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1,1-DIPHENYL-3-DIALKYLAMINO-1-SILACYCLOPENTANE DERIVATIVES: A NEW CLASS OF POTENT AND SELECTIVE 5-HT$_{2A}$ ANTAGONISTS

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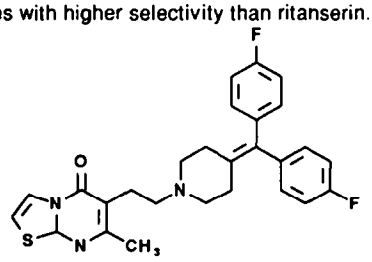
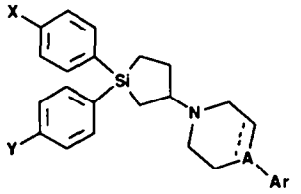
Abstract: *A new series of 1,1-diphenyl-3-dialkylamino-1-silacyclopentanes was synthesized, and most compounds demonstrated moderate to high affinity for the 5-HT$_{2A}$ receptor. A member of this series, compound* ***1p*** *displays potent antagonist activity after oral administration against both mescaline and DOI-induced head-twitches in mice and rats, with a long duration of action. The dextrorotatory isomer* ***(+)-1p*** *is highly more potent than the levorotatory isomer* ***(-)-1p*** *in in vitro and in in vivo assays.*

In the last four decades, the number of studies to understand both physiological and pharmacological actions of serotonin (5-HT, 5-hydroxytryptamine) have increased rapidly. Thus, appetite, memory, thermoregulation, sleep, sexual behaviour, anxiety, depression, and hallucinogenic behaviour are some of the processes that have been linked with the neurotransmitter serotonin [1]. To date, at least ten different serotonin receptors are known [2]. The 5-HT$_{2A}$ subtype is one of the best characterized, due to the availability of several increasingly selective antagonists [3]. Ritanserin was the first compound discovered with reasonable separation of 5-HT$_{2A}$ and non-5-HT effects. Clinical studies of this drug indicate that this 5-HT$_{2A}$ antagonist may be effective in anxiety or disthymic disorders [4]

The present paper describes the synthesis and SAR of a new series of 1,1-diphenyl-3-dialkylamino-1-silacyclopentanes **1d-t** [5] (Table 1) structurally unrelated to ritanserin. One of them, compound **1p** and especially its dextrorotatory isomer **(+)-1p** shows potent *in vitro* and *in vivo* 5-HT$_{2A}$ antagonist activities with higher selectivity than ritanserin.



ritanserin

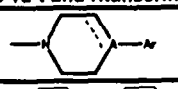
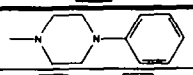
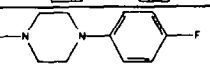
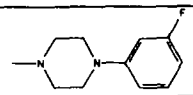
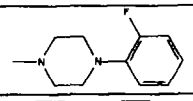
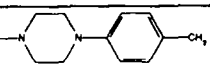
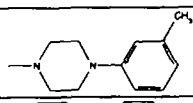
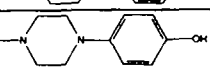
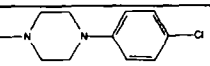
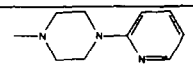
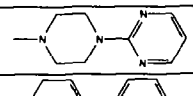
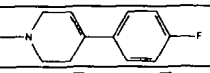
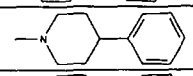
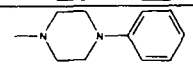
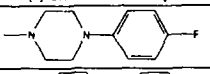
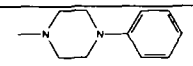
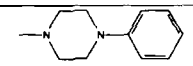
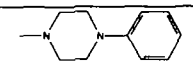


1d-t (see Table 1)

SYNTHESIS:

Compounds **1d-r** were prepared in a straightforward manner according to the sequence described in Scheme 1, which involves a global two-step synthesis from the readily available 1-silacyclopent-2-enes **2a-c** [6]. Conversion of **2a-c** to **8d-r** is a one-pot procedure Thus, silacyclopent-2-enes **2a-c**

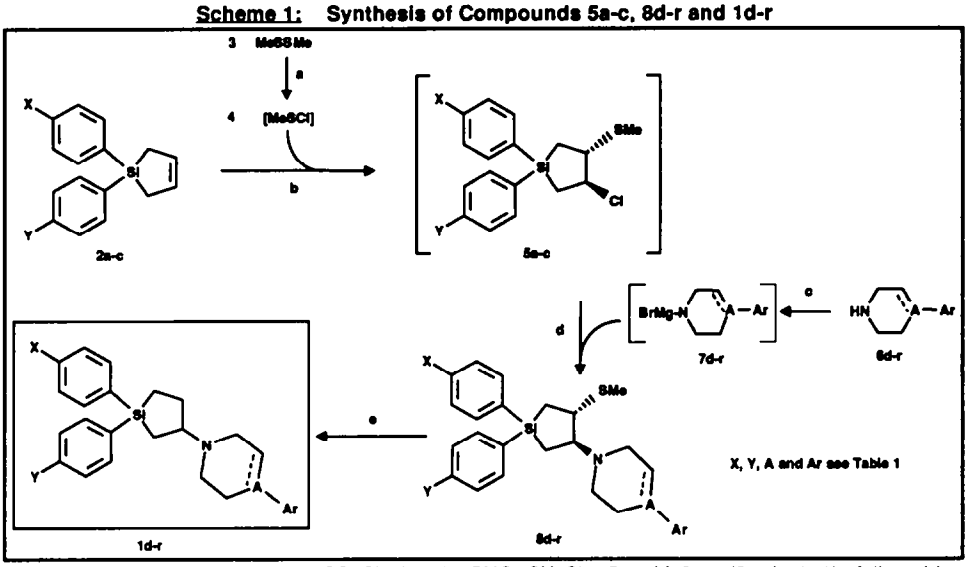
Table 1: *In Vitro* Activities of 1,1-Diphenyl-3-dialkylamino-1-silacyclopentane Derivatives 1d-t and ritanserin.

1	X	Y		IC_{50} (nM)[a]
1d	H	H		1
1e	H	H		0.9
1f	H	H		34
1g	H	H		100
1h	H	H		10
1i	H	H		33
1j	H	H		46
1k	H	H		25
1l	H	H		29
1m	H	H		80
1n	H	H		14
1o	H	H		53
1p	F	F		2
(+)-1p	F	F	(+) enantiomer of 1p	3
(-)-1p	F	F	(-) enantiomer of 1p	25
1q	F	F		18
1r [12] A/B isomers	H,F	H,F		16
1s A isomer	H	F		20
1t B isomer	F	H		27
ritanserin				1.7

[a] IC_{50} values (nM) are the mean of the last 3 determinations each with 6 concentrations of test compounds in triplicate

reacted with methanesulfenyl chloride **4**, generated from dimethyldisulfide **3** and sulfuryl chloride in dichloromethane at -50°C [7], to give **5a-c** which were used in the next step without purification.

Scheme 1: Synthesis of Compounds 5a-c, 8d-r and 1d-r



Reaction conditions: a) 3 (1eq.), SO_2Cl_2 (1eq.), -50°C, CH_2Cl_2, 5mn **b)** **2a-c** (2eq.), rt, 1h, followed by evaporation of CH_2Cl_2 and then addition of THF **c)** **6d-l** and **6k-r** (2eq.), PhMgBr (2eq.), 35°C, THF, 1h; **6j** (2eq.), PhMgBr (4eq.), 35°C, THF, 1h **d)** rt, 1 night **e)** Raney® nickel catalyst (50% slurry in water, pH>9, ≈ 2.5g/mmol of **8d-r**); for compound **1d**: methanol-water mixture 1-1, pressure of hydrogen: 40 bars, 70°C, 24h; for compound **1e**: methanol, pressure of hydrogen: 60 bars, 70°C, 100h; for compounds **8f,g, 8l, 8k, 8n** and **8q,r**: ethyl acetate, pressure of hydrogen: 1 bar, 40°C, 40-100 hrs; for compounds **8h, 8j, 8l,m** and **8o,p**: ethyl acetate-methanol 2-1, pressure of hydrogen: 1 bar, 40°C, 40-100 h.

The nucleophilic substitution of the chlorine atom by various amino moieties was performed by action of bromomagnesium amides **7d-r** [8] to give pure 3-dialkylamino-4-methylthio-1-silacyclopentanes **8d-r** in moderate to good (22-63%) overall yield. By comparison with analogous addition reactions [9], we suppose that methanesulfenyl chloride **4** reacts with the silacycloalkenes **2a-c** stereospecifically in a *trans* manner to afford **5a-c**. The chlorine atom was replaced by an amino group with retention of configuration to give **8d-r** as one diastereoisomer [10].

The second step is the reduction of the methylthio group of compounds **8d-r** by hydrogenation with Raney® nickel catalyst in methanol, ethyl acetate, methanol-water mixture or ethyl acetate-methanol mixture (see scheme 1). Pure 1,1-diphenyl-3-dialkylamino-1-silacyclopentanes **1d-r** [11] were obtained by flash-chromatography on silica gel.

After hydrogenation of **8r**, the two diastereoisomers **1s** and **1t** were obtained in 2/3 molar ratio [12]. Diastereoisomer separation of **1r** by HPLC using a column packed with Kromasil silica gel (mobile phase: ethyl acetate/*n*-hexane/diethylamine 10/90/0.02, detection: UV (265 nm), flow-rate: 1ml/mn, pressure: 25 bars) gave compounds **1s** and **1t** [11] with a purity of more than 95% (evaluated by HPLC).

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).

BIOLOGICAL ACTIVITY:

In vitro studies: The affinities of compounds **1d-t** and ritanserin for 5-HT_{2A} receptors were evaluated in *in vitro* binding assays using [^{3}H]-ketanserin as selective ^{3}H-ligand and rat cortical membranes [13]. The IC_{50} values for compounds **1d-t** are shown in Table 1.

Among the compounds prepared, the silacyclopentane derivatives **1d,e** and **1p** are the most interesting compounds with regards to their 5-HT_{2A} binding potency ($IC_{50} \leq 2nM$).

According to the binding data, the following structure-activity relationships were observed.

- Introduction of a fluorine atom at the 2- or 3-position of the phenyl ring of the piperazine group of compound **1d** highly reduced the 5-HT_{2A} binding potencies (**1f** and **1g** *vs.***1d**) while compound **1e** bearing the fluorine atom on the 4-position retained high potency ;
- Introduction of a fluorine atom at the 4-position of one of the phenyl rings born by the silicon atom of **1d** reduced 5-HT_{2A} binding potencies ($IC_{50} \geq 20nM$, **1s** and **1t** *vs.* **1d**). In addition, the two diastereoisomers **1s** and **1t** possessed almost the same potencies ,
- Introduction of two fluorine atoms at the 4-position of the two phenyl rings born by the silicon atom of **1d** retained high activity (**1p** *vs* **1d**), whereas the same modifications on the fluorinated compound **1e** dramatically reduced potency (**1q** *vs.* **1e**) ;
- Substitution of the fluorine atom of compound **1e** by a methyl (**1h**) group, a hydroxyl (**1j**) group or a chlorine atom (**1k**) reduced the binding activity ($IC_{50} \geq 10nM$) ;
- Replacement of the phenyl group of compound **1d** by heterocyclic moieties such as 2-pyridyl (**1l**) or 2-pyrazinyl (**1m**) groups highly reduced the 5-HT_{2A} binding activities ($IC_{50} \geq 29$ nM) ;
- Substitution of the 4-(4-fluorophenyl)-piperazinyl group of compound (**1e**) by 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridinyl group (**1n**) or 4-phenyl-piperidinyl (**1o**) groups also reduced the binding activity ($IC_{50} \geq 14nM$).

Given the potent 5-HT_{2A} binding activity of racemic **1p**, we went further and examined both enantiomers **(+)-1p** and **(-)-1p** of this compound. The two enantiomers were prepared in optically pure form by HPLC using a column packed with a chiral stationary phase [cellulose *tris* (3,5-dimethylphenylcarbonate-coated silica gel)]. Ten runs (recycling included) were necessary for the separation, starting from 0.7g of compound **1p** [mobile phase: *n*-hexane/2-propanol 95/5, flow-rate: 10 bars, detection: UV (265 nm), see Table 2].

Table 2: Chromatographic separation of enantiomers (+)-1p and (-)-1p

	retention time	weight [a]	yield [a]	$[\alpha]_D^{20}$
(+)-1p	14 0 mn	0 12 g	34%	+ 9 9° ± 0.5° (c=1, MeOH)
(-)-1p	15 1 mn	0 07 g	20%	- 9.3° ± 0 5° (c=1, MeOH)

[a]: after crystallisation

Enantiomeric homogeneity of both enantiomers (>99% e.e.) was evaluated by HPLC using Chiralcel OD as chiral stationary phase [mobile phase: *n*-hexane/2-propanol 95/5, flow-rate: 1ml/mn, pressure: bars, detection: UV (245nm), selectivity: 1.20].

Both enantiomers **(+)-1p** and **(-)-1p** were tested for their 5-HT_{2A} binding activities.The dextrorotatory isomer **(+)-1p** displayed 8-fold superior potency for the 5-HT_{2A} than did the levorotatory isomer **(-)-1p** (Table 1).

In vivo studies : The most potent *in vitro* silacyclopentane derivatives [**1d,e**, **1p** and **(+)-1p**] of this class of compounds and **(-)-1p** were tested *in vivo* . Central 5-HT_2 antagonist activity was assessed by the ability of these compounds to antagonize mescaline- and DOI-induced head-twitches[13] in mice and rats (Table 3). Among these compounds, **1p** showed the most potent *in vivo* activities (*sc* and *po*) with long duration of action at low dose. Thus, in the mescaline-induced head-twitches tests in rats, **1p** showed ED_{50}s of 0.48mg/kg (*po, 6 hours*) and 1.25mg/kg (*po, 16 hours*). This compound is 3 to 15-fold more potent *in vivo* by *po* route than ritanserin at 6 and 16 hours respectively. By *sc* route (1 hour), ritanserin was, however, more potent than **1p**.

In the DOI-induced head-twitches tests in mice, ritanserin invariably showed a higher potency than **1p** (*po and sc*). We cannot comment on why, in the mescaline-induced head-twitches tests in rats or mice, compound **1p** seems to be more active *po* than *sc*, since comparative pharmacokinetic studies have been performed.

Very interesting results were obtained with the dextrorotatory isomer **(+)-1p**. This isomer showed high *in vivo* activities both, in mescaline- and DOI-induced head-twitches in rats and mice, unlike isomer **(-)-1p** which is inactive. Thus, in the mescaline test in rats, compound **(+)-1p** exibited almost the same level of activity and the same long duration of action as **1p** by *po* route, while on the other hand it was 6-fold more potent by *sc* route. In the DOI test, compound **(+)-1p** showed the same level of activity as **1p** (*po* and *sc*).

Table 3: *In Vivo* Activities of compounds 1d,e, 1p, (+)-1p, (-)-1p and ritanserin
Mescaline- and DOI-induced head-twitches (ED_{50} mg/kg [a])

		t (h) [b]	1d	1e	1p	(+)-1p	(-)-1p	ritanserin
Mescaline	**mice**	1 5 (po)	4 5	15	0 44			0 09
		1 (sc)	6 8	10	1 38			0 29
	rats	1 (po)	8 4		1 93	2 03	in 2 5	2 55
		6 (po)			0 48	<0 63		1 54
		16 (po)			1 25	<2 5		18 4
		1 (sc)			10	1 56	in 2 5	0 38
DOI	**mice**	1 5 (po)			0 59	0 62	in 5 0	0 08
		1 (sc)			0 73	0 59	> 5 0	0 05

[a]: The ED_{50}values (mg/kg) are defined as the dose which protected 50% of the animals from head-twitches

[b]: Pretreatment time

In addition, compounds **1p** and **(+)-1p** are very selective for 5-HT_{2A} receptors. Binding are 30 to 500-fold lower for α_1-adrenergic [$IC_{50(1p)}$ =86nM; $IC_{50((+)-1p)}$ =100nM], D_2-dopamine [$IC_{50(1p)}$ =140nM; $IC_{50((+)-1p)}$ =100nM], muscarinic [$IC_{50(1p \text{ and } (+)-1p)}$ >1000nM] and H_1-histamine [$IC_{50(1p \text{ and } (+)-1p)}$ > 1000nM] receptors. In addition, compounds **1p** and **(+)-1p** respectively are 2- and 1.5-fold more

selective than ritanserin for 5-HT_{2A} receptors with regard to α_1-adrenergic receptors. It remains to be determined whether **1p** and **(+)-1p** also interact with the other subtypes of the 5-HT_2 receptor (5-HT_{2B} and 5-HT_{2C}) for which ritanserin has high affinities.

In conclusion, compound **(+)-1p** represents a very interesting drug candidate as a potential antidepressant and anxiolytic agent. Details of its pharmacological properties will be reported elsewhere.

Acknowledgements. We wish to thank A. Renaudon and C. Do-Huu for technical assistance,M. Chevé, F. Beaudoin, D. Lurier and G. Ducrotoy for the HPLC separations and M. Vuilhorgne and co-workers for analytical assistance.

References and Notes

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-6- Synthesis of **2a**: see: Manuel, G; Mazerolles, P; Cauquy, G; *Syn. React. Inorg. Metal-org. Chem.*, **1974**, 4(2), 133; **2b** was easily prepared in 86% yield by the condensation of 4-fluorophenyl magnesium bromide (2 eq.) to 1,1-dichloro-1-silacyclopent-3-ene (Damrauer, R.; Laporterie, A.; Manuel. G.; Park. Y.T.; Simon, K.; Weber, W.P.; *J. Organometal. Chem.*, **1990**, 7, 391) in THF, rt, 24h; **2c** was prepared in 91% yield by the condensation of 4-fluorophenyl magnesium bromide (1eq.) to 1-chloro-1-phenyl-1-silacyclopent-3-ene [Liao Xiugao; K., Young; H., Manuel; G., Weber; W.P.; *Polym.Bull.*, **1991**, 25(1), 63] in THF, rt, 24h

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-10- ^{1}H-NMR analysis of **8d-r** showed resonances for a single stereoisomer.

-11-

1	1d	1e	1f	1g	1h	1i	1j	1k	1l
yield(%)	45	26	43	32	52	56	45	30	25
mp(°C)	99	200	236	215	250	230	210	250	215
salt [c]	-	oxal	2HCl	2HCl	HCl	HCl	HCl	1.5HCl	2HCl

a HPLC separation (see text)

b colourless oil

c white solid

1	1m	1n	1o	1p	(+)-1p	(-)-1p	1q	1r	1s	1t
yield(%)	26	33	5	45	34	20	44	72	29[a]	51[a]
mp(°C)	192	134	212	160	71	73	226	67	*(b)*	*(b)*
salt [c]	HCl	HCl	HCl	HCl	-	-	1.5HCl	-	-	-

-12- ^{1}H-NMRand HPLC analysis of **1r** showed a 2/3 molar ratio of two diastereoisomers.

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