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(E) AND (Z)-3-STYRYLPIPERIDINES AS SIGMA LIGANDS.

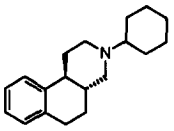
Sergio Mantegani*, Enzo Brambilla, Paolo Cremonesi, Carla Caccia, Maria Gioia Fornaretto, Nicola Carfagna, Monica Colombo, Robert A. McArthur and Mario Varasi.

Pharmacia & Upjohn S.p.A.-CNS Research-Viale Pasteur 10, 20014 Nerviano (Milan) Italy

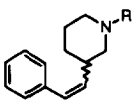
Abstract. A class of (E) and (Z)-3-styrylpiperidine derivatives was prepared as racemates and evaluated for affinity at σ binding sites labeled with [^{3}H]-(+)-SKF-10,047. Some of these compounds exhibited high affinity and selectivity for σ *versus* D_1 and D_2 binding sites. © 1997 Elsevier Science Ltd.

Sigma receptors have attracted much attention on account of being implicated in several biochemical and physiological processes.[1] For example, σ ligands might constitute novel antipsychotic agents lacking the side effects associated with classical neuroleptic therapy. Moreover their ability to affect the motor system and to protect from neuronal damage suggests potential clinical application in the treatment of motor disorders such as dystonia, and in the damaging effects of stroke insult or ischemia.[2]

Several classes of compounds have been reported to bind to the σ binding sites. These classes include benzomorphans, N, N'-disubstituted guanidines, cyclohexyldiamine analogues and a diverse array of phenylpiperidine derivatives.[3] Recently compound **1**, a member of a novel class of *trans*-octahydrobenz[f]isoquinoline analogues, has been shown to display one of the highest affinities at the σ recognition sites labeled with [^{3}H]-DTG and selectivity over the D_2 receptor reported so far.[4] This finding led us to explore some classes of compounds related to **1** in an effort to identify novel highly selective σ ligands. This paper describes the synthesis of some (E) and (Z)-3-styrylpiperidine derivatives **2** that can be envisioned as an open form of **1**. The novel compounds of this study were evaluated for σ, dopamine D_1 and D_2 receptor binding.



1

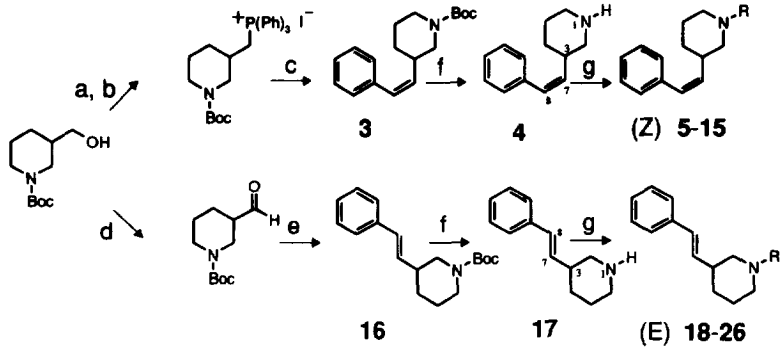


2

Fax: +39 2 4838.3937; E. mail: sergio mantegani @eu.pnu.com

Chemistry

The compounds of this study were synthesised according the routes according to the following scheme:



(a) I_2, $(Ph)_3P$, imidazole, THF
(b) $(Ph)_3P$, xylene, reflux
(c) PhCHO, tertBuOK, DMF
(d) $Py.SO_3$, TEA, DMSO
(e) $PhCH_2P^+(Ph)_3I^-$, 50% NaOH, DCM
(f) 0.1 N HCl, THF
(g) RX, N-Ethyldiisopropylamine (Hunig's base), DMF, or RCOCl, TEA, Py, followed by $LiAlH_4$, THF

The unsaturated intermediates **3** and **16** were prepared by stereoselective Wittig reaction between the appropriate aldehyde and the corresponding ylide.[5] The degree of stereoselectivity was markedly influenced by the nature of the ylide. In fact, the Wittig reaction afforded mostly the Z isomer **3** (composition of the reaction's mixture Z/E~8.7/1.3) when the more reactive triphenylphosphonium-(1-tert-butyloxycarbonyl-piperidin-3-yl)methylenylide was employed. Conversely, with the more stabilised triphenylphosphonium-benzylidenylide, the E isomer **16** was formed predominantly (composition of the reaction's mixture E/Z~9/1).[6]

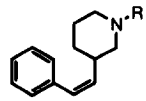
The pure **3** and **16** diastereoisomers were obtained by chromatography of the reaction mixture and characterized by ^{1}H-NMR. After removal of the N-tert-butyloxycarbonyl group by acidolysis to furnish the nor-derivatives **4** and **17** [7], the piperidine nitrogen was alkylated by reaction with the appropiate alkyl bromides or chlorides (catalytic NaI was required) in DMF or acetonitrile and in the presence of Hünig's base. Alternatively, the alkylation was carried out in a two step process. First by acylation of the basic piperidine nitrogen with the appropriate acyl chloride in chloroform in the presence of triethylamine, followed by reduction of the resulting tertiary amide with lithium aluminium hydride in tetrahydrofuran.

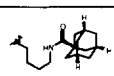
Results and discussion

The compounds **4-15** and **17-26** were examined for their affinity at σ sites labeled with [^{3}H]-(+)-SKF-10,047 [8] in fresh whole brain from male Wistar rat, and D_1 and D_2 sites labeled with [^{3}H]-SCH-22390 [9] and [^{3}H]-Spiperone [10] in Sprague Dawley male rat striatum respectively.

The results, shown in **Table I** and **II** (affinity expressed as IC_{50} in μM, standard errors are ± 10% of the mean reported values), reveal a spectrum of σ receptor affinities ranging from subnanomolar to hundred nanomolar values.

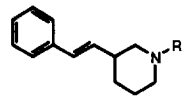
Table I. (Z)-3-styrylpiperidine derivatives.

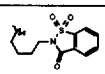


Cp	R	σ	D_1	D_2
4	H	0.064	>10	0.87
5		0.001	0.32	0.16
6		0.002	>10	1.12
7		0.007	>10	5.44
8		0.0008	0.63	0.12
9		0.0006	2.2	0.15
10		0.007	5.84	1.44
11		0.015	N.T.	N.T.
12		0.015	N.T.	N.T.
13		0.027	N.T.	N.T.
14		0.64	N.T.	N.T.
15		0.023	N.T.	N.T.

N.T not tested

Table II. (E)-3-styrylpiperidine derivatives.



Cp	R	σ	D_1	D_2
17	H	0.423	>10	>10
18		0.004	>10	>10
19		0.038	1.33	0.18
20		0.012	N.T.	N.T.
21		0.006	>10	5.12
22		0.023	N.T.	N.T.
23		0.01	N.T.	N.T.
24		0.006	>10	2.4
25		0.004	1.55	1.24
26		0.033	N.T.	N.T.

N.T. not tested

σ Site Affinity and Selectivity *versus* D_1 and D_2 Component.

The purpose of this study was to evaluate σ affinity and selectivity *versus* D_1 and D_2 receptor sites for this class of compounds. The unsubstituted **4** and **17** had little affinity for the σ sites. Generally, affinity was increased upon substitution of the piperidine nitrogen with alkyl, alkylidene or arylalkyl group. For instance, the allyl derivative **18** is endowed with high σ affinity and selectivity. The latter being more than two thousand fold in respect to the D_1 and D_2 component. On the contrary an increase in steric bulk and lipophilicity seem to produce a loss in affinity and selectivity as shown by **5-7**, **19-21**. Incorporation of a polar moiety in the nitrogen's substituent as in **11-15** and **22**, **26** improves the affinity in comparison with **3** and **13** as indicated in **Table I** and

Table II only slightly. Such modification seems to be detrimental for the σ affinity when comparing **10** with **11**.Affinity increased in the two series when phenyl alkyl side chains were present as in **8-10** and **23-25**. Elaboration of the chain length of the alkyl spacer between the basic nitrogen and the phenyl ring from 1 to 3 methylene units as in **8-9** and **23-25** resulted in an increase in affinity. Among the compounds considered in this study, **8** and **9** displayed the highest (subnanomolar) σ affinity and showed more than one hundred fold selectivity *versus* D_1 and D_2 receptor sites. However, when the chain length was increased further by one methylene unit as in the case of **10,** this resulted in a 10 fold decrease in affinity.

As far as selectivity is concerned, a decrease was observed by lengthening the chain in the (E)-3-styrylpiperidine derivatives **24** and **25** (**Table II**). For the (Z)-3-styrylpiperidine derivatives it was more difficult to draw a clear picture (**Table I**). Examination of the σ receptor affinities of the 3-styrylpiperidine derivatives and comparison with the geometry of the double bond indicated that a cisoid double bond geometry (Z) is not required for high affinity. This is exemplified by the high affinity of **18**, **21**, **24**, **25**, all of which contain the double transoid bond (E). However, by comparing the results in **Table I** and **Table II**, a cisoid double bond geometry would be more qualified to achieve higher affinity. The data presented in this study and those reported for the more conformational restricted trans-octahydrobenz[f]isoquinolines were not immediately compareable considering that the two different σ ligands used in each.

Conclusion.

In summary, two novel series of (E) and (Z)-3-styrylpiperidine derivatives have been uncovered as novel σ ligands. Affinity and selectivity and for σ sites over D_1 and D_2 receptors appears to be governed by the chemical nature of the nitrogen substituent and in some extent by the geometry of the double bond. The highest affinity was found with the phenylpropyl derivative **9** belonging to the (Z) series. Conversely, the highest selectivity was provided by the allyl derivative **18** belonging to the (E) series.

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7. Spectral data for **4**.HCl.
^{1}H-NMR (200 MHz, DMSO-d_6) δ : 1.3-1.9 (m, 4 H, CH_2-4, CH_2-5); 2.5-3.3 (m, 5 H, CH_2-2, CH_2-6, H-3); 6.19 (dd, J=6.3, 16.1 Hz, 1 H, H-7); 6.47 (d, J=16.1 Hz, 1 H, H-8); 7.2-7.4 (m, 5 H, aromatic's H); 9.21 (br s, 2 H, NH^+_2-1).
MS : *m/z* 187 (100, $[M]^+$); 129 (42, $[M-C_3H_6NH_2]$); 115 (44, $[M-C_4H_8NH_2]$).
Analysis : Calcd $C_{13}H_{18}ClN$, C 69.79, H 8.11, Cl 15.85, N 6.26. Found C 69.71, H 8.27, N 6.23.
mp 159-161 °C.
Spectral data for **17**.HCl.
^{1}H-NMR (200 MHz, DMSO-d_6) δ : 1.3-2.0 (m, 4 H, CH_2-4, CH_2-5); 2.6-3.3 (m, 5 H, CH_2-2, CH_2-6, H-3); 5.41 (dd, J=9.7, 11.6 Hz, 1 H, H-7); 6.49 (d, J=11.6 HZ, 1 H, H-8); 7.2-7.4 (m, 5-H, aromatic's H); 9.4 (br s, 2 H, NH^+_2-1).
MS : *m/z* 187 (78, $[M]^+$); 129 (100, $[M-C_3H_6NH_2]$); 115 (96, $[M-C_4H_8NH_2]$).
Analysis : Calcd $C_{13}H_{18}ClN$, C 69.79, H 8.11, Cl 15.85, N 6.26. Found C 69.61, H 8.24, N 6.19.
mp 202-204 °C.
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Note. After our work was completed, some compounds herein reported were disclosed in the patent : Brown , T. H. et al."Compounds as Calcium Channel Antagonists. WO 93/15052"; 930805

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