Bioorganic & Medicinal Chemistry Letters, Vol.3, No.2, pp. 205-208, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

SYNTHESIS AND 5-HT$_3$ RECEPTOR AGONIST ACTIVITY OF ARYLUREAS DERIVED FROM HISTAMINE.

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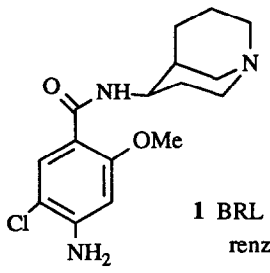
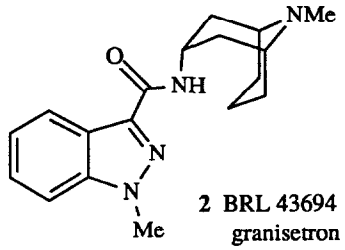
(*Received in USA* 5 *October* 1992)

Abstract. The synthesis of a series of aryl ureas derived from histamine is described. The compounds are shown to be 5-HT$_3$ receptor agonists by their ability to initiate the Bezold-Jarisch reflex and to displace [^{3}H]-BRL 43694 from central 5-HT$_3$ receptors with a potency equivalent to that of 5-HT.

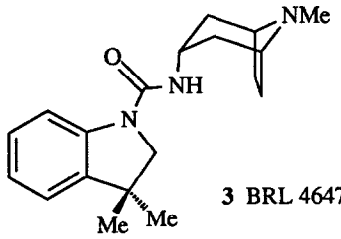
Although there have been many reports of potent and selective 5-hydroxytryptamine 5-HT$_3$ receptor antagonists, for example from our laboratories, BRL 24924 (**1**, renzapride),[1] BRL 43694 (**2**, granisetron)[2] and BRL 46470 (**3**),[3] very few selective 5-HT$_3$ receptor agonists have been reported.



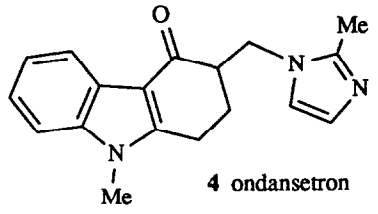
1 BRL 24924
renzapride



2 BRL 43694
granisetron



3 BRL 46470

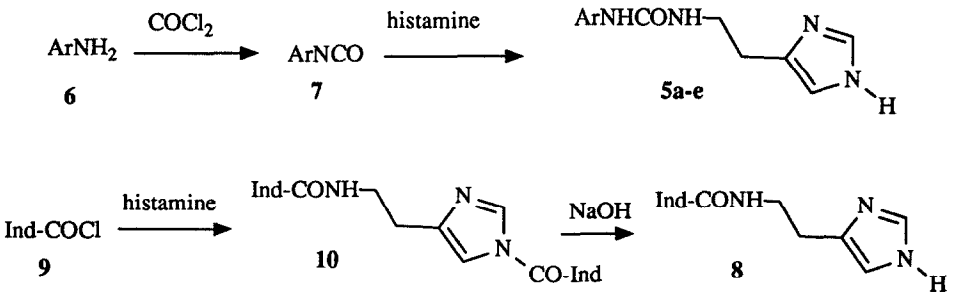


4 ondansetron

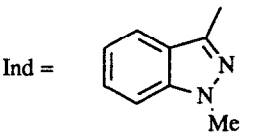
The standard alternative to 5-HT has been 2-methyl-5-HT.[4] However recent reports have suggested that this compound is a partial agonist.[5] By comparison, 1-(m-chlorophenyl)-biguanide has been reported to have a very high affinity for the 5-HT$_3$ receptor *in vitro*,[6] but has a much

lower potency *in vivo* which has prompted the suggestion that it has a higher affinity for the desensitised form of the receptor.[5] For these reasons there are currently no suitable 5-HT_3 receptor agonists for the investigation of central *in vivo* pharmacology.

In an earlier publication we described a series of aryl ureas which were potent 5-HT_3 receptor antagonists.[7] In that series the basic side chain, a common feature of all 5-HT_3 receptor antagonists, consisted of a saturated azabicycle. A second series of 5-HT_3 receptor antagonists, exemplified by ondansetron, **4**,[8] has an imidazole as the basic moiety. As a part of our attempts to combine the salient features of both series, we prepared a series of ureido derivatives of histamine (Scheme I).



Scheme I: Synthesis of **5a-e** and **8**.

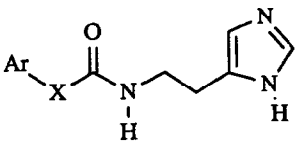


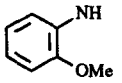
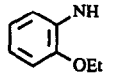
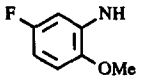
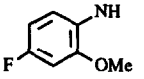
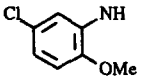
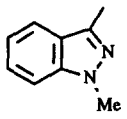
For commercially available isocyanates **7**, histamine was reacted directly to give the target compounds **5**. Alternatively the isocyanate was prepared *in situ* from the aniline **6** and phosgene.[7] We also prepared the amide **8** derived from histamine and 1-methylindazolecarboxylic acid by analogy with granisetron **1**. However, the reaction of histamine with 1-methylindazole-3-carbonyl chloride **9** could not be controlled to give the mono-aroylated product. The di-aroylated product **10** was therefore prepared and the more labile aroyl-imidazole cleaved by base hydrolysis.

None of these compounds exhibited any significant 5-HT_3 receptor antagonist activity in terms of the inhibition of the 5-HT evoked Bezold-Jarisch reflex. However it was noted that, on dosing prior to the 5-HT challenge, the compounds themselves evoked a reflex bradycardia, indicative of 5-HT_3 agonist activity. A number of compounds were prepared and the results are presented for both *in vivo* and *in vitro* activies in the Table, which includes 5-HT for comparison. Binding data was obtained using [^{3}H]-BRL 43694 (0.3 nM, specific activity 61 Ci/mmol; NEN Research Products, Dupont) by essentially the previously reported procedure.[9,10]

All the compounds **5a-e** and **8** had a higher 5-HT_3 receptor affinity than 5-HT but were

Table: Structure and 5-HT_3 receptor properties of **5a-e** and **8**.



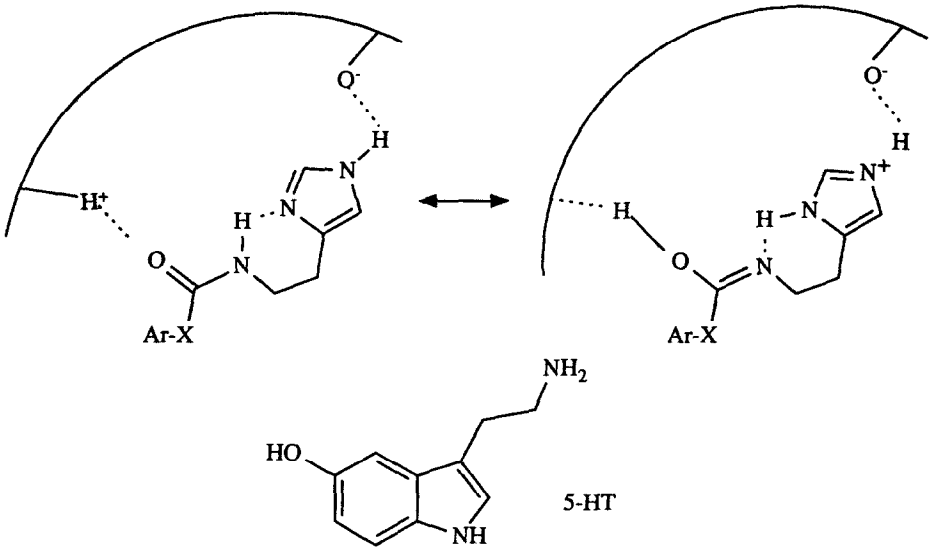
Compd No.	Ar-X	-log ED_{50} Bezold-Jarisch	pK_i	Slope
	5-HT	7.4	6.84 ± 0.01	1.62 ± 0.16
5a		7.0	7.55 ± 0.05	1.18 ± 0.01
5b		7.2	7.35 ± 0.03	1.14 ± 0.05
5c		7.4	7.69 ± 0.04	1.09 ± 0.03
5d		7.0	7.39 ± 0.01	1.26 ± 0.04
5e		6.8	8.86 ± 0.03	1.05 ± 0.04
8		6.9	7.84 ± 0.03	1.04 ± 0.09

marginally less potent *in vivo* except for **5c**. Equivalent activity was found with both the ortho-methoxy **5a** (BRL 45507) and ortho-ethoxy **5b** compounds. Introduction of a small fluorine in **5c** (BRL 48381) and **5d** also made little difference to potency. In marked contrast to the urea class of 5-HT_3 antagonists,[7] the 5-chloro analogue **5e** also retained good activity, though **5e** had a much greater potency difference between the two test systems. A similar larger difference was also noted with the indazole carboxamide **8**.

We have previously proposed a pharmacophoric model by which the 5-HT_3 receptor antagonists may bind to the receptor.[11] Using a similar hypothesis it could be considered that the ureas **5a-e** could intra-molecularly hydrogen bond in such a way as to mimic the basic NH_2 and the OH of

5-HT, yet retain sufficient flexibility that the activation of the receptor by a required conformational change is still possible (Scheme II). 5-HT is included in it's proposed binding

Scheme II: Representation of the interaction of the 5-HT_3 agonists with the 5-HT_3 receptor.



conformation for comparison.

Compounds (5a-e) and (8) represent a novel series of potent 5-HT_3 receptor agonists which could help to define further the role of 5-HT_3 receptors in peripheral and central disorders.

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10. Entorhinal cortical and hippocampus tissue was homogenised for 10 secs. at 20,500 rpm in 40 vols. ice cold HEPES buffer (50 mM, pH 7.5). Homogenates were allowed to stand at room temperature for 15 min and replaced on ice until required. Frozen tissue preparations were used throughout. Binding assays consisted of 0.1 mL [^{3}H]-BRL 43694, 0.1 mL displacing drug and 0.6 mL tissue in a total volume of 1 mL made up with HEPES buffer. Specific binding was defined as the excess over blanks in the presence of unlabelled metoclopramide (0.1 mM).
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