropylamino)ethyl]malonic acid diethyl ester (3k): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 0.94 (d, $J = 6.8$ Hz, 12H), 1.22 (t, $J = 7.3$ Hz, 6H), 1.85−1.93 (m, 2H), 2.35−2.43 (m, 2H), 2.92−2.98 (m, 2H), 3.23 (s, 2H), 4.16 (q, $J = 7.3$ Hz, 4H), 7.13−7.26 (m, 5H).

2-Benzyl-2-[2-(diethylamino)ethyl]malonic acid diethyl ester (3l): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 0.98 (t, $J = 7.1$ Hz, 6H), 1.21 (t, $J = 7.2$ Hz, 6H) 1.93 (t, $J = 7.7$ Hz, 2H), 2.50 (q, $J = 7.1$ Hz, 4H), 2.44−2.55 (m, 2H), 3.23 (s, 2H), 4.17 (q, $J = 7.2$ Hz, 4H), 7.07−7.25 (m, 5H).

2-Benzyl-2-(2-piperidin-1-ylethyl)malonic acid diethyl ester (3m): MS: 361.1 (7%, [M$^{•+}$]).

2-Benzyl-2-(2-morpholin-4-ylethyl)malonic acid diethyl ester (3n): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.24 (t, $J = 7.3$ Hz, 6H), 1.96 (t, $J = 7.2$ Hz, 2H), 2.35−2.41 (m, 6H), 3.24 (s, 2H), 3.66 (t, $J = 4.5$ Hz, 4H), 7.05−7.25 (m, 5H), 4.20 (q, $J = 7.3$ Hz, 4H). MS: 363.3 (1%, [M$^{•+}$]).

2-Benzyl-2-(2-pyrrolidin-1-yl-ethyl)malonic acid diethyl ester (3o): ^{1}H NMR (CDCl$_3$, 400 MHz, δ [ppm]) = 1.20 (t, $J = 7.3$ Hz, 6H), 1.72 (bs, 4H), 1.98−2.02 (m, 2H), 2.45−2.50 (m, 6H), 3.22 (s, 2H), 4.14 (q, $J = 7.3$ Hz, 4H), 7.07−7.23 (m, 5H). MS: 347.1 (2%, [M$^{•+}$]).

2-Benzyl-2-[2-(dimethylamino)propyl]malonic acid diethyl ester (3p): MS: 335.2 (0.2%, [M$^{•+}$]).

2-Benzyl-2-[2-(dimethylamino)ethyl]malonic Acid (4a). A solution of **3a** (33.5 g, 0.1 mol), NaOH (14 g, 0.35 mol), ethanol (100 mL) and water (50 mL) were refluxed for 4 h. The resulting suspension was evaporated and the residue dissolved in water (50 mL). Acetic acid was added dropwise while cooling (5 °C) until a white solid was formed. The solid product was filtered, washed with cold water (2 × 30 mL) and ethanol (20 mL), and dried in a vacuum oven at 50 °C for 2 days to give a white-yellow solid (20.4 g, 77%).

2-[2-(Dimethylamino)ethyl]indan-1-one (5a). **4a** (13.25 g, 50 mmol) was added to polyphosphoric acid (80 g) at 90−120 °C with overhead stirring. After the addition, the resulting brown reaction mixture was heated to 140−150 °C and stirred for 20 min at this temperature range. The reaction was quenched with the cautious addition of ice chips, neutralized with K_2CO_3 (2 M), and basified with NaOH (3 M). The mixture was extracted with ether (3 × 100 mL), washed with water (100 mL), dried (Na_2SO_4), and evaporated to give a yellow oil (4.2 g, 41%) ^{1}H NMR (CDCl$_3$, 200 MHz, dδ [ppm]) = 1.59−1.64 (m, 1H), 2.10−2.16 (m, 1H), 2.23 (s, 6H), 2.39−2.45 (m, 2H), 2.69−2.75 (m, 1H), 2.79 (dd, ^2J = 17.3 Hz, J = 4.4 Hz, 1H), 3.31 (dd, ^2J = 17.3 Hz, J = 9.4 Hz, 1H), 7.28 (d, J = 7.4 Hz, 1H), 7.38 (t, J = 7.4 Hz, 1H), 7.53 (t, J = 7.4 Hz, 1H), 7.69 (d, J = 7.4 Hz, 1H). MS: 203.2 (4%, [M•+]).

The following analogues were prepared using the procedure outlined for **5a** above.

2-[2-(Dimethylamino)ethyl]-6-methylindan-1-one (5b): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.39−1.57 (m, 1H), 1.99−2.13 (m, 1H), 2.15 (s, 6H), 2.30 (s, 3H), 2.31−2.40 (m, 2H), 2.70 (dd, ^2J = 17.4 Hz, J = 4.4 Hz, 1H), 3.21 (dd, ^2J = 17.4 Hz, J = 9.3 Hz, 1H), 7.24−7.44 (m, 3H).

2-[2-(Dimethylamino)ethyl]-6-methoxyindan-1-one (5c): MS: 233.2 (25%, [M•+]).

6-Chloro-2-[2-(dimethylamino)ethyl]indan-1-one (5d): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.45−1.59 (m, 1H), 2.00−2.15 (m, 1H), 2.13 (s, 6H), 2.24−2.32 (m, 2H), 2.61−2.67 (m, 1H), 2.68−2.78 (m, 1H), 3.21 (dd, ^2J = 17.5 Hz, J = 9 Hz, 1H), 7.24−7.54 (m, 3H).

2-[2-(Dimethylamino)ethyl]-6-methylsulfanylindan-1-one (5e): IR (NaCl, ν [cm^{-1}]) = 1700 (C=O).

2-[2-(Dimethylamino)ethyl]-6-fluoroindan-1-one (5f): IR (NaCl, ν [cm^{-1}])) = 1710 (C=O).

2-[2-(Dimethylamino)ethyl]-5-methylindan-1-one (5 g): MS: 217 (5%, [M•+]).

2-[2-(Dimethylamino)ethyl]-5-methoxyindan-1-one (5h): IR (NaCl, ν [cm^{-1}]) = 1700 (C=O).

5-Chloro-2-[2-(dimethylamino)ethyl]indan-1-one (5i): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.51−1.65 (m, 1H), 2.03−2.13 (m, 1H), 2.18 (s, 6H), 2.25−2.41 (m, 2H), 2.65−2.73 (m, 1H), 2.75−2.82 (m, 1H), 3.29 (dd, ^2J = 17.4 Hz, J = 4.4 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.40 (s, 1H), 7.63 (d, J = 8.1 Hz, 1H). MS: 239.1 (0.4%) and 237.1 (1%) [M•+].

2-(2-Morpholin-4-ylethyl)indan-1-one (5j): IR (NaCl, ν [cm^{-1}]) = 1695 (C=O).

2-(2-Pyrrolidin-1-ylethyl]indan-1-one (5k): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.63−1.75 (m, 5H), 2.10−2.22 (m, 1H), 2.47−2.61 (m, 6H), 2.62−2.71 (m, 1H), 2.81 (dd, ^2J = 17.4 Hz, J = 4.4 Hz, 1H), 3.32 (dd, ^2J = 17.4 Hz, J = 9.4 Hz, 1H), 7.28−7.78 (m, 4H).

2-(2-Piperidin-1-ylethyl]indan-1-one (5l): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.31−1.45 (m, 6H), 1.58−1.69 (m, 1H), 2.02−2.14 (m, 1H), 2.28−2.40 (m, 6H), 2.54−2.68 (m, 1H), 2.76 (dd, ^2J = 17 Hz, J = 4.3 Hz, 1H), 3.24 (dd, ^2J = 17 Hz, J = 7.9 Hz, 1H), 7.27−7.68 (m, 4H). MS: 242.9 (10%, [M•+]).

2-[2-(Diethylamino)ethyl]indan-1-one (5m): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 0.99 (t, J = 7.1 Hz, 6H), 1.52−1.66 (m, 1H), 2.06−2.21 (m, 1H), 2.45−2.56 (m, 4H), 2.55−2.68 (m, 3H), 2.78 (dd, ^2J = 17.4 Hz, J = 4.4 Hz, 1H), 3.31 (dd, ^2J = 17.4 Hz, J = 9.3 Hz, 1H), 7.28−7.77 (m, 4H).

2-[2-(Diisopropylamino)ethyl]indan-1-one (5n): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.00 (m, 12H), 1.47−1.54 (m, 1H), 2.09−2.16 (m, 1H), 2.59 (m, 2H), 2.77−2.86 (m, 2H), 3.02−3.08 (m, 2H), 3.34 (dd, ^2J = 18.5 Hz, J = 8.3 Hz, 1H), 7.30−7.75 (m, 4H).

2-[2-(Benzylmethylamino)ethyl]indan-1-one (5o): IR (NaCl, ν [cm^{-1}]) = 1705 (C=O).

2-[2-(Dimethylamino)propyl]indan-1-one (5p): IR (NaCl, ν [cm^{-1}]) = 1705 (C=O).

Dimethyl{2-[5-methyl-3-(1-pyridin-2-ylethyl)-1H-inden-2-yl]ethyl}amine (6). To a solution of 2-ethylpyridine (2.35 g, 22 mmol) in dry ether (40 mL) was added 1.6 M butyllithium (12.5 mL, 20 mmol) at −78 °C under nitrogen and stirred for 2 h at this temperature. To the dark red solution, **5b** (2.18 g, 10 mmol) was added dropwise and stirred overnight at RT. The reaction was quenched with cold water, washed with saturated NaHCO$_3$ (2 × 50 mL) and extracted with HCl (20%) (2 × 25 mL). The water layer was refluxed for 1 h, cooled to RT, basified with NH$_4$OH sol. and extracted with ether (3 × 50 mL). The ether was dried (Na$_2$SO$_4$) and evaporated to leave a brown oil. This oil was purified by flash chromatography eluting with toluene: acetone: methanol: NH$_4$OH concentrated 60:30:8:2, to yield a yellow oil (1.94 g, 63%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ [ppm]) = 1.75 (d, J = 7.2 Hz, 3H), 2.22 (s, 3H), 2.25 (s, 6H), 2.37−2.52 (m, 2H), 2.61−2.74 (m, 2H), 3.33 (s, 2H), 4.45 (q, J = 7.2 Hz, 1H), 6.85−7.51 (m, 6H), 8.60 (d, J = 4.8 Hz, 1H). MS: 306.1 (44%, [M•+]). Anal. (C$_{21}$H$_{26}$N$_2$·C$_4$H$_4$O$_4$· 0.1H$_2$O) C, H, N, mp 117−118 °C.

The following analogues were prepared using the procedure outlined for **6** above.

{2-[5-Methoxy-3-(1-pyridin-2-ylethyl)-1H-inden-2-yl]methyl}dimethylamine (7): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.74 (d, J = 6.8 Hz, 3H), 2.28 (s, 6H), 2.47−2.54 (m, 2H), 2.67−2.76 (m, 2H), 3.32 (s, 2H), 3.65 (s, 3H), 4.44 (q, J = 6.8 Hz, 1H), 6.58−6.63 (m, 2H), 7.05−7.24 (m, 3H), 7.46−7.54 (m, 1H), 8.59 (d, J = 4.9 Hz, 1H). MS: 322.2 (1%, [M•+]). Anal. (C$_{21}$H$_{26}$N$_2$O·C$_4$H$_4$O$_4$) C, H, N, mp 117−118 °C.

{2-[5-Chloro-3-(1-pyridin-2-ylethyl)-1H-inden-2-yl]methyl}dimethylamine (8): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.72 (d, J = 7.3 Hz, 3H), 2.23 (s, 6H), 2.41−2.48 (m, 2H), 2.59−2.67 (m, 2H), 3.34 (s, 2H), 4.43 (q, J = 7.3 Hz, 1H), 6.96−7.19 (m, 5H), 7.46−7.50 (m,1H), 8.59 (d, J = 4.5 Hz, 1H). MS: 326.0 (16%, [M•+]). Anal. (C$_{20}$H$_{23}$ClN$_2$·C$_4$H$_4$O$_4$) C, H, N, mp 118−119 °C.

Dimethyl{2-[5-methylsulfanyl-3-(1-pyridin-2-ylethyl)-1H-inden-2-yl]ethyl}amine (9): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.74 (d, J = 7.3 Hz, 3H), 2.32 (s, 6H), 2.35 (s, 3H), 2.49−2.77 (m, 4H), 3.35 (s, 2H), 4.45 (q, J = 7.3 Hz, 1H), 6.96−7.26 (m, 5H), 7.48−7.55 (m, 1H), 8.60 (d, J = 4.8 Hz, 1H). Anal. (C$_{21}$H$_{26}$N$_2$S·C$_4$H$_4$O$_4$·0.02H$_2$O) C, H, N, mp 97−98 °C.

{2-[5-Fluoro-3-(1-pyridin-2ylethyl)-1H-inden-2-yl]ethyl}dimethylamine (10): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.72 (d, J = 7.2 Hz, 3H), 2.23 (s, 6H), 2.45−2.53 (m, 2H), 2.66−2.74 (m, 2H), 3.32 (s, 2H), 4.43 (q, J = 7.2 Hz, 1H), 6.67−6.76 (m, 2H), 7.01−7.23 (m, 3H), 7.46−7.54 (m, 1H), 8.59 (d, J = 4.9 Hz, 1H). Anal. (C$_{20}$H$_{23}$FN$_2$·C$_4$H$_4$O$_4$) C, H, N, mp 131−132 °C.

{3-[6-Methyl-3-(1-pyridin-2-ylethyl)-1H-inden-2-yl]ethyl}dimethylamine (11): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.72 (d, J = 7.2 Hz, 3H), 2.22 (s, 3H), 2.26 (s, 6H), 2.42−2.49 (m, 2H), 2.63−2.70 (m, 2H), 3.34 (s, 2H), 4.43 (q, J = 7.2 Hz, 1H), 6.85−7.49 (m, 6H), 8.60 (d, J = 4.8 Hz, 1H). Anal. (C$_{21}$H$_{26}$N$_2$·C$_4$H$_4$O$_4$·0.05H$_2$O) C, H, N, mp 120−121 °C.

{3-[6-Methoxy-3-(1-pyridin-2-ylethyl)-1H-inden-2-yl]ethyl}dimethylamine (12): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.72 (d, J = 7.5 Hz, 3H), 2.26 (s, 6H), 2.42−2.49 (m, 2H), 2.63−2.70 (m, 2H), 3.34 (s, 2H), 3.75 (s, 3H), 4.43 (q, J = 7.5 Hz, 1H), 6.58−6.64 (m, 1H), 6.86−6.90 (m, 1H), 6.95−6.96 (m, 1H), 7.03−7.09 (m, 1H), 7.13−7.17 (m, 1H), 7.44−7.52 (m, 1H), 8.60 (d, J = 4.8 Hz, 1H). Anal. (C$_{21}$H$_{26}$N$_2$O·C$_4$H$_4$O$_4$) C, H, N, mp 119−120 °C.

{2-[6-Chloro-3-(1-pyridin-2-ylethyl)-1H-inden-2-yl]ethyl}dimethylamine (13): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.72 (d, J = 7.3 Hz, 3H), 2.23 (s, 6H), 2.41−2.48 (m, 2H), 2.59−2.67 (m, 2H), 3.34 (s, 2H), 4.44 (q, J = 7.3 Hz, 1H), 6.87−6.95 (m, 1H), 7.00−7.17 (m, 3H), 7.31 (m, 1H), 7.46−

7.50 (m, 1H), 8.59 (d, J = 4.5 Hz, 1H). Anal. ($C_{20}H_{23}ClN_2$·$C_4H_4O_4$) C, H, N, mp 115−116 °C.

{2-[6-Chloro-3-(1-pyridin-2-ylpropyl)-1H-inden-2-yl]ethyl}dimethylamine (14): ^{1}H NMR (CDCl₃, 200 MHz, δ [ppm]) = 0.93 (t, J = 7.4 Hz, 3H), 2.30 (s, 6H), 2.44−2.81 (m, 6H), 3.39 (s, 2H), 4.13−4.21 (m, 1H), 7.01−7.31 (m, 5H), 7.42−7.51 (m, 1H), 8.58 (d, J = 4.8 Hz, 1H). Anal. ($C_{21}H_{25}ClN_2$·$C_4H_4O_4$) C, H, N, mp 119−120 °C.

2-{1-[2-(2-Piperidin-1-ylethyl)-1H-inden-2-yl]ethyl}pyridine (15): ^{1}H NMR (CDCl₃, 400 MHz, δ [ppm]) = 1.41−1.44 (m, 2H), 1.60 (quint, 4H), 1.75 (d, J = 7.3 Hz, 3H), 2.44−2.57 (m, 6H), 2.72−2.77 (m, 2H), 3.37 (s, 2H), 4.47 (q, J = 7.3 Hz, 1H), 6.99−7.08 (m, 4H), 7.16 (m, 1H), 7.35 (m, 1H), 7.47 (m, 1H), 8.59 (d, J = 4.9 Hz, 1H). MS: 332.1 (2%, [M⁺]). Anal. ($C_{23}H_{28}N_2$·$C_4H_4O_4$·0.16H₂O) C, H, N, mp 114−115 °C.

4-{-2-[3-(1-Pyridin-2-ylethyl)-1H-inden-2-yl]ethyl}morpholine (16): ^{1}H NMR (CDCl₃, 200 MHz, δ [ppm]) = 1.78 (d, J = 7.3 Hz, 3H), 2.47−2.60 (m, 6H), 2.70−2.79 (m, 2H), 3.41 (s, 2H), 3.71 (t, J = 5.9 Hz, 4H), 4.48 (q, J = 7.3 Hz, 1H), 7.0−7.21 (m, 5H), 7.33−7.40 (m, 1H), 7.47−7.52 (m, 1H), 8.61 (d, J = 4.5 Hz, 1H). MS: 334.3 (2%, [M⁺]). Anal. ($C_{22}H_{26}N_2O$·$C_4H_4O_4$) C, H, N, mp 119−120 °C.

2-{1-[2-(3-Pyrrolidin-1-ylethyl)-1H-inden-2-yl]ethyl}pyridine (17): ^{1}H NMR (CDCl₃, 200 MHz, δ [ppm]) = 1.72−1.80 (m, 7H), 2.57−2.82 (m, 8H), 3.40 (s, 2H), 4.48 (q, J = 7.4 Hz, 1H), 6.98−7.11 (m, 4H), 7.17−7.20 (m, 1H), 7.34−7.39 (m, 1H), 7.48−7.53 (m, 1H), 8.60 (d, J = 6.3 Hz, 1H). Anal. ($C_{22}H_{26}N_2$·$C_4H_4O_4$·0.66 H₂O) C, H, N, mp 131−132 °C.

Diethyl{2-[3-(1-pyridin-2-ylethyl)-1H-inden-2-yl]ethyl}amine (18): ^{1}H NMR (CDCl₃, 200 MHz, δ [ppm]) = 1.04 (t, J = 7.6 Hz, 6H), 1.75 (d, J = 7.3 Hz, 3H), 2.56 (q, J = 7.6 Hz, 4H), 2.51−2.74 (m, 4H), 3.39 (s, 2H), 4.48 (q, J = 7.3 Hz, 1H), 7.00−7.11 (m, 4H), 7.14−7.17 (m, 1H), 7.33−7.40 (m, 1H), 7.46−7.52 (m, 1H), 8.59 (d, J = 4.5 Hz, 1H). Anal. ($C_{22}H_{28}N_2$·$C_4H_4O_4$) C, H, N, mp 90−91 °C.

Diisopropyl{2-[3-(1-pyridin-2-ylethyl)-1H-inden-2-yl]ethyl}amine (19): ^{1}H NMR (CDCl₃, 200 MHz, δ [ppm]) = 1.04 (m, 12H) 1.77 (d, J = 7.3 Hz, 3H), 2.62 (m, 4H), 3.06 (m, 2H), 3.41 (s, 2H), 4.46 (q, J = 7.3 Hz, 1H), 7.00−7.22 (m, 5H), 7.33−7.37 (m, 1H), 7.43−7.48 (m, 1H), 8.59 (d, J = 3.9 Hz, 1H). Anal. ($C_{24}H_{32}N_2$·$C_7H_8SO_3$) C, H, N. Exact mass ($C_{24}H_{33}N_2^+$·$C_7H_7SO_3^−$): 349.2638 ± 1.2 ppm, mp 175−176 °C.

Dimethyl{3-[5-methyl-3-(1-pyridin-2-ylethyl)-1H-inden-2-yl]propyl}amine (22): ^{1}H NMR (CDCl₃, 200 MHz, δ [ppm]) = 1.20−1.27 (m, 2H), 1.73 (d, J = 7.2 Hz, 3H), 2.26 (s, 6H), 2.43−2.51 (m, 2H), 2.66−2.74 (m, 2H), 3.36 (s, 2H), 4.44 (q, J = 7.2 Hz, 1H), 6.99−7.26 (m, 6H), 7.49−7.57 (m, 1H), 8.61 (d, J = 4.8 Hz, 1H). Anal. ($C_{21}H_{26}N_2$·$C_4H_4O_4$) C, H, N, mp 149−150 °C.

Dimethyl{2-[3-(1-pyridin-2-ylpropyl)-1H-inden-2-yl]ethyl}amine (23): ^{1}H NMR (CDCl₃, 200 MHz, δ [ppm]) = 0.93 (t, J = 7.4 Hz, 3H), 2.27 (s, 6H), 2.43−2.78 (m, 6H), 3.39 (s, 2H), 4.15−4.23 (m, 1H), 7.03−7.47 (m, 7H), 8.58 (d, J = 4.8 Hz, 1H). Anal. ($C_{21}H_{26}N_2$·$C_4H_4O_4$) C, H, N, mp 118−119 °C.

Dimethyl{2-[3-(1-pyridin-2-ylbutyl)-1H-inden-2-yl]ethyl}amine (24): ^{1}H NMR (CDCl₃, 200 MHz, δ [ppm]) = 0.94 (t, J = 7.2 Hz, 3H), 1.24−1.39 (m, 2H), 2.09−2.23 (m, 2H), 2.29 (s, 6H), 2.42−2.53 (m, 2H), 2.71−2.86 (m, 2H), 3.40 (s, 2H), 4.27−4.34 (m, 1H), 7.01−7.50 (m, 7H), 8.57−8.60 (d, J = 4.8 Hz, 1H). Anal. ($C_{22}H_{28}N_2$·$C_4H_4O_4$) C, H, N, mp 107−108 °C.

Dimethyl{2-[3-(phenylpyridin-2-ylmethyl)-1H-inden-2-yl]ethyl}amine (25): ^{1}H NMR (CDCl₃, 200 MHz, δ [ppm]) = 2.13 (s, 6H), 2.25−2.33 (m, 2H), 2.52−2.61 (m, 2H), 3.43 (s, 2H), 5.82 (s, 1H), 6.79−7.38 (m, 11H), 7.51−7.60 (m, 1H), 8.58 (d, J = 4.5 Hz, 1H). MS: 91.1 (100%, [C_7H_7⁺]). Anal. ($C_{25}H_{31}N_2$·$C_4H_4O_4$·H₂O) C, H, N, mp 146−147 °C.

Dimethyl{2-[3-(1-methyl-1-pyridin-2-ylethyl)-1H-inden-2-yl]ethyl}amine (26): ^{1}H NMR (CDCl₃, 200 MHz, δ [ppm]) = 1.81 (s, 6H), 2.28 (s, 6H), 2.50−2.58 (m, 2H), 2.84−2.92 (m, 2H), 3.44 (s, 2H), 6.46 (d, J = 7.3 Hz, 1H), 6.85−7.50 (m, 6H), 8.59 (d, J = 4.8 Hz, 1H). Anal. ($C_{21}H_{26}N_2$·$C_4H_4O_4$) C, H, N, mp 128−129 °C.

Dimethyl[2-(3-pyridin-2-ylmethyl-1H-inden-2yl)ethyl]amine (27): ^{1}H NMR (CDCl₃, 200 MHz, δ [ppm]) = 2.34 (s, 6H), 2.55−2.63 (m, 2H), 2.76−2.84 (m, 2H), 3.41 (s, 2H), 4.09 (s, 2H), 7.05−7.52 (m, 7H), 8.52 (d, J = 4.9 Hz, 1H). MS: 278.4 (0.1%, [M⁺]). Anal. ($C_{19}H_{22}N_2$·$C_4H_4O_4$) C, H, N, mp 139−140 °C.

Dimethyl[2-(3-pyridin-4-ylmethyl-1H-inden-2yl)ethyl]amine (28): ^{1}H NMR (CDCl₃, 200 MHz, δ [ppm]) = 2.22 (s, 6H), 2.40−2.50 (m, 2H), 2.63−2.73 (m, 2H), 3.41 (s, 2H), 3.90 (s, 2H), 6.96−7.20 (m, 5H), 7.37−7.43 (m, 1H), 8.42 (d, J = 4.9 Hz, 2H). Anal. ($C_{19}H_{22}N_2$·$C_4H_4O_4$·0.07H₂O) C, H, N, mp 147−148 °C.

Dimethyl[3-(1-pyridin-2-ylethyl)-1H-inden-2-ylmethyl]amine (31): ^{1}H NMR (CDCl₃, 200 MHz, δ [ppm]) = 1.75 (d, J = 7.3 Hz, 3H), 2.24 (s, 6H), 3.34 (d, ^2J = 14 Hz, 1H), 3.40 (d, ^2J = 14 Hz, 1H), 3.51 (s, 2H), 4.59 (q, J = 7.3 Hz, 1H), 7.05−7.16 (m, 5H), 7.39−7.41 (m, 1H), 7.48 (dt, J = 7.8 Hz, ^4J = 1.9 Hz, 1H), 8.60 (d, J = 4.4 Hz, 1H). Anal. ($C_{19}H_{22}N_2$·$C_4H_4O_4$) C, H, N, mp 162−163 °C.

Isopropylmethyl[3-(1-pyridin-2-ylethyl)-1H-inden-2-ylmethyl]amine (32). ^{1}H NMR (CDCl₃, 400 MHz, δ [ppm]) = 1.06 (d, J = 6.8 Hz, 6H), 1.75 (d, J = 6.8 Hz, 3H), 2.19 (s, 3H), 2.98 (sept, J = 6.8 Hz, 1H), 3.50 (s, 2H), 3.56 (s, 2H), 4.58 (q, J = 6.8 Hz, 1H), 7.05−7.16 (m, 5H), 7.36−7.53 (m, 2H), 8.58−8.60 (m, 1H). Anal. ($C_{21}H_{24}N_2$) C, H, N, oil.

Benzylmethyl{2-[[3-(1-pyridin-2-ylethyl)-1H-inden-2-yl]ethyl}amine (39): ^{1}H NMR (CDCl₃, 200 MHz, δ [ppm]) = 1.72 (d, J = 7.3 Hz, 3H), 2.28 (s, 3H), 2.58−2.77 (m, 4H), 3.33 (s, 2H), 3.56 (s, 2H), 4.43 (q, J = 7.3 Hz, 1H), 7.03−7.49 (m, 12H), 8.58 (d, J = 4.9 Hz, 1H).

Methyl{2-[3-(1-pyridin-2-ylethyl)-1H-inden-2yl]ethyl}amine (40). To a solution of **39** (4.8 g, 12.7 mmol) in ethanol (30 mL) was added formic acid (95%) (2.5 g, 51 mmol). This solution was added to freshly activated palladium on charcoal (10%) (0.72 g) in ethanol (20 mL) and stirred for 12 h under H₂. The catalyst was filtered and the solvent evaporated to leave an orange oil. The oil was purified by flash chromatography (silica gel) eluting with toluene:acetone:methanol: NH₄OH concentrated 60:30:8:2 to give a yellow oil (1.68 g, 47.6%). ^{1}H NMR (CDCl₃, 200 MHz, δ [ppm]) = 1.75 (d, J = 7.3 Hz, 3H), 2.45 (s, 3H), 2.73−2.85 (m, 4H), 3.38 (s, 2H), 4.50 (q, J = 7.3 Hz, 1H), 6.96−7.16 (m, 4H), 7.25 (d, J = 7.8 Hz, 1H), 7.31−7.38 (m, 1H), 7.54 (dt, J = 7.3 Hz, ^4J = 2 Hz, 1H), 8.54 (d, J = 4.9 Hz, 1H).

(2-Fluoroethyl)methyl{2-[3-(1-pyridin-2-ylethyl)-1H-inden-2-yl]ethyl}amine (20). To a suspension of K₂CO₃ (1.4 g, 10 mmol) in acetone (20 mL) was added **40** (1.39 g, 5 mmol) and 1-bromo-2-fluoro-ethan (0.63 g, 5 mmol). The reaction mixture was refluxed for 4 h. The suspension was filtered and the solvent was evaporated to leave a yellow oil. This oil was purified by flash chromatography (silica gel) eluting with toluene: acetone: methanol: NH₄OH concentrated 60:30:8:2 to give a yellow oil (0.48 g, 29%). ^{1}H NMR (CDCl₃, 200 MHz, δ [ppm]) = 1.75 (d, J = 7.3 Hz, 3H), 2.35 (s, 3H), 2.60−2.74 (m, 4H), 2.74 (dt, J_{HF} = 27.3 Hz, J_{HH} = 4.9 Hz, 2H), 3.39 (s, 2H), 4.47 (q, J = 7.3 Hz, 1H), 4.53 (dt, J_{HF} = 47.3 Hz, J_{HH} = 4.9 Hz, 2H), 7.02−7.11 (m, 4H), 7.17 (d, J = 7.8 Hz, 1H), 7.49 (dt, J = 7.3 Hz, ^4J = 2 Hz, 1H), 8.59 (d, J = 4.9 Hz, 1H). Anal. ($C_{21}H_{25}FN_2$·$C_4H_4O_4$) C, H, N, mp 118−119 °C.

The following analogue was prepared using the procedure outlined for **20** above.

Isopropyl-methyl-{2-[3-(1-pyridin-2-yl-ethyl)-1H-inden-2-yl]ethyl}-amine (21): ^{1}H NMR (CDCl₃, 200 MHz, δ [ppm]) = 1.00 (d, J = 6.8 Hz, 6H), 1.76 (d, J = 6.8 Hz, 3H), 2.25 (s, 3H), 2.56−2.74 (m, 4H), 2.87 (sept, J = 6.8 Hz, 1H), 3.39 (s, 2H), 4.47 (q, J = 6.8 Hz, 1H), 6.98−7.10 (m, 4H), 7.18 (d, J = 7.8 Hz, 1H), 7.43−7.37 (m, 1H), 7.48 (dt, J = 7.3 Hz, ^2J = 2 Hz, 1H), 8.58 (d, J = 4.9 Hz, 1H). Anal. ($C_{22}H_{28}N_2$·$C_4H_4O_4$) C, H, N.

Dimethyl{2-[3-(1-phenylethyl)-1H-indene-2-yl]ethyl-amine (30). To a solution of 1-brom*o*-ethyl-benzene (3.7 g, 20 mmol) in dry ether (50 mL) was added lithium (0.14 g, 20 mmol) under nitrogen and stirred for 1 h. **5a** (4.05 g, 20 mmol) was added dropwise and the reaction mixture was stirred

overnight. The suspension was quenched with ice chips. The organic layer was washed with water (2 × 30 mL) and extracted with HCl (20%) (2 × 25 mL). The water layer was refluxed for 1 h, basified with NH$_4$OH (pH>10), and extracted with ether (3 × 30 mL). The ether layer was dried (Na$_2$SO$_4$) and evaporated to leave a brown oil. This oil was purified by flash chromatography (silica gel) eluting with toluene: acetone: methanol: NH$_4$OH concentrated 60:30:8:2 to give a yellow oil (0.62 g, 21%). ^{1}H NMR (CDCl$_3$, 400 MHz, dδ [ppm]) = 1.68 (d, J = 7.2 Hz, 3H), 2.27 (s, 6H), 2.41−2.54 (m, 4H), 3.37 (s, 2H), 4.37 (q, J = 7.2 Hz, 1H), 6.96−7.36 (m, 9H). MS: 291 (0.2%, [M$^{+•}$]). Anal. (C$_{21}$H$_{25}$N·C$_4$H$_4$O$_4$) C, H, N, mp 159−160 °C.

[2-(1*H*-Inden-2-yl)ethyl]dimethylamine (38). To a solution of **5a** (8.1 g, 40 mmol) in ethanol (100 mL) was added sodiumborohydride (0.96 g, 40 mmol) portionwise with stirring. The reaction mixture was refluxed for 2 h, concentrated in vacuo and diluted with water (150 mL). The emulsion was extracted with ether (3 × 100 mL), dried (Na$_2$SO$_4$) and evaporated to give a yellow oil of 2-[2-(dimethylamino)-ethyl]-indan-1-ole. To this oil acetic acid (90 mL) and HCl concentrated (35 mL) were added and refluxed for 90min. Most of the solvent was evaporated in vacuo, the residue diluted with water (100 mL), basified with NH$_4$OH (pH>10), extracted with ether (2 × 100 mL), dried (Na$_2$SO$_4$) and concentrated to give a yellow oil (7.2 g, 96%). ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 2.30 (s, 6H), 2.54−2.69 (m, 4H), 3.33 (s, 2H), 6.53 (s, 1H), 7.08−7.38 (m, 4H).

Dimethyl[2-(3-pyridin-3-ylmethyl-1*H*-inden-2-yl)ethyl]-amine (29). To a solution of **38** (0.94 g, 5.0 mmol) in THF (50 mL) was added butyllithium 1.6 M (3.1 mL, 5.0 mmol). This mixture was stirred for 1 h at −78 °C under nitrogen. 3-Chloromethylpyridine (0.64 g, 5.0 mmol) was added, the reaction mixture was stirred for 6 h at RT and the solvent was evaporated. The residue was diluted with ether (50 mL), washed with water (2 × 30 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo to leave a brown oil. This oil was purified by flash chromatography (silica gel) eluting with toluene: acetone: methanol: NH$_4$OH concentrated 60:30:8:2 to give a yellow oil (0.9 g, 64%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ [ppm]) = 2.27 (s, 6H), 2.47−2.51 (m, 2H), 2.70−2.74 (m, 2H), 3.41 (s, 2H), 3.90 (s, 2H), 7.04−7.17 (m, 3H), 7.22−7.25 (m, 1H), 7.38 (m, 1H), 7.44−7.47 (m, 1H), 8.39−8.41 (m, 1H), 8.53 (m, 1H). Anal. (C$_{19}$H$_{22}$N$_2$·C$_4$H$_4$O$_4$) C, H, N, mp 116−117 °C.

The following analogues were prepared using the procedure outlined for **29** above.

3-Pyridin-2-ylmethyl-1*H*-indene-2-carboxylic acid 2-(dimethylamino)ethyl ester (33): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 2.35 (s, 6H), 2.72 (t, J = 5.8 Hz, 2H), 3.76 (s, 2H), 4.39 (t, J = 5.8 Hz, 2H), 4.68 (s, 2H), 7.04−7.09 (m, 1H), 7.18−7.34 (m, 3H), 7.44−7.56 (m, 3H), 8.51 (d, J = 4.4 Hz, 1H). Anal. (C$_{20}$H$_{22}$N$_2$O$_2$·2 C$_4$H$_4$O$_4$·0.42 H$_2$O) C, H, N, mp 134−135 °C.

3-Pyridin-3-ylmethyl-1*H*-indene-2-carboxylic acid 2-(dimethylamino)ethyl ester (34): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 2.32 (s, 6H), 2.67 (t, J = 5.8 Hz, 2H), 3.75 (s, 2H), 4.36 (t, J = 5.8 Hz, 2H), 4.46 (s, 2H), 7.10−7.59 (m, 6H), 8.41 (m, 1H), 8.61 (m, 1H). Anal. (C$_{20}$H$_{22}$N$_2$O$_2$·2 C$_4$H$_4$O$_4$·0.16 H$_2$O) C, H, N, mp 77−78 °C.

3-Pyridin-2-ylmethyl-1*H*-indene-2-carboxylic acid 2-(dimethylamino)ethyl amide (35): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 2.23 (s, 6H), 2.51−2.58 (m, 2H), 3.52−3.61 (m, 2H), 3.73 (s, 2H), 4.28 (s, 2H), 7.07−7.28 (m, 3H), 7.40−7.45 (m, 3H), 7.57−7.62 (m, 1H), 8.43 (d, J = 4.3 Hz, 1H), 9.85 (m, 1H). Anal. (C$_{20}$H$_{23}$N$_3$O·C$_4$H$_4$O$_4$·0.13H$_2$O) C, H, N, mp 114−115 °C.

3-Pyridin-3-ylmethyl-1*H*-indene-2-carboxylic acid 2-(dimethylaminoethyl) amide (36): ^{1}H NMR (CDCl$_3$, 400 MHz, δ [ppm]) = 2.25 (s, 6H), 2.47 (t, J = 5.9 Hz, 2H), 3.42−3.47 (m, 2H), 3.67 (s, 2H), 4.47 (s, 2H), 6.54 (m, 1H), 7.10−7.13 (m, 2H), 7.24−7.27 (m, 2H), 7.32−7.35 (m, 1H), 7.43−7.45 (m, 1H), 7.62 (m, 1H), 8.37 (d, J = 3.8 Hz, 1H), 8.60 (m, 1H). Anal. (C$_{20}$H$_{23}$N$_3$O·2 C$_4$H$_4$O$_4$) C, H, N, mp 116−117 °C.

3-Pyridin-4-ylmethyl-1*H*-indene-2-carboxylic acid 2-(dimethylamino)ethyl amide (37): ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 2.23 (s, 6H), 2.45−2.51 (m, 2H), 3.41−3.49 (m, 2H), 3.70 (s, 2H), 4.48 (s, 2H), 6.59 (m, 1H), 7.21−7.28 (m, 5H),

7.44−7.46 (m, 1H), 8.42 (m, 2H). Anal. (C$_{20}$H$_{23}$N$_3$O·2 C$_4$H$_4$O$_4$) C, H, N, mp 126−127 °C.

Benzyl(2-chloroethyl)methylamine Hydrochloride (41a). To 2-(benzyl-methyl-amino)-ethanol (40.3 g, 0.2 mol) was added dropwise HCl (15%) to pH<2. Chloroform (200 mL) was added and the emulsion was refluxed under Dean−Stark conditions until water was no longer separated. Chloroform was evaporated and to the oily residue was added dropwise thionyl chloride (35.7 g, 0.3 mol) under external ice-cooling. The reaction mixture was then refluxed for 3 h. The excess of thionyl chloride was evaporated in vacuo, the residue was washed with cold ethanol (100 mL) and dried in a vacuum oven overnight at RT to give a white solid (41.7 g, 94%). CHN theory/found (%): C: 54.76/54.82 H: 6.87/7.01 N: 6.36/6.35. (2-Chlor*o*-ethyl)-diisopropylamine **(41b)** was prepared by using the procedure outlined for **41a** above.

1*H*-Indene-2-carboxylic Acid 2-(dimethylamino)ethyl Ester (42a). The reagents indene (11.6 g, 100 mmol) and oxalyl bromide (10.8 g, 50 mmol) were heated neat to 90 °C for 5 h. The dark reaction mixture was cooled to RT and diluted with THF (100 mL). 2-Dimethylaminoethanol (4.45 g, 50 mmol) was added and heated to reflux for 2 min. The suspension was concentrated in vacuo, and the residue was diluted with HCl (5%) (200 mL), washed with CH$_2$Cl$_2$ (3 × 50 mL), basified with NH$_4$OH and extracted with CH$_2$Cl$_2$ (3 × 50 mL). The organic layer was washed with water (3 × 50 mL), dried (MgSO$_4$), and evaporated to leave a yellow oil (6.4 g, 56%). The product was used without further purification. 1*H*-Indene-2-carboxylic acid (2-(dimethylamino)ethyl)amide **(42b)** was prepared using *N,N*-dimethylethane-1,2-diamine in the procedure above.

2-(Dimethylaminomethyl)indan-1-one Hydrochloride (43) (Method A).[22] To a solution of indan-1-one (5.3 g, 40 mmol) in ethanol (30 mL) were added paraformaldehyde (3.3 g) and dimethylamine hydrochloride (4.8 g, 60 mmol). The mixture was refluxed for 15 min. Then, two drops of concentrated HCl were added in order to dissolve the surplus paraformaldehyde, and the homogeneous mixture was allowed to stand at RT overnight. The hygroscopic white solid was filtered under nitrogen and dried in a vacuum oven at RT for 24 h (5.8 g, 64%).

2-[(Isopropylmethylamino)methyl]indan-1-one (44) (Method B).[22] To a solution of indan-1-one (2.6 g, 20 mmol) in ethanol (60 mL) was added paraformaldehyde (0.6 g, 20 mmol) and isopropylmethylamine hydrochloride (2.0 g, 20 mmol). The mixture was refluxed until a homogeneous solution was formed. The addition of paraformaldehyde (0.6 g, 20 mmol) was repeated twice for a total of three additions. Concentrated HCl (1.5 mL) was subsequently added in order to dissolve the surplus paraformaldehyde. The mixture was concentrated, NaOH (2 M) (100 mL) was added and the basic layer was extracted with ether (3 × 100 mL). The ether layer was dried (Na$_2$SO$_4$) and concentrated in vacuo to give a yellow oil (2.65 g, 61%).

2-Isopropylpyridine (45). To a solution of 2-ethyl-pyridine (16.5 g, 0.154 mol) in THF (50 mL) was added 1.6 M butyllithium (94.4 mL, 0.151 mol) at −78 °C under nitrogen and stirred for 2 h at this temperature. Iodomethane (21.4 g, 0.151mol) was added dropwise to the resulting dark red solution and stirred overnight at RT. The solvent was evaporated and the residue diluted with ether (200 mL). The organic layer was washed with water (2 × 100 mL), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo to give a brown oil. The oil was purified by distillation at 153 °C with a spinning band column (13.2 g, 71%). ^{1}H NMR (CDCl$_3$, 200 MHz, δ [ppm]) = 1.27 (d, J = 6.9 Hz, 6H), 3.02 (sept, J = 6.9 Hz, 1H), 7.02−7.14 (m, 2H), 7.52−7.60 (m, 1H), 8.50 (d, J = 4.4 Hz, 1H).

Pharmacology. Muscarinic Receptor Binding Studies. Radioligand binding studies at the five cloned human muscarinic receptors stably expressed in CHO-K1 cells were performed by the methods described by Dörje et al.[29] and Buckley et al.[30] with the following modifications. Transfected CHO-K1 cells were grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum, 100 IU/mL penicillin

G, 100 µg/mL streptomycin, 2 mM glutamine, and 0.1 mM nonessential amino acids. At confluence, they were washed, scraped into ice-cold binding buffer, and homogenized for 45 s using a Branson Sonifier. Membranes were pelleted at 30.600g, rehomogenized, and stored at –80 °C. Protein concentrations were determined according to the method of Lowry et al.[31] using a Bio-Rad protein assay kit. Final membrane protein concentrations in the assay were (mg/mL): $M_1 = 2$, $M_2 = 6$, $M_3 = 2$, $M_4 = 2$, $M_5 = 5$.

Binding buffer consisted of 20 mM HEPES (pH 7.4), 10 mM MgCl$_2$, and 100 mM NaCl. Incubations were carried out at 25 °C for 2 h with 0.2 nM [^{3}H]NMS (78–85 Ci/mmol; Amersham International, Bucks, England). Assays were terminated by filtration through a Brandell cell harvester onto Whatman GF/B filters. Membranes were washed three times with 1 mL buffer, transferred to 3 mL of scintillant (Quickszint 2000, Zinsser Analytik, Frankfurt, Germany or Lumasafe Plus, Packard Bioscience, Dreieich, Germany), and counted in a Wallac beta counter.

Data were analyzed by a curve fitting procedure using the program GraphPad Prism. The K_i values of the test compounds were derived from IC$_{50}$ values using the Cheng-Prusoff equation,[32] $K_i = IC_{50}/(1 + L/K_d)$, with the radioligand concentration $L = 0.2$ nM and the following equilibrium dissociation constants K_D of [^{3}H] NMS, determined in previous saturation binding experiments (nM): M_1: $0.19 = M_2 = 0.33$; $M_3 = 0.17$; $M_4 = 0.10$; $M_5 = 0.48$.

Histamine Receptor Binding Studies. Radioligand binding studies at the human histamine H$_1$ receptor, stably expressed in CHO-K1 cells, were carried out as described for the muscarinic binding assay. The final membrane protein concentration was 18 µg/mL, and nonspecific binding was determined by adding 0.1 mM terfenadine. The radioligand was [^{3}H]mepyramine (1.0 nM; 28 Ci/mmol, Amersham Bioscience Europe, Freiburg, Germany), the equilibrium dissociation constant of which (0.84 ± 0.09 nM) was determined in previous saturation experiments.

All affinity data (pK_i values) are presented as arithmetic means ± SD from at least three experiments performed in duplicate.

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