Solid Phase Synthesis of 7-Hydroxy-3,10-dihydro-1*H*-[1,4]diazepino[5,6-*b*]indol-2-ones

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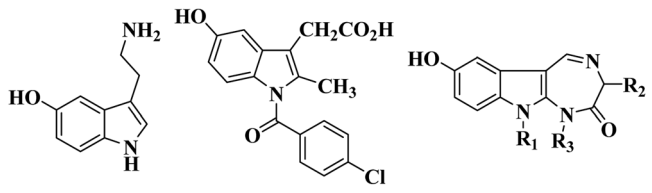
Indoles probably represent the most important of all structural classes in drug discovery.[1] The indole nucleus is a fundamental constituent of a number of natural and synthetic products with biological activity. Actually there are so many compounds containing this ring that it is nearly impossible to catalog their complete range of biological activity. This basic skeleton for example presents itself in the neurotransmitter Serotonin [**1**, 5-hydroxytryptamine, (5-HT)], which plays an important role in a variety of processes through the activation of 5-HT receptors.[2] Other indoles are present in drugs with a remarkable range of activities as demonstrated by the non-steroidal anti-inflammatory agent Indomethacin **2**,[3] the peptidal mimetic somatostatin agonist,[4] selective dopamine D4 receptor agonist cyanoindole derivatives[5] and potent and selective factor Xa inhibitors,[6] to name a few. Therefore, many reports, have been described in the solution-phase synthesis of heterocyclic fused indole derivatives.[7] However, the solid-phase synthesis of heterocyclic fused indoles has been scarcely reported in the research field of drug-like library construction, composed with their simple aromatic substituted derivatives.

Thus, we were interested in constructing heterocyclic fused indole libraries on solid-phase to find novel hit compounds toward multiple biological targets. Especially, we speculated that indole derivatives bearing 7-membered diazepine ring might serve for this purpose. Herein, we would like to report our results of an efficient procedure for the synthesis of 7-hydroxy-3,10-dihydro-1*H*-[1,4]diazepino-[5,6-*b*]indol-2-one (Indole- diazepine) derivatives **3** on solid-phase.

The reaction sequence is illustrated in Scheme 1. We selected resin-bound *N*1-substituted-2-amino-5-hydroxy-1*H*-indole-3-carbaldehyde **8** as the key intermediate for synthesis of these derivatives on solid-phase, since it can afford various diazepine fused indole compounds and easily release final products from the solid support under 10% trifluoroacetic acid (TFA) in dichloromethane (DCM) condition. The starting compound, 2-chloro-5-hydroxy-1*H*-indole-3-carbaldehyde **4**, was prepared *via* the Vilsmeier chloroformylation of 5-hydroxy-1,3-dihydroindol-2-one. The solid phase synthesis was initiated by treating a polystyrene-2-chlorotrityl chloride resin with **4** in DCM/DMF in the presence of *i*-Pr_2EtN to give the resin-bound indole **5**. The polystrene-2-chlorotrityl chloride resin was selected as a polymer support since the chloride in the trityl resin is suitable for the introduction of a 2-chloro-5-hydroxy-1*H*-indole-3-carbaldehyde **4** through the ether linker which would also serve as an efficient protecting group for the hydroxy group against the subsequent reactions. The loading was confirmed by the appearance of the aldehyde band at 1664 cm^{-1} by attenuated total reflection (ATR) FT-IR on single beads.

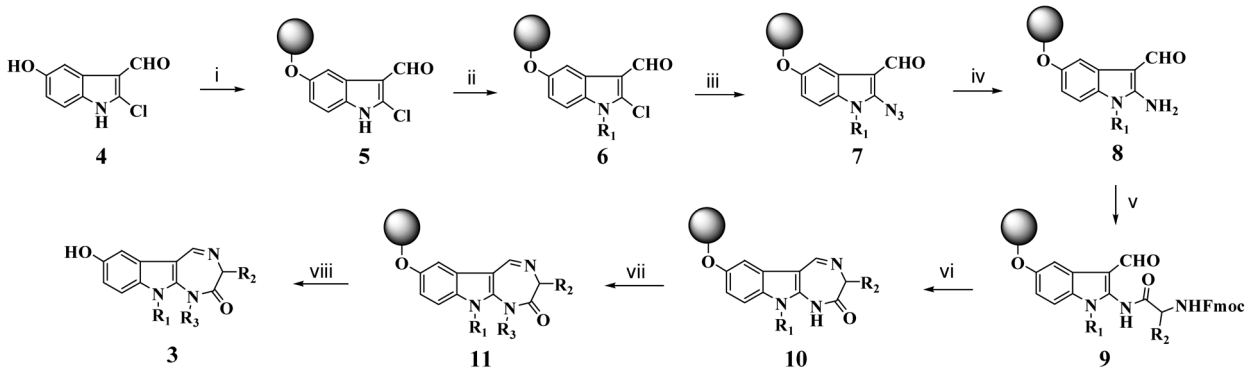


Serotonin 1 Indomethacin 2 3

Figure 1

For the initial variation on the *N*1-position of the indole resin **5**, various alkyl groups were introduced by a nucleophilic substitution reaction with alkyl halides[8] and potassium *t*-butoxide. To obtain the 2-amino indole resins **8** as the key intermediate, at first, chloride group of indole resin **6** was treated with NaN_3 in DMF/DMSO (10/1) in the presence of *n*-Bu_4NI to afford 2-azide indole resins **7**. The introduction of azide group was confirmed by the prominent azide band at 2133 cm^{-1}. And then, reduction of azide **7** with $NaBH_4$ in DMF/MeOH (5/1) gave the desired amine resins **8**.

With obtained amine resins **8**, we tried to react with the various amino acids for the second diversification. The amine resins **8** were acylated with Fmoc-amino acids[9] by using 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) in DCM to yield amide resins **9**. Deprotection of Fmoc group of resins **9** with 20% piperidine in DMF generated the desired products in very low yields. In contrast, deprotection and the subsequent cyclization of **9** were conducted *in situ* to provide the cyclic product resins **10** by using 50% morpholine in DCM. These reaction were confirmed by the disappearance of the Fmoc carbamate and aldehyde carbonyl bands at 1717 cm^{-1} and 1657 cm^{-1} in IR spectroscopy. Alkylations of **10** with alkyl halides[10] as the third diversification were achieved in DMF by using K_2CO_3



Scheme 1. Reagents and conditions: (i) polystyrene-2-chlorotrityl chloride resin, DIEA, DCM/DMF, rt, 24 h; (ii) alkyl halides, KI, *t*-BuOK, DMF, 50 °C, 24 h; (iii) NaN_3, *n*-Bu_4NI, DMF/DMSO (10/1), rt, 16 h; (iv) $NaBH_4$, DMF/MeOH (5/1), rt, 4 h; (v) Fmoc-amino acids, EEDQ, DCM, rt, 24 h; (vi) 50% morpholine/DCM, rt, 24 h; (vii) alkyl halides, KI, K_2CO_3, rt, 24 h; (viii) 10% TFA/DCM, rt, 1 h.

Table 1. Representative 7-hydroxy-3,10-dihydro-1*H*-[1,4]diazepino-[5,6-*b*]indol-2-one **3**

Product	R_1	R_2 (amino acids)	R_3	Yield (%)[a]	Purity (%)[b]
3abb	Me	Ala	benzyl	20	91
3abc	Me	Ala	CH_2CO_2Et	15	90
3acc	Me	Ile	CH_2CO_2Et	17	90
3aab	Me	Gly	benzyl	12	88
3adc	Me	Phe	CH_2CO_2Et	18	91
3bca	benzyl	Ile	Me	17	90
3bcc	benzyl	Ile	CH_2CO_2Et	15	90
3bda	benzyl	Phe	Me	20	90
3bdc	benzyl	Phe	CH_2CO_2Et	16	91
3cbb	4-chlorobenzyl	Ala	benzyl	19	95
3cca	4-chlorobenzyl	Ile	Me	21	94
3cea	4-chlorobenzyl	Tyr[c]	Me	18	93
3cec	4-chlorobenzyl	Tyr[c]	CH_2CO_2Et	17	92
3cda	4-chlorobenzyl	Phe	Me	21	91
3dba	4-methoxybenzyl	Ala	Me	15	85
3dcc	4-methoxybenzyl	Ile	CH_2CO_2Et	17	83

[a]Isolated yields after column chromatography (eight-step overall yield). [b]Determined on the basis of LC/MS spectroscopy. [c]Protected OH group with Boc.

as a base. Treatment of resins **11** with 10% TFA in DCM resulted in a very efficient cleavage from solid-support to furnish 60 individual derivatives of 7-hydroxy-3,10-dihydro-1H-[1,4]diazepino[5,6-*b*]indol-2-one **3**.

The yields of 12%-21% for the eight-step processes were determined from the mass balance of pure material after column chromatography. ^{1}H NMR and MS spectra of all the products were recorded to confirm the structures.[11]

In conclusion, a solid-phase strategy has been developed for the synthesis of 7-hydroxy-3,10-dihydro-1*H*-[1,4]diazepino[5,6-*b*]indol-2-ones **3**, using N1-substituted-2-amino-5-hydroxy-1*H*-indole-3-carbaldehyde **8** as a key intermediate. The polystrene-2-chlorotrityl chloride resin was suitable for the introduction of a 2-chloro-5-hydroxy-1*H*-indole-3-carbaldehyde **4** and the subsequent reactions to obtain the desired derivatives **3**. The construction of a large library of 7-hydroxy-3,10-dihydro-1*H*-[1,4]diazepino[5,6-*b*]indol-2-one derivatives with this methodology and biological evaluation of the library against a number of therapeutically relevant targets are in progress.

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8. Alkyl halides applied used were methyl iodide (**a**), benzyl bromide (**b**), 4-chlorobenzyl bromide (**c**) and 4-methoxybenzyl chloride (**d**).
9. Fmoc-amino acids applied used were glycine (**a**), alanine (**b**), isoleucine (**c**), phenyl- alanine (**d**), tyrosine (**e**).
10. Alkyl halides applied used were methyl iodide (**a**), benzyl bromide (**b**), ethyl bromoacetate (**c**).
11. Representative spetral data: (7-Hydroxy-3,10-dimethyl-2-oxo-3,10-dihydro-2*H*-[1,4]diazepino[5,6-*b*]indol-1-yl)acetic acid ethyl ester (**3abc**, R_1 = methyl, R_2 = methyl, R_3 = ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.80 (s, 1H), 7.16 (d, 1H, J = 2.1 Hz), 6.97 (d, 1H, J = 8.7 Hz), 6.78 (dd, 1H, J = 6.6, 2.1 Hz), 4.77 (d, 1H, J = 17.7 Hz), 4.65 (d, 1H, J = 17.7 Hz), 4.27 (q, 2H, J = 7.2 Hz), 4.11 (q, 1H, J = 6.9 Hz), 3.64 (s, 3H), 1.58 (d, 3H, J = 6.9 Hz), 1.32 (t, 3H, J = 7.2 Hz); LC/MS (*m/z*): 329.