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Multistep Solution-Phase Parallel Synthesis of Spiperone Analogues

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Abstract—A flexible, multistep parallel synthesis of spiperone analogues is described. A library of 4-substituted piperidines, assembled utilizing reductive amination and acylation protocols, was alkylated either homogeneously or heterogeneously, exploiting a product release only concept, to afford an oxa-series of spiperone analogues. Screening of the products at 5-HT_2 and D_2 receptors revealed 5-HT_{2A} antagonists with improved selectivity compared to spiperone and AMI-193. © 2000 Published by Elsevier Science Ltd.

The antipsychotic agent spiperone (Fig. 1), a potent mixed dopamine D_2 and serotonin antagonist, is a rare example of a 5-HT ligand binding with any selectivity at the 5-HT_{2A} subclass of serotonin receptors.[1] Surprisingly, little effort has been devoted to studying and optimizing this interesting feature of spiperone. Recently, Glennon et al.[2] investigated the influence of imidazolidinone substituents on affinity and selectivity at 5-HT_2 and D_2 receptors. Analogues with smaller substituents replacing the phenyl group, especially the methyl analogue, were found to possess lower affinity than spiperone itself, but higher selectivity. Introduction of substituents at the lactam nitrogen had little influence on the 5-HT_{2A} affinity, but reduced the 5-HT_{2A}/D_2 ratio, a trend also observed by others.[3] In an important earlier study,[4] Glennon et al. reported that improved 5-HT_{2A} selectivity (versus 5-HT_{2C} and D_2 receptors) resulted upon replacing the aminobutyrophenone portion of spiperone with an aryl ether functionality. The *p*-fluorophenoxy analogue (AMI-193; Fig. 1) was reported to have the highest selectivity.[4]

The current interest in selective 5-HT_{2A} antagonists[5] as potential antipsychotic agents prompted us to revisit the spiperone pharmacophore in a combinatorial context. In particular, we reasoned that oxa-analogues based on AMI-193 would constitute an interesting family of targets. In this communication, our synthetic strategy is exemplified by the solution-phase synthesis of a 240-membered (5×8×6) rehearsal library.

The preparation of the required series of 4-substituted piperidines is outlined in eqn (1) and Figure 2. Com-

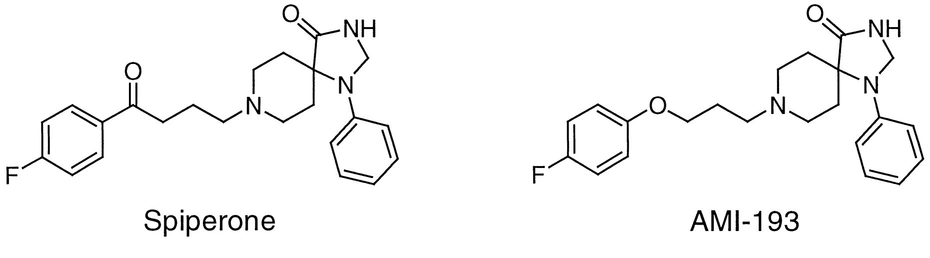

Figure 1.

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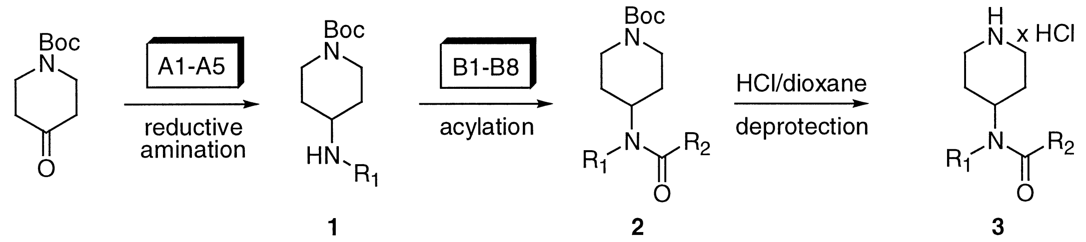
Equation 1.



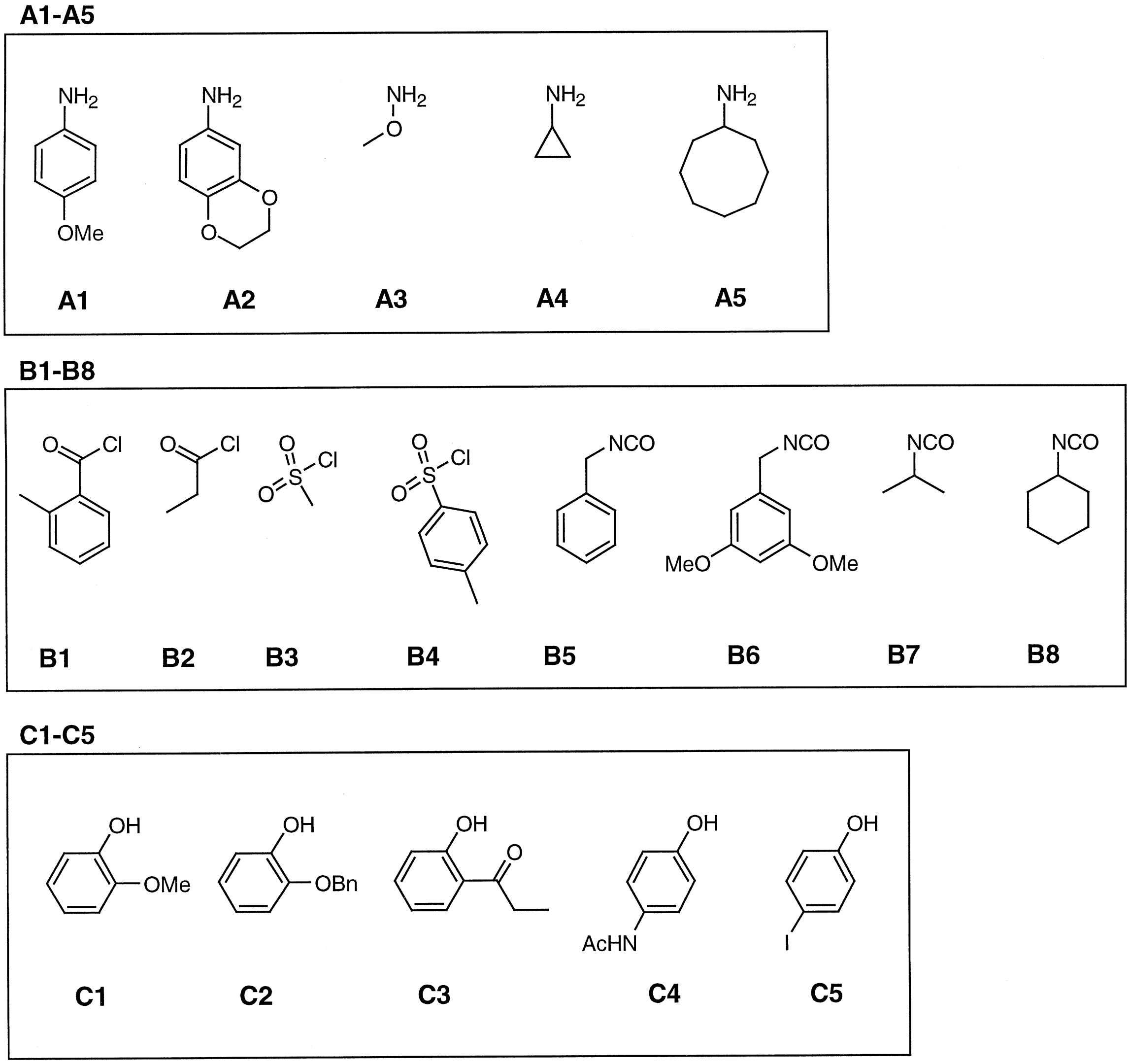


Figure 2. Building blocks.

mercially available Boc-protected piperidone was chosen as a convenient starting material enabling facile extractive purification of the intermediates as the synthesis progressed. Alternately, basic and neutral products were encountered, permitting simple and efficient liquid/liquid extraction for purification of the proceeding library. The 4-aminopiperidines **1** were synthesized via reductive amination[6] with an excess of the piperidone in order to ensure complete consumption of the amine (**A1**–**A5**). Extractive purification returned **1** with high purities (Table 1) and in yields of over 85% except for **1-A3**, which was obtained in 40% yield. Acylation of the amines **1** was performed with acid chlorides[7] (**B1**, **B2**), sulfonyl chlorides[7] (**B3**, **B4**), and isocyanates[8] (**B5**–**B8**), resulting in a library of Boc-protected piperidines **2**. The products were obtained in acceptable purities, provided that sequestration of excess isocyanates was undertaken in the latter cases (Table 1). Deprotection by treatment with 4 M HCl in dioxane for 2 h left building blocks **3** ready for further alkylation.

In general, the products derived from isocyanate acylation were of higher purity than the amides or sulfonamides (Table 1). In these latter series, a number of entries

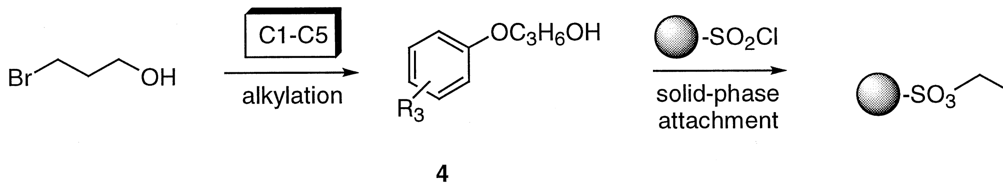
Table 1. Purities[a] for selected compounds

Compound	Purity (UV/MS)	Compound	Purity (UV/MS)	Compound	Purity (UV/MS)	Compound	Purity (UV/MS)
1-A1	100/97	**2-A1-B6**	100/89	**3-A1-B8**	93/93	**7-A4-B6-C1**	100/81
1-A2	100/97	**2-A1-B7**	100/92	**4-C1**	89/93	**7-A1-B7-C3**	97/83
1-A3	90/78	**2-A1-B8**	100/89	**4-C2**	66/79	**7-A1-B8-C2**	—/100
1-A4	95/99	**3-A1-B1**	65/78	**4-C3**	67/81	**8-A4-B1**	95/81[b]
1-A5	100/95	**3-A1-B2**	99/80	**4-C4**	97/84	**8-A4-B2**	100/82[b]
2-A1-B1	68/93	**3-A1-B3**	68/63	**4-C5**	96/—	**8-A4-B3**	100/73[b]
2-A1-B2	100/100	**3-A1-B4**	82/73	**7-A1-B5-C4**	100/88[b]	**8-A3-B5**	100/90[b]
2-A1-B3	77/61	**3-A1-B5**	89/92	**7-A1-B6-C4**	92/94[b]	**8-A3-B6**	100/80[b]
2-A1-B4	12/91	**3-A1-B6**	92/90	**7-A1-B7-C4**	88/89[b]	**8-A3-B7**	100/90[b]
2-A1-B5	100/81	**3-A1-B7**	100/98	**7-A1-B8-C4**	95/85[b]	**8-A3-B8**	100/92[b]

[a] Purities were measured on an HP1100 LC-MS using DAD/MSD electrospray detection. Eluent: 8 mM ammoniumacetate in MeCN/water. UV-data were measured at UV_{max}. Matrix characterization by NMR, performed on a quarter of the products, corroborated LC-MS results.

[b] Purity after ion-exchange chromatography on ISOLUTE SCX cartridges.

Equation 2.

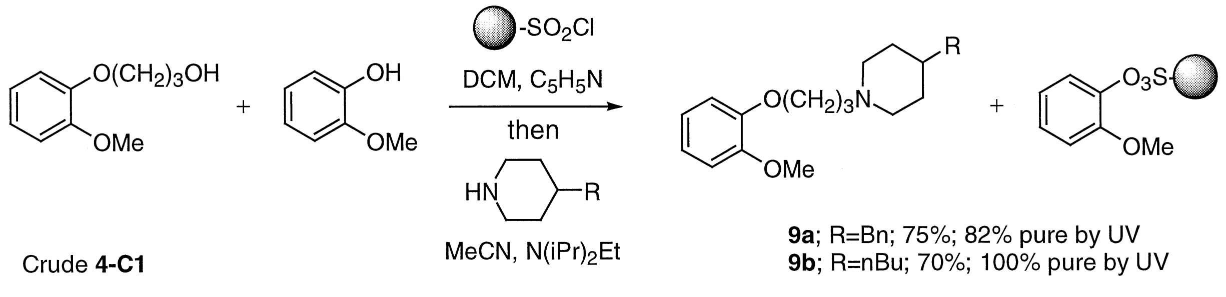


contained minor amounts of acylated 4-hydroxypiperidine, obviously arising from reduction of the ketone in the first step. Diacylated piperidines were also observed in some cases, the appearance of which was attributed to partial premature hydrolysis of the Boc-group.

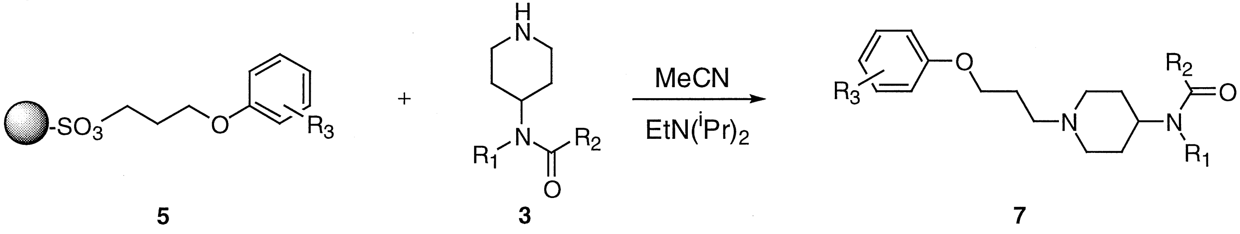
The 3-aryloxy-1-propanols **4** (eqn (2)) were synthesized in parallel by alkylation of an excess of the selected phenols (**C1**–**C5**).[10] Extraction with aqueous base was used to remove the bulk of excess phenol. However, by activating the crude alcohols **4** via attachment to solid-supported sulfonyl chloride,[11] residual phenols were efficiently scavenged, since only the primary sulfonates reacted under the nucleophilic conditions employed in the releasing step (illustrated for the synthesis of **9a**,**b** in eqn (3)). Alternatively, crude **4** could be passed through a short plug of silica gel to give products of high purity. The coupling to solid support was performed in CH_2Cl_2/pyridine 1:1 as reported.[12] For **4-C1** and **4-C3** the anchoring was confirmed by IR spectroscopy.

Before their use in parallel synthesis, the five solid-supported tosylates **5** were evaluated in a reaction with 4-butylpiperidine.[13] All five expected products were

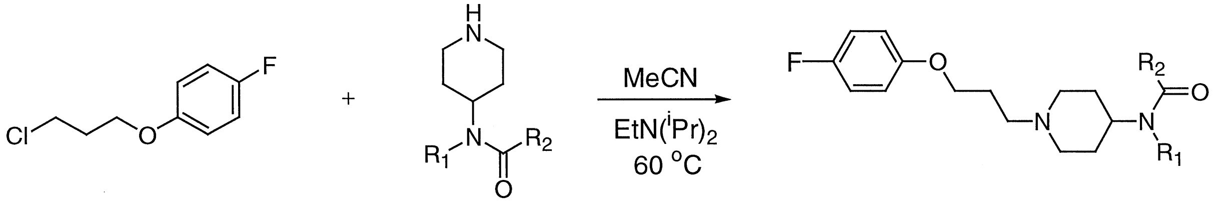
Equation 3.



Equation 4.



Equation 5.



6 **3** **8**

obtained in good yields (average 75%), and high purities (average 90%). Surprisingly, as we utilized the hydrochlorides **3** as nucleophiles towards **5** in the presence of *N*-ethyldiisopropylamine, the alkylation reaction failed. The major products isolated were the corresponding *N*-(aryloxypropyl)pyridinium salts,[14] presumably formed during activation of the alcohols on the solid support, and only released in the presence of chloride counter ions. In accordance with this assumption, when the piperidines **3** were alkylated as the free bases, the desired products **7** (eqn (4)) were obtained in high purities (Table 1). Good conversion was accomplished by heating **3** at 60 °C for 8–12 h with an excess of **5** in acetonitrile.

A procedure for alkylation in solution was also developed.[15] The piperidines **3** were readily alkylated with an excess of the commercially available **6** (eqn (5)), and the target compounds **8** were successfully purified by ion-exchange chromatography (Table 1).

The library of spiperone analogues **7** and **8** was assayed for antagonism and inverse agonism at the 5-HT$_{2A}$ receptor using R-SAT™ (Fig. 3).[16] R-SAT™ is a mammalian cell-based assay technology that provides a sensitive measure of receptor function. Cells are transiently transfected with vectors encoding the receptor target and a reporter enzyme gene, incubated with drug, and the reporter enzyme quantified after incubation. The degree of receptor activation correlates with the quantity of reporter enzyme produced by cells. In the case of measuring receptor inverse agonist activity, receptor constitutive activity is elevated and the ability of compounds to reverse the constitutive activation is measured.

Gratifyingly, a number of analogues turned out to possess activity as 5-HT$_{2A}$ inverse agonists and antagonists. Even though the new compounds disclosed herein were generally less potent (2–3 orders of magnitude) than the reference AMI-193 (pIC$_{50}$ = 9.5 as inverse agonist), preliminary profiling at the 5-HT$_{2A}$, 5-HT$_{2B}$, 5-HT$_{2C}$, and D$_2$ receptors using R-SAT™ revealed analogues with improved and potentially explorable selectivities.

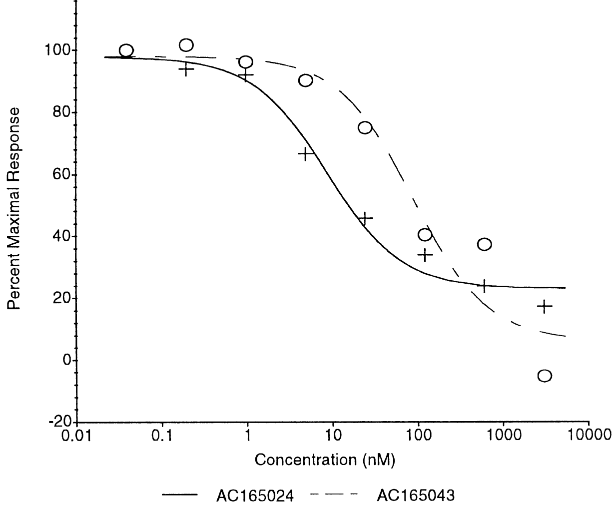
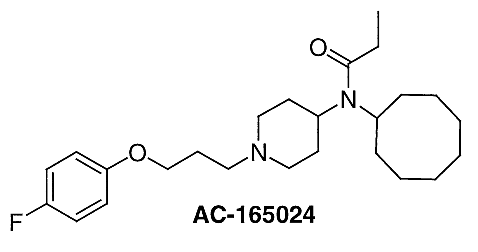


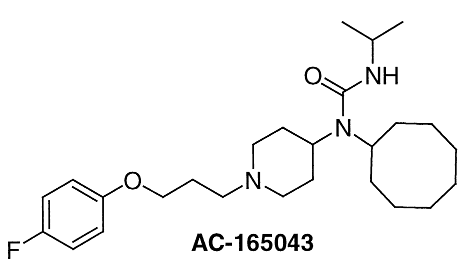
Figure 3. 5-HT$_{2A}$ Inverse Agonism.

For example, the cyclooctyl derivative **8-A5-B2,** AC-165024, displayed reasonable potency as an inverse agonist with an average pIC$_{50}$ of 7.9 from three determinations at the 5-HT$_{2A}$ receptor, and yet did not have significant inverse agonist activity at the 5-HT$_{2B}$ or 5-HT$_{2C}$ receptors up to 3000 nM. This compound also lacked D$_2$ R-SAT™ antagonist activity when tested up to a high dose of 3000 nM. In antagonist testing at the 5-HT$_{2A}$ receptor, using 5-HT as the agonist, potent and efficacious antagonism of 5-HT$_{2A}$ activity was observed, with a K_i of 20 nM. AC-165024 lacked antagonist activity against the muscarinic m1 and histamine H1 receptors and lacked agonist activity at the 5-HT$_{1A}$ receptor. The analogue AC-165043 also displayed strong repression of 5-HT$_{2A}$ activity (pIC$_{50}$ = 7.1 as inverse agonist) without significant effects at the other receptors tested.

In conclusion, we have developed a practical, multistep, solution-phase protocol for parallel synthesis of spiperone analogues. A combination of homogeneous and heterogeneous extractive purification, reagent seques-



AC-165024



AC-165043

tration and polymer-anchored reagents was employed in order to secure adequate product purities. Preliminary in vitro pharmacological characterization of a 240-membered rehearsal library revealed new compounds with greatly improved selectivity for the 5-HT$_{2A}$ receptor compared to spiperone and AMI-193.

Acknowledgements

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5. For a recent review, see: Meltzer, H. Y. *Neuropsychopharmacology* **1999**, *21*, S106.
6. Reductive amination: *tert*-Butyl-4-oxo-1-piperidinecarboxylate (10 mmol) was dissolved in MeOH (5 mL). The amine (5 mmol) in MeOH (3 mL) was added, followed by AcOH in MeOH (1 M, 6.7 mL) and $NaCNBH_3$ in MeOH (0.3 M, 22 mL). The mixture was stirred at rt. After 48 h, water (2 mL) was added, and the mixture was concentrated and redissolved in ether. The organic solution was extracted with HCl (0.1 N, 3–4 times). The combined aqueous layers were treated with NaOH (0.2 N) until pH >8, then extracted with ether (2×10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give the amines **1**.
7. Acylation with acid chlorides and sulfonyl chlorides: The amine **1** (approx. 0.45 mmol) was dissolved in dry CH_2Cl_2 (1 mL). *N*-Ethyldiisopropylamine (3.3 equiv) and the acid chloride (2.2 equiv) were added. The mixture was stirred at rt. After 20 h, the mixture was diluted with ether (20 mL), sequentially washed with water (20 mL), NaOH (1 N, 2×20 mL), HCl (0.1 M, 20 mL), dried (Na_2SO_4) and concentrated to give the products **2**.
8. Acylation with isocyanates: The amine **1** (approx. 0.45 mmol) was dissolved in dry CH_2Cl_2 (1 mL). The isocyanate (2 equiv) was added, and the mixture was stirred at rt. After 20 h, *N,N*-dimethylaminoethylamine (5 equiv)[9] was added, and the mixture was stirred for another 20 h. Ether (20 mL) was added, and the mixture was washed with HCl (0.1 N, 5×10 mL), water (1×10 mL), dried ($MgSO_4$) and concentrated to give the products **2**.
9. Siegel, M. G.; Hahn, P. J.; Dressman, B. A.; Fritz, J. E.; Grunwell, J. R.; Kaldor, S. W. *Tetrahedron Lett.* **1997**, *38*, 3357.
10. Synthesis of **4**: The phenol (10 mmol) was dissolved in KOH/EtOH (1.2 M, 10 mL) and stirred at rt. After 1 h, 3-bromo-1-propanol (0.9 equiv) was added. The mixture was stirred at 50 °C. After 16 h, the mixture was cooled to rt, concentrated, and redissolved in EtOAc (20 mL), washed with NaOH (2 N, 4×10 mL), dried ($MgSO_4$) and concentrated to give the alcohol **4**.
11. The polystyrene sulfonyl chloride was purchased from Argonaut Technologies.
12. Argonaut Technologies Catalogue '*Resins and Reagents*', 2000; p. 71. For a similar procedure, see: Rueter, J. K.; Nortey, S. O.; Baxter, E. W.; Leo, G. C.; Reitz, A. B. *Tetrahedron Lett.* **1998**, *39*, 975.
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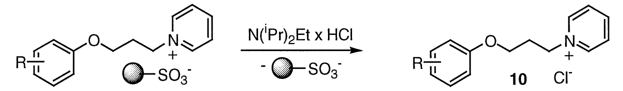
14. Pyridinium analogues **10** were released from the solid support in the presence of chloride. A confirmatory experiment employing the hydrochloride of Hünigs base as a chloride source gave the same result. **10** could be removed by ion-exchange chromatography.



15. Alkylation in solution: The amine **3** (approx. 0.45 mmol) was dissolved in MeCN (2 mL). *N*-Ethyldiisopropylamine (10 equiv) and 1-(3-chloropropoxy)-4-fluorobenzene (3–5 equiv) were added. The mixture was stirred at 60 °C. After 19 h, the mixture was concentrated and purified on ISOLUTE SCX to give the product **8**.
16. Brann, M. R. US Patent 5,707,798, 1998; *Chem. Abstr.* **1998**, *128*, 111548.