Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry Letters 13 (2003) 405–408

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

SLV310, a Novel, Potential Antipsychotic, Combining Potent Dopamine D_2 Receptor Antagonism with Serotonin Reuptake Inhibition

Rolf van Hes, Pieter Smid,* Cees N. J. Stroomer, Koos Tipker, Martin Th. M. Tulp, Jan A. M. van der Heyden, Andrew C. McCreary, Mayke B. Hesselink and Chris G. Kruse

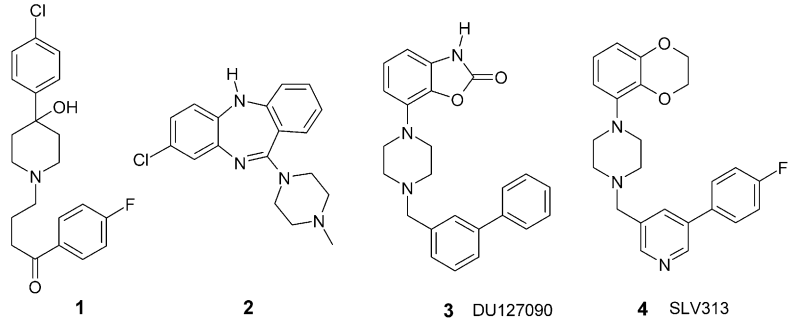
Solvay Pharmaceuticals Research Laboratories, PO Box 900, 1380 BA, Weesp, The Netherlands

Received 7 August 2002; accepted 4 November 2002

Abstract—In this paper, SLV310 is presented as a novel, potential antipsychotic displaying the interesting combination of potent dopamine D_2 receptor antagonism and serotonin reuptake receptor inhibition in one molecule. As such, SLV 310 could be useful in treating a broad range of symptoms in schizophrenia. This paper describes the structure–activity relationship in a series of compounds leading to SLV310 (**6b**, 2-{4-[4-(5-fluoro-1*H*-indol-3-yl)-3,6-dihydro-*2H*-pyridin-1-yl]-butyl}-phthalimide) together with pharmacological data showing the unique profile of this compound.

Introduction

Schizophrenia is a serious illness affecting about 1% of the world's population. Its toll in human suffering is probably exemplified best by the high suicide rate[1] for people having the disease. In addition, the economic losses and costs associated with schizophrenia are substantial. Therefore, the search for an effective treatment of the complete spectrum of symptoms of this disease is still progressing on many fronts. Schizophrenia is a complex disease characterised by: (a) positive symptoms, such as hallucinations; (b) negative symptoms (apathy, social withdrawal and difficulties with speaking) and (c) cognitive symptoms, for example, thought disorders and concentration problems. In addition, co-morbidity with other psychiatric disturbances like depression and different forms of anxiety is frequently observed. The usefulness of dopamine D_2 receptor antagonists such as haloperidol (**1**) for the treatment of schizophrenia has been well established.[2] However, haloperidol predominantly acts by attenuating the dopaminergic neurotransmission in the mesolimbic system of the brain, thereby only affecting

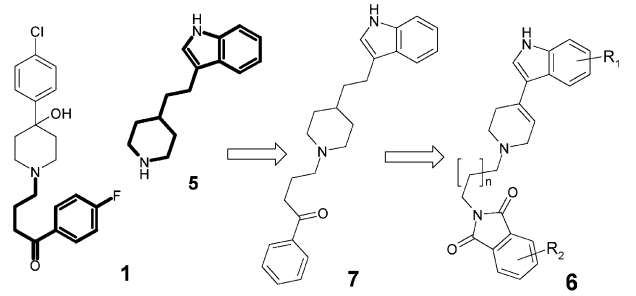


1 **2** **3** DU127090 **4** SLV313

*Corresponding author. Fax: +31-294-477138; e-mail: pieter.smid@solvay.com

0960-894X/03/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0960-894X(02)00996-4

the positive symptoms and not in a significant degree the accompanying symptoms of the disease. In addition, treatment with haloperidol or other typical antipsychotics has a number of drawbacks. Thirty percent of patients do not respond to treatment and the development of extra-pyramidal side effects (EPS) as well as cardiovascular side effects can become treatment limiting. Atypical antipsychotics show a broader efficacy caused by the combination of activity on the dopamine system with affinity for other (often serotonergic) receptors. For example, clozapine (**2**) has moderate dopamine D_2 receptor antagonism and strong affinity for serotonin receptor subtypes,[3] which is thought to offer the additional efficacy on the negative and cognitive symptoms and the reduction of potential side effects such as EPS. However, clozapine has serious side effects as agranulocytosis and weight gain, which limit the use of this compound in the clinic. Hence, there still is an unmet, clinical need for antipsychotics having broad efficacy but not the side effects of the traditional drugs. Recently, we have shown that 4-(biarylmethylene)-1-bicycloheteroaryl-piperazines [such as DU127090 (**3**)[4] and SLV313 (**4**)[5]] both displaying dopamine D_2 and serotonin $5HT_{1A}$ receptor affinity, are promising broad-spectrum antipsychotics with reduced liability for EPS. The research[6] reported in this paper is based on clinical studies showing that co-administration of an antipsychotic drug with a serotonin reuptake inhibitor (SRI) offers significant improvement for the treatment of both positive and negative symptoms.[7] In addition, the existence of a chemical entity displaying concomitant in vivo dopamine D_2 receptor antagonism and SRI activity was at the start of this research unknown in the literature.[8] In this paper, we will report the synthesis of compounds of type **6**, which are the result of the synthetic combination of the known SRI indalpine (**5**) with the butyrophenone chain of haloperidol (**1**) into one single molecule.[6] Compound **6b** of this series shows promising pre-clinical results (both on in vivo and in vitro experiments of dopamine D_2 receptor antagonism and serotonin reuptake inhibition) and represents a novel profile antipsychotic having a wider spectrum of therapeutic effects than the existing agents to date.



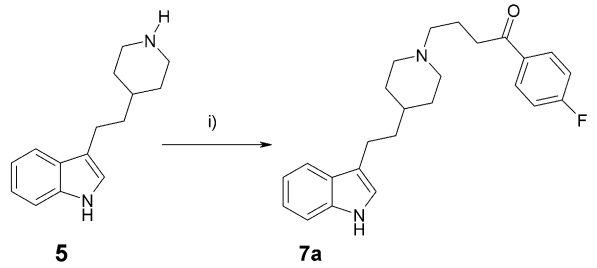
Chemistry

In a first attempt to combine D_2 and SRI affinity into one molecule, we prepared a series of compounds **7** having the butyrophenone chain attached to the piperidine moiety of indalpine (**5**).[9]

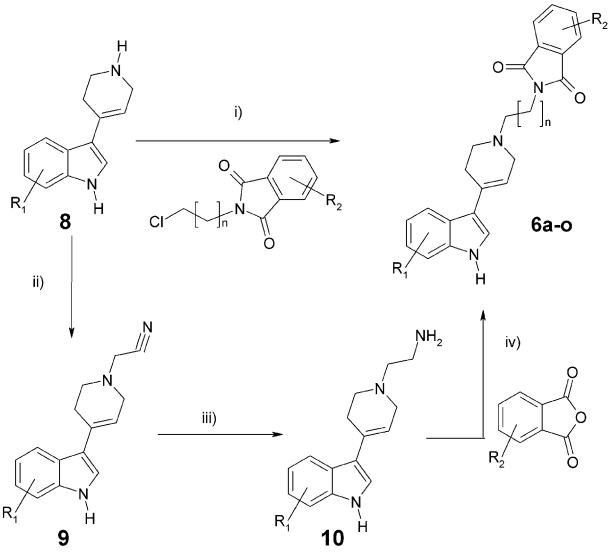
Compound **7a** (see Scheme 1) could be prepared by refluxing 4-chloro-butyrophenone derivatives with **5** in the presence of potassium iodide and diisopropylethylamine (DIPEA). Further research led to compounds **6**, the synthesis of which is depicted in Scheme 2. The starting 3,4-dehydro piperidine indole derivative **8** was prepared as described in the literature.[10] Alkylation of **8** with *N*[chloroalkyl]-phthalimides to **6** could be accomplished by refluxing the reagents in acetonitrile in the presence of DIPEA and KI. Alternatively, compounds **6** could be obtained from the ethylamine derivative of **8**, which was obtained via alkylation of **8** with bromoacetonitrile to **9**, followed by the reduction of the nitrile to **10**. Subsequently, compound **10** could be converted to **6** by refluxing **10** and a phthalic anhydride in DMF. The yields of **6** vary from 25 to 50% based on the starting indole **8**. The details of the syntheses are described in the corresponding patents.[6,11] An overview of the compounds discussed in this paper is shown in Table 1.

Results and Discussion

The affinity for dopamine D_2-receptors in a membrane preparation of CHO-cells transfected with the human



Scheme 1. (i) 4-Chloro-4′-fluorobutyrophenone, KI, DIPEA in acetonitrile, reflux.



Scheme 2. (i) Chloro-alkylphthalimides, acetonitrile, KI, DIPEA, 18 h, reflux; (ii) bromoacetonitrile, K_2CO_3, KI in acetonitrile, 18 h, reflux; (iii) $LiAlH_4$ in THF, rt to reflux, 2 h; (iv) phthalic anhydride, reflux in DMF, 48 h.

Table 1. R-groups of compounds **6**

Compd	*n*	R_1	R_2
6a	3	H	H
6b	3	5-F	H
6c	3	7-Me	H
6d	3	5-Cl	H
6e	1	5-F	H
6f	2	5-F	H
6g	5	5-F	H
6h	3	H	4-F
6i	3	H	5-F
6j	3	H	4-Me
6k	3	H	5-Me
6l	3	5-F	4-F
6m	3	5-F	5-F
6n	3	5-F	4-Me
6o	3	5-F	5-Me

D_2L receptor was measured by binding studies using [^{3}H]-spiperone as the ligand. The affinity for serotonin reuptake sites in rat frontal cortex membranes was measured using [^{3}H]-paroxetine. The results on these receptors obtained with the compounds described in this paper are given in Table 2. The affinities are expressed as K_i and are calculated from at least three independent experiments. The dopaminergic antagonist and serotonin reuptake activity were examined in vivo by antagonising apomorphine induced climbing behaviour[12] in mice (APO) and the potentiation of 5-hydroxytryptophan (5-HTP; the precursor of serotonin) induced serotonin syndrome like behaviour[13] in mice, respectively.

It is clear from Table 2 that the receptor binding activities of haloperidol (**1**) and indalpine (**5**) can be combined indeed into a single molecule. For example, we found that attachment of the *p*-F-butyrophenone chain of haloperidol to the piperidine moiety of indalpine giving **7a** induces the dopaminergic affinity (from not active of indalpine to 40 nM in **7a**) with the conservation of SRI activity. However, compound **7a** possessed only a moderate in vivo activity of 11 mg/kg in the APO test in mice and moreover, **7a** was inactive in the 5HTP potentiation test. Other compounds (not presented in this paper) from structure class **7**, having other substituents in the aromatic group of the butyrophenone chain, were equally or less active both in vitro and in vivo. However, the encouraging in vitro results obtained with structural class **7** urged us to investigate closely related structures. An interesting group of compounds appeared to be compounds **6** which were designed from compound class **7** in the following manner: (a) the indole ethyl piperidine moiety was changed into a 3,4-dehydropiperidine indole moiety (see compound **8**) which on itself is moderately active on the dopamine D_2 receptor and possess a good SRI activity; (b) the butyrophenone chain became part of a cyclic system (i.e., a phthalimide).

Compound **6a** was one of the first derivatives prepared and showed the desired activity on the D_2 receptor and serotonin transporter binding (25 and 2.5 nM, respectively) and promising results on the APO (14 mg/kg) and 5HTP test (7.1 mg/kg). A lead optimisation program around **6a** was started on three points of the molecule: (1) substitution on the indole moiety, (2) varying the chain length of the spacer between the phthalimide and the 3,4-dehydropiperidine, and (3) introduction of substituents into the phthalimide ring. Compounds **6b–d** having a 5-F, 7-Me or 5-Cl substituent in the indole ring were prepared and the test results on these compounds clearly showed that the 5-fluoro derivative **6b** is the most potent. Both in vitro (D_2 5 nM and SRI 2.5 nM) and in vivo (APO 5.6 mg/kg and 5-HTP 5.9 mg/kg) our criteria were met. Shortening (**6e** and **6f**) or prolonging (**6g**) the spacer length had a negative effect on the D_2 receptor binding in respect to **6b**. On the other hand, **6f** and **6g** did show an improvement in the SRI receptor binding with a factor 3. Finally, we tried to optimise **6b** by introducing substituents in the phthalimide ring. Table 2 shows that **6h–o** having either a fluorine or a methyl on the 4- or 5-position in the phthalimide lowered the dopamine D_2-receptor activity with at least a factor 2, but on the other hand improved the SRI activity in about the same extend. It is of interest to note that a compound as **6h** having the fluorine on the phthalimide instead of the indole (such as **6b**) looses the activity in the APO test, while the compounds **6l–m** having a fluorine on both the indole and the phthalimide have a comparable (to **6b**) in vivo activity on the APO and 5-HTP tests. It can be concluded that varying the spacer length or the substitution pattern in the phthalimide ring of **6b** resulted in a larger difference in affinity for the D_2-receptor and the SRI site. Since an equal potency on both targets was

Table 2. In vitro and in vivo test results on D_2 receptors (receptor binding and APO, respectively) and serotonin reuptake sites (receptor binding and 5HTP, respectively)

Compd	In vitro		In vivo	
	D_2, K_i (nM)[a]	SRI, K_i (nM)[a]	APO[c] ED_{50} (mg/kg po)	5HTP[d] ED_{50} (mg/kg po)
1	3	na[b]	0.1	
5	na	2.5		
7a	40	2	11	>30
8[e]	200	6		
6a	25	2.5	14	7.1
6b[f]	5	2.5	5.6	5.9
6c	40	1.3		
6d	20	16		
6e	20	25		
6f	16	0.6		
6g	25	0.8		
6h	25	0.8	>20	<50
6i	40	2		
6j	100	1		
6k	40	2		
6l	12	0.4	6.1	10
6m	10	1.3	5	10
6n	25	1		
6o	20	3		

[a]Calculated from three independent experiments.
[b]na, not active (>1 μM).
[c]Antagonising apomorphine induced climbing behaviour in mice (po).
[d]5-HTP induced serotonin syndrome like behaviour (po).
[e]Compound **8** with R_1 = H.
[f]Compound **6b** was tested as the hydrochloric acid salt.

considered to offer the highest potential for a broad antipsychotic profile in the clinic, **6b** was selected for further studies. Compound **6b** is potently active in the antagonising of apomorphine induced climbing behaviour in mice and equally potent in the potentiation of the behavioural effects of 5HTP in mice, clearly showing that the compound also acts as a dopamine D_2 receptor antagonist and a serotonin reuptake inhibitor in the brain. The antipsychotic potency of **6b** was demonstrated by the fact that **6b** significantly disrupted avoidance behaviour[14] in a conditioned avoidance response paradigm in three independent groups of trained rats ($ED_{50} = 17.5$ mg/kg, po, based on the HCl salt of **6b**).

It can be concluded that **6b** is a promising novel antipsychotic indeed, combining strong dopamine D_2-receptor antagonism with SRI effects in the same dose range. Consequently, compound **6b** was subjected to a thorough preclinical profiling and selected for clinical development under the acronym SLV310. More pharmacological details around SLV310 have been published elsewhere.[15]

Acknowledgements

We thank Mrs Alice Borst and Mr Karel Stegman for the supply and interpretation of the spectral data.

References and Notes

1. The suicide rate for schizophrenia patients is difficult to estimate, but several studies indicate a range of 9–24% of people having the disease will die by committing suicide: Conwell, Y.; Cholette, J.; Duberstein, P. R. *Medscape Mental Health* **1998**, 3. Black, D. W.; Winokur, G. *Psychobiology of Suicidal Behaviour*; Academy of Sciences: New York, 1986; p 106. Caldwell, C. B.; Gottesman, I. I. *Schizophr. Bull.* **1990**, *16*, 571.
2. Gray, J. A. *Schizophrenia Bull.* **1998**, *24*, 249.
3. King, D. J. *Eur. Neuropschychopharmacol.* **1998**, *8*, 33. Galletly, C. A.; Clark, C. R.; McFarlane, A. C.; Weber, D. L. *Psychiatry Res.* **1997**, *72*, 161.
4. Feenstra, R. W.; de Moes, J.; Hofma, J. J.; Kling, H.; Kuipers, W.; Long, S. K.; Tulp, M.; Th, M.; van der Heyden, J. A. M.; Kruse, C. K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2345.
5. Feenstra, R. W. et al. Document in preparation.
6. Tulp, M. Th. M.; van Vliet, B. J.; Tipker, J.; van Hes, R.; Visser, G.; Kruse, C. G.; van der Heyden, J. A. M.; WO00/23441, *Chem. Abstr.*, **2000**, *132*, 293673. van Hes, R.; van der Heyden, J. A. M.; Kruse, C. G.; Long, S.; WO00/69424; *Chem. Abstr.* **2000**, *134*, 534.
7. Goff, D. C.; Midha, K. K.; Sarid-Segal, O.; Hubbard, J. W.; Amico, E. *Psychopharmacology (Berl)* **1995**, *117*, 417. Silver, H.; Barash, I.; Aharon, N.; Kaplan, A.; Poyurovsky, M. *Int. Clin. Psychopharmacol.* **2000**, *15*, 257.
8. Recently, the Bristol-Myers Squibb company claimed the results of a research program leading to indole piperidine derivatives having the profile of D_2 receptor antagonism with SRI activity; Bristol-Myers Squibb Company; Mattson, R. J.; Yevich, J. P.; Yuan, J.; Eison, A. S.; DenHart, D.; WO 01/43740; *Chem. Abstr.* **2000,** *135*, 46175.
9. Gueremy, C.; Audiau, F.; Champseix, A. *J. Med. Chem.* **1980**, *23*, 1306.
10. Perregaard, J.; Andersen, K.; Hyttel, J.; Sanchez, C. *J. Med. Chem.* **1992**, *35*, 4813. Guillaume, J.; Dumont, C.; Laurent, J.; Nedelec, L. *Eur. J. Med. Chem.* **1987**, *22*, 33.
11. Analytical data for compound **6b** (SLV310, 2-{4-[4-(5-fluoro-1H-indole-3-yl)-3,6-dihydro-*2H*-pyridin-1-yl]-butyl}-phthalimide): mp 178–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.2 (s, 1H, NH-indole); 7.78–7.88 (m, 4H-phthalimide); 7.46–7.50 (dd, $J = 2$ Hz, $J = 10.5$ Hz, 1H, H4-indole); 7.1 (d, $J = 3$ Hz, 1H, H2-indole); 7.34–7.38 (dd, $J = 4.5$ Hz, $J = 8.1$ Hz, 1H, H7-indole); 6.88–6.94 (dt, $J = 3$ Hz, $J = 8.1$ Hz, $J = 10.5$ Hz, 1H, H6-indole); 6.4 (bs, 1H, C=CH); 3.60–3.66 (t, 2H, CH_2–N–Pht); 3.20–3.55 (bs, 2H) 2.75–2.8 (bs, 2H); 2.50–2.60 (m, 4H); 1.52–1.72 (m, 4H).
12. Costall, B.; Naylor, R. J.; Nohria, V. *Eur. J. Pharmacol.* **1978**, *1*, 39.
13. Jacobs, B. L. *Life Sci.* **1976**, *19*, 777.
14. Van der Heyden, J. A. M.; Bradford, D. *Behav. Brain Res.* **1988**, *31*, 61.
15. Tuinstra, T.; Herremans, A. H. J.; van der Heyden, J. A. M.; McCreary, A. C.; Hesselink, M. B.; Kruse, C. G.; Long, S. K. *Eur. Neuropsychopharmacol.* **2001**, *11*, S251. Hesselink, M. B.; van Vliet, B.; Kruse, C. G.; Long, S. K. *Eur. Neuropsychopharmacol.* **2001**, *11*, S252.