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NEW INDOLE DERIVATIVES AS POTENT AND SELECTIVE SEROTONIN UPTAKE INHIBITORS

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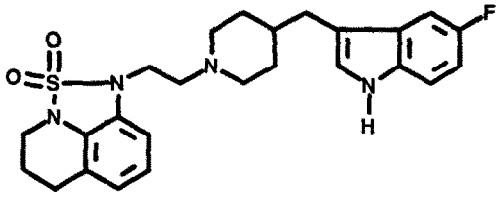
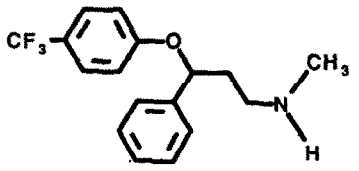
Abstract: *A new series of serotonin uptake inhibitors is described. Compounds* ***2c,f,g,o*** *and* ***r*** *exhibit potent and selective activities in a binding assay for the 5-HT uptake site. Compounds* ***2c, 2f*** *and* ***2g*** *behave like strong in vivo serotonin uptake inhibitors.*

The last decade has witnessed a growing interest in receptors for serotonin (5-hydroxytryptamine, 5-HT)[1], and to date at least seven subtypes of these 5-HT receptors have been identified. [2] In addition to the search for 5-HT receptor antagonists, the quest for potent and specific 5-HT uptake inhibitors has been important in attempts to discover new antidepressant drugs. [3] Several 5-HT uptake inhibitors are known[4], including fluoxetine[5], indalpine[6], and zimelidine. [7]

In our previous paper[8], we described indole derivatives as potential antidepressant drugs. One of them, 1-[2-[4-((5-fluoro-1H-indol-3-yl)-methyl)-1-piperidinyl]-ethyl]-5,6-dihydro-1H,4H-1,2,5-thiadiazole[4,3,2-ij]quinoline-2,2-dioxide **1** (**RP 68303**) displayed strong activity as serotonin uptake inhibitor (IC_{50}=1.2nM), and was found *in vivo* to be as active as fluoxetine in potentiating head shakes induced by 5-HTP.



1 RP 68303

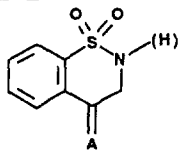
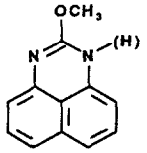
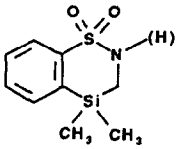
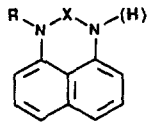
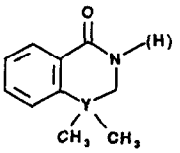
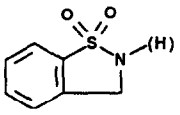
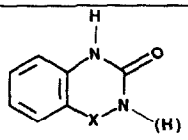
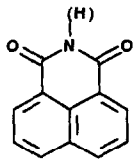
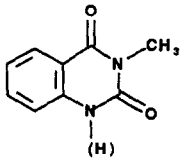
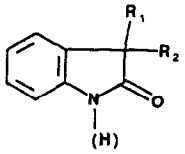
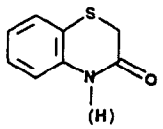


fluoxetine

As already mentioned[8], the presence of the 2-[4-((5-fluoro-1H-indol-3-yl)-methyl)-1-piperidinyl]-ethyl moiety seems to be critical for 5-HT uptake inhibitor activity. We therefore decided to keep this constant, and to replace the thiadiazoloquinoline-2,2-dioxide ring of **1** by other heterocyclic moieties, in order to find new potent 5-HT uptake inhibitors[9], and in addition to obtain more information about structure-activity relationships in this family.

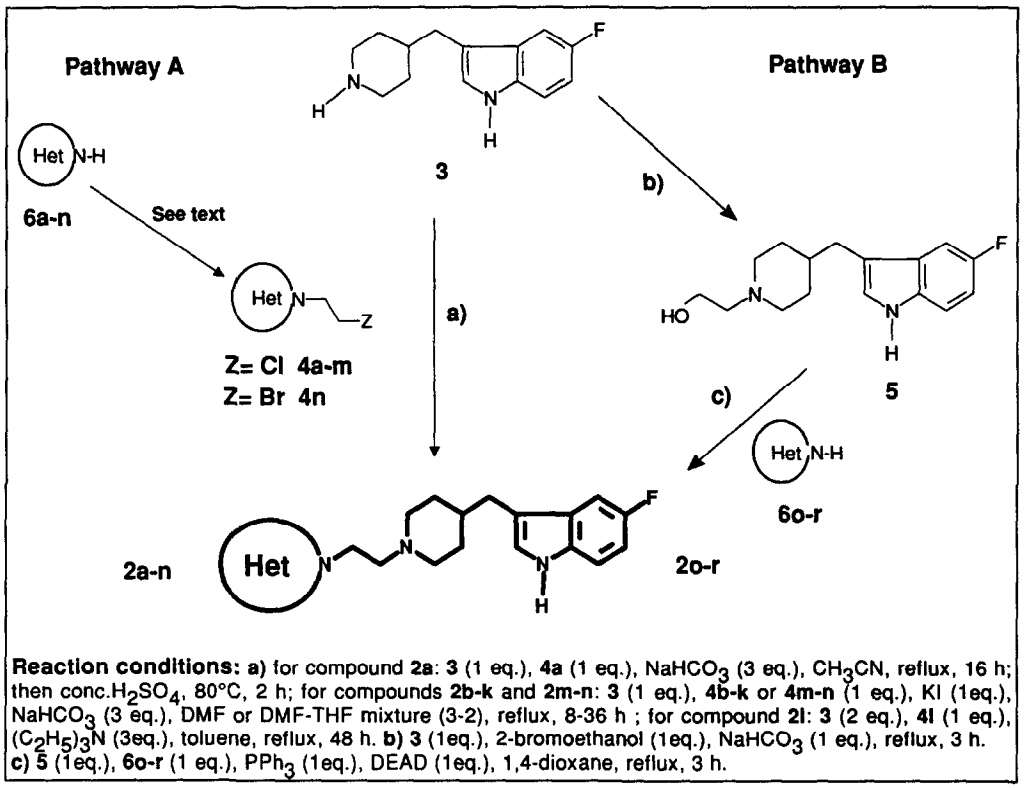
The present paper reports on the synthesis of novel compounds **2a-r** (Table 1), on their inhibition of 5-HT uptake, and on their *in vivo* activities.

Table 1: Chemical structures of compounds 2a-r and 6a-r.

Het N-(H)	Compounds 6a-i	Compounds 2a-i	Het N-(H)	Compounds 6j-n	Compounds 2j-n
	**6a** A= $-O(CH_2)_2O-$	**2a** A= O	$C_6H_5-SO_2N(H)R$	**6j** R= H **6k** R= $-CH_3$	**2j** R= H **2k** R= $-CH_3$
	**6b**	**2b**		**6l**	**2l**
	**6c** X= CO R= H **6d** X= SO_2 R= H **6e** X= SO_2 R= $-CH_3$	**2c** X= CO R= H **2d** X= SO_2 R= H **2e** X= SO_2 R= $-CH_3$		**6m** Y= C **6n** Y= Si	**2m** Y= C **2n** Y= Si
	**6f**	**2f**		**6o** X= CO **6p** X= SO_2	**2o** X= CO **2p** X= SO_2
	**6g**	**2g**		**6q**	**6q**
	**6h** $R_1 = R_2 = H$ **6i** $R_1 = R_2 =$ $-CH_2-CH_2-$	**2h** $R_1 = R_2 = H$ **2i** $R_1 = R_2 =$ $-CH_2-CH_2-$		**6r**	**2r**

Compounds **2a-r** were synthesized by the two approaches shown in Scheme 1, and the chemical structures of heterocycle **6a-n** are shown in Table 1.

Scheme 1: Synthesis of Compounds 2a-r.



Reaction conditions: **a)** for compound **2a**: **3** (1 eq.), **4a** (1 eq.), $NaHCO_3$ (3 eq.), CH_3CN, reflux, 16 h; then conc.H_2SO_4, 80°C, 2 h; for compounds **2b-k** and **2m-n**: **3** (1 eq.), **4b-k** or **4m-n** (1 eq.), KI (1eq.), $NaHCO_3$ (3 eq.), DMF or DMF-THF mixture (3-2), reflux, 8-36 h ; for compound **2l**: **3** (2 eq.), **4l** (1 eq.), $(C_2H_5)_3N$ (3eq.), toluene, reflux, 48 h. **b)** **3** (1eq.), 2-bromoethanol (1eq.), $NaHCO_3$ (1 eq.), reflux, 3 h. **c)** **5** (1eq.), **6o-r** (1 eq.), PPh_3 (1eq.), DEAD (1eq.), 1,4-dioxane, reflux, 3 h.

The **first approach (pathway A)** was the reaction of the readily available indolylpiperidine **3** [8,10] with the alkylchlorides **4a-m** or alkylbromide **4n** to give **2a-n** in moderate to high yields. [11]

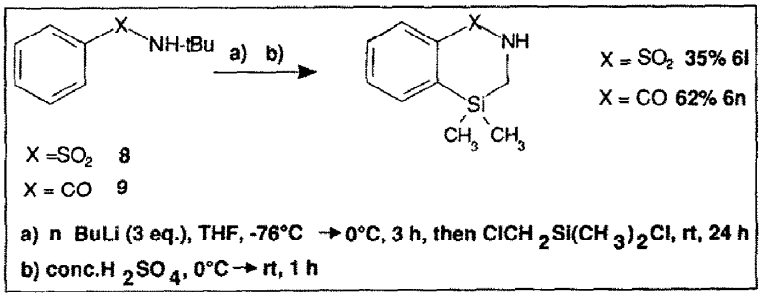
Compounds **4a,b**, and **d-m** were synthesized in 10-95% yields by reaction of the sodium salt of the heterocyclic compounds **6a,b**, and **d-m** [NaH (1 eq.), DMF, 20°C for 3 h then 100°C for 2h] with 1-bromo-2-chloroethane (DMF, 80°C, 16h), whereas **4c** was prepared from **4b** in a 98% yield by reaction of concentrated HCl in ethanol as solvent. Compound **4n** was obtained in a two-step synthesis in a 59% overall yield, from the corresponding silaheterocycle **6n**, by reaction of the lithium amide of **6n** (*n* BuLi, THF, -70°C→ rt, 3 h) with ethylene oxide (autoclave, rt, 48 h) followed by bromination of the resulting alcohol with phosphorus tribromide (THF,rt,12h).

The **second approach (pathway B)** required the addition of 2-bromoethanol to the same starting material **3** to provide **5** with a 95% yield. Then, under the Mitsunobu reaction

conditions, the reaction of alcohol **5** with the heterocyclic compounds **6o-r** afforded the expected compounds **2o-r** in moderate yields. [11]

The heterocycles **6g,h,j,k,o** and **r** are commercially available, whereas **6a,d-f,i,m,p** and **q** were prepared according to the methods cited in the literature.[12] Compound **6b** was obtained in 80% yield by addition of tetramethyl orthocarbonate to 1,8-diaminonaphthalene in pure phase (reflux, 4 h), and the heterocycles **6l** and **n** were prepared as described in Scheme 2. The first step was an ortho-lithiation reaction of the benzenesulfonamide **8** or benzamide **9** with an excess of *n* butyl lithium followed by the addition of (chloromethyl)dimethylchlorosilane, then acidic hydrolysis gave the silaheterocycles **6l** and **6n** respectively.

Scheme 2 : Synthesis of Compounds 6l and 6n



All new compounds have been caracterized by ^{1}H-NMR, IR and Mass spectroscopy, and have given satisfactory combustion analyses (C, H, N, O, S).

As shown in Table 2, except for compounds **2b,d,** and **k** all compounds cited are significant 5HT uptake inhibitors. *In vitro* inhibition of serotonin uptake by compounds **2c,f,g,o** and **r** was much greater than by fluoxetine [8] (IC_{50} equal or less than 1.8 *vs.*15 nM), and for compounds **2c,f,g,o** and **r** close to that of **1** [8] (IC_{50} equal or less than 1.8 *vs.*1.2nM).

Note that unlike the 2-[4-((5-fluoro-1H-indol-3-yl)-methyl)-1-piperidinyl]-ethyl moiety, the thiadiazoloquinoline-2,2-dioxide ring of **1** is not indispensable for binding to the 5-HT uptake site and can be replaced by other heterocycles, such as **6c, 6f** and **6g** .

On the basis of the binding data, the following structure-activity relationships were observed: **1)** Introduction of a sulfone group in the heterocyclic ring in place of the corresponding carbonyl group reduced 5-HT uptake inhibitory activities (**2o** *vs.* **2p**, **2c** *vs.* **2d**, and **2m** *vs.* **2l**); **2)** Ring enlargement by introduction of a carbonyl group into the ring system of **2f** also reduced 5-HT uptake inhibitory activities (**2f** *vs.* **2a**); **3)** Replacement of the 2-methoxy-pyrimidine moiety of **2b** by the corresponding pyrimidin-2-one (**2c**) increased the 5-HT inhibitory activities; **4)** Replacement of the naphtothiadiazine-2,2-dioxide ring of **2c** by the closely related heterocycle 1,8-napthalenedicarboximide (**2g**) did not change the 5-HT uptake inhibitory

activity; **5)** Substitution of the carbon atom of **2m** by the silicon atom (**2n**) weakly increased the activity of **2m**; **6)** Substitution of the acyclic sulfonamides (**2j** or **2k**) by the benzisothiazole moiety (**2f**) markedly increased 5-HT uptake inhibitory activities.

Table 2: In Vitro[13] and In Vivo[14] Activities for 2[4-((5-fluoro-1H-indol-3-yl)-methyl)-piperidinyl]ethyl Derivatives 2a-r , fluoxetine, and 1.

	IC_{50}, nM [a] [^{3}H] paroxetine binding	ED_{50}, mg/kg [b] 5-HTP		IC_{50}, nM [a] [^{3}H] paroxetine binding	ED_{50}, mg/kg [b] 5-HTP
2a	5.4	>20 (*po*)	**2j**	6.0	>20 (*po*)
2b	22.6	ND	**2k**	30.0	ND
2c	1.5	2.0(*po*), 4.0 (*sc*)	**2l**	14.0	ND
2d	12.0	ND	**2m**	3.8	20 (*po*)
2e	3.7	>20 (*po*)	**2n**	2.6	>20 (*po*)
2f	1.0	7.2 (*po*), 4.5 (*sc*)	**2o**	0.5	20 (*po*)
2g	1.8	2.3 (*po*), 6.1 (*sc*)	**2p**	2.1	>20 (*po*)
2h	3.1	ND	**2q**	5.9	20 (*po*)
2i	4.0	>20 (*po*)	**2r**	1.1	>20 (*po*)
fluoxetine	15.0	7.47 (*po*), 6.3 (*sc*)	**1**	1.2	2.89 (*po*), 5.1 (*sc*)

a IC_{50} values (nM) are the mean of at least 3 determinations each with 6 concentrations of test compounds in triplicate.
b ED_{50} values (mg/kg) are those that give half-maximal potentiation of the number of head-twitches observed with 5-HTP administered 1h (*sc*) or 1h30 (*po*) after giving the test compound. At least six doses were used for each compound, with groups of five mice/dose.
ND: not determined.

In contrast to compounds **2o, 2p** and **2r**, compounds **2c**, **2f**, and **2g** were found to be very active both in vitro and in vivo, and in addition were as active orally as fluoxetine or **1**.

None of compounds **2a-r** showed appreciable affinity (IC_{50}>100nM) for muscarinic, D_2 dopamine and α_1 adrenergic receptors, although certain had moderate affinities (between 10 and 100nM) for 5-HT_2 serotonin and H_1 histamine receptors.

This study showed that the thiadiazoloquinoline-2,2-dioxide ring of **1** can be replaced by other moieties such as **6c**, **6f**, and **6g**. Compounds **2c**, **2f**, and **2g** represent very interesting drug candidates as antidepressants. Details of their pharmacological properties will be reported elsewhere.

Acknowledgements. We wish to thank Mr. F. Gay, B. Just , J-C. Szmigel, and Ms. R. Kerphirique and Ms. B. Martin for technical assistance, and Mr. M. Vuilorgne and coworkers for analytical assistance.

References and Notes

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10. Gray, A. P.; Kraus, H. *J. Org. Chem.*, **1961**, 26, 3368.
11. Isolated yield, melting point (°C), and recrystallization solvent of **2a-r**: **2a**: cream-coloured semisolid, R_f=0.3 in dichloromethane-methanol mixture 97.5-2.5, compound **2a** was obtained in a 27% overall yield by the condensation of **4a** with **3** to give the corresponding acetal followed by an acidic hydrolysis (conc. H_2SO_4); **2b**. 13%, white solid, 198°C (oxalate salt, acetone), **2c**. 22%, white solid, 170°C (oxalate salt, acetone); **2d** 3%, cream-coloured solid, 155°C (acetonitrile); **2e**. 29.5%, white solid, 162°C (oxalate salt, DMF); **2f**. 22%, white solid, 130°C (acetonitrile); **2g**. 23%, yellow solid, 214°C (methyethylketone); **2h**. 25%, white solid, 173°C (ethanol); **2i**, 36%, yellow solid, 190°C (ethanol); **2j**. 60%, yellow oil (R_f=0.38 in dichloromethane-methanol mixture 9-1); **2k**. 36%, white solid, 130°C (oxalate salt, acetone); **2l**. 66%, white solid, 159°C (oxalate salt, acetone); **2m**. 83%, cream-coloured solid, 160°C (acetonitrile); **2n** 74%, white solid, 225°C (methanol-ethyl acetate mixture 1-1); **2o**. 6%, white solid, 250°C; **2p**. 15%, white solid, 208°C (1-methyl ethanol); **2q**. 15%, white solid, 195°C (ethanol); **2r**. 13%, cream-coloured solid, 180°C (oxalate salt, acetone).
12. Synthesis of: **6a**: see Zinnes, H.; Comes, R.A.; Zuleski, F. R.; Caro, A. N.; Shavel, J. *J. Chem. Soc.*, **1965**, 30, 2241; **6d** and **e**: Comte, M. T.; Gueremy, C.; Malleron, J-L.; Peyronel, J-F.; Truchon, A. *Eur. Pat.*, 433149, **1982**, CA: 74-111707; **6f** see: Jabre, I., Saquet, M., Tuillier, A. *J. Chem. Res., Synop.*, **1990**, 4, 106; **6i** see Kauffman, R. F, Hay, S. J. *J. Med. Chem.*, **1987**, 30, 824; **6m** see: Ben-Ishai, A.; *J. Heterocycl. Chem.*, **1970**, 7, 615; **6p** see: Girard, Y., Atkinson, G. J., Rokach, J. *J. Chem. Soc. Perkin I* **1979**, 1043; **6q** see: Hess, H-J, Cronin, T. H., Scriabine, A. *J. Org. Chem*, **1968**, 11, 130.
13. The indole derivatives shown in Table 2 were tested as 5-HT uptake inhibitors by mesuring their ability to inhibit [^{3}H] paroxetine binding to rat cortical membranes, and the procedures for the biological assays are described in detail in: Habert, E.; Graham, D.; Tahraoui, L.; Claustre, Y.; Langer, S. Z. *Eur. J. Pharmacol.*, **1985**, 118, 107.
14 Potentiation of 5-hydroxytryptophan-induced behavioral symptomatology in mice was used to measure the *in vivo* activity of compounds **2**, and the procedures for these assays are described in detail in: Corne, S. J.; Pickering, R. W.; Warner, B. T.; *Brit. J. Pharmacol.* **1963**, 20, 106.