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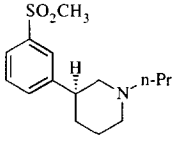
REGIOSELECTIVE SYNTHESIS OF 3-ARYL SUBSTITUTED PYRROLIDINES *VIA* PALLADIUM CATALYZED ARYLATION: PHARMACOLOGICAL EVALUATION FOR CENTRAL DOPAMINERGIC AND SEROTONERGIC ACTIVITY.

Clas Sonesson[1]*, Håkan Wikström[2a], Martin W. Smith[2b], Kjell Svensson[2b], Arvid Carlsson[2c], and Nicholas Waters[2c]

Medicinal Chemistry Unit, Department of Pharmacology, University of Göteborg, Sweden.

Abstract: A series of 3-arylpyrrolidines has been synthesised *via* palladium catalyzed arylation and evaluated for dopaminergic and serotonergic activity *in vitro* and *in vivo*. Compounds substituted by electron withdrawing groups on the *meta* position of the aromatic ring, were found to be preferential dopamine autoreceptor antagonists.

Recently we reported on a series of dopamine receptor antagonist like, substituted phenylpiperidines with preference for dopamine DA-D_2 type autoreceptors. Compound **1** (*S*-(-)-OSU6162) was found to be one of the most interesting in this respect.[3] Unlike classical neuroleptics, these agents appear to have a preference for autoreceptors and, as a consequence, they produce a weak behavioural activation in the rat when the baseline activity is low. However, when the baseline activity is raised by means of dopaminergic stimulatory agents such as apomorphine, amphetamine or cocaine, compound **1** counteracts the behavioural stimulation, decreasing it to the normal baseline activity. Thus, such stabilizing compounds may have potential for therapeutic intervention in central nervous system disorders such as schizophrenia, parkinsons disease and drug addiction.



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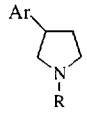


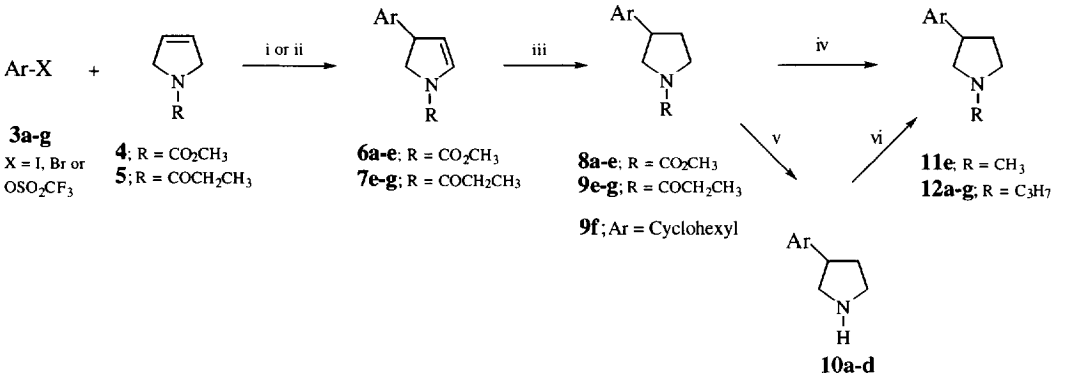
2

As part of a medicinal chemistry program investigating the structure activity relationship for this class of CNS stabilizers, we required a short and efficient procedure for the preparation of pyrrolidines bearing an aromatic or heteroaromatic substituent at the C-3 position (**2**). Recently we reported on a simple way to access this molecular framework using palladium catalyzed arylation of the cyclic olefins **4** and **5**, outlined in Scheme 1.[4]

Competing double-bond migration of the olefin's **4** and **5** to the corresponding 2-pyrrolines yields undesired 2-aryl-pyrrolines. Thus, an initial problem was to attain a high degree of regioselectivity in the preparation of compounds **6a-e** and **7e-g**. We also set out to reduce the competing diarylation of compounds **6a-e** and **7e-g** to 2,4-diaryl pyrrolines and improve the generally low yields, by a careful choice of reaction conditions.

Fax number : + 46-31-821.795 E-mail : chemistry@pharm.gu.se

Scheme 1



Reagents and conditions: **3a** Ph-I, **3b** Naphtyl-1-I, **3c** *m*-$MeSO_2$Ph-Br, **3d** *m*-CF_3Ph-I, **3e** Pyr-3-OTf, **3f** cyclohexenyl-1-OTf, **3g** *m*-MeOPh-I (**i**) X = I or Br: ArX (3 mmol), *i*-Pr_2NEt (4 eq), **4** or **5** (10 eq), Ag_2CO_3 (0.7 eq), $Pd(OAc)_2$ (0.05 eq), P(*o*-Tol)$_3$ (0.11 eq), DMF (8 ml), 100 °C, 4-8 h. (**ii**) X = OTf: ArX (3 mmol), *i*-Pr_2NEt (4 eq), **4** or **5** (10 eq), LiCl (3 eq), $Pd(OAc)_2$ (0.05 eq), P(2-Furyl)$_3$ (0.11 eq), DMF (8 ml), 100 °C, 4-8 h. (**iii**) **6** a-e or **7** e-g (2 mmol), HCO_2NH_4 (2 eq), Pd/C (30 mg), MeOH (25 ml), N_2 (g), Δ 4 h. (**iv**) **9**e-g (1.5 mmol), $LiAlH_4$ (3.5 eq), diethyl ether (30 ml), Δ 2 h. (**v**) **8** a-e (1.7 mmol), MeOH or EtOH (5 ml), 8 N HCl (15 ml), Δ 24-48 h. (**vi**) **10** a-d (1.5 mmol), I-C_3H_7 (1.2 eq), K_2CO_3 (3 eq), CH_3CN (20 ml), 50°C, 12 h.

The phosphine ligand was found to be of great importance in determining the regioselectivity. Bidentate ligands (e.g. dppp) yielded 50:50 mixtures of 2- and 3-arylated pyrrolines, while the monodentate ligands (e.g. P(o-Tol)3, P(2-Furyl)3) improved the selectivity in favour of 3-substitution to more than 95:5 for both aryl-halides and aryl-triflates. For arylhalides, it was also found that addition of a silversalt (e.g. Ag2CO3) completely suppressed the formation of 2-arylpyrrolines.

The second problem of diarylation was more difficult to overcome. Using a large excess (10 eq) of the olefins **4** or **5** decreased the amount of diarylated side products to 15-25 %. The yield of arylated compound was found to depend mainly on the choice of ligand and reaction temperature. Thus, using the optimized reaction conditions **i** and **ii** (Scheme 1), it was possible to obtain pure **6a-e** and **7e-g** in satisfactory yields of 50-68 %.[4] These arylated pyrrolines were converted in high yields to the corresponding pyrrolidines (**8a-e**, **9e-g**) by catalytic hydrogenation using Pd/C and excess ammonium formate in methanol at reflux.[4] When compound **7f** was reduced the cyclohexenyl moiety was also saturated to give the corresponding cyclohexyl analog **9f**.

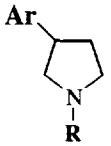
The secondary amines **10a-d** were quantitatively obtained from the methyl carbamates (**8a-d**) by heating in a mixture of aqueous HCl (8 N) and ethanol or methanol as cosolvent. The *N*-propyl derivatives **12a-d** were prepared from **10a-d** by alkylation with 1-iodopropane and powdered potassium carbonate in acetonitrile. Reduction of the methyl carbamate **8e** and the propenone analogues **9e-g** with LAH in diethyl ether afforded *iso*-Nicotine **11e** and the *N*-propylated pyrrolidines **12e-g**, respectively.

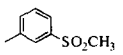
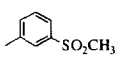
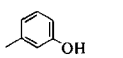
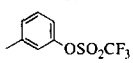
The phenol substituted pyrrolidine (**13**) was prepared from the corresponding methoxy analogue **12g** by demethylation in 48% aqueous HBr. Finally, treatment of **13** with triflic anhydride afforded the triflate ester (**14**) in high yield.

PHARMACOLOGICAL RESULTS AND DISCUSSION

The data in Table 2 suggest that the pharmacological profiles of compounds **12c-d** and **14** are similar to **1**.[3] Thus, in a single dose study they increased DA synthesis rates, measured as DOPA formation, in striatal, limbic and cortical brain regions. Although the efficacy of these compounds is only slightly lower than haloperidol[5] they do not induce hypomotility or catalepsy in the rat (100 μmol/kg). This may suggest that compounds **12c-d** and **14** are more efficacious antagonists at DA autoreceptors than at postsynaptic DA receptors.

Table 1. *In Vitro* Binding Data and Calculated logP Values.



Comp	Ar	R	Receptor Binding[a] (Ki nM) 5-HT1A	5-HT2	D2	D3	ClogP[b]
10a		H	>1,000[c]	>1,000[c]	486 ± 48[d]	>2,440	1.55
10b		H	95 ± 9	40 ± 5	264 ± 26	>1,000[c]	2.73
10c		H	>1,000[c]	>1,000[c]	>1,000[c]	>1,000[c]	-0.09
10d		H	174 ± 10	227 ± 22	100 ± 14	633 ± 223	2.44
11e		Me	>1,000[c]	>1,000[c]	>1,000[c]	>1,000[c]	0.92
12a		n-Pr	453 ± 36	> 1,000[c]	625 ± 58[d]	>2,500	3.46
12b		n-Pr	73 ± 4	113 ± 17	71 ± 3	>1,000[c]	4.63
12c		n-Pr	807 ± 139	>1,000[c]	>1,000[c]	>1,000[c]	1.82
12d		n-Pr	351 ± 48	569 ± 167	151 ± 9	35 ± 9	4.34
12e		n-Pr	>1,000[c]	>1,000[c]	>1,000[c]	>1,000[c]	1.98
12f		n-Pr	>1,000[c]	>1,000[c]	>1,000[c]	>1,000[c]	4.45
13		n-Pr	201 ± 23	>1,000[c]	68 ± 9	52 ± 28	2.79
14		n-Pr	652 ± 58	>1,000[c]	162 ± 31	62 ± 15	4.68

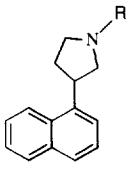
Footnotes: [a] All receptor binding measurements were made from cloned mammalian receptors expressed in CHO-K1 cells (using [^{3}H]-8-OH-DPAT for 5-HT$_{1A}$ receptors, [^{3}H]-ketanserin for 5-HT$_2$ receptors, [^{3}H]-U86170 for D$_2$ receptors and [^{3}H]-spiperone for D$_3$ receptors. Values were obtained with 11 drug concentrations in duplicate. [b] Calculated by version 3.5 of CLOGP available from Daylight Chemical Information Systems III, Rue Iberville #610, New Orleans LA 10130. [c] IC$_{50}$ estimated to be >1,000 nM based on single concentration study. [d] IC$_{50}$ was found to be > 1,000 nM in 11-point competition curve. All other Ki values were derived from IC$_{50}$ values <1,000 nM.

A comparison between compounds **1** and **12c** regarding their relative *in vivo* antagonist potency at DA receptors is not justified, since the piperidine **1** is a pure enantiomer whilst the pyrrolidine **12c** is a racemate. The racemic trifluoromethylphenyl-piperidine analogue of **12d**, has been reported to increase the DOPA accumulation to 168 and 229 % of saline controls in limbic and striatal regions, respectively (100 μmol/kg).[6] This is only slightly less than for **12d** and indicates similar *in vivo* efficacy for piperidine- and pyrrolidine-analogues at DA autoreceptors. Interestingly, pyrrolidines **12d** and **14** displayed a 4- and 3-fold selectivity, for the D_3 over the D_2 receptor, respectively, while the methylsulfonyl analogue (**12c**) has no DA receptor affinity *in vitro*. We have erlier reported that for the phenylpiperidines there is no correlation between the *in vitro* DA receptor affinity and the *in vivo* antagonist efficacy at DA autoreceptors.[3] This seems to be true also for the pyrrolidine analogues and may indicate that the *in vitro* DA receptor affinity (these compounds also lack affinity for DA D_1 and D_4 receptors), has nor relation to the *in vivo* affinity/efficacy at DA autoreceptors.

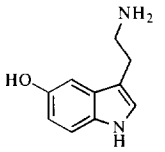
In reserpine pretreated rats, **13** has earlier been reported to have weak DA agonist properties.[7] In nonpretreated rats **13** increased DOPA accumulation in the striatum (Table 2). In addition, in contrast to compounds **12c-d** and **14**, **13** was found to decrease the locomotor activity to 20% of control (Table 2), suggesting a similar pharmacological profile to the partial DA agonist *S*-(-)-3-(3-hydroxyphenyl)-1-propylpiperidine ((-)-3-PPP).[8]

In a *in vivo* SAR study of the phenyl piperidines, we found a strong correlation between the efficacy (maximal increase in DOPA acc.) and the group dipole moment of the substituent on the aromatic ring.[3] In the phenyl pyrrolidine series it appears that this property also plays an important role in determining *in vivo* antagonist efficacy at DA receptors. This is demonstrated by compounds **12c-d** and **14**. However, since compounds **12c-d** and **14** are all substituted with powerful electron withdrawing groups it may be speculated that the antagonistic properties is mainly depending on the low electron density in the aromatic ring, and a weak π-π interaction with the receptor.[9a] Indeed, **12f**, in which the aromatic ring has been substituted with a saturated cyclohexyl ring, was found to be devoid of *in vitro* affinity and *in vivo* activity at the DA receptors (Table 1 and 2). An explanation may be that the cyclohexyl ring, in contrast to the phenyl ring, lacks the possibility of electrostatic interactions. These preliminary data may indicate that the *in vivo* antagonistic properties in the phenylpyrrolidine series mainly depend on (1) the dipole-dipole interaction between the substituent on the aromatic ring and the receptor in combination with a weak π-π interaction or (2) charge transfer interactions between the substituent and the receptor.[9b] The substituent on the basic nitrogen was also found to be an important factor. The antagonistic efficacy at DA receptors, for compounds **10a-d** (secondary amines) were found to be improved by *N*-propylation (comp. **12a-d**, Tab. 2).

The 1-naphthyl substituted pyrrolidine (**10b**) represents a semirigid bioisostere analog of 5-hydroxytryptamine (5-HT, **15**). The lack of the hydroxy group on the aromatic ring as well as the indole nitrogen (possible hydrogen bond-accepting/-donating functionalism) in **10b**, may suggest that this compound will act as an antagonist at 5-HT_{1A} receptors. The *in vitro* data in Table 1 shows that **10b** displays intermediate affinity for 5-HT_{1A} and 5-HT_2 receptors. However, **10b** was found to be devoid of *in vivo* activity at 5-HT and DA receptors (Table 2). Substitution the secondary amine in **10b** with a propyl group (**12b**) did not improve the affinity for 5-HT_{1A} receptors, but *in vivo*, **12b** displays full intrinsic activity at 5-HT_{1A} receptors (Table 2).



10b R = H
12b R = *n*-Pr



15 5-HT

The difference *in vivo* activity between **10b** and **12b** may be related to inability for **10b** to pass the blood-brain barrier since both **10b** and **12b** displays similar *in vitro* affinity for 5-HT_{1A} receptors. However, since **10b** is a relative lipophilic compound (CLOGP, Table 1) compared to other ligands in this series (e.g. **10d**) which are able to influence the *in vivo* biochemistry, this explanation does not seem to be realistic. A more sound interpretation of the data would be that the structural elements of **10b** contribute to 5-HT_{1A} affinity, but the lack of a propyl group on the nitrogen prevents it from having intrinsic efficacy at these receptors. It is also worth noting that **12b** displays relatively high affinity for D_2 receptors while it was found to be devoid of affinity for the D_3 site.

In compounds **11e** (*iso*-Nicotine) and **12e** the aromatic ring has been substituted by a pyridine ring. This was found to be detrimental for *in vitro* affinity for 5-HT_{1A} and D_2/D_3 receptors as well as effects on *in vivo* biochemistry mediated *via* these receptors (Table 1 and 2). Interestingly, both pyridine analogues depressed the locomotor activity with **12e** being the most efficient one (Table 2). Interestingly, *iso*-Nicotine has recently been reported to display affinity for the nicotine receptors.[10] However, the underlying mechanism to this behavioural phenomena is unclear and has to be further elucidated.

Table 2: Maximal Effects on *In Vivo* DA and 5-HT Biochemistry and Locomotor Activity (LMA) in Normal Rats at 100 μmol/kg s.c.[11]

Comp.	DOPA accumulation[a]			5-HTP accumulation[a]			LMA[b]
	Stri.	Limb.	Cort.	Stri.	Limb.	Cort.	% of ctrl
ctrls	100	100	100	100	100	100	100
1	317 ± 19***[c]	228 ± 17***	165 ± 8***	85 ± 4	83 ± 3**	78 ± 2**	135 ± 17
10a	81 ± 2	98 ± 3	107 ± 6	89 ± 2	86 ± 4	81 ± 4**	95 ± 15
10b	82 ± 5	92 ± 6	104 ± 2	93 ± 2	94 ± 11	86 ± 9	129 ± 9
10c	91 ± 7	89 ± 7	104 ± 9	92 ± 7	96 ± 5	98 ±7	71 ± 8
10d	163 ± 9***	113 ± 7	72 ± 2***	82 ± 5**	70 ± 1***	70 ± 4**	74 ± 10
11e	112 ± 6	112 ± 6	126 ± 4**	112 ± 5	72 ± 5*	79 ± 8	47 ± 8**
12a	66 ± 1**	96 ± 7	130 ± 7*	81 ± 4**	92 ± 10	83 ± 3**	115 ± 19
12b	177 ± 10**	118 ± 11	115 ± 8	54 ± 8***	53 ± 12***	57 ± 6***	80 ± 6
12c	256 ± 23***	207 ± 17***	143 ± 7***	78 ± 8**	97 ± 15	92 ± 8	126 ± 32
12d	297 ± 18***	205 ± 8***	131 ± 8**	78 ± 3**	97 ± 9	87 ± 2	89 ± 14
12e	108 ± 10	111 ± 8	132 ± 10**	104 ± 16	90 ± 8	94 ± 1	15 ± 4***
12f	95 ± 6	116 ± 11	119 ± 2*	103 ± 6	102 ± 10	88 ± 9	87 ± 7
13	153 ± 3***	113 ± 6	88 ± 7	68 ± 2**	74 ± 3*	79 ± 3	20 ± 5***
14	290 ± 13***	211 ± 1***	114 ± 5	86± 2*	85 ± 8	98 ± 2	93 ± 18
haloperidol	310***[d]	214***[d]					2 ± 1***[d]

Footnotes: [a] Animals were injected with test drug 65 min and with NSD 1015 (100 mg/kg s.c.) 30 min before death. Controls received corresponding saline injections. Values are expressed as percent of saline controls; means ± SEM. DOPA acc. = 3,4-Dihydroxyphenylalanine accumulation. 5-HTP acc. = 5-Hydroxytryptophan accumulation. [b] Locomotor activity. The activity was measured for 30 min after injection of drug. Values are expressed as percent of saline controls; mean ± SEM. c * $p<0.01$, ** $p<0.05$, *** $p<0.001$. [d] 0.07 mg/kg s.c. data taken from ref. 5.

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References and Notes:

1. Medicinal Chemistry Unit, Dept. of Pharmacology, University of Göteborg, Medicinargatan 7, S-41390 Göteborg, Sweden.
2 a) Dept. of Medicinal Chemistry, University of Groningen, Antonius Deusinglaan 2, NL-9713 AW, Groningen, The Netherlands. b) Pharmacia & Upjohn, 301 Henrietta St., Kalamazoo, MI 49007, USA. c) Dept. of Pharmacology, University of Göteborg, Medicinargatan 7, S-41390 Göteborg, Sweden.
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11. For a description of the methods used see: Svensson, K., Johansson, A.M., Magnusson, T., Carlsson, A. *Naunyn-Schmideberg's Arch. Pharmacol.* **1986**, *334*, 234.
12. All new compounds were fully characterized by ^{1}H-NMR (300 MHz, $CDCl_3$), ^{13}C-NMR (75.4 MHz, $CDCl_3$), MS *m/z* (relative intensity, 70 eV) and either elemental analysis (±0.4%) or high resolution mass spectrometry. The synthesis and analytical data for compounds **6a-e**, **7g**, **8a-e**, **9g**, **10a-d**, **11e**, **12g** and **13** have already been described in reference 4. Following are the yields, melting points, MS, ^{1}H- and ^{13}C-NMRs for each new compound: **7e** (1-(3-Pyridin-3-yl-2,3-dihydropyrrol-1-yl)propane-1-one), Method **ii** (scheme 1); Colorless oil, yield 0.31 g (51 %); eluent dichloromethane/methanol (19/1, v/v); MS 202 (M^+, 51), 146 (100), 145 (92), 117 (59), 68 (51);^{1}H NMR δ 1.1-1.3 (m, 3H), 2.2-2.5 (rotamers, q, *J* = 7.5 Hz, 2H), 3.6-3.8 (rotamers, dd, *J* = 5.4 Hz, 1 H), 4.1-4.4 (m, 3 H), 4.7, 4.9 (m, 1 H), 5.25 (m, 1 H), 6.7 (dd, *J* = 4.3, 2.0 Hz, 1 H), 7.25 (dd, J = 7.6, 4.8 Hz, 1H), 7.5 (m, 1H), 8.4-8.55 (m, 2H). **7f** (1-(3-Cyclohex-1-enyl-2,3-dihydropyrrol-1-yl)propane-1-one), method **ii** (scheme 1); Colorless oil, yield 0.32 g (52 %); eluent dichloromethane/methanol (19/1, v/v); MS 205 (M^+, 91), 149 (100), 106 (67), 68 (81), 67 (72);^{1}H NMR δ 1.1-1.3 (m, 3H), 1.5-1.7 (m, 3H), 1.8-2.0 (m, 4H), 2.1-2.4 (m, 3H), 3.4-3.9 (m, 3 H), 5.1 (m, 1 H), 5.5 (m, 1H), 6.5 (dd, *J* = 4.4, 2.0 Hz, 1 H). **9e** (1-(3-Pyridin-3-yl-pyrrolidine-1-yl)propane-1-one), Method **iii** (scheme 1); Colorless oil, yield 0.24 g (80 %); eluent dichloromethane/methanol (19/1, v/v); MS 204 (M^+, 40), 147 (13), 119 (12), 106 (100), 57 (28);^{1}H NMR δ 1.1-1.2 (m, 3H), 1.8-2.4 (m, 4H), 3.3-4.1 (m, 5H), 7.15 (m, 1H), 7.5 (m, 1H), 7.55 (m, 1H), 8.5 (m, 2H). **9f** (1-(3-Cyclohexylpyrrolidin-1-yl)propan-1-one), Method **iii** (scheme 1); Colorless oil, yield 0.27 g (82 %); eluent EtOAc; MS 209 (M^+, 27), 127 (30), 126 (100), 57 (19), 55 (18); ^{1}H NMR δ 0.9 (m, 2H), 1.1-1.3 (m, 6H), 1.4-2.1 (m, 8H), 2.25 (q, 2H), 2.9 (m, 1H), 3.25 (m, 1H), 3.5 (m, 1H), 3.7 (m, 1H). **12a** (3-Phenyl-1-propylpyrrolidine), Method **vi** (scheme 1); Colorless oil, yield 0.20 g (78 %); eluent CH_2Cl_2/ methanol (19/1, v/v); MS 189 (M^+, 7), 160 (100), 131 (17), 91 (25), 84 (26);^{1}H NMR δ 0.95 (t, 3H), 1.6 (sex, 2H), 1.9 (m, 1H), 2.3-2.6 (m, 4H), 2.7 (m, 1H), 2.9 (m, 1H), 3.15 (t, 1H), 3.4 (p, 1H), 7.1-7.3 (m, 5H); ^{13}C NMR δ 12.0, 21.9, 33.0, 43.3, 54.7, 58.6, 62.1, 126.2, 2 x 127.3, 2 x 128.4, 144.9. **12b** (3-Naphthalen-1-yl-1-propylpyrrolidine), Method **vi** (scheme 1); yield 0.26 g (82 %); eluent CH_2Cl_2/methanol (9/1, v/v); m.p. gum (HCl); MS 239 (M^+, 20), 211 (17), 210 (100), 141 (15), 84 (23);^{1}H NMR δ 1.0 (t, 3H), 1.7 (sex, 2H), 2.2 (m, 1H), 2.5-3.0 (m, 5H), 3.1 (m, 1H), 3.35 (m, 1H), 4.3 (p, *J* = 8.6 Hz, 1H), 7.4-7.6 (m, 4H), 7.73 (d, *J* = 8 Hz, 1H), 7.85 (dd, *J* = 7.6 Hz, 2.2 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR δ 11.8, 21.1, 31.7, 38.6, 54.3, 58.4, 60.2, 122.6, 123.5, 125.5, 125.7, 126.2, 127.2, 128.9, 131.8, 133.9, 138.6. **12c** (3-(3-Methanesulfonylphenyl)-1-propylpyrrolidine), Method **vi** (scheme 1); yield 0.33 g (80 %); eluent CH_2Cl_2/methanol (9/1, v/v); m.p. 156-158 °C (HCl, recryst. from MeOH / diethyl ether); MS 267 (M^+, 5), 239 (16), 238 (100), 129 (6), 84 (8);^{1}H NMR δ 0.9 (t, 3H), 1.55 (sex, 2H), 1.85 (m, 1H), 2.2-2.9 (m, 6H), 3.0-3.1 (m, 4H), 3.45 (m, 1H), 7.5 (t, *J* = 7.8 Hz, 1H), 7.58 (dt, *J* = 8.1 Hz, 1.6 Hz, 1H), 7.75 (dt, *J* = 7.8 Hz, 1.4 Hz, 1H), 7.82 (t, *J* = 1.7 Hz, 1H); **12d** (1-Propyl-3-(3-trifluoromethylphenyl)pyrrolidine), Method **vi** (scheme 1); yield 0.12 g (80 %); eluent CH_2Cl_2/methanol (9/1, v/v); m.p. syrup (HCl); MS 257 (M^+, 6), 229 (14), 228 (100), 199 (8), 84 (9);^{1}H NMR δ 0.95 (t, 3H), 1.55 (sex, 2H), 1.85 (m, 1H), 2.2-2.6 (m, 4H), 2.7 (m, 1H), 2.85 (m, 1H), 3.1 (dd, *J* = 9.3 Hz, 7.9 Hz, 1H), 3.45 (m, 1H), 7.35-7.6 (m, 4H); **12e** (3-(1-Propylpyrrolidin-3-yl)pyridine), Method **v** (scheme 1); yield 0.15 g (40 %); eluent CH_2Cl_2/methanol (3/1, v/v); MS 190 (M^+, 7), 162 (12), 161 (100), 84 (16), 57 (9);^{1}H NMR δ 0.95 (t, 3H), 1.55 (sex, 2H), 1.9 (m, 1H), 2.2-2.6 (m, 4H), 2.7-2.9 (m, 2H), 3.1 (t, *J* = 8.6 Hz, 1H), 3.45 (p, *J* = 7.9 Hz, 1H), 7.21 (dd, *J* = 7.8, 4.6 Hz, 1H), 7.6 (dt, *J* = 7.8, 1.9 Hz, 1H), 8.43 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.49 (d, *J* = 2.2 Hz, 1H); **12f** (3-Cyclohexyl-1-propylpyrrolidine), Method **v** (scheme 1); yield 0.11 g (60 %); eluent CH_2Cl_2/methanol (3/1, v/v); m.p. 138-140 °C (HCl, precipitate from diethyl ether); MS 195 (M^+, 6), 167 (14), 166 (100), 81 (18), 55 (12);^{1}H NMR δ 0.9 (m, 4H), 1.1-1.3 (m, 4H), 1.4-2.05 (m, 12H), 2.2-2.45 (m, 3H), 2.6-2.8 (m, 2H); **14** (Trifluoromethanesulfonic acid 3-(1-propylpyrrolidin-3-yl)phenyl ester); yield 0.38 g (84 %); eluent CH_2Cl_2/ methanol (9/1, v/v); m.p. 100-104 °C (HCl, precipitate from diethyl ether); MS 337 (M^+, 5), 309 (20), 308 (100), 175 (28), 84 (8);^{1}H NMR δ 0.95 (m, 3H), 1.55 (p, 2H), 1.85 (m, 1H), 2.3-2.6 (m, 4H), 2.75 (m, 2H), 3.0 (t, 1H), 3.4 (m, 1H), 7.1 (dt, 1H), 7.2 (s, 1H), 7.3-7.4 (m, 2H); ^{13}C NMR δ 12.0, 22.0, 33.2, 43.0, 54.5, 58.3, 61.8, 118.7 (q, *J* = 317 Hz, CF_3), 118.8, 120.2, 127.4, 130.1, 148.9, 149.7.

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