1-(Arylalkyl)quinolizidine Derivatives and Thio-Isosteric Analogues as Ligands for Sigma Receptors

by **Anna Sparatore***[a]), **Federica Novelli**[b]), and **Fabio Sparatore**[b])

[a]) Istituto di Chimica Farmaceutica, Università di Milano, Viale Abruzzi 42, I-20131 Milano (tel.: +39 02 50317554; fax: +39 02 50317565; e-mail: anna.sparatore@unimi.it)

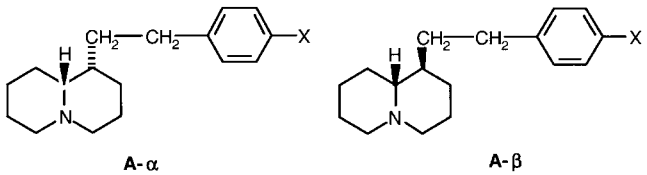
[b]) Dipartimento di Scienze Farmaceutiche, Università di Genova, Viale Benedetto XV 3, I-16132 Genova

A set of 1-(arylalkyl)quinolizidines, isosteric thioanalogues, and variously functionalized congeners were synthesized (see **1**–**25**) and tested for affinity to sigma 1 and sigma 2 receptor subtypes, by displacing [^{3}H]-(+)-pentazocine and [^{3}H]DTG from guinea pig brain and rat brain preparations, respectively. All compounds exhibited a good affinity for the σ_1 subtype, with subnanomolar K_i values for the best of them, while only modest or poor affinity for the σ_2 subtype was observed (*Tables 1* and *2*). Some structure–activity relationships were put forward.

Introduction. – Sigma receptors occur in at least two classes of binding sites, namely σ_1 and σ_2, which are widely distributed in the central nerve system (CNS) and in several peripheral tissues [1][2] and also expressed in some human and rodent tumor cell lines [3][4]. The functional roles of the two receptor subtypes are being progressively defined, particularly in the pathogenesis of psychiatric and motor disorders, but also outside of the nervous system [5–7], which accounts for the large number of attempts to obtain selective sigma binding-site ligands. Many structurally unrelated compounds have been described as being able to bind to sigma receptors, but only few display high affinity and selectivity for the sigma receptor subtypes [8–13].

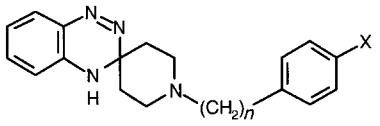
Recently we described two novel types of ligands for sigma receptors that correspond, respectively, to the general structures **A-*α*** or **A-*β*** ((1*R*, 9a*R*) or (1*S*, 9a*R*)-1-(2-arylethyl)octahydro-2*H*-quinolizines) and **B** (1′-substituted-(spiro[1,2,4-benzotriazine-3(4*H*),4′-piperidines])) [14][15]. Many compounds of both types exhibited high affinity for the σ_1 receptor subtype, with K_i in the low nM range, while the affinity for σ_2 subtype of compounds so far tested was ten to more than 100 times lower. In type **B** compounds, the lengthening of the aliphatic chain from one to four CH_2 units did not change significantly the affinity, which was, however, improved when five CH_2 units are present. On the other hand, in a set of *N*-(arylalkyl)piperidines [8][9][16], of which compounds of type **A-*α*** or **A-*β*** could be considered 'closed' analogues with an imposed conformation, the affinity and the selectivity for the σ_1 subtype increased with the increasing distance between the aromatic ring and the basic N-atom.

Therefore, we deemed it worthwhile to investigate whether the latter structural feature would improve affinity for the σ_1 subtype also in type A-α and A-β compounds in spite of the rigidity and bulkiness of the terminal quinolizine ring. Thus additional compounds whose aromatic and octahydro quinolizine (quinolizidine) nuclei are separated by one to four C- and/or S-atoms were prepared, taking into account the



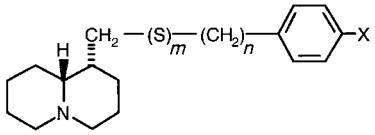
A-α

A-β

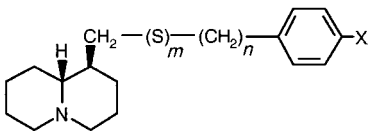


B

well-known bioisosterism of a CH_2 unit to a S-atom. These compounds correspond to the general formulae **C-*α*** and **C-*β*** (absolute configurations; **11** is racemic), which include also the previously described compounds of types **A-*α*** and **A-*β***, *i.e.*, compounds **1**–**18**.



C-α

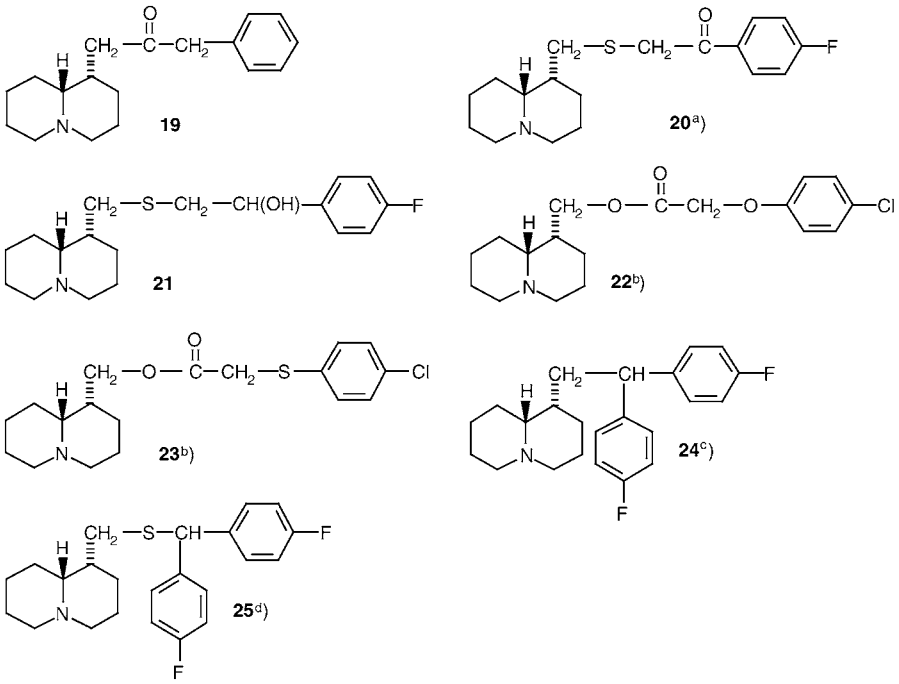


C-β

1	*m*=0, *n*=0, X=H	**11**[b]	*m*=0, *n*=0, X=F
2[a]	*m*=0, *n*=1, X=H	**12**[a]	*m*=0, *n*=1, X=H
3[a]	*m*=0, *n*=1, X=F	**13**[a]	*m*=0, *n*=1, X=F
4	*m*=0, *n*=2, X=H		
5	*m*=1, *n*=0, X=H	**14**	*m*=1, *n*=0, X=H
6	*m*=1, *n*=0, X=F	**15**	*m*=1, *n*=0, X=F
7	*m*=1, *n*=1, X=H	**16**	*m*=1, *n*=1, X=H
8	*m*=1, *n*=1, X=Cl	**17**	*m*=1, *n*=1, X=Cl
9	*m*=1, *n*=2, X=H	**18**	*m*=1, *n*=2, X=H
10	*m*=1, *n*=2, X=F		

[a]) Previously described [14]. [b]) Racemate (only one stereoisomer is represented).

To further investigate the observed [14] negative influence of the presence of oxygenated functions on the affinity for the σ_1 receptor and, more generally, to investigate the influence of the nature of the chain that links the quinolizidine and benzene moieties, a group of miscellaneous compounds (*i.e.*, **19**–**23**) was also tested. Compounds **20** [17] and **22** and **23** [18] were already described by us. Finally, the claimed [8][16] existence in the σ_1 receptor of a bulk-tolerating region at a given distance from the proton-donor site was explored by testing the two previously described quinolizidine derivatives **24** [19] and **25** [20], bearing two aromatic moieties linked to the same C-atom, which is separated from the basic N-atom by three or four atoms.

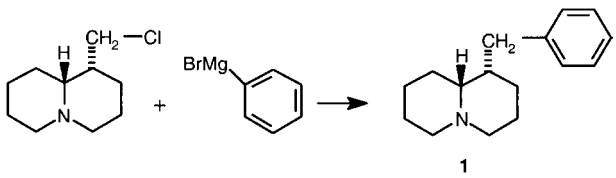


[a])–[d]) Previously described compounds : **20** [17], **22** and **23** [18], **24** [19], and **25** [20].

In this paper, the synthesis and the biological evaluation of compounds **1**–**25** are reported.

Syntheses. – For the preparation of compound **C-*α*** with $m = n = 0$, *i.e.*, of **1**, the coupling of *ω*-chlorolupinane (=(1*R*,9a*R*)-1-(chloromethyl)octahydro-2*H*-quinolizine) with PhMgBr was firstly assayed (*Scheme 1*), but the reaction gave only a modest yield of the expected (1*S*,9a*R*)-octahydro-1-(phenylmethyl)-2*H*-quinolizine. Probably due to steric hindrance, the rate of the coupling reaction was very low, and the competitive intra- and/or intermolecular quaternarization of chlorolupinane prevailed.

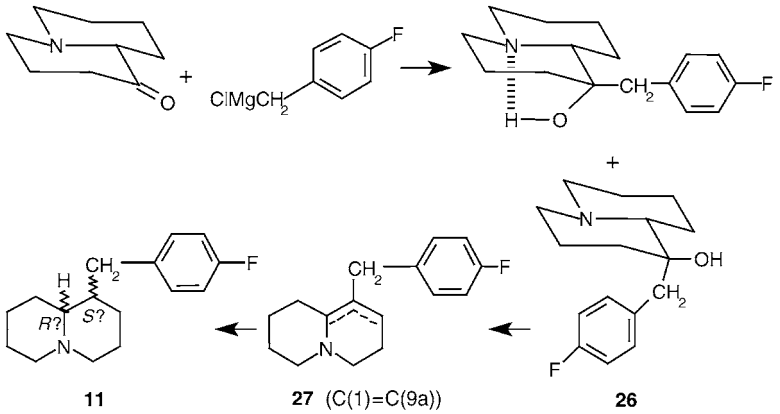
Scheme 1



Therefore, another possibility was explored, although, unavoidably, a mixture of stereoisomers resulted: 1-quinolizidinone (octahydroquinolizin-1-one) was reacted with (4-fluorobenzyl)magnesium chloride, followed by dehydration of the formed tertiary alcohol and reduction of the unsaturated compound (*Scheme 2:* only one of the

possible stereoisomers is represented). Quinolizidin-1-one exists predominantly (90%) in the *trans* fused chair-chair conformation [21] and reacts with *Grignard* reagents to give mixtures of epimeric alcohols. In the reaction with arylmagnesium bromides, the axial alcohols largely prevail [22][23], while, with MeMgI, the ratio of epimeric alcohols is inverted [24]. In our reaction of quinolizidin-1-one with (4-fluorobenzyl)-magnesium chloride, only a single racemate was isolated, whose sturdy resistance to dehydration suggests it to be the equatorial alcohol **26**. However, by reacting this alcohol with P_2O_5 in phosphoric acid at 165°, an unsolitary (by TLC) unsaturated compound **27** was finally obtained. (^{1}H-NMR: δ 3.3 (*s*, 1.8 H, CH_2 between Ar and C=C); 5.38–5.47 (*m*, 0.2 H, olefinic H), suggesting that, in the dehydration, the angular H-atom was preferentially eliminated to form the enamine **27**.

Scheme 2

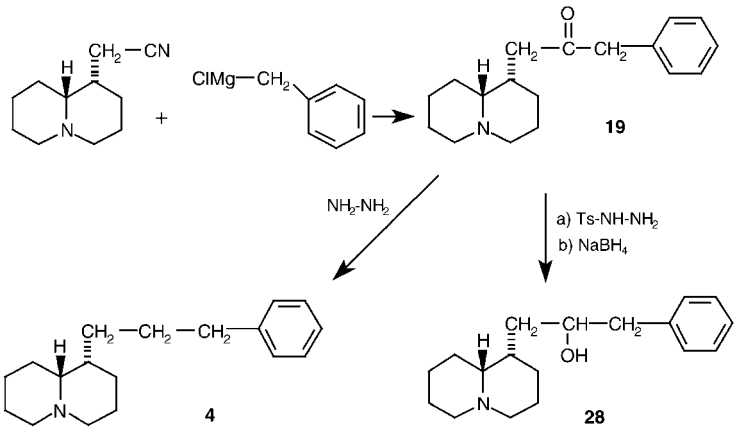


The presence of a tetrasubstituted C=C bond in **27** accounts for the very slow absorption of 1 mol of H_2 in the presence of 10% Pd/C, giving, apparently, a single saturated compound (by TLC and NMR). The protons of the quinolizidinylmethylene moiety of this saturated compound give rise, in the ^{1}H-NMR spectrum, to a sequence of *multiplets* between δ 0.80 and 3.10, whose overall outline is quite similar to that which characterizes several *epi*-lupinane derivatives, thus suggesting that the 4-fluorobenzyl residue is linked equatorially to the quinolizidine nucleus. Therefore, the compound obtained is tentatively assigned as the racemate of (1*RS*,9a*SR*)-1-[(4-fluorophenyl)-methyl]-octahydro-2*H*-quinolizine (**11**).

To obtain the (1*R*,9a*R*)-octahydro-1-(3-phenylpropyl)-2*H*-quinolizine (**4**), the cross-coupling between chlorolupinane and PhEtMgBr was attempted, but it failed completely even in the presence of the Cu^I catalyst suggested by *Tamura et al.* [25][26].

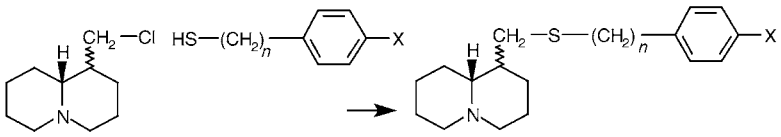
On the contrary, good results were obtained when the BnMgCl was reacted with ω-cyanolupinane (=(1*S*,9a*R*)-octahydro-2*H*-quinolizine-1-acetonitrile), and the resulting ketone **19** was reduced with hydrazine under *Huang–Minlon* conditions [27] (*Scheme 3*). To avoid the drastic conditions required by this reaction, the reduction of the corresponding ketone tosylhydrazone with $NaBH_4$ suggested by *Caglioti* [28] was initially attempted, but only the corresponding alcohol (as mixture of diastereoisomers) was obtained.

Scheme 3



S-Aryl- or *S*-(arylalkyl)thiolupinines (**5**–**9**) and -epithiolupinines (**14**–**18**) [(1*R*,9a*R*)- and (1*S*,9a*R*)-1-[(arylthio)methyl]- or (1-{[(ω-arylalkyl)thio]methyl}octahydro-2*H*-quinolizines], respectively, were obtained, without any particular difficulty, by reacting ω-chlorolupinane or ω-chloroepilupinane with benzene- and 4-fluorobenzenethiol, benzene- and 4-chlorobenzenemethanethiol, and benzeneethanethiol (*Scheme 4*). Due to higher steric hindrance, the reaction with the axial chlorolupinane was sluggish and gave the expected sulfides **5**–**9** in lower yields than the reaction with the equatorial ω-chloroepilupinane (→ **14**–**18**).

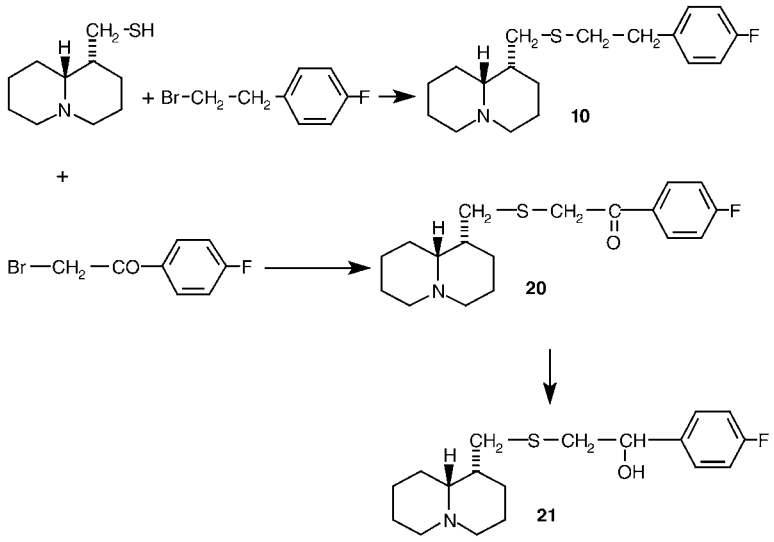
Scheme 4



5, **14** *n* = 0, X = H
6, **15** *n* = 0, X = F
7, **16** *n* = 1, X = H
8, **17** *n* = 1, X = Cl
9, **18** *n* = 2, X = H

S-(4-Fluorophenethyl)thiolupinine (=(1*R*,9a*R*)-1-({[2-(4-fluorophenyl)ethyl]thio}methyl)octahydro-2*H*-quinolizine; **10**) was of particular interest for comparing its affinity for σ receptors with that of the previously described *S*-(4-fluorophenacyl)thiolupinine (=1-(4-fluorophenyl)-2-{[(1*R*,9a*R*)-(octahydro-2*H*-quinolizin-1-yl)methyl]thio}ethanone; **20**) [14][17]. Since the 4-fluorobenzeneethanethiol is as yet, far unknown and unavailable, **10** was obtained by reacting 4-fluorophenethyl bromide with thiolupinine (=(1*R*,9a*R*)-octahydro-2*H*-quinolizine-1-methanethiol) [17] (*Scheme 5*). Finally, 1-(4-fluorophenyl)-2-({(1*R*,9a*R*)-octahydro-2*H*-quinolizin-1-yl]methyl}thio)-ethanol was prepared by reduction of *S*-(4-fluorophenacyl)thiolupinine (**20**) with

Scheme 5



$NaBH_4$; the alcohol **21** was obtained as a mixture of diastereoisomers. No attempts to resolve the mixture were made, and it was tested as such (*Scheme 5*).

Biological Evaluation and Discussion. – Novel and previously described compounds **1**–**25** were tested *in vitro* to evaluate their affinities for the σ_1 receptor subtypes through the displacement of [^{3}H]- (+)-pentazocine from guinea pig brain preparations. Selected compounds were also assayed for affinity to σ_2, $5HT_{2A}$, and D_2 receptor subtypes by displacing [^{3}H]DTG, [^{3}H]ketanserin and [^{3}H]nemonapride, respectively, from rat brain (σ_2, $5HT_{2A}$), and rat striatum (D_2) preparations.

Results of binding assays for compounds **1**–**18** to σ_1 and σ_2 receptor subtypes are collected in *Table 1*, while results concerning compounds **19**–**25** are collected in *Table 2*. The reported data show that all compounds exhibit good affinity for the σ_1 receptor subtype, with subnanomolar K_i values for the best of them. On the contrary, a clear trend for modest or poor affinity to the σ_2 subtype was observed, although only representative compounds were assayed in this case.

Affinity for the σ_1 subtype increased with the increasing distance between the benzene ring and the quinolizidine moieties, however, also the nature of the connecting chain influenced the increase.

Indeed, while the expected bioisosterism between a S-atom and a CH_2 group was, in principle, confirmed, the actual bioequivalence of these groups is lower when the S-atom is directly linked to the benzene ring as in compounds **5**, **6**, **14**, and **15**. Moreover, the introduction of an oxygenated function (hydroxy or oxo) at the aliphatic chain produced a decrease in affinity (compare compounds **4** and **10** with **19**, **20**, and **21**), but to a lesser extent than previously observed for compounds of structure **A** [14]. Thus, the negative effect of the presence of an oxygenated function seems to be largely counterbalanced by the positive effect of the elongation of the aliphatic chain. Similar

Table 1. *Binding Affinities of* **1**–**18** *for* σ_1 *and* σ_2 *Receptor Subtypes*

Ligand	K_i[a]) [nM]		Ratio K_i σ_2/K_i σ_1
	σ_1	σ_2	
*(1*R*)-Substituted quinolizidines*			
1	35.2[c])		
2[b])	38.0[d])	300[g])	7.9
3[b])	6.6[e])	220[g])	33.3
4	4.2[c])		
5	89.0[f])		
6	13.2[c])	463[h])	35.1
7	3.2[f])		
8	1.0[f])	186[h])	186.0
9	0.63[f])	155.7[h])	247.1
10	0.63[f])	147[h])	233.3
*(1*S*)-Substituted quinolizidines*			
(±)-**11**	11.0[c])		
12[b])	6.5[d])	405[h])	114.9
13[b])	3.7[e])	1297[i])	350.5
14	10.0[f])		
15	4.4[c])	578[h])	131.4
16	0.52[f])		
17	0.23[f])	233.6[h])	1015.6
18	0.38[f])	138.4[h])	364.2

[a]) Means of duplicate experiments: each value differed from the mean by less than 10%. [b]) Previously published data [14], included for comparison. K_i (nM) of reference ligand haloperidol used in σ_1 experiments: [c]) 4.4. [d]) 3.64. [e]) 2.01. [f]) 1.45. K_i (nM) of reference ligand haloperidol used in σ_2 experiments: [g]) 91.0. [h]) 78.7. [i]) 88.2.

considerations apply also to the 1-lupinine esters **22** and **23** (4-chlorophenoxy- and 4-chlorophenylthioacetate, resp.), which still exhibited K_i of 37 and 24 nM, respectively. Thus, the intercalation of an ester function might represent an easy way to increase the distance between the quinolizidine and benzene moieties, overcoming the difficulties of synthesizing long-chain arylalkyl quinolizidines.

It is worth noting that compounds somewhat similar to **22**, and **23**, such as 2-(4-chlorophenoxy- or chlorophenylthio)propanoic and -butanoic acid esters of tropanol, (=(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]octan-3-ol) have been recently found [29][30] to exhibit rather poor affinity for the σ_1 receptor subtype. Such differences in affinity might be due to the different bicyclic aminoalcohol, or possibly to the branching of the aliphatic chain in the relevant esters.

All compounds bearing the arylalkyl chain in the β-position at C(1) of the quinolizidine ring displayed higher affinities than those bearing the same chain in the α-position, as already observed for the 1β-(arylethyl)quinolizidine derivatives **A-*β*** [14]. However, the difference in affinity in each couple of epimers decreased with the increasing length of the chain. The introduction of F or Cl at the *para*-position of the phenyl ring strongly increased the affinity for the σ_1 receptor subtype, but also this effect was quenched by the increasing length of the aliphatic chain; thus, compounds **9** and **10** exhibited the same K_1 value (0.63 nM).

Table 2. *Binding Affinities of* **19**–**25** *for the* σ_1 *Receptor Subtype*

Ligand	K_i[a]) (nM)
19	10.2[b])
20	9.0[c])
21	9.2[b])
22	36.9[b])
23	24.2[b])
24	49[c])
25	6.4[b])

[a]) Mean of duplicate experiments: each value differed from the mean by less than 10%. [b]) K_i (nM) of reference ligand haloperidol 1.45. [c]) K_i (nM) of reference ligand ifenprodil 1.4 (see [14]).

The affinity-enhancing effect of the mentioned structural features (length of chain, equatorial position of the substituent at the quinolizidine moiety, presence of a halogen atom on the aromatic ring) showed additive character; when (1*R*,9a*R*)-octahydro-1-[(phenylthio)methyl]-2*H*-quinolizine (**5**; $K_i = 89$ nM) and (1*S*,9a*R*)-octahydro-1-({[4-chlorophenyl)methyl]thio}methyl)-2*H*-quinolizine (**17**; $K_i = 0.23$ nM) are compared, a 387-fold increase in affinity is observed.

Finally, for compounds **24** and **25**, each bearing two fluorophenyl residues, a high affinity for the σ_1 subtype was still observed, albeit lower than that of the related compounds **3** and **7**, that each bear only a single halobenzene moiety. The increasing distance between the basic N-atom and the aromatic part of the molecule produces a significant increase in affinity also in these compounds, which exhibit a K_i of 49 and 6.4 nM, respectively.

Taken together, these results support further the σ_1-receptor pharmacophore model proposed by *Glennon* and co-workers [8][9][31], which consists of a primary hydrophobic binding site situated 6–10 Å from the basic N-atom binding site, with a secondary binding site, associated with a region of bulk tolerance, situated 2.5–3.9 Å from the amine site. Thus, the aromatic part of our ligands **1**–**23** could interact with either the primary or secondary hydrophobic site of the receptor, depending on the effective distance from the basic N-atom, taking into account the possible folding of the aliphatic chain. On the other hand, the two 4-fluorophenyl rings of compounds **24** and **25** should better accommodate in the secondary hydrophobic bulk-tolerating region.

Concerning the affinity for the σ_2 receptor subtype, compounds tested so far exhibit K_i values that were one to more than two orders of magnitude lower than those found for the σ_1 subtype. Moreover, the above structural features, which improved the affinity for the σ_1 subtype, particularly the equatorial position of the substituent at the quinolizidine moiety and the presence of a halogen atom, did not play an identical role in the case of the σ_2 subtype.

Compound **17**, which displays the highest affinity for the σ_1 subtype and the highest selectivity *vs.* the σ_2 subtype, was also tested for affinity to serotonin 5-HT_{2A} and dopamine D_2 receptor subtypes that are implicated, though in different measures, in the

activity of conventional and atypical neuroleptic drugs. As was previously observed for compounds **12** and **13** [14], in this case only modest affinity for 5-HT_{2A} ($K_i = 183$ nM) was found, while affinity for the D_2 subtype was once more very poor, with only 40% inhibition of [^{3}H]nemonapride binding at a 10 μM concentration.

Conclusions. – Several functions of σ_1 receptors have been progressively uncovered, but the interest in selective ligands for this receptor subtype is now addressed mainly because of their neuroprotective and anti-amnesic potentials in aging-related pathologies [5]. Recently, 4-phenyl-1-(4-phenylbutyl)piperidine was found to afford neuroprotection in experimental stroke, through attenuation of neuronal nitric oxide synthase activity and ischemia-evoked NO production [32].

The (arylalkyl)quinolizidines, their isosteric thioanalogs, and the variously functionalized congeners presently considered (**1**–**25**) behave as good ligands for the σ_1 receptor subtype with subnanomolar binding constants for the best compounds, while they display a manifold lower, or definitely poor, affinity for σ_2, 5 HT_{2A}, and D_2 receptor subtypes. Therefore, this class of quinolizidine derivatives deserves further investigation toward development of still more potent and selective compounds.

The proper length of the benzene-quinolizidine-connecting aliphatic chain represents an important structural feature that defines a good ligand. On the other hand, the demonstrated good affinity of thio ethers and esters permit facile construction of new sets of quinolizidine derivatives with aliphatic chains of variable length and nature, overcoming the difficulties of synthesizing long chain (arylalkyl)quinolizidines. In this manner, a larger molecular diversity can also be introduced in the new ligands, which will be useful for studying the receptor requirements around the central proton donor site.

The financial support from the Italian '*Ministero dell'Istruzione, dell'Università e Ricerca*' (MIUR) is gratefully acknowledged.

Experimental Part

General. All commercially available solvents and reagents were used without further purification, unless otherwise stated. CC = column chromatography. M.p.s: *Büchi* apparatus; uncorrected. IR Spectra: *Perkin-Elmer Paragon-1000-PC* spectrophotometer; KBr pellets for solid, and neat for liquid; $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR Spectra: *Varian Gemini-200* spectrometer; $CDCl_3$ with Me_4Si as internal standard; δ in ppm, J in Hz; Q = octahydroquinolizine ring. Elemental analyses were performed on a *Carlo-Erba EA-1110* CHNS–O instrument in the Microanalysis Laboratory of the Department of Pharmaceutical Sciences of Genoa University.

*(1S,9aR)-Octahydro-1-(phenylmethyl)-2*H*-quinolizine* (**1**). To a soln. of ω-chlorolupinane [33] (1.69 g, 9 mmol) in dry Et_2O (5 ml), 3M phenylmagnesium bromide soln. in Et_2O (*Aldrich*; 5 ml, 15 mmol) was added, and the soln. was heated under reflux for 17 h. After cooling, 1N HCl (25 ml) was added dropwise, and the acid soln. was extracted with Et_2O. The aq. phase was alkalinized with 2N NaOH and extracted with Et_2O. After evaporation, the residue was distilled at 115–120° (air-bath temp.)/0.05 Torr: **1** (0.28 g, 13.6%). Oil which solidified on standing. M.p. 30–33°. ^{1}H-NMR ($CDCl_3$): 1.10–2.20 (*m*, 14 H, Q); 2.60–2.80 (*m*, 1 H, ArCH_2Q); 2.80–3.00 (*m*, 1 H of ArCH_2Q, 2 H_α near N of Q); 7.10–7.40 (*m*, 5 arom. H). Anal. calc. for $C_{16}H_{23}N$: C 83.78, H 10.11, N 6.11; found: C 83.55, H 10.26, N 6.10.

*(±)-(1*RS*,9a*RS*)-1-[(4-Fluorophenyl)methyl]octahydro-2*H*-quinolizin-1-ol* (**26**). A soln. of freshly distilled 4-fluorobenzyl chloride (1.5 g, 10.4 mmol) in dry Et_2O (20 ml) was added dropwise to 0.25 g (10 mmol) of Mg-turnings covered with dry Et_2O, and the mixture was refluxed under N_2 until all Mg was dissolved. A soln. of octahydro-2*H*-quinolizin-1-one [34] (1.6 g, 10 mmol) in dry Et_2O (10 ml) was added, and the soln. was refluxed for 18 h. The soln. was extracted with 0.1N HCl, and the acid soln. was alkalinized and extracted with Et_2O. After

evaporation, the oily residue (2.43 g) was purified by CC (neutral alumina (1:15), CH_2Cl_2, then CH_2Cl_2 containing 0.5% (*v*/*v*) of MeOH): **26** (2.08 g, 78.6%). Oil that soon solidified. Repeated crystallization from hexane gave 1.12 g (42.4%) of **26**. M.p. 80–81°. ^{1}H-NMR ($CDCl_3$): 1.00–2.20 (*m*, 13 H, Q); 2.45 (*dd*, *J* = 14, 1 H, ArCH_2); 2.60–2.80 (*dm*, 1 H, ArCH_2); 2.80–3.05 (*m*, 2 H_{eq} near N of Q, OH collapsing with D_2O); 6.90–7.05 (*m*, 2 arom. H); 7.10–7.25 (*m*, 2 arom. H). Anal. calc. for $C_{16}H_{22}FNO$: C 72.97, H 8.42, N 5.32; found: C 73.27, H 8.32, N 5.41.

*1-[(4-Fluorophenyl)methyl]-3,4,6,7,8,9-hexahydro-2*H*-quinolizine* (**27**). Phosphorous pentoxide (1.5 g) was added to a soln. of **26** (1.1 g, 4.2 mmol) in polyphosphoric acid (PPA; 10 g). The mixture was heated to 165° and stirred at 165° for 1 h. After cooling, H_2O (30 ml) was added, and the mixture neutralized with Na_2CO_3 and alkalinized to pH 10 by 6N NaOH. By extraction with Et_2O, impure **27** (0.93 g, 90%) was obtained. Light brownish oil. TLC (alumina, CH_2Cl_2): very minor spot just behind the main spot. IR (neat): no OH band. ^{1}H-NMR ($CDCl_3$): 1.00–3.10 (*m*, 14 H, Q); 3.30 (*s*, 1.8 H, ArCH_2C=C); 5.38–5.47 (*m*, 0.2 H, >C=CH); 6.80–7.20 (*m*, 4 arom. H).

*(±)-(1*RS*,9a*SR*)-1-[(4-Fluorophenyl)methyl]octahydro-2*H*-quinolizine* (**11**). Compound **27** (0.90 g) was dissolved in EtOH (20 ml) and hydrogenated at r.t. and atmospheric pressure over 10% Pd/C (0.5 g) until the absorption of H_2 ceased. Catalyst and solvent were removed, and the residue was purified twice by CC (neutral alumina (1:20), CH_2Cl_2) pure (TLC) **11** (0.57 g, 62.8%). Colorless oil. ^{1}H-NMR ($CDCl_3$): 0.80–2.20 (*m*, 14 H, Q); 2.60–3.10 (*m*, therein *dd*, *J* = 14, 11, 4 H, 2 H_{eq}. near N of Q, ArCH_2Q); 6.85–7.20 (*m*, 4 arom. H). Anal. calc. for $C_{16}H_{22}FN$: C 77.69, H 8.96, N 5.66; found: C 77.41, H 9.20, N 5.54.

*1-[(1*S*,9a*R*)-Octahydro-2*H*-quinolizin-1-yl]-3-phenylpropan-2-one* (**19**). This ketone was first described in [35]. A soln. of freshly distilled ω-cyanolupinane [36] (1.78 g, 10 mmol) in a few ml of dry Et_2O was added to 1M benzylmagnesium chloride soln. in Et_2O (*Aldrich*; 18 ml, 18 mmol), previously diluted with dry Et_2O (10 ml). The mixture was heated under reflux for 11 h and then, under ice cooling, 1N HCl (38 ml) was added, and the acid soln. was further washed with Et_2O. The aq. phase was alkalinized with 30% KOH soln. and extracted with Et_2O, the extract evaporated, and the residue crystallized from petroleum ether: **19** (2.13 g, 78.6%). M.p. 73–74°. IR (KBr): 1690 (C=O). Anal. calc. for $C_{18}H_{25}NO$: C 79.66, H 9.29, N 5.16; found: C 79.44, H 9.35, N 5.37.

*(1*R*,9a*R*)-Octahydro-1-(3-phenylpropyl)-2*H*-quinolizine* (**4**). Na (0.19 g, 8.26 mmol) was dissolved in diethylene glycol (6 ml), hydrazine monohydrate (0.39 ml, 7.7 mmol) and **19** (0.75 g, 2.76 mmol) were added in this order, and the mixture was heated at 205–210° for 4 h. After cooling, H_2O was added, the soln. extracted with toluene, the org. phase washed with H_2O, dried (Na_2SO_4), and evaporated, and the residue bulb-to-bulb distilled at 130–145° (air bath temp/0.06 Torr): **4** (0.57 g, 80%). Colorless oil. ^{1}H-NMR ($CDCl_3$): 1.15–2.05 (*m*, 16 H of Q, CH_2Q); 2.50–2.65 (*m*, $CH_2CH_2CH_2$); 2.72–2.88 (*m*, PhCH_2); 7.10–7.35 (*m*, 5 arom. H). Anal. calc. for $C_{18}H_{27}N$: C 83.99, H 10.57, N 5.44; found: C 84.05, H 10.60, N 5.70.

Hydrochloride **4**·HCl: M.p. 149–151°. Anal. calc. for $C_{18}H_{27}N \cdot HCl \cdot 0.25\ H_2O$: C 72.45, H 9.63, N 4.69; found: C 72.66, H 9.82, N 4.87.

*(1*S*,9a*R*)-Octahydro-α-(phenylmethyl)-2*H*-quinolizine-1-ethanol* (**28**). Tosylhydrazide (=4-methylbenzenesulfonic acid hydrazide; 0.616 g, 3.24 mmol) was added to a soln. of **19** (0.447 g, 1.65 mmol) in MeOH (34 ml), which was heated under reflux for 3.5 h. $NaBH_4$ (0.625 g; 16.2 mmol) was added to the ice-cooled soln., which was subsequently refluxed for 3 h. The solvent was evaporated, the residue taken up in H_2O and extracted with Et_2O, the org. phase evaporated and the residue distilled at 177° (air-bath temp./0.06 Torr) diastereoisomer mixture **28** (0.36 g, 80%). Oil. IR (neat): 3390 (OH), no C=O band. ^{1}H-NMR ($CDCl_3$): 1.15–2.10 (*m*, 16 H of Q ring QCH_2); 2.58–2.74 (*m*, 1 H, ArCH_2); 2.75–2.92 (*m*, 1 H of ArCH_2, 2 H_α near N of Q); 3.80–3.95, 4.00–4.15 (2*m*, C*H*OH); 6.40 (br. *s*, OH, collapsing with D_2O); 7.10–7.38 (*m*, 5 arom. H). Anal. calc. for $C_{18}H_{27}NO$: C 79.07, H 9.95, N 5.12; found: C 79.17, H 10.05, N 5.30.

*(1*R*,9a*R*)- and (1*S*,9a*R*)-1-[(Arylthio)methyl]- or 1-[[(ω-Arylalkyl)thio]methyl]-Octahydro-2*H*-quinolizines* **5**–**9** *and* **14**–**18**, resp.: *General Method*. To a soln. of 4-substituted benzenethiol or 4-substituted benzene alkanethiol (6 mmol) in abs. EtOH (3–6 ml), ground NaOH (6 mmol) was added, and the mixture was heated to reflux under N_2. After a clear soln. was obtained, ω-chlorolupinane [33] or ω-chloroepilupinane [37] (1.13 g, 6 mmol) was added, and the soln. was further refluxed for 6 h under N_2. To obtain **18**, ω-bromoepilupinane [38] was used. The mixture was diluted with H_2O, acidified with 1M HCl to pH 2, and washed with Et_2O to remove the unreacted thiol. The aq. soln. was then strongly alkalinized with 4M NaOH and extracted with Et_2O, the extract evaporated, and the residue distilled at 0.04–0.06 Torr. At 80–90° (air-bath temp.), the unreacted halo compound was removed, while the target compound distilled at 140–170°. In the case of **15** and **17**, after removing the chloroepilupinane, the residues were crystallized from petroleum ether and dry Et_2O, respectively.

*(1*R*,9a*R*)-Octahydro-1-[(phenylthio)methyl]-2*H*-quinolizine* (**5**): Yield 68%. M.p. 23–24.5°. B.p. 139–147°/0.04 Torr. ^{1}H-NMR ($CDCl_3$): 1.10–2.15 (*m*, 14 H, Q); 2.75–2.95 (*m*, 2 H_α near N of Q); 3.07 (*dd*,

$J = 12.64$, 9.88, 1 H, QCH_2SPh); 3.25 (*dd*, $J = 12.64$, 4.32, 1 H QCH_2SPh); 7.10–7.45 (*m*, 5 arom. H). Anal. calc. for $C_{16}H_{23}NS$: C 73.53, H 8.87, N 5.36, S 12.24; found: C 73.65, H 8.80, N 5.50, S 11.90.

*(1*R*,9a*R*)-1-{[(4-Fluorophenyl)thio]methyl}octahydro-2*H*-quinolizine* (**6**): Yield 40%. Oil that solidified on standing. B.p. 148–152°/0.05 Torr. ^{1}H-NMR ($CDCl_3$): 1.10–2.15 (*m*, 14 H, Q); 2.75–2.95 (*m*, 2 H_α near N of Q); 3.03 (*dd*, $J = 12.64$, 9.88, 1 H, QCH_2SAr); 3.18 (*dd*, $J = 12.64$, 4.32, 1 H, QCH_2SAr); 6.90–7.10, 7.25–7.45 (2*m*, each 2 arom. H (*p*-subst.)). Anal. calc. for $C_{16}H_{22}FNS$: C 68.77, H 7.94, N 5.01, S 11.48; found: C 68.51, H 7.90, N 5.03, S 11.11.

*(1*R*,9a*R*)-Octahydro-1-{[(phenylmethyl)thio]methyl}-2*H*-quinolizine* (**7**): Yield 70%. Oil. B.p. 145–152°/0.05 Torr. ^{1}H-NMR ($CDCl_3$): 1.10–2.10 (*m*, 14 H, Q); 2.55–2.85 (*m*, 2 H_α near N of Q, QCH_2S); 3.7 (*s*, PhCH_2S); 7.15–7.40 (*m*, 5 arom. H). Anal. calc. for $C_{17}H_{25}NS$: C 74.14, H 9.15, N 5.09, S 11.62; found: C 74.36, H 9.05, N 5.20, S 11.31.

*(1*R*,9a*R*)-1-{{[(4-Chlorophenyl)methyl]thio}methyl}octahydro-2*H*-quinolizine* (**8**): Yield 72%. M.p. 29–30°. B.p. 168–171°/0.09 Torr. ^{1}H-NMR ($CDCl_3$): 1.05–2.00 (*m*, 14 H, Q); 2.50–2.83 (*m*, 2 H_α near N of Q, CH_2S); 3.60 (*s*, PhCH_2S); 7.15–7.35 (*m*, 4 arom. H (*p*-subst.)). Anal. calc. for $C_{17}H_{24}ClNS$: C 65.88, H 7.81, N 4.52, S 10.35; found: C 65.92, H 7.73, N 4.46, S 10.48.

*(1*R*,9a*R*)-Octahydro-1-{[(2-phenylethyl)thio]methyl}-2*H*-quinolizine* (**9**): Yield 33%. Oil. B.p. 160–167°/0.05 Torr. ^{1}H-NMR ($CDCl_3$): 1.18–2.05 (*m*, 14 H, Q); 2.65–2.94 (*m*, CH_2CH_2SCH_2Q, 2 H_α near N of Q); 7.18–7.35 (*m*, 5 arom. H).

Hydrochloride **9**·HCl: M.p. 113–114°. Anal. calc. for $C_{18}H_{27}NS \cdot HCl$: C 66.33, H 8.66, N 4.30, S 9.84; found: C 66.15, H 8.74, N 4.29, S 9.51.

*(1*S*,9a*R*)-Octahydro-1-[(phenylthio)methyl]-2*H*-quinolizine* (**14**): Yield 94%. M.p. 59–60.5°. B.p. 130–139°/0.05 Torr. ^{1}H-NMR ($CDCl_3$): 1.00–2.15 (*m*, 14 H, Q); 2.70–2.90 (*m*, therein *dd* at 2.78, $J = 12.48$, 7.63, 2 H_α near N of Q, 1 H of QCH_2S); 3.16 (*dd*, $J = 12.48$, 2.95, 1 H, QCH_2S); 7.10–7.40 (*m*, 5 arom. H). Anal. calc. for $C_{16}H_{23}NS$: C 73.53, H 8.87, N 5.36, S 12.24; found: C 73.60, H 8.90, N 5.55, S 11.80.

*(1*S*,9a*R*)-1-{[(4-Fluorophenyl)thio]methyl}octahydro-2*H*-quinolizine* (**15**): Yield 93%. M.p. 63–63.5°. ^{1}H-NMR ($CDCl_3$): 0.95–2.20 (*m*, 14 H, Q); 2.60–2.90 (*m*, therein *dd* at 2.71, $J = 12.48$, 7.63, 2 H_α near N of Q, 1 H of QCH_2SAr); 3.08 (*dd*, $J = 12.48$, 2.95, 1 H, QCH_2SAr); 6.90–7.10, 7.25–7.45 (2*m*, each 2 arom. H (*p*-subst.)). Anal. calc. for $C_{16}H_{22}FNS$: C 68.77, H 7.94, N 5.01, S 11.48; found: C 68.84, H 7.96, N 5.04, S 10.98.

*(1*S*,9a*R*)-Octahydro-1-{[(phenylmethyl)thio]methyl}-2*H*-quinolizine* (**16**): Yield 92%. M.p. 44.5–45°. B.p. 152–161°/0.04 Torr. ^{1}H-NMR ($CDCl_3$): 0.90–2.15 (*m*, 14 H, Q); 2.27 (*dd*, $J = 12.6$, 7.6, 1 H, QCH_2S); 2.59 (*dd*, $J = 12.6$, 3.2, 1 H, QCH_2S); 2.70–2.90 (*m*, 2 H_α near N of Q); 3.68 (*s*, PhCH_2S); 7.20–7.45 (*m*, 5 arom. H). Anal. calc. for $C_{17}H_{25}NS$: C 74.14, H 9.15, N 5.09, S 11.62; found: C 73.98, H 9.30, N 5.07, S 11.80.

*(1*S*,9a*R*)-1-{{[(4-Chlorophenyl)methyl]thio}methyl}octahydro-2*H*-quinolizine* (**17**): Yield 96%. M.p. 92–92.5°. ^{1}H-NMR ($CDCl_3$): 0.90–2.15 (*m*, 14 H, Q); 2.27 (*dd*, $J = 12.6$, 3.0, 1 H, QCH_2S); 2.59 (*dd*, $J = 12.6$, 7.6, 1 H, QCH_2S); 2.70–2.90 (*m*, 2 H_α near N of Q); 3.68 (*s*, ArCH_2S); 7.20–7.40 (*m*, 4 arom. H). Anal. calc. for $C_{17}H_{24}ClNS$: C 65.88, H 7.81, N 4.52, S 10.35; found: C 66.21, H 7.61, N 4.55, S 10.00.

*(1*S*,9a*R*)-Octahydro-1-{[(2-phenylethyl)thio]methyl}-2*H*-quinolizine* (**18**): Yield 90%. M.p. 45–46°. B.p. 160–165°/0.05 Torr. ^{1}H-NMR ($CDCl_3$): 1.05–2.10 (*m*, 14 H, Q); 2.40 (*dd*, $J = 12.6$, 7.6, 1 H, QCH_2S); 2.66–2.96 (*m*, 7 H, ArCH_2CH_2S, 1 H of QCH_2S, 2 H_α near N of Q); 7.16–7.34 (*m*, 5 arom. H). Anal. calc. for $C_{18}H_{27}NS$: C 74.68, H 9.40, N 4.84, S 11.08; found: C 74.50, H 9.45, N 4.95, S 10.98.

*(1*R*,9a*R*)-1-{{[2-(4-Fluorophenyl)ethyl]thio}methyl}octahydro-2*H*-quinolizine* (**10**). A mixture of 4-fluorobenzeneethanol (2 g) and 48% hydrobromic acid (18 ml) was heated under reflux for 3 h. After cooling, H_2O was added, and the soln. was extracted with Et_2O. The org. phase was shaken with 10% $NaHCO_3$ soln., then with H_2O, dried, and evaporated. The 4-fluorophenethyl bromide was distilled (120°/10 Torr).

A soln. of 4-fluorophenethyl bromide (1.41 g, 7 mmol) in DMF (3 ml) was introduced into an *Aldrich* pressure tube flushed with N_2; freshly distilled thiolupinine [17] (1.29 g, 7 mmol) was added and the sealed tube heated at 140° for 18 h. DMF was evaporated, and the residue was dissolved in CH_2Cl_2 and treated with 0.5N HCl to remove the unreacted thiolupinine, while the title compound's hydrohalides remained in the org. phase. The solvent was evaporated, the residue dissolved in 0.5N HCl, and the acid soln. washed with Et_2O. The aq. phase was alkalinized and extracted with Et_2O, the extract evaporated, and the residue distilled at 160° (air-bath temp.)/0.01 Torr: **10** (1.13 g, 52.6%). Oil. ^{1}H-NMR ($CDCl_3$): 1.05–2.15 (*m*, 14 H, Q); 2.60–3.00 (*m*, 8 H, CH_2CH_2SCH_2Q, 2 H_α near N of Q); 6.90–7.10, 7.10–7.25 (2*m*, each 2 arom. H (*p*-subst)). Anal. calc. for $C_{18}H_{26}FNS$: C 70.32, H 8.52, N 4.56, S 10.43; found: C 70.52, H 8.90, N 4.53, S 10.08.

*4-Fluoro-α-{{[(1*R*,9a*R*)-octahydro-2*H*-quinolizin-1-yl]methyl}thio}methyl}benzenemethanol* (**21**). To a soln. of *S*-(4-fluorophenacyl)thiolupinine [17] (0.3 g, 0.93 mmol) in EtOH/H_2O 8:2 (10 ml), $NaBH_4$ (0.045 g) was added and the soln. heated under reflux for 3 h. The solvent was evaporated, and the residue was taken up in

H_2O and filtered. The collected product was dried (0.25 g) and crystallized from pentane: diastereoisomer mixture **21** (0.16 g, 53.3%). M.p. 64–77°. Anal. calc. for $C_{18}H_{26}FNOS$: C 66.84, H 8.10, N 4.33, S 9.91; found: C 66.74, H 8.25, N 4.38, S 9.70.

REFERENCES

[1] M. Abou-Gharbia, S. Y. Ablordeppey, R. A. Glennon, *Annu. Rep. Med. Chem.* **1993**, *28*, 1.
[2] S. D. Wyrick, R. G. Booth, *Drugs Future* **1995**, *20*, 1033.
[3] B. J. Vilner, C. S. John, W. D. Bowen, *Cancer Res.* **1995**, *55*, 408.
[4] R. H. Mach, C. R. Smith, J. Al-Nabulsi, B. R. Whirrett, S. R. Childers, K. T. Wheeler, *Cancer Res.* **1997**, *57*, 156.
[5] T. Maurice, B. P. Lockhart, *Prog. Neuro-Psychopharmacol. Biol. Psychiat.* **1997**, *21*, 69.
[6] W. D. Bowen, *Pharm. Acta Helv.* **2000**, *74*, 211.
[7] K. W. Crawford, W. D. Bowen, *Cancer Res.* **2002**, *62*, 313.
[8] R. A. Glennon, S. Y. Ablordeppey, A. M. Ismaill, M. B. El-Ashmawy, J. B. Fisher, K. B. Howie, *J. Med. Chem*. **1994**, *37*, 1214.
[9] S. Y. Ablordeppey, J. B. Fisher, R. A. Glennon, *Bioorg. Med. Chem*. **2000**, *8*, 2105.
[10] W. Quaglia, M. Giannella, A. Piergentili, M. Pigini, L. Brasili, R. Di Toro, L. Rossetti, S. Spampinato, C. Melchiorre, *J. Med. Chem*. **1998**, *41*, 1557.
[11] F. Berardi, S. Santoro, P. Perrone, V. Tortorella, S. Govoni, L. Lucchi, *J. Med. Chem*. **1998**, *41*, 3940.
[12] A. Marrazzo, O. Prezzavento, L. Pasquinucci, F. Vittorio, G. Ronsisvalle, *Farmaco* **2001**, *56*, 181.
[13] R. H. Mach, B. Yang, L. Wu, R. J. Kuhner, B. R. Whirrett, T. West, *Med. Chem. Res.* **2001**, *10*, 339.
[14] A. Sparatore, F. Novelli, F. Sparatore, *Med. Chem. Res.* **2002**, *11*, 1.
[15] F. Novelli, F. Sparatore, *Farmaco* **2002**, *57*, 871.
[16] S. Y. Ablordeppey, J. B. Fisher, K. J. Burke Howie, R. A. Glennon, *Med. Chem. Res.* **1992**, *2*, 368.
[17] F. Novelli, F. Sparatore, *Farmaco* **1993**, *48*, 1021.
[18] A. Sparatore, F. Sparatore, *Farmaco* **2001**, *56*, 169.
[19] I. Vazzana, F. Novelli, F. Sparatore, A. Sparatore, G. Fadda, C. Manca, *Farmaco* **1994**, *49*, 105.
[20] F. Novelli, B. Tasso, F. Sparatore, *Farmaco* **1999**, *54*, 354.
[21] S. F. Mason, K. Schofield, R. J. Wells, *Proc. Chem. Soc.* **1963**, 337.
[22] J. D. England, J. Sam, *J. Heterocycl. Chem*. **1966**, *3*, 482.
[23] D. L. Temple, J. Sam, *J. Heterocycl. Chem*. **1970**, *7*, 847.
[24] D. L. Temple, J. Sam, *J. Heterocycl. Chem*. **1968**, *5*, 441.
[25] M. Tamura, J. Kochi, *Synthesis* **1971**, 303.
[26] M. Tamura, J. Kochi, *J. Organomet. Chem.* **1971**, *31*, 289.
[27] H. Minlon, *J. Am. Chem. Soc*. **1946**, *68*, 7487.
[28] L. Caglioti, *Tetrahedron* **1966**, *22*, 487.
[29] R. H. Mach, L. Wu, T. West, B. R. Whirrett, S. R. Childers, *Life Sci*. **1999**, *64*, PL 131.
[30] O. Prezzavento, F. Gualtieri, A. Marrazzo, M. N. Romanelli, G. Ronsisvalle, E. Teodori, *Arch. Pharm. Pharm. Med. Chem*. **2002**, *335*, 39.
[31] S. Y. Ablordeppey, M. El-Ashmawy, J. B. Fisher, R. A. Glennon, *Eur. J. Med. Chem*. **1998**, *33*, 625.
[32] T. Goyagi, S. Goto, A. Bhardway, V. L. Dawson, P. D. Hurn, J. R. Kirsch, *Stroke* **2001**, *32*, 1613.
[33] F. Sparatore, V. Boido, P. Preziosi, E. Miele, G. De Natale, *Farmaco, Ed. Sci*. **1969**, *24*, 587.
[34] W. A. Reckhow, D. S. Tarbell, *J. Am. Chem. Soc*. **1952**, *74*, 4960.
[35] M. Ercoli, Ph. D. Thesis, University of Genoa, 1995.
[36] G. R. Clemo, J. Rudinger, *J. Chem. Soc.* **1951**, 2714.
[37] V. Boido, A. Sparatore, *Farmaco, Ed. Sci.* **1982**, *37*, 63.
[38] V. Boido, A. Boido, C. Boido-Canu, F. Sparatore, *Farmaco, Ed. Sci*. **1979**, *34*, 673.

Received August 21, 2003