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SYNTHESIS AND SEROTONERGIC ACTIVITY OF BENZOFURAN AND DIHYDROBENZOFURAN ANALOGUES OF 5-CARBOXAMIDOTRYPTAMINE.

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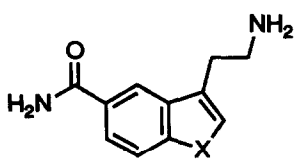
Abstract. The syntheses of the benzofuran (1) and dihydrobenzofuran (10) analogues of 5-carboxamidotryptamine (5-CT) were accomplished utilising a Horner-Emmons reaction on a benzofuranone. Compound 1 was a relatively potent 5-HT_{1D} agonist, although less potent than 5-CT. MO studies were carried out to investigate this difference.

To date at least fourteen different subtypes of serotonin (5-hydroxytryptamine, 5-HT) receptors have been identified,[1] which provide a rich source of targets for drug therapy.[2] In particular, the 5-HT_{1D} receptor has generated considerable recent interest[3,4] since the antimigraine drug sumatriptan is an agonist at this site.[5]

As part of our programme in the design of novel 5-HT_{1D} receptor agonists, we became interested in evaluating a benzofuran ring as a potential replacement for the indole nucleus in tryptamine derivatives. Indole and benzofuran have similar steric and geometric characteristics but their electronic features and functionality differ and thus may lead to variations in 5-HT receptor recognition and subsequent activation.

An early report[6] exists in which the benzofuran analogue of 5-HT appears to be a weaker agonist than 5-HT itself in the rat fundus strip, a preparation which has recently been shown to contain 5-HT_{2B} receptors.[7,8] Although McKenna et al.[9] found that *N*-methyl-*N*-isopropyltryptamine had 13-, 7- and 1.5-fold higher affinity than the benzofuran analogue at the 5-HT_{2A}, 5-HT_{1A} and 5-HT_{2B} sites, respectively, there has been little work since, until a recent paper from Tomaszewski et al.[10] which has prompted the disclosure of our own results. In their paper, the affinities of the benzofuran analogues of 5-methoxy-*N*,*N*-dimethyltryptamine and 5-methoxy-α-methyltryptamine were found to be about 20-30% lower than those of the indole counterparts at the 5-HT_{1A} receptor, whilst at the 5-HT_2 receptor the benzofurans had approximately one-third and one-sixth the affinity of the indoles. However, no binding affinities for benzofurans at the 5-HT_{1D} receptor have been published. For the purpose of this investigation, we targetted the novel benzofuran analogue (1) of 5-carboxamidotryptamine (5-CT), because 5-CT itself is one of the most potent 5-HT_{1D} agonists known.

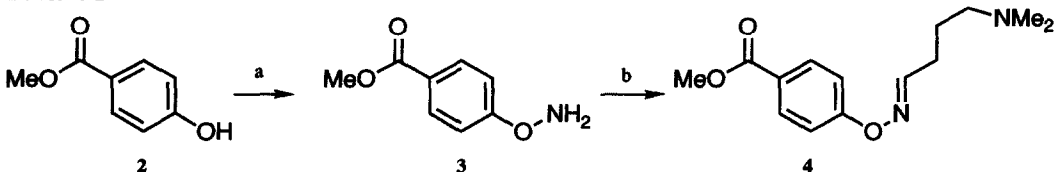


5-CT: X = NH
1: X = O

Although the benzofuran analogue of 5-HT has been prepared,[11,12] the syntheses are rather long and cumbersome. Among the many methods available for the synthesis of benzofurans,[13] two routes appeared attractive towards our goal due to their simplicity. The first involved a Fischer-like cyclisation of an oxime while the second utilised a Horner-Emmons reaction on a benzofuranone.

There are several examples in the literature[13,14] of forming 2-substituted benzofurans utilising *O*-aryl oximes derived from ketones, but we were not aware of any precedent for the cyclisation to proceed with oximes derived from aldehydes. We decided, therefore, to test the methodology with the readily accessible oxime **4** prepared by treating 4-(methoxycarbonyl)phenoxyamine (**3**) with dimethylaminobutanal dimethyl acetal (Scheme 1). Attempted cyclization of oxime **4** under a variety of acidic conditions (*e.g.* concd HCl in EtOH or HCO_2H-H_3PO_4) resulted only in decomposition to phenol **2**, a process which may occur by a Beckman rearrangement or an elimination to the nitrile, facilitated by the electron-withdrawing nature of the carboxy substituent. In support of this fragmentation, it was found that the reaction did proceed on the oxime derived from the same acetal and phenoxyamine itself in 29% yield using 98% HCO_2H-H_3PO_4 at 60° for 4 h.

Scheme 1



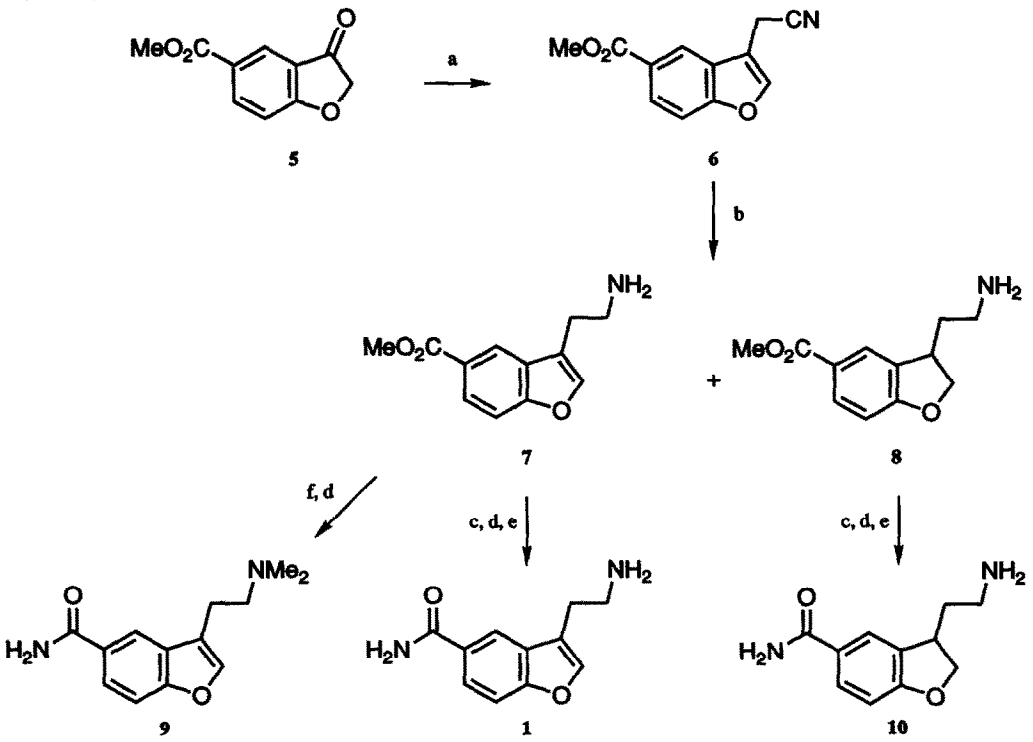
2 **3** **4**

Reagents and conditions: a) (2,4-dinitrophenoxy)amine, NaH, DMF, 58%; b) $(MeO)_2CH(CH_2)_3NMe_2$, EtOH, concd HCl, 60°, 2 h, 69%.

Having failed in our attempts to perform a Fischer-like cyclization on a suitable oxime, we turned our attentions to the second route. Although Wittig reactions of benzofuranones are known,[15] attempts to react methyl 3(2*H*)-benzofuranone-5-carboxylate (**5**)[16] with cyanomethylenetriphenylphosphorane led to only a low yield (12%) of the required 5-(methoxycarbonyl)-3-benzo[b]furylacetonitrile (**6**) with several by-products being observed. This transformation was, however, cleanly achieved using a Horner-Emmons reaction of **5** with diethyl cyanomethylphosphonate to give **6** in 57% yield, with no trace of exocyclic olefinic products (Scheme 2). Hydrogenation of **6** over platinum oxide afforded the benzofurylethylamine **7** in 70% yield, together with a small amount (4%) of the over-reduced 2,3-dihydrobenzofuran (**8**). Direct conversion of **7** into the required final target compound **1** with NaOMe and formamide[17] proceeded in low yield due to formylation of the ethylamino side chain. This side-reaction was avoided by protecting the amine using di-*tert*-butyl dicarbonate (99% yield), prior to conversion to the amide in 66% yield using the above conditions. Removal of the Boc group with trifluoroacetic acid then gave a quantitative yield of **1**.[18] The (*N*,*N*-dimethylamino)ethyl analogue (**9**) was prepared by reductive alkylation of **7** with formaldehyde and $NaCNBH_3$ (94% yield), followed by treatment with NaOMe and formamide (92% yield).

In addition, 3-(2-aminoethyl)-5-carboxamido-2,3-dihydrobenzofuran (**10**) was prepared from **8** in 35% overall yield utilising similar chemistry, in order to test the hypothesis that 2,3-dihydrobenzofuran may be a better indole bioisostere than benzofuran itself.[10]

Scheme 2



Reagents and conditions: a) $KN(SiMe_3)_2$, $(EtO)_2P(O)CH_2CN$, -78° to rt; b) H_2, PtO_2, $CHCl_3$, EtOH, 50 psi, 4 h; c) Boc_2O, CH_2Cl_2; d) NaOMe, H_2NCHO, DMF; e) CF_3CO_2H, CH_2Cl_2; f) CH_2O, $NaCNBH_3$, AcOH, MeOH.

The *in vitro* binding affinities of **1**, **9**, and **10** at various subtypes of the 5-HT receptor, compared to 5-CT, are shown in Table 1.

Table 1. Binding affinities of 1, 9, 10, and 5-CT for various serotonin receptor subtypes.

	$pIC_{50} \pm SEM$[a]				
compd	5-HT_{1A}[b]	5-HT_{1D}[c]	5-HT_{2A}[d]	5-HT_{2C}[e]	5-HT_3[f]
1	8.34 ± 0.09	7.37 ± 0.10	5.77 ± 0.04	6.18 ± 0.10	5.13 ± 0.07
9	8.04 ± 0.10	6.82 ± 0.07	5.47	5.38 ± 0.13	5.40 ± 0.10
10	7.14 ± 0.04	6.11 ± 0.09	<5.0	5.09 ± 0.02	5.37 ± 0.05
5-CT	9.53[g]	8.47	4.66[g]	6.23[g]	4.71 ± 0.23[h]

[a] SEM is the standard error mean from at least three experiments. Where SEM is not quoted the figures are the mean of two independent determinations. Full experimental details for 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 binding assays are given in ref. 19. [b] Displacement of [^{3}H]-8-OH-DPAT from pig cortex using 10 μM 5-HT to define nonspecific binding. [c] Displacement of [^{125}I]-GTI from pig caudate using 1 μM 5-HT to define nonspecific binding[20]. [d] Displacement of [^{3}H]-DOB from rat cortex homogenates using 1 μM cyproheptidine to define nonspecific binding. [e] Displacement of [^{3}H]-mesulergine from pig cortex using 10 μM 5-HT to define nonspecific binding. [f] Displacement of [^{3}H]-Q-ICS 205-930 from rat cortex homogenates using 10 μM MDL 72222 to define nonspecific binding. [g] Values from ref. 21. [h] Value from ref. 22 for displacement of [^{3}H]-ICS 205-930 from N1E-115 membranes.

It can be seen that 5-CT has higher affinity than 1 for the 5-HT_{1A} and 5-HT_{1D} receptors whereas 1 has a higher affinity for the 5-HT_{2A} subtype. They have equal affinities at the 5-HT_{2C} receptor. The order of potency of the other analogues at all subtypes, except 5-HT_3, is 1>9>10; i.e., the dihydrobenzofuran analogue is the least potent, a result which is in contrast to the suggestion by Tomaszewski et al.[10] that the 2,3-dihydrobenzofuran may be a good indole bioisostere. Their claim, however, is based on compounds[23] in which the aminoethyl side chain originates from the 4-position rather than the 3-position of the dihydrobenzofuran.

The functional assay performed on the rabbit saphenous vein,[24] which contains 5-HT_1-like receptors, shows that both 5-CT and 1 are full agonists in this preparation (Table 2). However, as is to be expected from the binding affinities, 1 is less potent than 5-CT.

Table 2. In vitro functional activity of 1 and 5-CT.

compd	$pEC_{50} \pm SEM$[a]	RM[b]
1	6.80 ± 0.26	1.20 ± 0.28
5-CT	7.55 ± 0.35	1.06 ± 0.02

[a] Contraction of the New Zealand white rabbit saphenous vein. The figures are the mean ± SEM of two (for 5-CT) or three (for 1) independent determinations. [b] RM = relative maximum and is defined as the maximum contraction relative to the maximum response obtained with 1μM 5-HT.

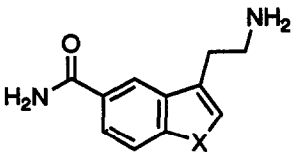
A possible explanation as to why the benzofuran analogue is less potent at the 5-HT_{1D} receptor may be that the indole NH is involved in a specific hydrogen bond to the receptor. However, it is likely that a good hydrogen bond donor group is not essential as Glennon et al.[4] found that naphthyl piperazines bind with high affinity to the 5-HT_{1D} site. An alternative explanation may be that the orientational preference of the amide group is different. In order to explore this possibility, MO studies were carried out in MOPAC[25] at the semiempirical level using AM1 with PRECISE convergence criteria and eigenvector following full geometry optimisation. Since 5-CT was not found in the Cambridge structural database, the starting structure geometry was taken from that found in the solid state for *N,N*-dimethyl-2-[5-[(3-amino-1,2,4-oxadiazol-5-yl)methyl]-1*H*-indol-3-yl]ethylamine,[19,26] suitably modified to incorporate the amide side chain at the 5-position. The neutral species was modelled since it is likely that in the receptor-bound state the charge on the amine is largely neutralised by the proposed aspartate counterion on the receptor, an approach taken in the classical study of tryptamine-receptor interactions by Green et al.[27]

Of the two possible orientations of the amide side chain, orientation 1 was significantly more stable than orientation 2 by some 2 kcal/mol for 5-CT but there was little difference for the benzofuran analogue 1 (Figure 1). Moreover, the calculated dipole moments (for the neutral species) suggest that in a higher dielectric environment there would be little effect on the preferred orientation of 5-CT but that in the benzofuran analogue 1 orientation 2 will become more favoured with respect to orientation 1.[28] Thus the variation in biological activity may be due to a change in orientational preference of the amide group.

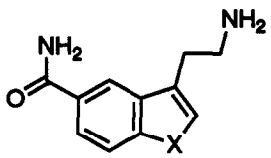
Since previous observations[19] on 5-(oxadiazolyl)tryptamines have shown that a hydrogen bond acceptor rather than a hydrogen bond donor group is required in this region for effective binding to the 5-HT_{1D} receptor, the possibilty that the carbonyl group of 5-CT may be a better hydrogen bond acceptor than the

benzofuran analogue **1** was also examined. However, calculations of atomic point charges by the esp-fit method[29] using orientation 1 suggested that the carbonyl oxygen of 5-CT would be only 0.004 e more negative than the equivalent atom in **1**, which is probably insufficient to explain all the observed difference in 5-HT_{1D} binding affinity. The full explanation may lie in a combination of some or all of these factors.

Figure 1



Orientation 1



Orientation 2

	X	Heat of formation (kcal/mol)	Dipole moment (D)
Orientation 1	NH	4.46	4.74
	O	-27.40	2.37
Orientation 2	NH	6.52	5.23
	O	-27.24	5.44

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28. The final conformations of the ethylamine side chains were close to that of the starting structure geometry. This is not inconsistent with the conformational space available to the rigid 5-HT_{1D} selective 5-CT analogue, 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (see King, F. D.; Brown, A. M.; Gaster, L. M.; Kaumann, A. J.; Medhurst, A. D.; Parker, S. G.; Parsons, A. A.; Patch, T. L.; Raval, P. *J. Med. Chem.* **1993**, *36*, 1918). Although it appears that this is the most likely binding orientation of 5-CT at the 5-HT_{1D} receptor, other side chain conformations were explored and generally found to show similar trends, favouring orientation 1 in a higher dielectric environment. One exception is the β-carboline-like conformations where the dipole moment for orientation 2 is larger than that for orientation 1. However, 1,2,3,4-tetrahydro-β-carboline itself has very low affinity for the 5-HT_{1D} site[4], so these conformations can be discounted.
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