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Solid-Phase Synthesis of 2,3-Disubstituted Indoles: Discovery of a Novel, High-Affinity, Selective h5-HT_{2A} Antagonist

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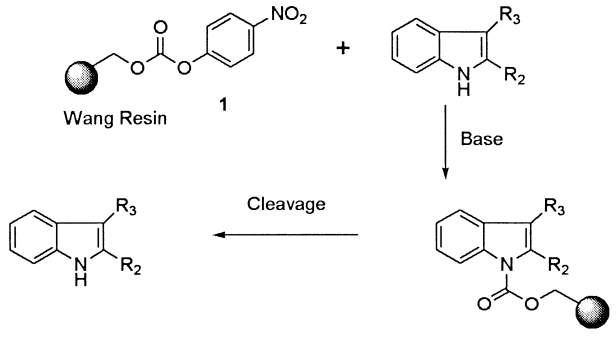
Abstract—The application of a novel solid-phase synthesis of 2,3-disubstituted indoles utilizing a carbamate indole linker is described resulting in the identification of the novel, high-affinity, selective h5-HT_{2A} antagonist **19**.

The last decade has witnessed an explosion of interest in the solid-phase synthesis of small organic molecules as a tool for medicinal chemists interested in accelerating the drug discovery process through combinatorial chemistry and automated high-speed parallel synthesis. Much of this work has focused upon elaboration of scaffolds of pharmaceutical relevance.[1] Indoles probably represent one of the most important of all structural classes in drug discovery—high-affinity indole ligands have been identified for a variety of G-protein coupled receptors and a large number of drugs are indole based. Several reports have appeared describing solid-phase synthetic approaches to indoles,[2] and we recently described some of our studies in this area.[3] We now report an extension of these studies involving a new linker for the indole N-H which we have successfully used for synthesizing parallel arrays of tryptamine derivatives and which lead to the identification of the 2-arylindole **19** as a high-affinity selective antagonist for the h5-HT_{2A} receptor.

During the course of our work, we wished to develop new methods for linking indoles to the solid phase in order to allow us to rapidly explore structure–activity relationships around indole leads. We have already reported the use of a THP-linker for indoles which was utilized in a Pd(0)-mediated synthesis of 2,3-disubstituted indoles.[3] We now report the use of an alternative indole carbamate linker which has proven to be extremely useful for immobilizing indole cores to resin, allowing further functionalization prior to cleavage. The synthetic strategy is highlighted in Scheme 1, whereby the indole core would be deprotonated and allowed to react with the readily available *p*-nitrophenylcarbonate derivative of Wang resin (**1**). Further functionalization should then be possible prior to cleavage of the Wang-carbamate linker.



Scheme 1.

The chemistry was evaluated through the synthesis of an array of 3-(3-aminopropyl)indole derivatives **7** as shown in Scheme 2.[4,5] It was found that pre-mixing the indole **2** (1.10 equiv) with the resin **1**, azeotroping with toluene, resuspending in toluene and treating with potassium bis(trimethylsilyl)amide (1.05 equiv) at −78 °C resulted in clean conversion to the resin-bound indole **3**.[6] Removal of the silyl protecting group was cleanly effected with HF–pyridine in THF to give the alcohol **4**. Activation of the alcohol and introduction of the amino substituent proved to be somewhat problematic. For example, the corresponding mesylate or tosylate was found to be relatively unreactive towards nucleophilic displacement by amines and required extensive heating for amination to occur. Under these conditions, the indole was displaced from the resin by nucleophilic attack of the amine on the carbamate

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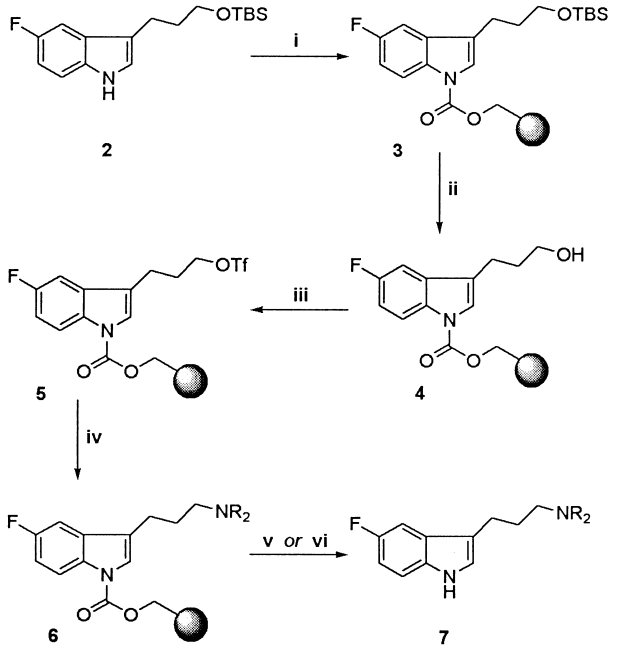
linker. However, the alcohol **4** was readily and cleanly converted to the more reactive triflate **5**, which was itself smoothly converted to the amino derivative **6** at ambient temperature. Cleavage of the resin under the TFA conditions usually associated with Wang resin were problematic, presumably due to reaction of the generated carbonium ion with the indole nucleus. However, the above observation that the indole could be cleaved from the resin by nucleophilic displacement with amines at elevated temperatures led to the successful use of 5% pyrrolidine in DMF at 90 °C as a means of cleavage, with evaporation leading to essentially pure products in many cases. An alternative hydrolytic cleavage by heating in acetic acid at 110 °C was also successfully employed, and in this case pure products were generally obtained by lyophilization of the resulting cleavage solution.[7] With both cleavage methods, compounds could often be purified in parallel if needed by use of SCX ion exchange chromatography[8] to give analytically pure material.

The scope and efficiency of the chemistry is illustrated in Table 1. For primary amines HNR_2, variable amounts of the indole dimer resulting from cross-linking of the mono-alkylated amine **6** with a neighbouring resin-bound triflate were observed. This was particularly noticeable with relatively unreactive amines such as aniline. This was not problematic with secondary amines, and uniformly high yields of these were obtained with a wide range of amines.

Having established the chemistry for introduction of 3-(aminoalkyl)indole substituents on solid phase, we wished to extend this chemistry in order to allow the introduction of substituents into the indole 2-position.

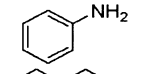
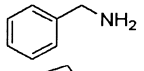
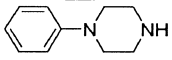


Scheme 2. Reagents: (i) **1**, KHMDS, toluene, −78 → 20 °C, 30 min; (ii) HF•py, THF, 20 °C, 30 min; (iii) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 20 °C, 2×30 min; (iv) HNR_2 (4 equiv), CH_2Cl_2, 20 °C, 1 h; (v) 5% pyrrolidine, DMF, 90 °C, 4 h; (vi) AcOH, 110 °C, 4 h.

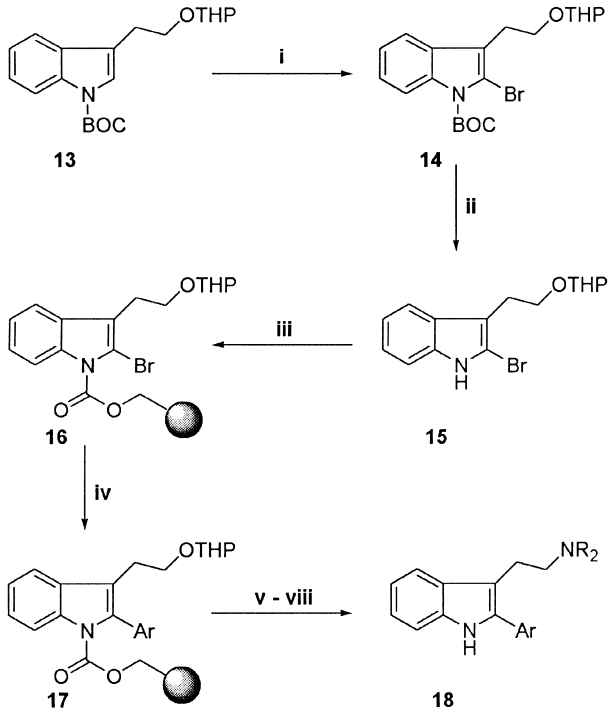
To this end, we decided to explore the solid-phase synthesis of 2-aryltryptamines **18** according to Scheme 3.

The tryptophol derivative **13** was cleanly brominated in the indole 2-position by lithiation with lithium 2,2,6,6-tetramethylpiperidide[9] followed by treatment with $BrCF_2CF_2Br$ to give **14**. Removal of the *tert*-butyloxycarbonyl group was effectively carried out using sodium methoxide to give the relatively unstable free 2-bromoindole **15**. This could be loaded onto the *p*-nitrophenylcarbonate derivative of Wang resin (**1**) as previously described to give the resin-bound 2-bromoindole **16**.

Table 1. Yields of products **7** with a range of amines HNR_2, together with yields of dimer

Example	Amine HNR_2	Yield **7**[a] (%)	Yield dimer[a] (%)
8		51	35
9		75	15
10		86	0
11		91	0
12		91	0

[a]Isolated yield based upon initial loading of *p*-nitrophenylcarbonate resin **1**, utilizing 5% pyrrolidine in DMF cleavage at 90 °C for 4 h.

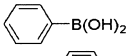
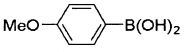
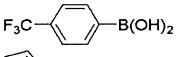
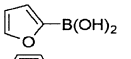
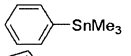
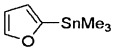


Scheme 3. Reagents: (i) LiTMP (2 equiv), THF, −78 °C *then* $BrCF_2CF_2Br$ (2 equiv); (ii) NaOMe, MeOH, 20 °C; (iii) **1**, KHMDS, toluene, −78 → 20 °C, 30 min; (iv) Ar-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, THF–H_2O, 100 °C, 16 h; *or* Ar-$SnMe_3$, $Pd(PPh_3)_4$, toluene, 105 °C, 16 h; (v) PPTS, 10% EtOH–DCE; (vi) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 20 °C, 30 min; (vii) HNR_2 (4 equiv), CH_2Cl_2, 20 °C, 1 h; (viii) AcOH, 110 °C, 4 h.

Considerable effort was spent investigating the introduction of the 2-aryl substituent (**16**→**17**). Suzuki-type reactions[10,11] were examined utilizing the Pd(0)-mediated coupling of arylboronic acids with the 2-bromoindole **16**. A number of reaction condition variants were examined, but the standard $Pd(PPh_3)_4/Na_2CO_3$/aqueous THF conditions proved to be amongst the best. Double couplings were required to push the reaction to completion, and under these conditions some hydrolysis of the indole–resin linkage was observed. This resulted in somewhat reduced overall yields of the final products **18**, although they were generally obtained with good purity.

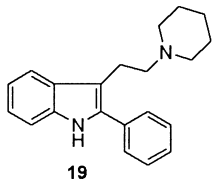
The corresponding Stille coupling with arylstannanes[10,12] proved to be a better reaction, often proceeding to completion with a single coupling reaction and not suffering the partial resin linker hydrolysis observed under the Suzuki reaction conditions. This reaction is, however, hampered by the lack of commercially available arylstannanes which generally had to be prepared via reaction of aryl Grignards with Me_3SnCl.[13]

Table 2. Comparison of Suzuki and Stille couplings on solid-phase synthesis of 2-aryltryptamine derivatives (HNR_2 = piperidine)

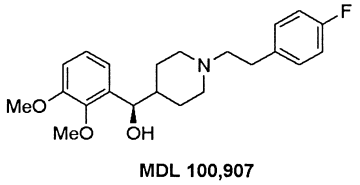
Reagent	Number of couplings	Purity[a] (%)	Yield[b] (%)
	2	92	45
	2	94	47
	2	89	44
	2	84	35
	1	94	65
	1	89	61

[a]HPLC purity of crude product produced by AcOH cleavage (230 nm).
[b]Isolated yield of purified product based upon initial loading of *p*-nitrophenylcarbonate resin **1**.

Table 3.



19



MDL 100,907

Compound	K_i (nM) h5-HT_{2A}[a]	hD_2[b]
19	2.7	900
MDL 100,907	0.3	1300

[a]Displacement of [^{3}H]-ketanserin from CHO cells stably expressing h5-HT_{2A} receptors.[15]
[b]Displacement of [^{3}H]-spiperone from CHO cells stably expressing hD_2 receptors.[17]

Removal of the THP protecting group from the 2-arylindoles **17** was readily accomplished with PPTS, and the resulting resin-bound 2-aryltryptophols were converted through to the desired 2-aryltryptamines **18** without incident using the previously described chemistry. An indication of the overall relative efficiencies of the Suzuki and Stille coupling routes is given in Table 2.

With efficient solid-phase chemistry now available for synthesizing arrays of 2-aryltryptamine derivatives, a number of such libraries were synthesized and screened in various assays within Merck. One such assay was against the cloned human 5-HT_{2A} receptor with the cloned human D_2 receptor being used as a counter-screen, looking for antagonists showing selectivity for 5-HT_{2A} over D_2 for the possible development of an atypical neuroleptic. This revealed that compound **19** is a high-affinity antagonist[14–16] at the h5-HT_{2A} receptor with good selectivity over hD_2 activity (Table 3), comparable to the selective h5-HT_{2A} antagonist **MDL 100,907** reported to be in phase III clinical trials for chronic schizophrenia.[18] The development of the series based upon **19** as part of a selective 5-HT_{2A} antagonist medicinal chemistry program will be described in subsequent communications.

Acknowledgements

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References and Notes

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4. Step **i** was carried out in a round bottom flask; step **ii** was carried out in a PTFE flask; steps **iii**–**vii** were carried out using an Advanced Chemtech ACT 496 solid-phase synthesis robot.
5. Solid-phase reactions were monitored by diffuse reflectance FT-IR spectroscopy.
6. The resin **1** (2.97 g, 0.59 mmol/g) and indole **2** (590 mg, 1.92 mmol) were mixed in a 100 mL round bottom flask and azeotroped with toluene (10 mL) on a rotary evaporator. Failure to do this may result in hydrolysis during the next step. Toluene (20 mL) was added, and the flask cooled to −78 °C. Potassium bis(trimethylsilyl)amide (3.70 mL of a 0.5 M solution in toluene) was added dropwise, and the reaction was then allowed to warm to room temperature over 30 min. The resin was filtered washing successively with toluene, CH_2Cl_2,

MeOH and Et_2O and dried to give 3.27 g of resin **3** (0.52 mmol/g). IR indicated complete conversion of **1** to **3** (C=O signal). The resin was treated with Ac_2O:pyridine:CH_2Cl_2 (1:3:5) for 30 min in order to cap any Wang resin resulting from hydrolysis of **1**.
7. The pyrrolidine cleavage method leaves small amounts of bis-pyrrolidine urea as an impurity in the cleaved products. The AcOH cleavage method acetylates unprotected alcohols, but otherwise is generally clean.
8. The sample was loaded in MeOH onto a Varian SCX benzenesulfonic acid ion exchange solid-phase extraction column, washed with MeOH, and the compound then eluted off with 2 M NH_3 in MeOH.
9. LiTMP was found to be much more effective than LDA at lithiation of the indole 2-position.
10. Reactions were carried out in a Quest 210 solid-phase reactor under a N_2 atmosphere.
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14. In h5-HT_{2A} transfected CHO cells, compound **19** alone at 1 μM had no effect but antagonized the 5-HT mediated accumulation of inositol phosphates.
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