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N-Substituted-3-arylpyrrolidines: Potent and Selective Ligands at Serotonin 1A Receptor

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Abstract: 3-Arylpyrrolidines are synthesized through the coupling of *N*-benzyl-3-(methanesulfonyloxy)pyrrolidine with diarylcuprates. Pharmacological evaluation of a series of *N*-substituted-3-arylpyrrolidines toward several neurotransmitter receptors indicated that some of them are good ligands for serotonin 1A receptor. Particularly, *N*-[(*N*-saccharino)butyl]pyrrolidines were found to be potent and selective ligands. A preliminary biological evaluation for several selected compounds indicated that they are potentially effective antianxiety and antidepressant agents.

The development of selective and potent ligands for serotonin 1A receptor (5-HT_{1A}) has attracted a considerable interest since they are promising drug candidates for treatment of mood and anxiety disorders[1,2]. In addition to their biological aspects, the development of selective and potent ligands for 5-HT and other neurotransmitter receptors is of importance for studying the receptor pharmacology. A large number of ligands for various 5-HT receptor subtypes have been developed, and most of them can be simply categorized as indole, aminotetraline, arylpiperazine, and benzodioxane derivatives according to their common heterocycle structure.[3] Here we wish to report the synthesis of 3-arylpyrrolidines and their pharmacological evaluation toward several neurotransmitter receptors. From the study, selective ligands with high affinity at 5-HT_{1A} receptor have been developed. Originally, the 3-arylpyrrolidine system was designed for the development of ligands for dopamine receptors. After analyzing numerous ligand structures known, 3-arylpyrrolidines were deduced as new type of lead structure for dopamine receptors. However, from pharmacological evaluation, several *N*-substituted-3-arylpyrrolidine derivatives synthesized were found to be more potent ligands toward 5-HT_{1A} receptor[4] than dopamine receptors.

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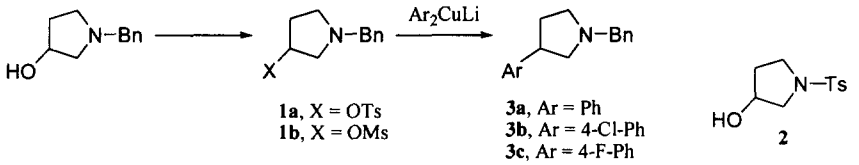
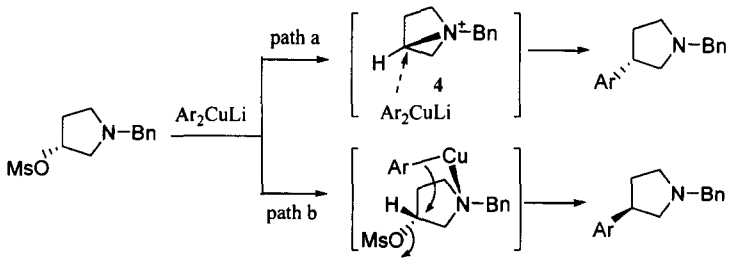
Synthesis of 3-arylpyrrolidines.

A literature survey indicated that there are limited methods that can be generally applicable to the synthesis of various 3-arylpyrrolidine derivatives[5]. As a more direct route we studied a direct nucleophilic coupling of 3-*p*-toluenesulfonyloxy- or 3-methanesulfonyloxy-pyrrolidine **1** with diarylcuprates as shown in Scheme 1.[6]



Scheme 1.

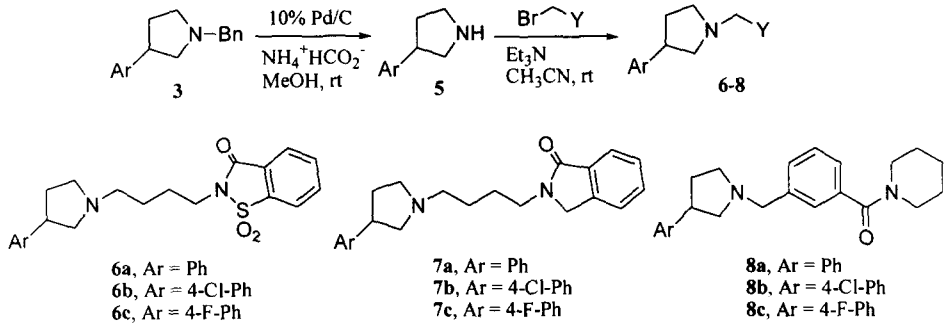
The starting materials **1** can be accessible in an enantiomeric form, starting from commercially available 3(*R*)-hydroxypyrrolidine. Treatment of *N*-benzyl-3-hydroxypyrrolidine, prepared from 3-hydroxypyrrolidine, with *p*-toluenesulfonyl chloride in the presence of an equimolar amount of triethylamine in dichloromethane at room temperature, however, gave 30% of the desired tosylate **1a** with 44% of a side product. The side product was found to be *N*-(*p*-toluenesulfonyl)-3-hydroxypyrrolidine **2**. Carrying out the reaction with the aid of 5 mol% DMAP reduced the formation of side product, thus providing 77% of *O*-tosylated product **1a** and 12% of the rearrangement product **2**. It was found that a similar reaction with methanesulfonyl chloride under the latter conditions in acetonitrile (0.8 M solution) at 0 °C for 10 min gave only the desired mesyloxypyrrolidine **1b**[7] in a near-quantitative yield after purification by column chromatography on silica gel. Next, the coupling of mesylate **1b** with diarylcuprates was carried out in diethyl ether.



Scheme 2.

The coupling yield was dependent on both the equivalents of the cuprate used and the reaction temperature. With three equivalents of the cuprate and at below 0 °C, reasonable yields were obtained (**3a**, 78%; **3b**, 65%; **3c**, 45%).[8] When 3-phenylpyrrolidine was synthesized starting from enantiopure 3(*R*)-hydroxypyrrolidine, the optical purity was found to be less than 10% ee.[9] This result may be explained by evoking the neighboring group participation of the *N*-benzyl nitrogen (path a), as depicted in the Scheme 2. The *N*-benzyl nitrogen also seemed to

influence the rate of the cuprate addition, because *N*-(*p*-toluenesulfonyl)-3-(methanesulfonyloxy)pyrrolidine did not give the coupling product under the same reaction conditions. As depicted in path b, a nitrogen-assisted cuprate reaction may be operating. The observed low enantiopurity suggests that both the routes (path a and b) are favorably competing in the coupling process. Finally, debenzylation of **3** was carried out under transfer hydrogenation conditions to give 3-arylpyrrolidines **5** in over 90% yields. Interestingly, *N*-benzylpyrrolidines **3** themselves exhibited significant affinity at dopamine receptors (K_i values for D_1 and D_2 receptors are several hundred μM levels). We have synthesized various *N*-substituted-3-arylpyrrolidine derivatives from the lead structure **5** (Scheme 3).



Scheme 3.

Thus, the coupling of pyrrolidine **5** with appropriate bromides in the presence of triethylamine at room temperature for 12 h (in the case of **7** and **8**) or at reflux temperature (for **6**) afforded the corresponding products in moderate to good yields after purification by column chromatography on silica gel (**6a**, 66%; **6b**, 46%; **6c**, 60%; **7a**, 41%; **7b**, 48%; **7c**, 52%; **8a**, 57%; **8b**, 53%; **8c**, 42%).[10] Among the three types of *N*-substituted derivatives **6-8**, *N*-[*N*-(saccharino)butyl]pyrrolidines **6** exhibited selective and strong affinity at 5-HT_{1A} receptor.

Binding affinity.

Some selected data on the binding affinity of the 3-arylpyrrolidines at several neurotransmitter receptors (5-HT_{1A}, 5-HT_{2A}, D_1, D_2, and α_2-adrenergic receptors) are listed in the Table 1.[11] The *in vitro* affinity was evaluated by standard radioligand binding assays.[12] Notably, arylpyrrolidines **6a-6c** exhibited strong affinity at 5-HT_{1A}, showing K_i values of nanomolar concentrations. 3-Phenyl-substituted derivative **6a** exhibited intermediate affinity at both 5-HT_{2A} and adrenergic α_2 receptors, weak affinity at D_2 receptor, but poor affinity at D_1 and muscarine receptors 1 and 2 (those K_i values toward muscarine receptors 1 and 2 are >700 nM and are not listed in the table). Similarly, other ligands showed weak or poor affinities toward dopamine and muscarine receptors. Of particular note is that 3-(4-fluorophenyl)-substituted analog **6c** exhibited good selectivity, showing weak affinity toward 5-HT_{2A}, adrenergic α_2, and D_2 receptors. This substituent effect on the receptor selectivity would be a valuable guideline for a further improvement of the selectivity. This selectivity is important for

clinical use because interactions with other receptors would cause undesirable side effects.[13]

Table 1. Receptor Binding Profile of Arylpyrrolidines **6-8** (K_i, *n*M)

	5-HT_{1A}	5-HT_{2A}	α2	D_1	D_2
6a	2.7	34	16	12,502	195
6b	2.6	232	56	1,567	327
6c	4.2	>367	334	6,668	263
7a	11.5	46	11	1,954	77
7b	30.4	184	12	1,622	185
8a	30.6	320	24	88,099	783
8b	15.3	46	44	37,581	334

A comparison of the *N*-substituents between **6-8** suggests that the *N*-substitutent containing saccharine moiety is better than that of indoline in terms of the affinity and selectivity toward 5-HT_{1A} receptor. The former moiety is the *N*-substituent of ipsapirone,[3] a well-known arylpiperazine ligand of 5-HT_{1A}.

A further evaluation of arylpyrrolidine **6a** in the following tests for rat indicated that it would be a potentially effective antianxiety and antidepressant agent: (a) corticosterone secretion test, (b) body temperature change test, (c) forced swimming test, (d) face-to-face test, and (e) isolation-induced aggregation test. Also, from a comparative pharmacokinetics study, arylpyrrolidine **6a** was found to have roughly twice bioavailability compared to buspirone,[14] a known antianxiety drug.

In summary, we have synthesized a series of 3-arylpyrrolidines, starting from 3-hydroxypyrrolidine using standard organocuprate chemistry. Among a variety of *N*-substituted derivatives thus synthesized from the arylpyrrolidines, arylpyrrolidine derivatives **6a-6c**, particularly **6c**, exhibited potent and selective affinity at 5-HT_{1A} receptor. A preliminary biological evaluation of compound **6a** suggested that they would be potentially effective antianxiety and antidepressant agents. A detailed biological evaluation for a variety of 3-arylpyrroline derivatives will be reported in due course.

References and Notes

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3. Hibert MF, Mir AK, Fozard JR: serotonin (5-HT) receptors. In: Sammes PG, Taylor JB, editors. Comprehensive Medicinal Chemistry, Vol. 3. Oxford: Pergamon Press, 1990:567-600.
4. Recently, *N*-Substituted-3-arylpyrrolidine derivatives having high affinity at 5-HT_{1A} receptor (for an

example, *N*-{2-[3-(2-naphthyl)-1-pyrrolidinyl]ethyl}-*N*-(2-pyridyl)cyclohexanecarboxamide: IC_{50}, 3 nM) have been reported as a patent (DE 19615232). We thank the referee who called our attention to this information. Other *N*-substituted-3-arylpyrrolidine derivatives with different pharmacological behavior have been reported from Abbott laboratories, see: (a) Zelle RE, Hancock AA, Buchner SA, Basha FZ, Tietje K, DeBernardis JF, Meyer MD. Bioorg. Med. Chem. Lett. 1994:4;1319-1322. (b) Basha FZ, DeBernardis JF. Pure & Appl. Chem. 1994:66;2201-2204. (c) Hancock AA, Buckner SA, Giardina WJ, Brune ME, Lee JY, Morse PA, Oheim KW, Stanisic DS, Warner RB, Kerkman DJ, DeBernardis JF. J. Pharmacol. Exp. Ther. 1995:272;1160-1169). Also, a Swedish group has reported different 3-arylpyrrolidine derivatives as potential DA receptor antagonists, see: Sonesson C, Wikström H, Smith MW, Svensson K, Carlsson A, Waters N. Bioorg. Med. Chem. Lett. 1997:7;231-246..

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7. Gmeiner P, Orecher F, Thomas C, Weber K. Tetrahedron Lett. 1995;36:381-382.
8. A representative procedure: To a suspension of CuBr-Me_2S complex (2.29 g, 11.16 mmol) in dry Et_2O (20 mL) under an argon atmosphere at 0 °C was added PhLi (3 molar equiv, 18.6 mL, 1.2 M in cyclohexane/Et_2O), and the resulting mixture was stirred for 1 h at the same temperature. To this cuprate solution at −78 °C was added dropwise a solution of 3-(methanesulfonyloxy)pyrrolidine **1b** in dry Et_2O through a cannula. The reaction temperature was raised to 0 °C and the mixture was stirred for 15 min before quenching with an aqueous ammonium hydroxide solution. After being extracted with Et_2O, the organic phase was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel (eluent: 10% ethyl acetate in hexanes) afforded the product **3a** in 78% yield (685 mg).
9. It was determined by converting the product to the known 3-phenylpyrrolidine and comparing its specific rotation with that of optically pure compound ($[\alpha]_D$ +22.7 (*c* 2.36, EtOH): Tseng CC, Terashima S, Yamada S. Chem. Pharm. Bull. 1977;25:166-170).
10. Spectroscopic data for representative compounds. **6a**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.05-8.06 (m 1H), 7.83-7.93 (m, 3H), 7.14-7.31 (m, 5H), 3.84 (t, 2H, J = 7.4 Hz), 3.37 (dt, 1H, J = 7.8, 17.4 Hz), 3.07 (t, 1H, J = 8.8 Hz), 2.83-2.90 (m, 1H), 2.48-2.70 (m, 4H), 2.30-2.36 (m, 1H), 1.85-2.00 (m, 3H), 1.62-1.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.4, 145.9, 138.1, 135.1, 134.7, 128.8, 127.7, 127.6, 126.5, 125.5, 121.3, 62.7, 56.1, 55.1, 43.8, 39.7, 33.6, 27.0, 26.5. **7a**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.16-7.33 (m 7H), 7.05 (t, 1H, J = 7.5 Hz), 6.87 (d, 1H, J = 7.7 Hz), 3.76 (t, 2H, J = 7.0 Hz), 3.54 (s, 2H), 3.32-3.38 (m, 1H), 3.09 (t, 1H, J = 8.7 Hz), 2.84-2.92 (m, 1H), 2.50-2.72 (m, 4H), 2.28-2.40 (m, 1H), 1.89-1.96 (m, 1H), 1.73-1.84 (m, 2H), 1.59-1.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.4, 145.5, 128.8, 128.2, 127.7, 126.6, 126.3, 125.1, 124.9, 122.6, 108.8, 62.5, 56.2, 55.0, 43.7, 40.1, 36.2, 33.6, 26.4, 25.8. **8a**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.17-7.51 (m, 9H), 3.65-3.75 (m, 4H), 3.32-3.41 (m, 3H), 3.02 (dd, 1H, J = 8.1, 9.0 Hz), 2.70-2.82 (m, 2H), 2.54 (dd, 1H, J = 7.5, 9.0 Hz), 2.29-2.41 (m, 1H), 1.85-1.96 (m, 1H), 1.67 (br s, 4H), 1.50 (br s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.8, 146.1, 140.1, 136.9, 130.1, 128.8, 128.5, 127.7, 127.4, 126.5, 125.8, 62.7, 60.6, 55.0, 49.2, 43.8, 43.5, 33.8, 26.8, 26.0, 25.0.
11. All the compounds tested were racemic. The binding study for enantiopure (*R*)-**6c** and (*S*)-**6c**, synthesized in

a different approach, indicated that the (*S*)-isomer was about twice potent than the (*R*)-isomer: Unpublished results.

12. Ligand binding assays were performed according to the standard protocols using [^{3}H]8-OH-DPAT for 5-HT_{1A} receptors of the rat hippocampus, [^{3}H]ketanserin for 5-HT_{2A} receptor of rat cerebrial cortex, [^{3}H]RX821002 for adrenergic α_2 receptor of rat cerebrial cortex, and [^{3}H]SCH23390 for dopaminergic D_1 and [^{3}H]raclopride for dopaminergic D_2 of rat striatum. Specific binding was measured by subtracting nonspecific binding out of total binding. Nonspecific binding was measured in the presence of specified concentrations of each non-labeled ligands under the same condition as that for measuring total binding.
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