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A Convenient Procedure for the Synthesis of Nonsymmetrical Bivalent Selective Serotonin Reuptake Inhibitors Using Polymer-Supported Reagents

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Abstract—A convenient synthesis of nonsymmetrical bivalent inhibitors of the serotonin transporter is described. The synthesis utilizes polymer-supported reagents that allow for rapid access to novel bivalent ligands without the need for isolation or purification of synthetic intermediates. © 2000 Elsevier Science Ltd. All rights reserved.

Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (Prozac)[1a] and paroxetine (Paxil),[1b] among others, have been developed for the treatment of depression and related psychological disorders (Fig. 1).[2a–h] We recently discovered an interesting aspect of the serotonin transporter (SERT) structure–activity relationships (SARs), namely that significant selectivity and potency can be achieved through use of a bivalent ligand approach.[3,4] The length of the linking chain could be used as a means to eliminate activity at the dopamine (DAT) and the norepinephrine transporters (NET). Our SAR studies thus far support the possible existence of dual binding sites at the SERT, where an enhancement of potency of greater than 8000-fold is achieved by bridging two neighboring recognition sites via a linking chain of five methylene units.[3] As such proximal binding sites at the SERT may differ in their topology, we sought a rapid means to synthesize a series of nonsymmetrical bivalent ligands to further explore the possibility to optimize the ligand potency and selectivity at the SERT. We envisioned a synthesis that utilizes polymer-supported reagents whereby a series of nonsymmetrical bivalent ligands can be rapidly and conveniently prepared in 5–100 mg quantities for complete in vitro and in vivo biological evaluation.

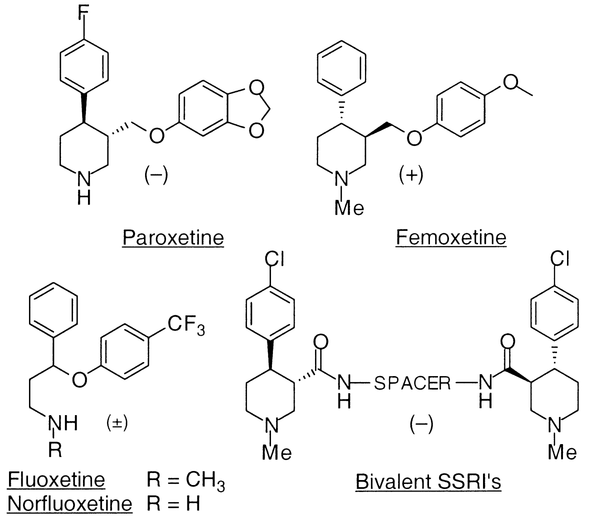

Figure 1.

Chemistry

Scheme 1 delineates the chemistry used to prepare the compounds in this series. Briefly, acid hydrolysis of (–)-methyl 4β-(4-chlorophenyl)-1-methylpiperidine-3α-carboxylate ((–)-**2**)[5] followed by the treatment of the acid intermediate with $(COCl)_2$ in CH_2Cl_2 gave the acid chloride **3** which was used without further purification in

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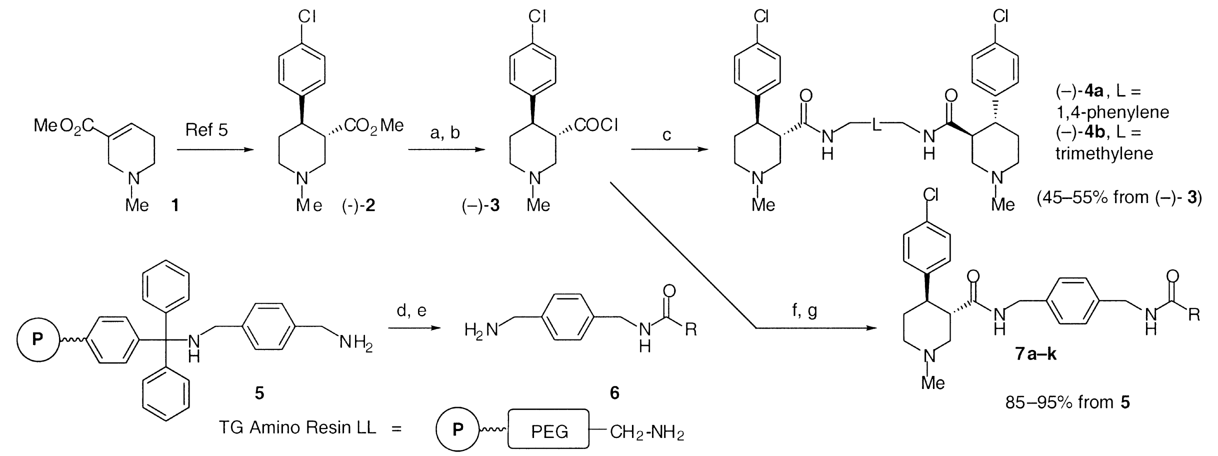

Scheme 1. Reagents and conditions: (a) HCl (10%); (b) $(COCl)_2$, CH_2Cl_2; (c) diamine spacer, TEA, CH_2Cl_2; (d) RC(O)Cl, TEA, CH_3CN; (e) TFA (5% in CH_2Cl_2); (f) **6**, TEA, CH_3CN; (g) TG amino resin.

the next step. In a parallel synthesis fashion, commercially available *p*-xylene diamine trityl resin **5** (Novabiochem) was reacted with the appropriate acid chloride in CH_3CN. The solvent was removed by filtration, and the resins were washed with CH_3CN. The tethered monosubstituted diamine was then released from the trityl resin support by treatment with TFA (5% in CH_2Cl_2). The solvent was removed in vacuo and the residue treated with TEA (4 molar equiv based on **5**) and acid chloride **3** (2 molar equiv based on **5**) in CH_3CN. NovaSyn® TG amino resin LL (Novabiochem, 2 molar equiv based on **5**) was added after agitation for 6 h to remove all of the unreacted acid chloride, and the mixture was filtered after an additional 6 h of mixing at 50 °C. Evaporation of the mother liquor gave the final compound. All of the compounds in this series were isolated as the free bases (Na_2CO_3 wash) and purified by chromatographic methods for biological evaluation purposes.[6]

All final compounds were tested for their ability to inhibit high affinity uptake of dopamine (DA), serotonin (5-HT), and norepinephrine (NE) into rat nerve endings (synaptosomes).[5] The uptake data are listed in Table 1.

In general, all compounds showed reasonably good affinity and selectivity for the SERT. In particular, compounds **4a** and **4b** exhibit remarkable potency and selectivity for the SERT as noted previously.[3] In fact, **4a** is one of the more potent SSRIs reported to date. However, none of the nonsymmetrical inhibitors (**7a–7j**) prepared in this series are as potent as the parent compounds **4a** and **4b**. This observation suggests that the two binding sites on the SERT complex may have similar affinity for the dimer head groups. Also, these data support the notion that the bivalent ligands bind to the SERT recognition sites in a manner that requires specific binding interactions, rather than some nonspecific interaction with a simple hydrophobic region located either in the surrounding membrane or in the SERT protein itself.

In conclusion, a general synthesis of a series of nonsymmetrical bivalent ligands is reported. The chemistry

Table 1. K_i values for selected bivalent inhibitors at dopamine, norepinephrine, and serotonin transporters

		[^{3}H]DA[a]	[^{3}H]NE[a]	[^{3}H]5-HT[a]	Selectivity ratio (K_is)	
Compound	R	Uptake K_i (nM)	Uptake K_i (nM)	Uptake K_i (nM)	DA/5-HT	NE/5-HT
Fluoxetine[b]	—	>2500	176±3.5	7.3±0.7	624	24
4a	—	2268±167	74±1.1	0.32±0.03	>7000	231
4b[c]	—	1960±200	399±6.7	1.2±0.1	1633	332
7a	Ph	[d]NT	NT	30±5.0	—	—
7b	3-Cl–Ph	>4000	1040±160	33±3.8	>121	32
7c	4-Cl–Ph	3710±210	1540±50	84±16	44	18
7d	2,4-Cl_2–Ph	NT	NT	139±64	—	—
7e	3-CF_3–Ph	>5000	508±147	35±0.22	>143	15
7f	4-CF_3–Ph	>4000	651±100	334±100	>12	1.9
7g	4-MeO–Ph	NT	NT	92±15	—	—
7h	4-Me–Ph	>7000	>1000	195±37	>36	>5
7i	CH_2CH_2Ph	>2000	>1000	67±12	>30	>15
7j	CH=CH(4-Cl–Ph)	>2000	>2000	69±0.23	>29	>29

[a] Data are mean±standard error of at least three experiments as described in ref 5b.
[b] See ref 5b.
[c] See ref 3.
[d] NT, not tested.

allows convenient and rapid access to a novel series of bivalent ligands without the need for the isolation or purification of the synthetic intermediates. Starting from trityl resin **5**, the synthesis can be completed in less than 48 h using as little as 15 mL of solvent per 100 mg of the resin. The present work thus broadens the scope of SAR to be used to better understand the structural motifs required to achieve high potency and selectivity at the SERT for the purposes of drug discovery, and is readily applicable to the synthesis of other bivalent ligands.

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6. Reagents and solvents were obtained from commercial suppliers and used as received. All the polymer-based reagents were purchased from Novabiochem Corp. All reactions were performed under an inert atmosphere of nitrogen. Final compounds described were purified by chromatography on silica gel, and were characterized by NMR and mass spectroscopy (sequential gas chromatography mass spectrometry measured in the EI mode at an ionization potential of 70 eV). Compounds **4a** and **4b** gave satisfactory C, H, N analyses.