Benzophenone Derivatives and Related Compounds as Potent Histamine H_3-Receptor Antagonists and Potential PET/SPECT Ligands[1)]

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Summary

Para-substituted aromatic ethers with benzophenone or related structural elements and a 3-(1*H*-imidazol-4-yl)propyloxy moiety were prepared by Mitsunobu-type ether synthesis or S_NAr reaction. Most of the title compounds possess high antagonist potency in histamine H_3-receptor assays in vitro as well as in vivo in mouse CNS following oral administration. After defining 4-(3-(1*H*-imidazol-4-yl)propyloxy)phenyl phenyl methanone as a new lead, structure-activity relationships were investigated for this new class of compounds. Substitution of the *meta'*-position of the benzophenone moiety with halogen atoms (e.g., iodine, fluorine) led to compounds with high antagonist potency in vitro as well as in vivo (K_i = 9.3 and 4.3 nM, ED_{50} = 0.7 and 0.47 mg/kg p.o., **18** and **12**, respectively). A receptor profile of several functional in vitro assays for several biogenic amine receptors for the *meta'*-iodinated derivative demonstrated high selectivity toward the histamine H_3 receptor.

Introduction

Histamine H_1 and H_2 receptors are well-known targets for selective antagonists[3]. A third histamine receptor, termed H_3 receptor, was identified as auto- and heteroreceptor in the central nervous system (CNS)[4]. Activation of presynaptically localized histamine H_3 receptors by histamine leads to an inhibition of the release of various neurotransmitters[5] including histamine[6] and to an inhibition of the synthesis of histamine in histaminergic neurons[7]. In vivo, histamine H_3-receptor antagonists inhibit the negative feedback of histamine on its own synthesis and release[8].

Several therapeutic applications have been proposed for H_3-receptor antagonists such as schizophrenia, attention-deficit hyperactivity disorder (ADHD), and Alzheimer's disease[9]. In order to study CNS disorders, non-invasive imaging in vivo techniques such as Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) are highly beneficial[10]. For these neuroimaging techniques radiolabeled ligands with high affinity as well as selectivity for the investigated receptor are needed. Although a large number of histamine H_3-receptor ligands has been described, e.g., thioperamide[8,11], FUB 372[12,13], and ciproxifan[14] (Chart 1, Table 1), and radioligands such as [^{125}I]iodoproxyfan for in vitro binding studies have been developed[15], suitable radiolabeled compounds for PET and SPECT are still lacking. Certain prerequisites for suitable compounds have to be met. First of all, the ligand should possess high affinity and selectivity for the histamine H_3 receptor, it should be able to cross the blood-brain barrier, thus showing high potency in the CNS, and it must contain an atom or functional group which is suitable for radiolabeling such as –F, –I, $–SCH_3$ or $–OCH_3$ at a final step of the synthesis. Unfortunately, previous developments have met these prerequisites with limited success[16–21]. According to published methods these structures may be radiolabeled by exchange or derivatisation to give [^{18}F], [^{11}C], or [^{123}I]labeled ligands[17,18]. Among other compounds, [^{123}I]iodoproxyfan[19], [^{18}F]VUF 5000[20], and [^{11}C]UCL 1829[21] have been described (Chart 1), but biodistribution studies revealed only low uptake into the brain.

In this study histamine H_3-receptor antagonists are described which have been developed after defining a novel lead and subsequent variation of the lead compound in order to assess structure-activity relationships. As fluorinated and iodinated derivatives showed high in vitro as well as in vivo potency at histamine H_3 receptors in rodents, further development for use as PET or SPECT ligand are proposed. Binding experiments and a broad funtional receptor profile have been performed for the most promising compound.

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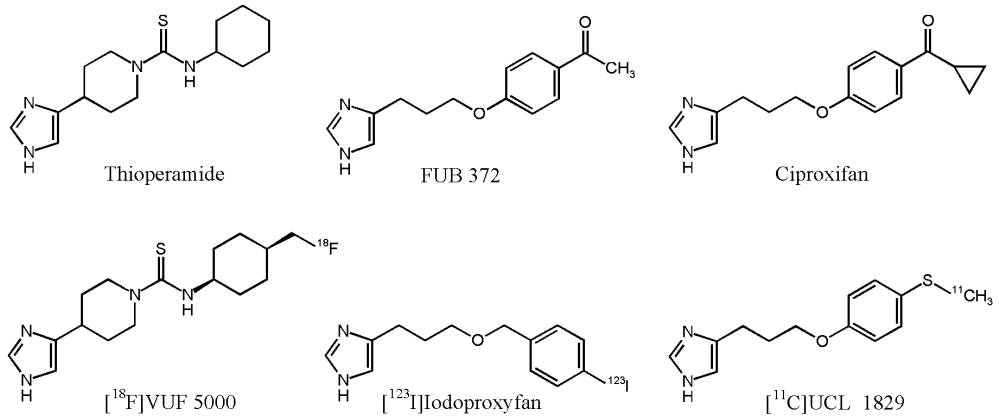
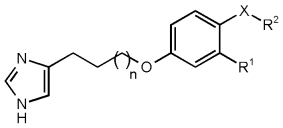


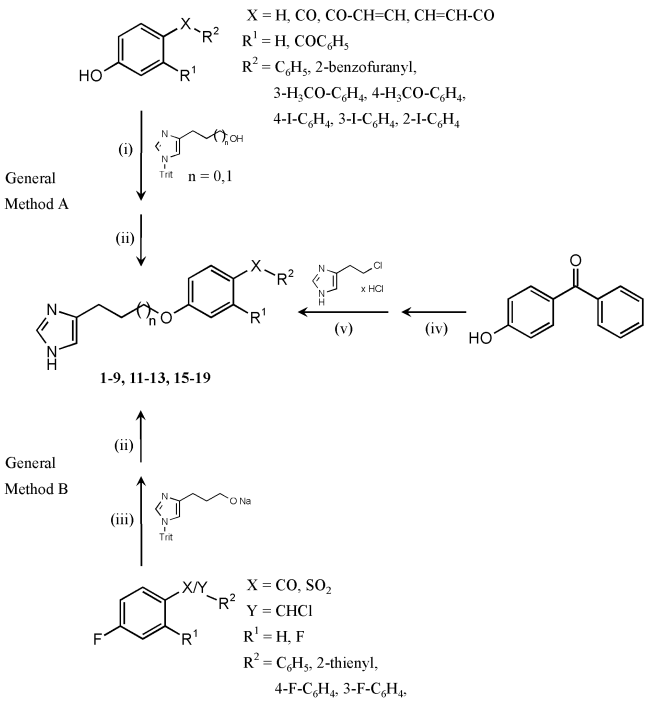
Chart 1

Table 1. Chemical structure and results of pharmacological assays of histamine H_3-receptor antagonists **1**–**19** in vitro as well as in vivo in rodents.

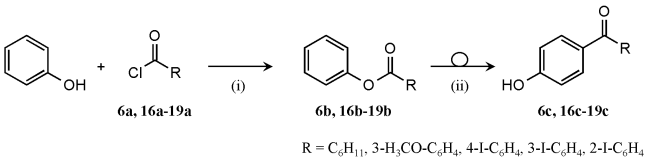


No.	*n*	R^1	X	R^2	K_i (nM)[a] ± s.e.m.	ED_{50} (mg/kg)[b] ± s.e.m.
1	0	H	CO	C_6H_5	54 ± 13	2.6 ± 0.5
2	1	H	CO	C_6H_5	3.2 ± 0.5	0.9 ± 0.1
3	1	CO-C_6H_5	H		n.d.[c]	6.7 ± 2.5
4	1	H	CO-CH=CH	C_6H_5	8.3 ± 1.4	0.18 ± 0.07
5	1	H	CH=CH-CO	C_6H_5	55 ± 13	~20
6	1	H	CO	C_6H_{11}	12 ± 2	0.88 ± 0.31
7	1	H	CO	2-benzofuranyl	n.d.[c]	1.6 ± 0.4
8	1	H	CO	2-thienyl	4.3 ± 1.4	1.0 ± 0.6
9	1	H	CO	4-F-C_6H_4	4.6 ± 1.2	0.71 ± 0.2
10	1	H	C=NOH	4-F-C_6H_4	54 ± 22	3.7 ± 1.3
11	1	H	SO_2	4-F-C_6H_4	95 ± 30	2.9 ± 1.0
12	1	H	CO	3-F-C_6H_4	4.3 ± 1.1	0.47 ± 0.25
13	1	F	CO	C_6H_5	n.d.[c]	3-10 (α^d ~ 0.4)
14	1	F	C=NOH	C_6H_5	39 ± 10	~10
15	1	H	CO	4-H_3CO-C_6H_4	n.d.[c]	4.5 ± 2.1
16	1	H	CO	3-H_3CO-C_6H_4	n.d.[c]	3.6 ± 1.6
17	1	H	CO	4-I-C_6H_4	14 ± 5	~10
18	1	H	CO	3-I-C_6H_4	9.3 ± 2.0	0.70 ± 0.34
19	1	H	CO	2-I-C_6H_4	263 ± 68	~25
Thioperamide[e]					4 ± 1	1.0 ± 0.5
FUB 372[f]	1	H	CO	CH_3	0.8 ± 0.2	0.24 ± 0.06
Ciproxifan[g]	1	H	CO	cyclopropyl	0.49 ± 0.09	0.14 ± 0.03
Imoproxifan[h]	1	H	C=NOH	CH_3	0.26 ± 0.03	0.034 ± 0.009

[a] Functional H_3-receptor assay on synaptosomes of rat cerebral cortex[30]; [b] Central H_3-receptor screening after p.o. administration to mice[30]; [c] n.d. = not determined; [d] α = intrinsic activity (histamine: α = 1.0); [e] Ref.[11]; [f] Ref.[12,13]; [g] Ref. [14]; [h] Ref. [29].



Scheme 1. Synthesis of ethers **1**–**9**, **11-13**, and **15**–**19** by Williamson, Mitsunobu (General Method A) or S_NAr (General Method B) type reaction. Trit = Trityl; (i) Ph_3P, DEAD, THF, ambient temperature, 3 d; (ii) 2N HCl, THF, reflux, 2 h; (iii) 15-crown-5, toluene, 70 °C, 8 h; (iv) NaH (60%), DMF, ambient temperature, 1 h; (v) TBAI, DMF, 100 °C, 48 h.



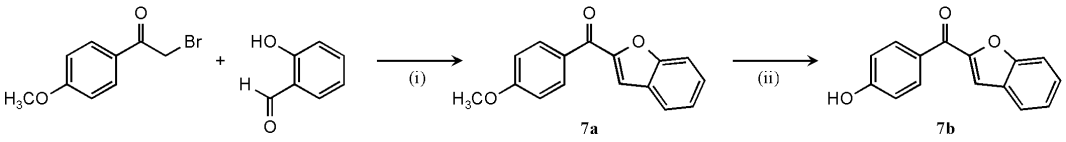
Scheme 2. Synthesis of ketones **6c** and **16c**–**19c** by esterification and Fries rearrangement. (i) Et_3N, Et_2O, reflux, 1 h; (ii) **6b**, **16b**: $AlCl_3$, 80 °C, 30 min; **17b**, **18b**: $AlCl_3$, nitrobenzene, 45 °C, 4 d.

Chemistry

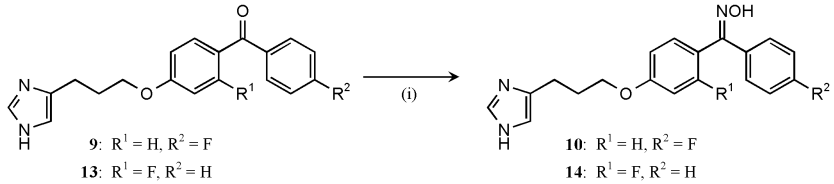
Ether **1** was prepared from 4-(2-chloroethyl)-1*H*-imidazole [22], ethers **2**–**19** were built up from trityl-protected 2-(1*H*-imidazol-4-yl)ethanol[23] or 3-(1*H*-imidazol-4-yl)-propanol[15] by reaction of corresponding substituted phenols or fluorobenzenes by a Williamson[24], Mitsunobu type (General Method A)[25], or S_NAr (General Method B)[26] reaction, respectively, and subsequent deprotection of the imidazole ring (**2**–**19**) (Scheme 1). The appropriate phenols for Mitsunobu synthesis were prepared by different synthetic pathways (Scheme 2, 3). α,β-Unsaturated ketones (**4a**, **5a**) were prepared by an aldol condensation of the appropriate ketone and aldehyde. Substituted 4-hydroxybenzophenone precursors **6c** and **16c**–**19c** were synthesized from phenol and the corresponding benzoic acid (Scheme 2). First, the phenyl esters (**6b**, **16b**–**19b**) were formed by standard methods, then a Fries rearrangement[27] using $AlCl_3$ at moderate temperature was conducted for the formation of the 4-hydroxybenzophenone derivatives (**6c**, **16c**–**19c**). 2-Benzofuranyl 4-hydroxyphenyl methanone (**7b**) was constructed up by reaction of 4-methoxyacetophenone bromide and salicylaldehyde and subsequent demethylation under mild conditions using boron tribromide (Scheme 3)[28]. Oximes (**10**, **14**) were prepared as described for imoproxifan[29] from their corresponding ketones (**9**, **13**) with hydroxylamine hydrochloride and sodium carbonate in ethanol (Scheme 4).

Pharmacological Results and Discussion

Histamine H_3-receptor antagonist properties were investigated in vitro in a functional model on synaptosomes of rat cerebral cortex, measuring [^{3}H]-histamine release[30]. All investigated compounds displayed affinity in the nanomolar concentration range (Table 1). The novel compounds were also screened for their ability to modulate N^{τ}-methylhistamine levels in mouse brain cortex after p.o. administration[30]. Unsubstituted benzophenone derivatives were investigated first in order to select a new lead structure. Variation of the chain length of the alkyl spacer between the imidazole nucleus and the benzophenone moiety (**1**, **2**) clearly favored the three carbon methylene spacer (**2**) in agreement with former observations on other classes of histamine H_3-receptor ligands with an ether[22,31] or carbamate[32] moiety. The *para*-position for acyl substitution on the phenyl ring has



Scheme 3. Synthesis of benzofurane precursors **7a** and **7b**. (i) K_2CO_3, DMF, 120 °C, 3 h; (ii) BBr_3, CH_2Cl_2, –80 °C → ambient temperature, 72 h.



Scheme 4. Synthesis of oximes **10** and **14**. (i) $NH_2OH \times HCl$, Na_2CO_3, EtOH, 60 °C, 9 h.

already been shown to lead to highly active compounds, e.g., FUB 372 and ciproxifan (Table 1)[12,13]. The present findings, demonstrating higher potency for *para*-substituted **2** than for *meta*-substituted **3**, are in line with these results. Compound **2** (K_i = 3.2 nM, ED_{50} = 0.9 mg/kg p.o.) is equipotent with thioperamide, the reference histamine H_3-receptor antagonist. Compound **2** was thus defined as the novel parent compound, and related compounds, as well as derivatives of **2**, were synthesized and investigated pharmacologically. Insertion of a vinyl group (**4**, **5**) next to the carbonyl moiety led to very different pharmacological potencies depending on the position of the vinyl group. For compound **4** the carbonyl moiety remained on the phenyl ether side of the molecule, and the in vitro antagonist potency was only lowered slightly compared to the lead **2**. Interestingly, in vivo antagonist potency of **4** was increased (ED_{50} = 0.18 mg/kg, p.o.) and it is equipotent with FUB 372. In the other case where the vinyl group is positioned next to the phenyl ether moiety (**5**), a drop in in vitro and especially in in vivo potency occurred. The observed different activities of **4** and **5** seem to be related to the position of the carbonyl group within the molecule, given that the electronic properties of **4** and **5** are quite similar, since both represent comparable mesomeric systems.

Exchange of the phenyl ring attached to the phenoxy carbonyl group with cyclohexyl (**6**) or heteroaromatics (**7**, **8**) hardly influenced H_3-receptor antagonist potency. In vitro, exchange by cyclohexyl (**6**) led to a decrease of potency, whereas in vivo no significant change was observed, presumably due to increased lipophilicity and consequently enhanced penetration through the blood–brain barrier. 2-Thienyl substitution did not increase in vitro or in vivo potency with **8** being equipotent to the lead **2**.

Thus, compound **2** seemed to be a most promising structure for further investigation into the structure-activity relationships of this new class of compounds. Derivatives and analogues of **2** were prepared with special interest in fluorinated, methoxylated or iodinated compounds which could be transformed to their corresponding radiolabeled potential PET or SPECT ligands.

Introduction of an electron-withdrawing fluoro-substitutent in *para*-position did not significantly affect in vitro and in vivo potency when compared to **2**. Unfortunately, transformation of the carbonyl group to an oxime moiety (**10**) decreased histamine H_3-receptor potency in vitro as well as in vivo. Recently, this transformation was described as a possibility to increase H_3-receptor potency of ketones (e.g., FUB 372 → imoproxifan[29], *cf.* Table1), although this is not generally applicable[29]. An exchange of the carbonyl moiety of **9** by a sulfone (**11**) also led to a decrease in H_3-receptor potency. Compound **9** was [^{18}F]-labeled ([^{18}F]FUB 272) and evaluated as a potential PET ligand[21]. However, the labeled compound was poorly taken up by the brain and distributed homogeneously, indicating that it is not suitable in this form for PET studies. Nevertheless, fluoro substitution was well tolerated with regard to histamine H_3-receptor assays in vitro and in vivo in rodents (K_i = 4.6 nM, ED_{50} = 0.71 mg/kg p.o.); thus diverse positions of fluoro substitution were investigated. On changing the fluorine atom from *para′*- to *meta′*-position (**12**), high in vitro potency was maintained, with increased in vivo antagonist activity after p.o. administration to mice (ED_{50} = 0.47 mg/kg).

On substitution of the phenyl ring bound to the alkyl ether moiety with fluorine in the *meta*-position (**13**), partial agonist activity of low potency was observed under in vivo conditions. The corresponding oxime **14** showed low antagonist potency in vitro as well as in vivo. Recently this striking partial agonist behavior has also been observed for a related class of *meta*-substituted phenyl ethers[33]. As agonism is not favorable for ligands in PET or SPECT imaging due to more complex binding behavior of (partial) agonists in general, no efforts were made to further investigate the structure-activity relationships of this pharmacologically different class of compounds. However, compounds derived from lead **2** with high antagonist potency in vitro as well as in vivo, possessing an atom that could be radiolabeled, such as the fluorine in **9** and **12**, were further investigated.

Introduction of a methoxy group in *para′*- or *meta′*-position led to low in vivo potency (**15**, **16**). Substitution with iodine in *para′*-, *meta′*-, or *ortho′*-positions (**17**–**19**) showed very interesting potency patterns. Whereas iodoproxyfan, a commonly used radioligand for binding studies[34], does not possess central in vivo activity and was not suitable as a SPECT ligand[19], the *meta′*-iodo substituted derivative **18** displayed high in vitro as well as in vivo antagonist potency. The *para′*-substituted analogue **17** was about equipotent in vitro, but showed highly decreased potency in vivo, which might be caused by pharmacokinetic properties of *para′*-iodo substitution of the phenyl ring. *Ortho′*-substituted **19** had only moderate potency in vitro as well as in vivo. The ligand–receptor interaction which is determined in vitro might be hindered by steric parameters of the *ortho′*-positioned iodine in **19** shielding the carbonyl group or forcing the phenyl group into another position. The importance of the position of the carbonyl group has been discussed for **4, 5**, **10**, and **11**, and in vitro results of **18** and **19** further strengthen the hypothesis that the carbonyl group of these compounds plays an important role in the close ligand-receptor interaction. Compound **18** was selected for further investigation. For this reason, a detailed functional receptor profile for several neurotransmitter receptors as well as H_3-receptor binding experiments with [^{3}H](*R*)-α-methylhistamine on membranes of rat cerebral cortex and a functional peripheral H_3-receptor assay on guinea-pig were performed (Figure 1). Compound **18** displayed a high H_3-receptor selectivity, as its potency at H_3 receptors was at least 100 times higher than at the other receptors investigated including H_1 and H_2 receptors.

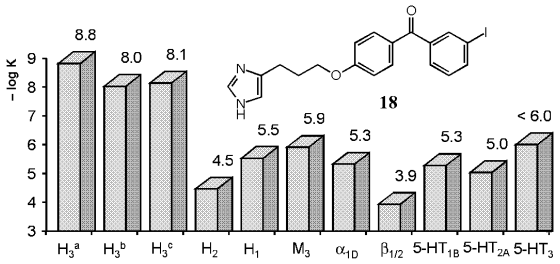


Figure 1. Functional receptor profile and binding data of compound **18**. [a] Histamine H_3-receptor potency in a binding assay on rat cerebral cortex membranes; [b] functional assay on synaptosomes of rat cerebral cortex synaptosomes; [c] functional assay on guinea-pig ileum.

Conclusion

Benzophenone derivatives and related compounds containing a 3-(1*H*-imidazol-4-yl)propoxy moiety were investigated for their histamine H_3-receptor antagonist potency. Two pharmacological assays were used to screen the potency of the novel compounds in vitro as well as in vivo. After defining a new lead structure (**2**) with high antagonist potency in vitro and in vivo, structural variations were performed in order to obtain structure-activity relationships for this new class of compounds. Substitution with iodine (**18**) or fluorine (**12**) in the *meta′*-position led to compounds showing high histamine H_3-receptor potency in vitro as well as in vivo (K_i = 9.3 and 4.3 nM, ED_{50} = 0.7 and 0.47 mg/kg p.o., respectively). These compounds might be used as pharmacological tools for SPECT or PET studies when labeled with [^{123}I] or [^{18}F]. For *meta′*-iodinated compound **18** histamine H_3-receptor binding studies and a functional receptor profile were determined, establishing high affinity and selectivity for the histamine H_3 receptor.

Acknowledgment

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Experimental

Chemistry

General Procedures. Melting points were determined on an Electrothermal IA 9000 digital or a Büchi 512 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Brucker DPX 400 Avance (400 MHz) spectrometer. Chemical shifts (δ) are expressed in ppm downfield from internal Me_4Si as reference. Mass spectra were obtained on an EI-MS Finnigan MAT CH7A. Elemental analyses (C, H, N) were measured for all final compounds on Perkin-Elmer 240 B or Perkin-Elmer 240 C instruments and were within ±0.4% of the theoretical values. Preparative, centrifugally accelerated, rotatory chromatography was performed using a Chromatotron 7924T (Harrison Research) and glass rotors with 4 mm layers of silica gel 60 F_{254} containing gypsum (Merck). Column chromatography was carried out using silica gel 63-200 μm (Macherey, Nagel & Co.). Thin layer chromatography (TLC) was performed on silica gel F_{254} plates (Merck).

General Method A (Mitsunobu-type Ether Synthesis)

Triphenylphosphine (6 mmol, 1.57 g), 2-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)ethanol[23] (5 mmol, 1.77 g) or 3-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)propanol[15] (5 mmol, 1.84 g), and 6 mmol of the corresponding phenol derivative were dissolved in 15 mL of freshly distilled THF under Ar atmosphere and cooled in an ice bath. Diethyl azodicarboxylate (DEAD) (6 mmol, 0.95 mL) was added dropwise. The mixture was stirred for 16–72 h at ambient temperature. Then the solvent was removed under reduced pressure and the crude reaction product purified by column chromatography (eluent: EtOAc). Pure fractions were detritylated by heating to reflux in 20 mL of 2N HCl and 40 mL of THF for 2 h. THF was evaporated under reduced pressure and the aqueous residue washed with Et_2O. The aqueous phase was basified with K_2CO_3 and extracted with Et_2O and CH_2Cl_2. The organic layer was separated and the solvent evaporated. The crude product was subjected to rotatory chromatography (eluent: CH_2Cl_2/MeOH (90/10), NH_3 atmosphere). Pure fractions were crystallized as free base or as hydrogen chloride, hydrogen maleate, or hydrogen oxalate from EtOH/Et_2O.

General Method B (S_NAr-type Ether Synthesis)

3-(1-(Triphenylmethyl)-1*H*-imidazol-4-yl)propanol[15] (5 mmol, 1.84 g) was stirred for 2 h with NaH (6 mmol, 240 mg of 60% suspension in paraffin oil) under Ar in 20 mL of dry toluene. Then a catalytic amount of 15-crown-5 (0.5 mmol, 0.1 g) and the appropriately substituted fluorobenzene (6 mmol) in 5 mL of toluene were added at ambient temperature and the mixture heated to 70 °C for 8 h. The solvent was evaporated, water was carefully added, and it was then heated to reflux in 20 mL of 2N HCl and 40 mL of THF for 2 h. Purification and crystallization were continued as described in General Method A.

General Method C (Preparation of Esters)

The appropriate carboxylic acid (50 mmol) was transformed into the carboxylic acid chloride with thionyl chloride (75 mmol) in 50 mL of THF by heating the mixture to reflux for 30 min. The solvent was removed under reduced pressure. The crude reaction product was directly added to a solution of phenol (50 mmol) and Et_3N (55 mmol) in 50 mL of Et_2O and heated to reflux for 1 h. The precipitate was filtered, dissolved in H_2O and extracted with Et_2O. The combined organic phases were washed with a saturated solution of K_2CO_3, 0.2N HCl, and brine, dried with Na_2SO_4, and concentrated.

General Method D (Fries Reaction I)

The phenyl ester (30 mmol) obtained from General Method C was mixed with $AlCl_3$ (150 mmol), stirred for 30 min at ambient temperature, and then heated to 80 °C for 30 min. The crude product was taken up in cold 0.5N HCl and extracted with Et_2O and CH_2Cl_2. The organic phases were dried (Na_2SO_4) and concentrated. The resulting dark oil was purified by column chromatography (eluent: CH_2Cl_2). Pure fractions were crystallized from solvents as indicated.

General Method E (Fries Reaction II)

The phenyl ester (30 mmol) obtained from General Method C and $AlCl_3$ (150 mmol) were dissolved in 30 mL of nitrobenzene, warmed to 45 °C, and stirred for 4 days. Work-up procedure as described in General Method D.

*4-(2-(1H-Imidazol-4-yl)ethyloxy)phenyl Phenyl Methanone (**1**)*

4-Hydroxybenzophenone (12 mmol, 2.38 g) in dry DMF (10 mL) was stirred with sodium hydride (6 mmol, 240 mg of 60% suspension in paraffin oil) for 1 h at room temperature. Then 4-(2-chloroethyl)-1*H*-imidazole hydrochloride[22] (1.2 mmol, 200 mg) and tetrabutylammonium iodide (catalytic amount) were added and the mixture was heated at 100 °C for 48 h. The mixture was then evaporated, acidified (2N HCl), washed (3 ×) with Et_2O, basified with K_2CO_3, and extracted with Et_2O (3 ×). The combined ether extracts were dried, concentrated, and the residue was treated with oxalic acid in 2-propanol to yield the solid as hydrogen oxalate. The latter was recrystallized from MeOH/Et_2O. Yield: 25%. Anal. ($C_{18}H_{16}N_2O_2 \times 1.3\ C_2H_2O_4$); M_r = 409.3; mp 193 °C; ^{1}H NMR (DMSO-d_6): δ 8.62 (s, 1H), 7.86 (d, *J* = 8.6 Hz, 2H), 7.78-7.59 (m, 5H), 7.36 (s, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 4.80 (t, *J* = 6.0 Hz, 2H), 3.28 (t, *J* = 7.3 Hz, 2H); C, H, N.

*4-(3-(1H-Imidazol-4-yl)propyloxy)phenyl Phenyl Methanone (**2**)*

Prepared from (4-fluorophenyl)phenylmethyl chloride according to General Method B. Yield: 30%. Anal. ($C_{19}H_{18}N_2O_2 \times C_4H_4O_4 \times 0.25\ H_2O$); M_r = 426.9; mp 126 °C; ^{1}H NMR (DMSO-d_6): δ 8.87 (s, 1H), 7.75 (d, *J* = 8.6 Hz, 2H), 7.70-7.53 (m, 5H), 7.31 (s, 1H), 7.07 (d, *J* = 8.7 Hz, 2H), 6.04 (s, 2H), 4.13 (t, *J* = 6.1 Hz, 2H), 2.81 (t, *J* = 7.5 Hz, 2H), 2.10 (m, 2H); C, H, N.

*3-(3-(1H-Imidazol-4-yl)propyloxy)phenyl Phenyl Methanone (**3**)*

Prepared from 3-hydroxybenzophenone according to General Method A, crystallized from 2-propanol and recrystallized from MeOH. Yield: 40%. Anal. ($C_{19}H_{18}N_2O_2 \times C_2H_2O_4 \times 0.2\ H_2O$); M_r = 336.0; mp 155 °C; ^{1}H NMR (DMSO-d_6): δ 8.38 (s, 1H), 7.65–7.57 (m, 5H), 7.46 (t, 1H), 7.24–7.21 (m,

2H), 7.22 (s, 1H), 4.05 (t, *J* = 6.2 Hz, 2H), 2.74 (t, *J* = 7.6 Hz, 2H), 2.07 (m, 2H); C, H, N.

*1-(4-Hydroxyphenyl)-3-phenyl-2-propen-1-one (**4a**)*

4-Hydroxyacetophenone (40 mmol, 5.5 g) was dissolved in 30 mL of water, 15 mL of EtOH, and 10 mL of 6N NaOH and stirred for 30 min at ambient temperature. Then benzaldehyde (42 mmol, 4.5 g) dissolved in H_2O/EtOH (2/1) was added slowly. The mixture was heated to reflux for 72 h and then acidified with 6N HCl. The crystalline product was filtered and recrystallized from EtOH. Yield. 80%; mp 173 °C (174 °C[35]); ^{1}H NMR (DMSO-d_6): δ 10.42 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 2H), 7.94–7.86 (m, 3H), 7.69 (d, *J* = 15.6 Hz, 1H), 7.49-7.45 (m, 3H), 6.92 (d, *J* = 8.5 Hz, 2H).

*1-(4-(3-(1H-Imidazol-4-yl)propyloxy)phenyl)-3-phenyl-2-propen-1-one (**4**)*

Prepared from **4a** according to General Method A. Yield: 65%. Anal. ($C_{21}H_{20}N_2O_2 \times C_2H_2O_4 \times 0.75\ H_2O$); M_r = 436.0; mp 169 °C; ^{1}H NMR (DMSO-d_6): δ 8.91 (s, 1H), 8.17 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 15.6 Hz, 1H) 7.90–7.87 (m, 2H), 7.71 (d, *J* = 15.6 Hz, 1H), 7.48–7.43 (m, 3H), 7.08 (d, *J* = 8.8 Hz, 2H), 4.15 (t, *J* = 6.1 Hz, 2H), 2.83 (t, *J* = 7.5 Hz, 2H), 2.13 (m, 2H); C, H, N.

*3-(4-Hydroxyphenyl)-1-phenyl-2-propen-1-one (**5a**)*

Prepared from 4-hydroxybenzaldehyde and acetophenone as described for **4a**. Yield. 80%; mp 183 °C (184 °C[35]); ^{1}H NMR (DMSO-d_6): δ 10.10 (s, 1H), 8.13 (d, *J* = 7.6 Hz, 2H), 7.75–7.70 (m, 4H), 7.67–7.64 (m, 1H), 7.56 (t, *J* = 7.6 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H).

*3-(4-(3-(1H-Imidazol-4-yl)propyloxy)phenyl)-1-phenyl-2-propen-1-one (**5**)*

Prepared from **5a** according to General Method A. Yield: 40%. Anal. ($C_{21}H_{20}N_2O_2 \times 0.5\ C_2H_2O_4 \times 0.75\ H_2O$); M_r = 391.0; mp 187 °C; ^{1}H NMR (DMSO-d_6): δ 9.00 (s, 1H), 8.14 (d, *J* = 7.5 Hz, 2H), 7.87–7.83 (m, 3H), 7.77 (d, *J* = 18.6 Hz, 1H), 7.70–7.65 (m, 1H), 7.60–7.56 (m, 2H), 7.47 (s, 1H), 4.11 (t, *J* = 6.0 Hz, 2H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.12 (m, 2H); C, H, N.

*Phenyl Cyclohexanecarboxylate (**6a**)*

Prepared from cyclohexanecarboxylic acid according to General Method C. Yield: 91%; b.p. 163 °C/21 Torr (163 °C/21 Torr [36]); ^{1}H NMR (DMSO-d_6): δ 7.40 (m, 2H), 7.25 (t, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 2H), 2.60 (m, 1H), 1.99-1.21 (m, 10H).

*Cyclohexyl 4-Hydroxyphenyl Methanone (**6b**)*

Prepared from **6a** according to General Method D and crystallized from light petroleum. Yield: 35%; mp 98 °C (98 °C[37]); ^{1}H NMR (DMSO-d_6): δ 10.31 (s, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 3.34 (m, 1H), 1.81-1.19 (m, 10H).

*Cyclohexyl 4-(3-(1H-Imidazol-4-yl)propyloxy)phenyl Methanone (**6**)*

Prepared from **6b** according to General Method A. Yield: 80%. Anal. ($C_{19}H_{24}N_2O_2 \times C_4H_4O_4$); M_r = 428.5; mp 103 °C; ^{1}H NMR (DMSO-d_6): δ 8.86 (s, 1H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.42 (s, 1H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.04 (s, 2H), 4.10 (m, 3H), 2.79 (t, *J* = 7.4 Hz, 2H), 2.09 (m, 2H), 1.76-1.20 (m, 10H); C, H, N.

*2-Benzofuranyl 4-(3-(1H-Imidazol-4-yl)propyloxy)phenyl Methanone (**7**)*

To a solution of 4-methoxyacetophenone bromide (8.7 mmol, 2.0 g) and salicylaldehyde (8.7 mmol, 1.06 g) in 30 mL of dry DMF, K_2CO_3 (8.7 mmol, 1.2 g) was added slowly (1 h) under nitrogen atmosphere. It was then heated to 100 °C for 3 h. The solvent was evaporated under reduced pressure and the oily residue taken up in a saturated solution of K_2CO_3. The precipitate was filtered, washed with H_2O, and recrystallized from EtOH (**7a**). The reaction product **7a** (12 mmol, 3.2 g) was dissolved in 40 mL of dry CH_2Cl_2 and cooled to –80 °C under Ar atmosphere. BBr_3 (40 mL of a 1 mol/L solution in CH_2Cl_2) (40 mmol, 10 g) was added slowly, maintaining the temperature below –60 °C. After complete addition of BBr_3, the mixture was stirred for 72 h at ambient temperature. The reaction was quenched after cooling to –80 °C by addition of dry MeOH (25 mL). The solvents were evaporated under reduced pressure and the residue taken up with water. On neutralization with K_2CO_3 2-benzofuranyl 4-hydroxyphenyl methanone (**7b**) crystallized and was recrystallized from EtOH. Yield: 80%*:* For the final step, **7b** was treated according to General Method A. Yield: 80%. Anal. ($C_{21}H_{19}N_2O_3 \times C_4H_4O_4 \times 0.5\ H_2O$); M_r = 471.5; mp 155 °C; ^{1}H NMR (DMSO-d_6): δ 8.84 (s, 1H), 8.06 (d, *J* = 8.8 Hz, 2H), 7.87 (s, 1H), 7.77 (m, 2H), 7.55 (dd, *J* = 7.8 Hz, 1H), 7.40 (m, 2H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.04 (s, 2H), 4.17 (t, *J* = 6.1 Hz, 2H), 2.83 (t, *J* = 7.5 Hz, 2H), 2.15 (m, 2H); C, H, N.

*4-(3-(1H-Imidazol-4-yl)propyloxy)phenyl 2-Thienyl Methanone (**8**)*

Prepared from 4-fluorophenyl 2-thienyl methanone according to General Method B. Yield: 10%. Anal. ($C_{17}H_{16}N_2O_2S \times C_2H_2O_4$); M_r = 402.4; mp 175 °C; ^{1}H NMR (DMSO-d_6): δ 8.47 (s, 1H), 8.08 (d, *J* = 5.1 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 2H), 7.72 (d, *J* = 3.1 Hz, 1H), 7.28 (t, *J* = 4.3 Hz, 1H), 7.24 (s, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 4.13 (t, *J* = 6.0 Hz, 2H), 2.78 (t, *J* = 7.6 Hz, 2H), 2.09 (m, 2H); C, H, N.

*4-Fluorophenyl 4-(3-(1H-Imidazol-4-yl)propyloxy)phenyl Methanone (**9**)*

Prepared from bis(4-fluorophenyl)methylchloride according to General Method B. Yield: 9%. Anal. ($C_{19}H_{17}N_2O_2 \times C_4H_4O_4$); M_r = 440.4; mp 127 °C; ^{1}H NMR (DMSO-d_6): δ 8.97 (s, 1H), 7.76 (m, 4H), 7.41 (m, 3H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.06 (s, 2H), 4.14 (t, *J* = 6.1 Hz, 2H), 2.84 (t, *J* = 7.4 Hz, 2H), 2.14 (m, 2H); C, H, N.

*4-Fluorophenyl 4-(3-(1H-Imidazol-4-yl)propyloxy)phenyl Methanone Oxime (**10**)*

Ketone **9** (free base, 1 mmol, 0.32 g), hydroxylamine hydrochloride (5 mmol, 0.35 g), and Na_2CO_3 (6 mmol, 0.64 g) were dissolved in 25 mL of dry EtOH and heated to 60 °C for 9 h. After filtration of inorganic salts, the solvent was evaporated under reduced pressure. The product was purified by column chromatography (eluent: CH_2Cl_2/MeOH (90/10); NH_3 atmosphere) and crystallized as hydrogen maleate from EtOH/Et_2O. Yield: 70%. Anal. ($C_{19}H_{18}FN_3O_2 \times C_4H_4O_4$); M_r = 455.5; mp 126 °C; ^{1}H NMR (DMSO-d_6): δ 11.29/11.17 (2s, 1H), 8.86 (s, 1H), 7.41–7.20 (m, 6H), 7.02 (s, 1H), 6.92 (d, *J* = 8.5 Hz, 2H), 6.04 (s, 2H), 4.02 (t, *J* = 6.1 Hz, 2H), 2.80 (t, *J* = 7.6 Hz, 2H), 2.07 (m, 2H); C, H, N.

*4-Fluorophenyl 4-(3-(1H-Imidazol-4-yl)propyloxy)phenyl Sulfone (**11**)*

Prepared from bis(4-fluorophenyl) sulfone according to General Method B. Yield: 38%. Anal. ($C_{18}H_{17}FN_2O_3S \times HCl$); M_r = 396.9; mp 235 °C; ^{1}H NMR (DMSO-d_6): δ 8.83 (s, 1H), 8.02-7.98 (m, 2H), 7.87 (d, *J* = 8.7 Hz, 2H), 7.45 (m, 3H), 7.13 (d, *J* = 8.7 Hz, 2H), 4.09 (t, *J* = 6.0 Hz, 2H), 2.79 (t, *J* = 7.5 Hz, 2H), 2.09 (m, 2H); C, H, N.

*3-Fluorophenyl 4-(3-(1H-Imidazol-4-yl)propyloxy)phenyl Methanone (**12**)*

Prepared from 3-fluorophenyl 4-fluorophenyl methanone according to General Method B. Yield: 15%. Anal. ($C_{19}H_{17}FN_2O_2 \times C_4H_4O_4 \times 0.25\ H_2O$); M_r = 445.0; mp 127 °C; ^{1}H NMR (DMSO-d_6): δ 8.84 (s, 1H), 7.76 (d, *J* = 8.6 Hz, 4H), 7.62-7.45 (m, 5H), 7.42 (s, 1H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.04 (s, 2H), 4.14 (t, *J* = 6.1 Hz, 2H), 2.82 (t, *J* = 7.5 Hz, 2H), 2.11 (m, 2H); C, H, N.

*2-Fluoro-4-(3-(1H-imidazol-4-yl)propyloxy)phenyl Phenyl Methanone (**13**)*

Prepared from 2,4-difluorophenyl phenyl methanone according to General Method B. Yield: 30%. Anal. ($C_{19}H_{17}FN_2O_2 \times C_4H_4O_4 \times H_2O$); M_r = 458.5; mp 146 °C; ^{1}H NMR (DMSO-d_6): δ 8.83 (s, 1H), 7.68 (m, 2H), 7.63 (dd, *J* = 7.22/7.11 Hz, 1H), 7.50 (m, 3H), 7.17 (s, 1H), 7.11 (d, *J* = 10.9 Hz, 1H), 6.94 (d, *J* = 7.59 Hz, 1H), 6.04 (s, 2H), 3.99 (t, *J* = 5.6 Hz, 2H), 2.27 (t, *J* = 7.4 Hz, 2H), 1.71 (m, 2H); C, H, N.

*2-Fluoro-4-(3-(1H-imidazol-4-yl)propyloxy)phenyl Phenyl Methanone Oxime (**14**)*

Prepared from **13** as described for **10**. Yield: 65%. Anal. ($C_{19}H_{18}FN_3O_2 \times C_2H_2O_4 \times 0.25\ H_2O$); M_r = 433.9; mp 197 °C; ^{1}H NMR (DMSO-d_6): δ 11.40 (s, 1H), 8.86 (s, 1H), 8.13 (s, 1H), 7.43-7.33 (m, 5H), 7.01 (d, *J* = 10.5 Hz, 1H), 6.89-6.82 (m, 3H), 4.03 (t, *J* = 6.1 Hz, 2H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.07 (m, 2H); C, H, N.

*4-Hydroxyphenyl 4-Methoxyphenyl Methanone (**15a**)*

Bis(4-hydroxyphenyl)methanone (15 mmol, 3.2 g) was dissolved in 50 mL of an aqueous solution of potassium hydroxide (10%). Dimethyl sulfate (15 mmol, 1.9 g) was added dropwise, the mixture was stirred for 30 min at ambient temperature and for an additional 30 min at 100 °C. It was acidified with 2N HCl and extracted with Et_2O. The solvent was evaporated, the product purified by column chromatography (eluent: CH_2Cl_2/MeOH (90/10)), and crystallized from EtOH. Yield: 33%; mp 154 °C (151 °C[38]); ^{1}H NMR (DMSO-d_6): δ 10.31 (s, 1H), 7.68 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 3.85 (s, 3H).

*4-(3-(1H-Imidazol-4-yl)propyloxy)phenyl 4-Methoxyphenyl Methanone (**15**)*

Prepared from **15a** according to General Method A. Yield: 50%. Anal. ($C_{20}H_{20}N_2O_3 \times HCl$); M_r = 373.5; mp 189 °C; ^{1}H NMR (DMSO-d_6): δ 9.02 (s, 1H), 7.70 (m, 4H), 7.48 (m, 1H), 7.07 (m, 4H), 4.13 (t, *J* = 6.3 Hz, 2H), 3.86 (s, 3H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.13 (m, 2H); C, H, N.

*Phenyl 3-Methoxybenzoate (**16a**)*

Prepared from 3-methoxybenzoic acid according to General Method C. Yield: 71%; mp 62 °C (61 °C[38]); ^{1}H NMR (DMSO-d_6): δ 7.73 (d, *J* = 7.6 Hz, 1H), 7.61 (s, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.34–7.30 (m, 2H), 7.28 (d, *J* = 7.7 Hz, 2H), 3.86 (s, 3H).

*4-Hydroxyphenyl 3-Methoxyphenyl Methanone (**16b**)*

Prepared from **16a** according to General Method D and crystallized from light petroleum. Yield: 17%; mp 134 °C (138 °C[38]); ^{1}H NMR (DMSO-d_6): δ 10.42 (s, 1H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.21–7.17 (m, 3H), 6.89 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H).

*4-(3-(1H-Imidazol-4-yl)propyloxy)phenyl 3-Methoxyphenyl Methanone (**16**)*

Prepared from **16b** according to General Method A. Yield: 65%. Anal. ($C_{20}H_{20}N_2O_3 \times C_4H_4O_4$); M_r = 452.5; mp 115 °C; ^{1}H NMR (DMSO-d_6): δ 8.90 (s, 1H), 7.75 (d, *J* = 8.7 Hz, 2H), 7.45 (m, 2H), 7.20 (m, 3H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.06 (s, 2H), 4.14 (t, *J* = 6.1 Hz, 2H), 3.82 (s, 3H), 2.82 (t, *J* = 7.5 Hz, 2H), 2.12 (m, 2H); C, H, N.

*Phenyl 4-Iodobenzoate (**17a**)*

Prepared from 4-iodobenzoic acid according to General Method C. Yield: 25%; mp 129 °C (133 °C[39]) ^{1}H NMR (DMSO-d_6): δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.47 (m, 2H), 7.30 (m, 3H).

*4-Hydroxyphenyl 4-Iodophenyl Methanone (**17b**)*

Prepared from **17a** according to general method E and crystallized from light petroleum. Yield: 18%; mp 185 °C; ^{1}H NMR (DMSO-d_6): δ 10.44 (s, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H).

*4-(3-(1H-Imidazol-4-yl)propyloxy)phenyl 4-Iodophenyl Methanone (**17**)*

Prepared from **17b** according to General Method A. Yield: 63%. Anal. ($C_{19}H_{17}IN_2O_2$); M_r = 432.3; mp 187 °C; ^{1}H NMR (DMSO-d_6): δ 7.92 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 8.7 Hz, 2H), 7.50 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.83 (s, 1H), 4.10 (t, *J* = 6.2 Hz, 2H), 2.64 (m, 2H), 2.03 (m, 2H); C, H, N.

*Phenyl 3-Iodobenzoate (**18a**)*

Prepared from 3-iodobenzoic acid according to General Method C. Yield: 62%; mp 57 °C; ^{1}H NMR (DMSO-d_6): δ 8.41 (s, 1H), 8.12 (m, 2H), 7.49–7.28 (m, 6H).

*4-Hydroxyphenyl 3-Iodophenyl Methanone (**18b**)*

Prepared from **18a** according to General Method E and crystallized from light petroleum. Yield: 33%; mp 188 °C; ^{1}H NMR (DMSO-d_6): δ 10.50 (s, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.95 (s, 1H), 7.67-7.64 (m, 3H), 7.34 (t, *J* = 7.7 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 1H).

*4-(3-(1H-Imidazol-4-yl)propyloxy)phenyl 3-Iodophenyl Methanone (**18**)*

Prepared from **18b** according to General Method A. Yield: 66%. Anal. ($C_{19}H_{17}IN_2O_2 \times HCl$); M_r = 468.7; mp 179 °C; ^{1}H NMR (DMSO-d_6): δ 9.03 (s, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.97 (s, 1H), 7.73 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.48 (s, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 4.14 (t, *J* = 6.2 Hz, 2H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.14 (m, 2H); C, H, N.

*Phenyl 2-Iodobenzoate (**19a**)*

Prepared from 2-iodobenzoic acid according to general method C. **19a** was a yellow oil at room temp. and crystallized at 4 °C. Yield: 60%; ^{1}H NMR (DMSO-d_6): δ 8.10 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.54-7.50 (m, 2H), 7.40-7.33 (m, 4H).

*4-Hydroxyphenyl 2-Iodophenyl Methanone (**19b**)*

Prepared from **19a** according to General Method E and crystallized from light petroleum. Yield: 51%; mp 112 °C; ^{1}H NMR (DMSO-d_6): δ 10.60 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.26 (t, *J* = 7.3 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H).

*4-(3-(1H-Imidazol-4-yl)propyloxy)phenyl 2-Iodophenyl Methanone (**19**)*

Prepared from **19b** according to General Method A. Yield: 55%. Anal. ($C_{19}H_{17}IN_2O_2 \times C_4H_4O_4$); M_r = 548.3; mp 98 °C; ^{1}H NMR (DMSO-d_6): δ 8.87 (s, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.43 (s, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 1H), 6.05 (s, 2H), 4.12 (t, *J* = 6.1 Hz, 2H), 2.81 (t, *J* = 7.5 Hz, 2H), 2.10 (m, 2H); C, H, N.

Pharmacology

General Procedures

Histamine H_3-Receptor Antagonist Potency in Vitro on Synaptosomes of Rat Cerebral Cortex

Compounds were tested for their histamine H_3-receptor antagonist potency in an assay using K^+-evoked depolarization induced release of [^{3}H]histamine from synaptosomes of rat cerebral cortex according to Garbarg et al.[30].

Histamine H_3-Receptor Potency in Vitro on Guinea-Pig Ileum

Histamine H_3-receptor potency was measured by concentration-dependent inhibition of electrically evoked twitches of isolated guinea-pig ileum segments induced by (*R*)-α-methylhistamine in the presence of the antagonist as described previously[34].

Histamine H_3-Receptor Binding Assay on Membranes of Rat Cerebral Cortex

Displacement of [^{3}H](*R*)-α-methylhistamine binding was performed on membranes of rat cerebral cortex as described by Garbarg et al.[30].

Histamine H_3-Receptor Potency in Vivo in Mouse

In vivo testing was performed after p.o. administration of the compounds to male Swiss mice as described by Garbarg et al.[30]. Brain histamine turnover was assessed by measuring the level of the main metabolite of histamine, N^τ-methylhistamine.

In Vitro Screening at Other Neurotransmitter Receptors

Histamine H_2-receptor activity on the isolated spontaneously beating guinea-pig right atrium, histamine H_1-receptor activity on the isolated guinea-pig ileum, and adrenergic α_{1D}-receptor activity on rat aorta were assessed by standard methods described by Hirschfeld et al.[40]. Muscarinic M_3-receptor assay on guinea-pig ileum, adrenergic $\beta_{1/2}$-receptor assay on guinea-pig right atrium, and serotonergic 5-HT_{2A}-receptor assay on rat tail artery were performed as described by Pertz and Elz.[41] Serotonergic 5-HT_{1B}-receptor potency was determined on guinea-pig iliac artery according to Pertz[42] and serotonergic 5-HT_3-receptor activity was conducted on guinea-pig ileum as described by Elz and Keller[43].

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