(±) 3-Amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole: A Conformationally Restricted Analogue of 5-Carboxamidotryptamine with Selectivity for the Serotonin 5-HT_{1D} Receptor

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Serotonin (5-HT) receptors have been classified in at least six subtypes, including 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT_2, and 5-HT_3. Part of our investigation on conformationally restricted analogues of serotonergic mediators was to identify a novel structural class of selective 5-HT_{1D} receptor agonists as potential drugs for the treatment of migraine. For the purpose of our investigation, we chose 5-carboxamidotryptamine (5-CT) as our starting compound, because replacement of the hydroxy group in 5-HT with the amide in 5-CT has reportedly given good selectivity for the 5-HT_{1A} and 5-HT_{1D} receptor subtypes.[2]

A number of investigations into the binding orientation of the ethylamino side chain of 5-HT at the 5-HT_{1A} receptor have come to the conclusion that a "northerly" orientation A was the binding orientation as depicted in Figure 1.[3,4] This conclusion was based upon structural comparisons with conformationally restricted 5-HT_{1A} ligands such as the ergot alkaloid **1**, the partial ergot structures, such as **2**, and the even simpler **3**.

In contrast there have been no investigations into the likely binding conformation of either 5-HT or 5-CT at the 5-HT_{1D} receptor. However the high affinity of some ergot alkaloids related to **1**, for example metergoline (pK_D 9.09[5]), would suggest that the preferred binding conformation of the indole ethylamines is also orientation A. In order to investigate this, we prepared a number of conformationally-restricted analogues of 5-CT which would mimic not only orientation A, but also many of the other possible orientations of the side chain. One such analogue was the 3-aminotetrahydrocarbazole, **4** (BRL 56905, Figure 2), in which the side chain has an "easterly" orientation B.

As shown in Scheme I, 4-aminocyclohexanol (**5**) was N-protected as the phthalimide and oxidized with pyridinium chlorochromate to give the ketone **6** (67%) required for the Fischer indole synthesis. Cyclization with 4-cyanophenylhydrazine in AcOH gave the carbazole **7** (60%). Deprotection with hydrazine gave 3-amino-6-cyanotetrahydrocarbazole which was also required for our SAR study. The 3-amino compound could not be efficiently hydrolyzed to the 6-amide **4** directly. However N reprotection as the t-BOC derivative, basic peroxide conversion of the nitrile to the amide, and N deprotection with HCl gave **4** in an overall yield of 45% from **6**.[6]

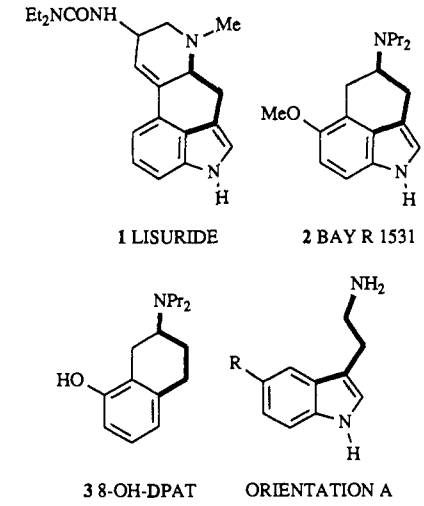


Figure 1.

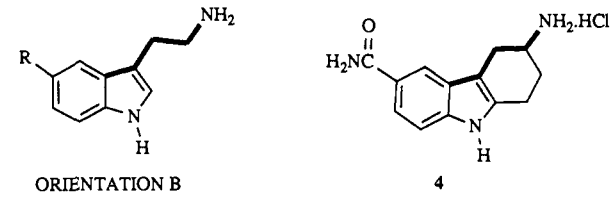
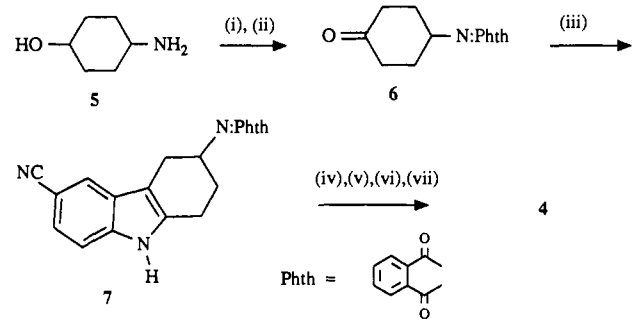


Figure 2.

Scheme I. Synthesis of 1[a]



[a] (i) Phth:NCO_2Et; (ii) $C_5H_5NH{\cdot}ClCrO_3$; (iii) *p*-CN-$C_6H_4N_2H_3{\cdot}$HCl/HOAc/NaOAc; (iv) $N_2H_4{\cdot}H_2O$ (v) $(t\text{-}BuOCO)_2O$; (vi) H_2O_2/NaOH; (vii) HCl.

The binding affinity of **4** at the 5-HT_{1A}, 5-HT_{1C}, 5-HT_{1D}, and 5-HT_2 receptors are shown in Table I. Sumatriptan (**8**)[7] has been included for comparison.

As mentioned earlier, 5-CT shows high potency and selectivity for both the 5-HT_{1A} and 5-HT_{1D} receptors. In contrast, whereas **4** has retained high 5-HT_{1D} affinity, equivalent to that of 5-HT, affinity at the 5-HT_{1A} receptor is about 1000-fold lower than that of 5-CT to give a compound now about 50-fold selective for the 5-HT_{1D} receptor. Interestingly, 5-HT_{1C} affinity of **4** is also much lower than that of 5-CT.

Receptor affinity alone gives no indication of the function of the compound and therefore the properties of **4** were investigated in two *in vitro* models of 5-HT_{1D} and/or 5-HT_1-like function, the dog isolated saphenous vein[7] and rabbit isolated basilar artery[12] models. The results are presented in Table II. For comparison, results for both 5-HT and **8** are included.

In both test systems, **4** was found to be a partial agonist with potency equal to or marginally greater than 5-HT. Whereas comparative binding data suggested only a trend toward greater 5-HT_{1D} receptor affinity of **4** over **8**, in

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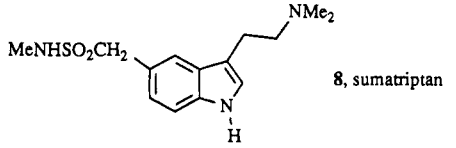
Table I. Serotonergic 5-HT_{1A}, 5-HT_{1C}, 5-HT_{1D}, and 5-HT_2 Affinities (pK_D) of 5-HT, 5-CT, 1, and 8



8, sumatriptan

compd	5-HT_{1A}	5-HT_{1C}	5-HT_{1D}	5-HT_2
5-HT	8.5[8]	7.5[8]	7.9[5]	5.5[8]
5-CT	9.5[8]	6.2[8]	8.8[5]	4.7[8]
1	6.3 ± 0.1[a]	4.3 ± 0.2[b]	8.0 ± 0.2[c]	>5.3[d]
8	5.5 ± 0.1[a]	4.8 ± 0.1[b]	7.6 ± 0.5[c]	>4.0[d]

[a] Piglet hippocampus [^{3}H]-8-OH-DPAT. [b] Piglet choroid plexus [^{3}H]mesulergine.[10] [c] Piglet caudate [^{3}H]-5-HT,[5] high affinity site. [d] Rat cortex [^{3}H]ketanserin.[11]

Table II. In Vitro Functional Results for 5-HT, 1, and 8

	dog saphenous vein[a]		rabbit basilar artery[a]	
compd	EC_{50}, μM (± SEM)	IA[b]	EC_{50}, μM (± SEM)	IA[b]
5-HT	0.21 ± 0.07	1.0	0.30 ± 0.08	1.0
1	0.07 ± 0.03	0.73	0.28 ± 0.09	0.73
8	0.40 ± 0.10	0.78	2.40 ± 0.70	0.74

[a] $n \geq 4$, EC_{50} = concentration for 50% of maximal response. [b] IA = intrinsic activity defined as the maximum contraction obtained relative to 5-HT (= 1).

both these *in vitro* models, 4 is between 5 and 8 times more potent than 8.

In conclusion, conformational restriction of the ethylamino side chain of 5-CT in an "easterly" orientation B in the form of the 3-aminotetrahydrocarbazole 4 has given a compound which is a potent and selective 5-HT_{1D} receptor partial agonist with an intrinsic activity comparable to 8 but with significantly greater potency. A conclusion that could be drawn from this result is that the binding orientation of the side chain of 5-CT at the 5-HT_{1D} receptor may be orientation B. Further studies are in progress on the SAR and detailed pharmacological properties of the tetrahydrocarbazoles, and their enantiomers, full details of which will be published later.

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(6) For full experimental details see WO 93/00086. For 4, Anal. ($C_{13}H_{16}ClN_3O$). Found (calcd): C, 58.6 (58.8); H, 6.1 (6.1); N, 15.9 (15.8); Cl, 13.5 (13.2).

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