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SYNTHESIS, BIOLOGICAL ACTIVITY AND ELECTROSTATIC PROPERTIES OF 3-[2-(DIMETHYLAMINO)ETHYL]-5-[(3-AMINO-1,2,4-THIADIAZOL-5-YL)METHYL]-1H-INDOLE, A NOVEL 5-HT$_{1D}$ RECEPTOR AGONIST.

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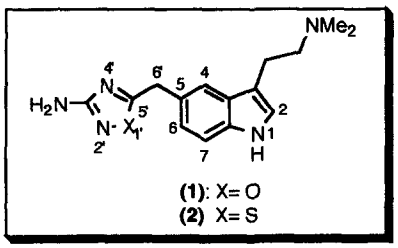
Abstract: The synthesis, biological activity and electrostatic properties of the thiadiazolyl-tryptamine (**2**), a novel 5-HT$_{1D}$ receptor agonist, are described The compound was synthesised in four steps from the readily available tryptamine ester (**7c**) and it was found to be remarkably more potent than the corresponding oxadiazole analogue (**1**), both in functional and binding assays.

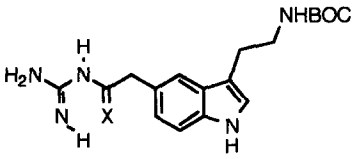
During the past decade there has been a renewed interest in the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) and a multitude of different receptor subtypes has been identified[1]. This heterogeneity offers the possibility for discovering selective agonists/antagonists in order to modulate serotonergic function in clinical disorders where alterations in 5-HT have been implicated[2]

As part of a program of work directed towards the identification of novel and selective 5-HT$_{1D}$ receptor agonists for the treatment of migraine[3], we became interested in the oxadiazole (**1**) and thiadiazole (**2**) tryptamines, molecules which, like sumatriptan[3], incorporate an indole C$_5$ substituent which is in principle capable of hydrogen-bonding donor and acceptor interactions at the 5-HT$_{1D}$ receptor The thiadiazole (**2**) proved to be an unexpectedly potent agonist at this receptor and its synthesis, biological activity and electrostatic properties are the subject of the present Letter.

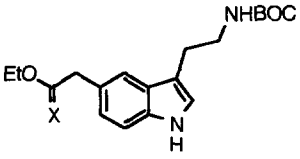
Chart 1



(1): X= O
(2) X= S



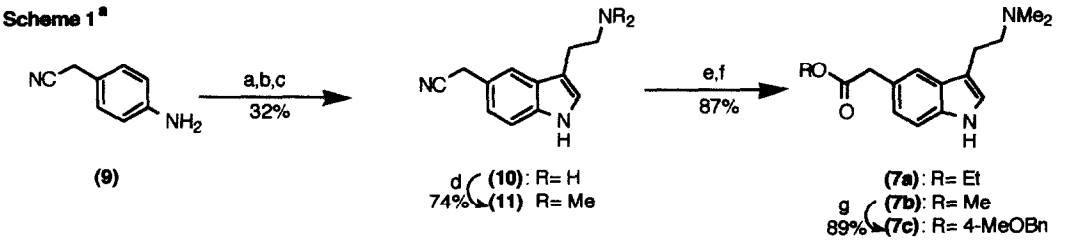
(3): X= S
(6): X= O



(4): X= S
(5): X= O

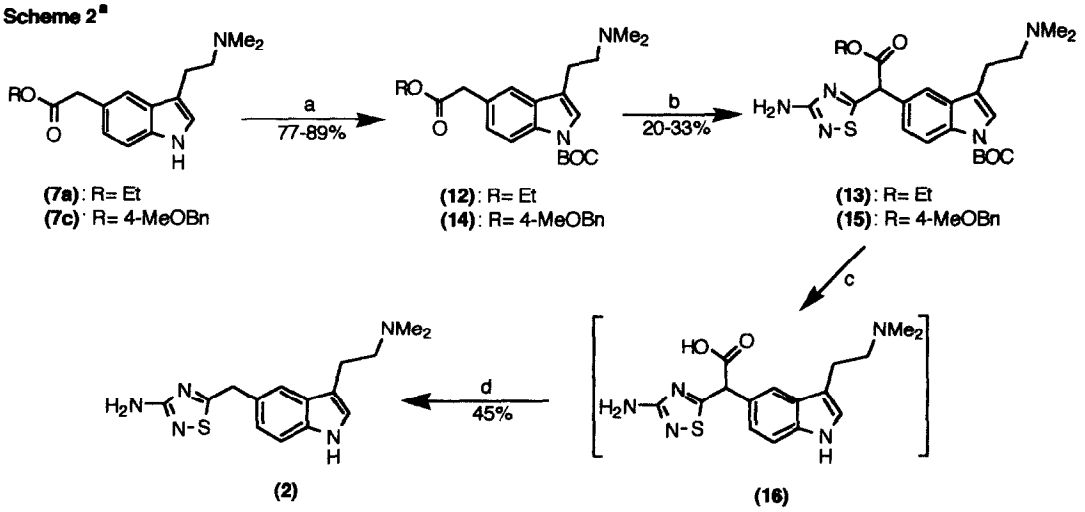
Two different approaches to the synthesis of (**2**), starting from readily available tryptamine-5-acetic acid derivatives, were envisaged The first route was based on the oxidation (e.g. bromine, DEAD)[4] of a thionoacylguanidine (**3**) which in turn could be prepared from guanidine itself and the thiono ester (**4**), or by thionation of an acylguanidine (**6**) (Chart 1). However, reaction of either (**5**) or (**6**) with Lawesson's reagent[5] (toluene, reflux) failed to produce the required products (**4**) or (**3**), respectively. Although other thionation methods or alternative ways to generate the thiono ester (**4**) could have been utilised, we instead turned our attention to the second approach which, indeed, afforded the target compound.

Scheme 1[a]



[a]Reagents and conditions: (a) $NaNO_2$ (1.05 eq), H_2O, concentrated HCl, -10°C, 0.5 h; (b) $SnCl_2.2H_2O$ (5.0 eq), concentrated HCl, -10°C, 20 min, (c) 4-chlorobutanal dimethylacetal (1.0 eq), EtOH-H_2O (5:1), reflux, 2-4 h; (d) HCHO (4.0 eq), $NaCNBH_3$ (2.2 eq), AcOH (5.0 eq), MeOH, 0° to 25°C, 1 5 h; (e) 2N NaOH (4.0 eq), EtOH-THF (2.5 1), reflux, 17 h; (f) $SOCl_2$ (3.5 eq), MeOH, 0° to 25°C, 2 h; (g) 4-methoxybenzyl alcohol (4.8 eq), n-BuLi (3.3 eq), THF, -78° to 25°C, 1 h.

Scheme 2[a]



[a]Reagents and conditions: (a) $(BOC)_2O$ (1.3 eq), MeCN, 4-DMAP (0.1 eq), 25°C, 3 h; (b) NaH (2.5 eq), DMF, 25°C, 20 min; 3-amino-5-chloro-1,2,4-thiadiazole (**8**) (2 1 eq), 25°C, 1 h; (c) TFA-CH_2Cl_2-H_2O (2:12:0.5), 25°C, 1 5 h; (d) MeOH, reflux, 10 min.

The second route relied on the alkylation of an ester (**7**) with 3-amino-5-chloro-1,2,4-thiadiazole (**8**)[6] using enolate chemistry, followed by hydrolysis and decarboxylation of the activated acid (**16**) (Schemes 1 and 2). Using the Grandberg modification of the Fischer indole synthesis[7], 5-cyanomethyltryptamine (**10**) was prepared in three steps from (**9**). N,N-Dimethylation of (**10**) followed by hydrolysis and esterification then produced esters(**7a**) or (**7b**). It was considered that protection of the indolic nitrogen as the BOC derivative would be advisable at this stage, both to promote the generation of the corresponding ester enolate and to avoid potential side reactions with the electrophile at this centre. Thus,treatment of (**7a**) with $(BOC)_2O$ in acetonitrile in the presence of a catalytic amount of DMAP cleanly afforded (**12**). Generation of the enolate of (**12**) with $KN(SiMe_3)_2$ (1 2 eq, THF, -70°C) and subsequent reaction with (**8**) (1.2 eq,-70 to 25°C, 5 h) produced, however, only trace amounts (*ca* 1%) of coupled material (**13**). After some experimentation, conditions were developed to achieve this transformation in moderate (*ca* 30%) yield: the enolate was generated with excess sodium hydride (2.5 eq) in DMF at room temperature for a short period of time, followed by treatment with the electrophile (2.5 eq) at the same

temperature for 1 hour. It is noteworthy that the coupling proceeds in the presence of the unprotected amino group of (**8**) under overtly basic conditions. Conversion of (**13**) into the final compound was not, however, trivial. Attempted hydrolysis of the ester under mild basic conditions failed, probably due to the generation of a highly stabilized enolate which protects the ester against further nucleophilic attack, and more vigorous conditions led to decomposition. It was, therefore, necessary to alter the nature of the ester functionality to permit cleavage under non-basic conditions. A p-methoxybenzyl (MPM) ester was chosen with the expectation that it could be removed under the acidic conditions required to unblock the indolic nitrogen. Thus, transesterification of (**7b**) (p-methoxybenzyl alcohol, nBuLi, THF) followed by reaction with $(BOC)_2O$ produced ester (**14**) which was coupled with (**8**), under the optimized conditions, to give (**15**) in 33% isolated yield. Removal of the BOC and MPM groups was now achieved under standard conditions (TFA-CH_2Cl_2-H_2O, 25°C) and, after elimination of solvents,the intermediate carboxylic acid (**16**) was decarboxylated by heating under reflux in methanol for a brief period of time to afford (**2**) in 45% yield[8]

The exchange of sulphur (**2**) for oxygen (**1**)[9] proved to have a dramatic effect on the biological profile (Table 1). Thus, the thiadiazole (**2**) exhibited a ten-fold higher affinity for the 5-HT_{1D} receptor in pig caudate[10] than the oxadiazole (**1**). Furthermore, in a 5-HT_{1D} functional assay, (**2**) was some fifty-fold more potent than (**1**) in contracting the rabbit saphenous vein[11], both compounds were full agonists on this preparation (as compared to 5-HT).

Table 1

Compound	pIC_{50}[a]	pEC_{50}[b]
(**1**)	7.6	6.3
(**2**)	8.7	8.0
5-HT	8.0	6.8
Sumatriptan	7 7	6.2

[a]Displacement of [^{3}H]-5-HT to 5-HT_{1D} recognition sites in pig caudate membranes. [b]Contraction of New Zealand white rabbit saphenous vein. Figures are a mean of $n \geq 3$.

Because the molecular geometries of the oxadiazole and thiadiazole moieties are very similar[12], alternative explanations were sought for these remarkable differences in biological activity. The molecular electrostatic potentials (MEP's), calculated for models of both compounds, were therefore examined. A model of (**1**) was constructed from the crystal structure by arbitrary selection of one conformer of the disordered ethylamino side chain, addition of hydrogen atoms to satisfy the valencies of all atoms and full optimisation performed using AM1 in MOPAC[13]. A model of (**2**) was similarly constructed by changing the oxygen of (**1**) to a sulfur and minimising the resulting structure in the same way. Direct calculation of the MEP's from the wavefunctions[14] suggested that the majority of the differences between (**1**) and (**2**) lay in the volume close to the C_5-heterocyclic rings. Thus, it can clearly be seen from Figure 1 that there is a fairly large area of negative potential in the region of the nitrogen-oxygen bond in (**1**); the corresponding area in (**2**) is somewhat smaller and its orientation is dominated by the 2-nitrogen of the 1,2,4-thiadiazole ring. These features can be expressed quantitatively by examining the esp-fit charges for the two molecules, derived using AM1 and the ESP keyword in MOPAC[15,16]. Atoms where these charges differed by more than 0.05 units in (**1**) and (**2**) are included in Table 2. It can be seen that the main effect of changing the heteroatom is reflected in the charge on the heteroatom itself and its immediate neighbours. Although the charge on the carbon atom at position 5 of the indole ring is clearly affected, this effect does not extend much further into the indole nucleus. In particular, there is no obvious effect on the indolic N-H which could have modified its hydrogen-bonding donor ability. It is, therefore, reasonable to suggest that the enhanced biological activity observed for (**2**) could be the direct result of improved electrostatic complementarity of the C_5-heterocyclyl substituent with the receptor[17].

Table 2[a]

Atom number	Type in (1)	Type in (2)	Charge in (1)	Charge in (2)	Difference in charge
5	C	C	0.0402	-0.0216	-0 0618
6'	C	C	-0 3733	-0 3147	0 0586
5'	C	C	0 1798	-0.1251	-0 3049
1'	O	S	-0 0012	0 3194	0.3206
2'	N	N	-0 2628	-0 3618	-0 0990
4'	N	N	-0 3315	-0 2420	0 0895

[a]See Chart 1 for atom numbering

Acknowledgement. We wish to thank Mrs Margaret Beer and Miss Kate Scholey (Biochemistry and Pharmacology Dpts , Terlings Park, UK) for conducting the binding and functional assays, and Dr Richard G. Ball (Biophysical Chemistry Dpt., Rahway, NJ) for the single crystal structure determination of (1)

References and notes

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3. 5-HT_{1D} agonists such as sumatriptan (3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methane sulphonamide) (GR43175) and dihydroergotamine are clinically effective in the treatment of migraine See for example W Feniuk, P P A Humphrey, *Drug Dev. Res.*, **1992**, *26*, 235; A V Deliganis, S J Peroutka, *Headache*, **1991**, *31*, 228. The mechanism of action of these compounds is still, however, open to debate: M. A. Moskowitz, *Trends Pharmacol. Sci.*, **1992**, *13*, 307.
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7. B. Robinson, *The Fischer Indole Synthesis;* John Wiley and Sons, 1982; pp. 487-495
8. The oxalate salt of (2) has mp 185-188°C (methanol-diethyl ether), δ_H(360 MHz, DMSO-d_6) 10.99 (1H, br s, indole N-H), 7 57 (1H, s, Ar-H), 7.34, (1H, d, J= 8 3 Hz, Ar-H), 7 08 (1H, dd, J= 8 3 and 1.5 Hz, Ar-H), 6 55 (2H, s, -NH_2), 4.32 (2H, s, Ar-CH_2-), 3 23 (2H, m, -CH_2-), 3 03 (2H, m, -CH_2-), 2.75 (6H, s, -NMe_2) (Found. C, 52 47, H, 5.42; N, 17 65 $C_{15}H_{19}N_5S$ x 1.0 $C_2H_2O_4$ requires. C, 52.16, H, 5,41, N, 17.89%).
9. Compound (1) can be prepared in a single step from ester (**7b**) and hydroxyguanidine sulfate in the presence of a base such as sodium methoxide in methanol Full chemical and biological data for a series of oxadiazole based 5-HT_{1D} agonists will be reported in a forthcoming paper Leslie J. Street, et al
10 M S. Beer, J A. Stanton, Y Bevan, N S Chauhan, D N. Middlemiss, *Eur J Pharmacol*, **1992**, *213*, 193 Affinities are given as pIC_{50} values (-log IC_{50} where IC_{50} is the molar concentration of drug necessary to inhibit specific binding by 50%)
11. G. R Martin, S J MacLennan, *Naunyn-Schmiedeb. Arch. Pharmacol.*,**1990**, *342*, 111. Potencies are expressed as pEC_{50} values (-log EC_{50} where EC_{50} is the molar concentration of drug necessary to produce 50% of the maximum contraction)
12. The RMS difference in the geometries of (1) and (2),optimised as described in the text and calculated over all non-hydrogen atoms, was 0.30Å.
13. None of these minimisations resulted in large deviations from the crystal structure geometry, and while lower energy geometries could be found, these were all within 1.7 kcal/mol (AM1 calculation) of the models used and all showed similar behaviour in the calculated electrostatics All minimisations were carried out using the PRECISE keyword and Herbert's test was satisfied in both cases MOPAC is available from QCPE, Programme No 455, Version 6.
14. H. B Broughton, S M Green, H S Rzepa, *J. Chem. Soc. Chem. Commun.*, **1992**, 37.
15. B H Besler, K M. Merz, P A Kollman, *J. Comp. Chem.*, **1990**, *11*, 431.
16. A semi-empirical AM1 calculation was chosen as a compromise between the computational time required for molecules of this size and the validity of the information obtained The reasonableness of these charges was confirmed by calculation of the esp-fit charges for 3-amino-5-methyl-1,2,4-oxadiazole with full geometry optimisation at the 6-31G* level (*Gaussian 90, Revision J*, Gaussian, Inc., Pittsburgh, PA) although the absolute magnitudes vary, the pattern is similar to that found using MOPAC AM1 esp-fit charges for (1)
17. Note however that the logD's , measured in octanol- pH 7.4 buffer, for (1) and (2) are -0.67 and -0 04, respectively The possibility of a difference in desolvation energy between (1) and (2) prior to binding at the 5-HT_{1D} receptor could therefore be an additional contributing factor to the difference in binding energy See for example D Grobelny, U B Goli, R E Galardy, *Biochemistry*, **1989**, *28*, 4948.

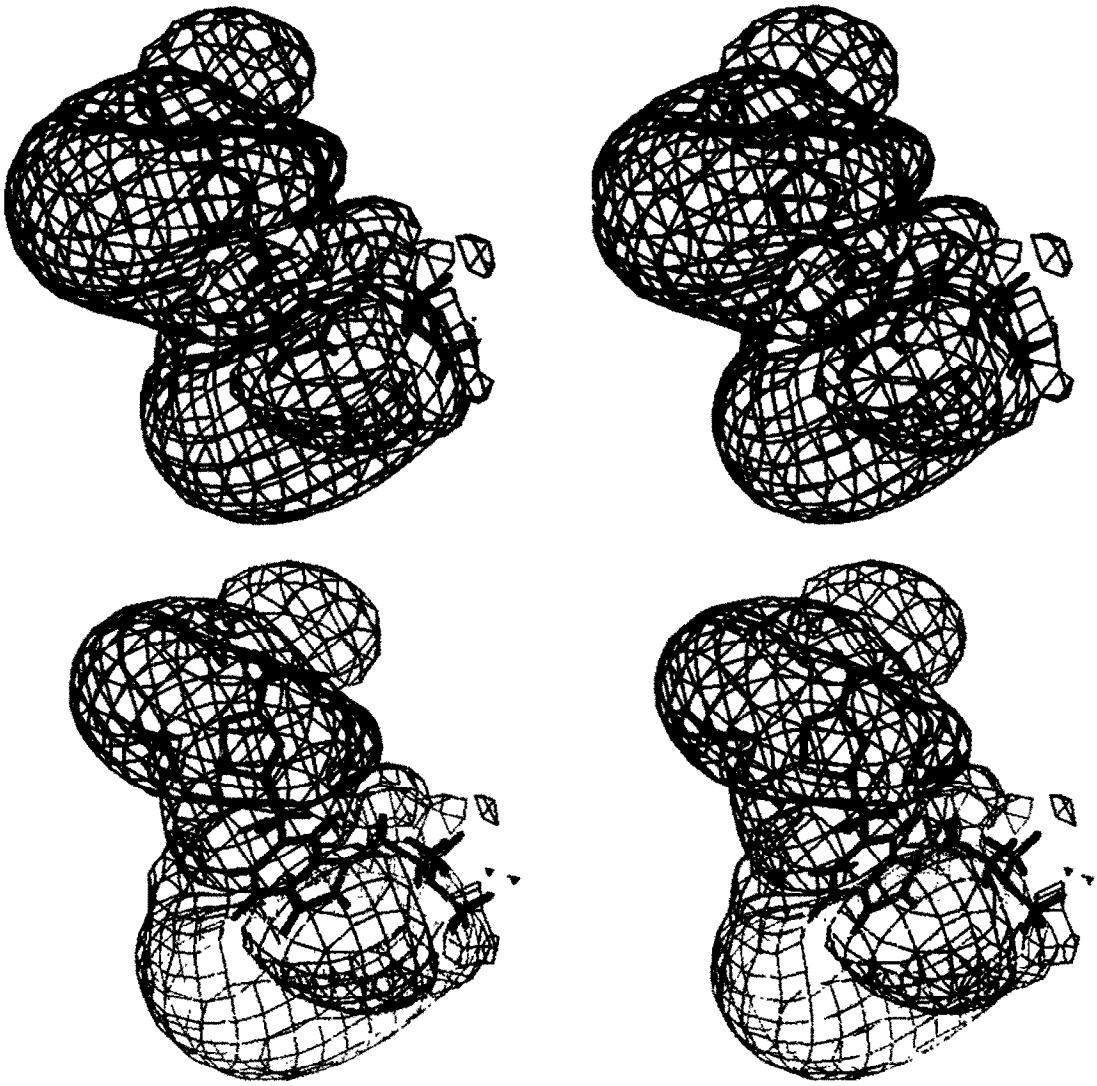

Figure 1: Stereo views of (1) (top) and (2) (bottom) with electrostatic potential isocontours at +4 (red/yellow) and -4 (blue/cyan) kcal/mol.