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Synthesis and Preliminary Pharmacological Evaluation of 2-Benzyloxy Substituted Aryl Ketones as 5-HT_4 Receptor Antagonists

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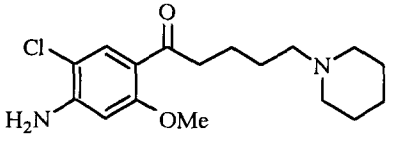
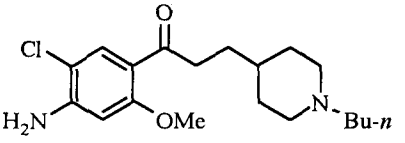
Abstract: Structural modification of the 2-methoxy group and at the 4-position of the piperidine ring of the 5-HT_4 partial agonist **1** led to analogues with increased affinity for the 5-HT_4 receptor and loss of agonist activity. Similar modification of **2** resulted in 2-(3,5-dimethoxy)benzyloxy derivatives (**23**,**24**,**26-28**) that were found to be 5-HT_4 receptor antagonists with subnanomolar affinity.

In the preceeding communication,[1] we reported that the aryl ketones **1** and **2** are partial agonists at the 5-HT_4 receptor of the rat esophagus. These compounds were derived from the 5-HT_4 receptor antagonist RS-23597,[2] the benzoate ester corresponding to ketone **1**. As a continuation of that work, we examined structure-activity relationships of the 2-alkoxy substituent of **1** and **2** and selected analogues. We now report that replacement of the 2-methoxy group of these partial agonists with substituted benzyloxy groups results in 5-HT_4 receptor antagonists with sub-nanomolar affinity. Other high affinity 5-HT_4 antagonists have recently been reported,[3] most notably the esters GR 1132808 (**3**)[4] and SB 204070 (**4**).[5]



1



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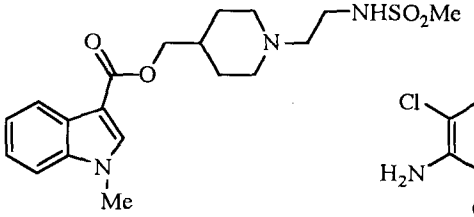
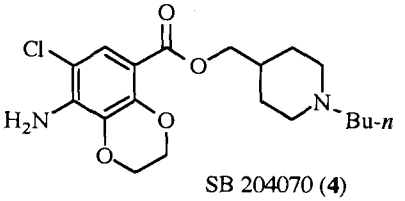


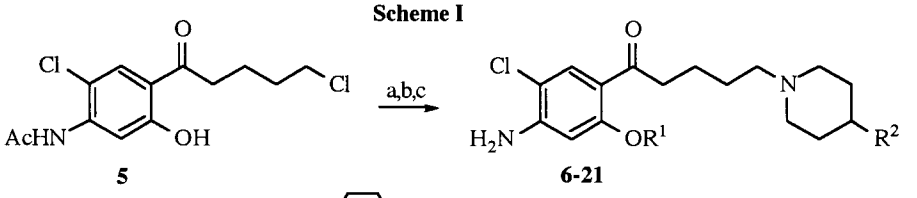
GR 113808 (**3**)



SB 204070 (**4**)

Replacement of the 2-methoxy substituent of the two aryl ketone series was accomplished as described in Schemes I and II. Phenol **5**, derived from Friedel-Crafts acylation of *N*-acetyl-6-chloro-*m*-anisidine with 5-chlorovaleryl chloride,[1] was alkylated with alkyl or benzyl halides under standard conditions. Treatment with the requisite piperidine, followed by hydrolysis of the acetamide then provided compounds **6-21** (Table 1). Benzyloxy derivatives **23-28** (Table 2) were prepared from methyl ethers **22**[1] via a demethylation-alkylation sequence. Yields in the alkylation step were moderate (40-60%), reflecting a certain amount of quaternization of the piperidine nitrogen.

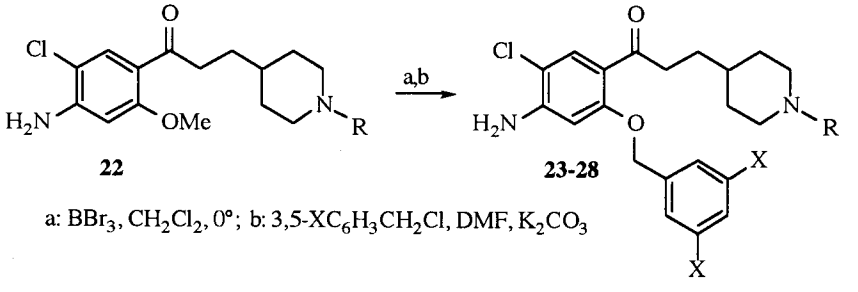
Scheme I



5 **6-21**

a: R^1X, DMF, K_2CO_3; b: HN⟨⟩–R^2, NaI, DMF; c: KOH, EtOH

Scheme II

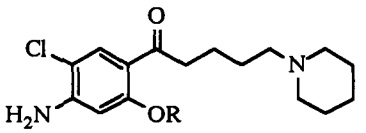


22 **23-28**

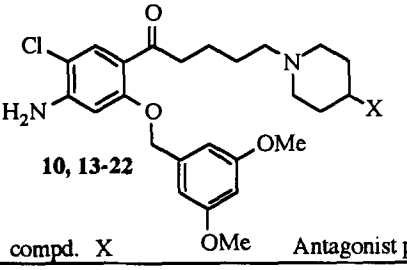
a: BBr_3, CH_2Cl_2, 0°; b: 3,5-$XC_6H_3CH_2Cl$, DMF, K_2CO_3

Initial structure-activity work centered on replacement of the 2-methoxy substituent or aryl ketone **1** with other alkoxy and arylalkoxy groups (Table 1). Compounds were tested for functional 5-HT_4 receptor antagonism in the rat esophagus as previously described.[6] It was found that replacement of the 2-methoxy group of **1** with benzyloxy resulted in increased affinity for the receptor and loss of partial agonist activity. In particular, dimethoxy substituted benzyloxy derivatives **9** and **10** were found to be reasonably potent 5-HT_4 receptor antagonists with pK_b values of 8.5. Homologation of the benzyl group of **9** to phenylethyl (**11**) gave a significant reduction in activity, implying a region of steric inaccessibility at the receptor. The acid lability of 3,4-dimethoxy derivative **9** precluded further evaluation; however, 3,5-dimethoxy analogue **10** demonstrated excellent stability and was chosed for further modification. Substitution at the 4-position of the piperidine moiety of **10** led to antagonist **20** with a pK_b value approaching the nanomolar range (Table 1). Substitution at this position also appeared to be sensitive to steric factors as evidenced by the low activity of the phenyl derivative **14** and the reduction in activity noted upon homologation of **20** to **21**.

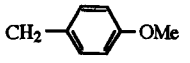
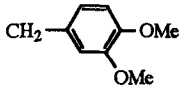
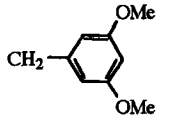
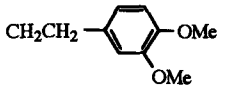
TABLE 1. 5-HT$_4$ Receptor Antagonist Activity for Compounds **6-21**



6-22



10, 13-22

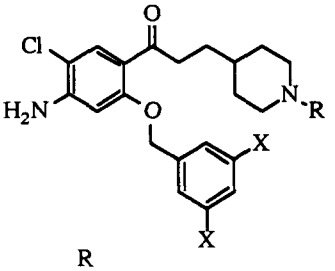
compd.	R	Antagonist pK_b[a]
1	Me	agonist[b]
6	Et	<7
7	Pr-*n*	agonist[c]
8		8.4 ± 0.1
9		8.5 ± 0.1
10		8.5 ± 0.1
11		6.8 ± 0.1
GR 113808		9.0 ± 0.1

compd.	X	Antagonist pK_b[a]
10	H	8.5 ± 0.1
12	Me	8.3 ± 0.1
13	Pr-*n*	7.7 ± 0.2
14	Ph	7.7 ± 0.1
15	OH	8.3 ± 0.1
16	OMe	8.4 ± 0.1
17	$CONH_2$	8.4 ± 0.1
18	$NHCONH_2$	8.5 ± 0.1
19	$NHSO_2Me$	8.4 ± 0.1
20	CH_2NHSO_2Me	8.9 ± 0.1
21	$CH_2CH_2NHSO_2Me$	8.1 ± 0.1

[a]Antagonism of 5-HT mediated relaxation of rat, carbachol contracted esophageal muscularis mucosae (± SEM). [b]pEC_{50} of 7.4 (0.70 intrinsic activity). [c]pEC_{50} of 5.7 (0.40 intrinsic activity).

Consideration of the structure-activity relationships developed from modifications of **1** (Table 1) led to the synthesis of the (3,5-dimethoxy)benzyloxy derivative of **2**. This analogue (**23**, Table 2) was found to have ca. 10-fold increased affinity for the 5-HT$_4$ receptor relative to progenitor **2** (pEC_{50} = 8.2 in the rat esophagus[1]) with a loss of agonist activity; both results were consistent with those observed in the conversion of **1** to **10**. In addition to evaluation for 5-HT$_4$ antagonist activity in the rat esophagus, **23** and selected analogues were tested for affinity at the 5-HT$_4$ receptor labeled by [^{3}H]GR 113808[7] in the guinea-pig striata (Table 2). Subnanomolar affinity was noted for **23** and related *N*-alkyl (**24**) and *N*-(sulfonamido)alkyl derivatives (**26-28**).

TABLE 2. 5-HT_4 Receptor Binding and Antagonist Activity for Compounds **23-28**



compd.	X	R	Binding pK_i[a]	Antagonist pK_b[b]
23	OMe	butyl-*n*	9.32 ± 0.11	8.9 ± 0.1
24	OMe	pentyl-*n*	9.09 ± 0.09	9.1 ± 0.1
25	H	$CH_2CH_2NHSO_2Me$	8.75 ± 0.08	8.1 ± 0.1
26	OMe	$CH_2CH_2NHSO_2Me$	9.13 ± 0.10	9.2 ± 0.1
27	OMe	$CH_2CH_2NMeSO_2Me$	9.33 ± 0.32	9.1 ± 0.1
28	OMe	$CH_2CH_2CH_2NHSO_2Me$	9.47 ± 0.06	8.8 ± 0.1
GR 113808			10.20 ± 0.04	9.0 ± 0.1
SB 204070			10.89 ± 0.08	10.3 ± 0.1

[a]Displacement of [^{3}H]GR 113808 from guinea-pig striata (± SEM). [b]Antagonism of 5-HT mediated relaxation of rat, carbachol contracted esophageal muscularis mucosae (± SEM).

On the basis of preliminary in vivo testing, compound **26** was chosen for further pharmacological evaluation. Receptor profiling by ligand binding techniques indicated that **26** was at least one thousand-fold selective for the 5-HT_4 receptor versus adrenergic, muscarinic, dopaminergic, and other serotonergic receptors. Although the 5-HT_4 receptor affinity of **26** is less than that of GR 113808 and SB 204070 (Table 2), **26** may be a more useful tool for probing 5-HT_4 receptor function in vivo since it lacks the metabolically labile ester functionality of these higher affinity ligands.[8]

References and Notes

1. Clark, R.D.; Jahangir, A.; Langston, J.A.; Weinhardt, K.K.; Miller, A.B.; Leung, E.; Eglen, R.M. *BioMed. Chem. Lett.* preceeding communication in this issue.
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8. Details of the complete in vitro and in vivo pharmacological characterization of compound **26** will be the subject of a forthcoming publication.

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