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Solid-phase synthesis of substituted 3-amino-3′-carboxy-tetrahydrocarbazoles

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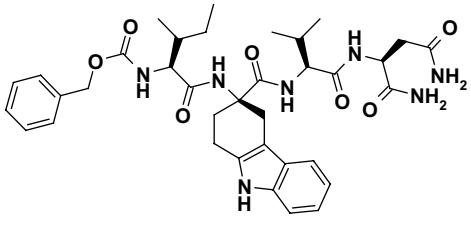
Abstract—Two related solid-phase synthesis routes have been developed allowing the synthesis of 3-amino-3′-carboxy substituted tetrahydrocarbazole derivatives. Diversity can be introduced at the amino and carboxy functionalities and at the nitrogen and the aromatic ring of the tetrahydrocarbazole moiety. Both routes rely on Fmoc-protected 1-amino-4-oxocyclohexanone carboxylic acid as central core element. Derivatization of the carboxy function is achieved with amines, derivatization of the amino functionality is possible by reaction with alkyl halides, isocyanates, activated alcohols, sulfonic acid chlorides or carboxylic acids. The tetrahydrocarbazole scaffold is generated by Fischer indole cyclization with phenyl hydrazine derivatives, thereby introducing diversity in the aromatic moiety. N-Alkylation at the indole nitrogen with alkyl halides delivers N-substituted derivatives.

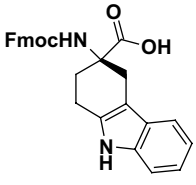
A screening campaign on GPCR antagonists within one of our GPCR projects revealed compound **1** as micromolar hit for the respective receptor. In order to exploit the tetrahydrocarbazole scaffold as valuable input structure for our GPCR-targeted library, it was decided to develop a solid-phase synthesis for the rapid generation of highly diverse libraries based on that core element. The initial solid-phase approach focused on the variation of the N- and C-terminus in 3/3′ position of the tetrahydrocarbazole scaffold and utilized preformed Fmoc-protected tetrahydrocarbazole amino acid **2**.

This building block was synthesized according to Britten and Lockwood.[1] Starting from 4,4-ethylendioxycyclohexanone, Bucherer–Strecker conditions for amino acid synthesis gave 1-amino-4,4-ethylendioxycyclohexane carboxylic acid, which under acid-catalyzed conditions of Fischer indolization undergoes hydrolysis and cyclization to the tetrahydrocarbazole. Fmoc-protection according to Ten Kortenaar[2] and subsequent separation of enantiomers by chiral HPLC yields the required building block.

This synthesis route, however, does not allow to introduce diversity elements in the aromatic ring of the tetrahydrocarbazole scaffold. For more flexibility, it was therefore decided to develop a solid-phase synthesis with on-resin Fischer indole cyclization. The required building block **3** could easily be obtained from the ketal-protected amino acid intermediate of the previous route by



1



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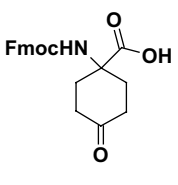

3

Keywords: Tetrahydrocarbazole; Solid phase; Fischer indolization.
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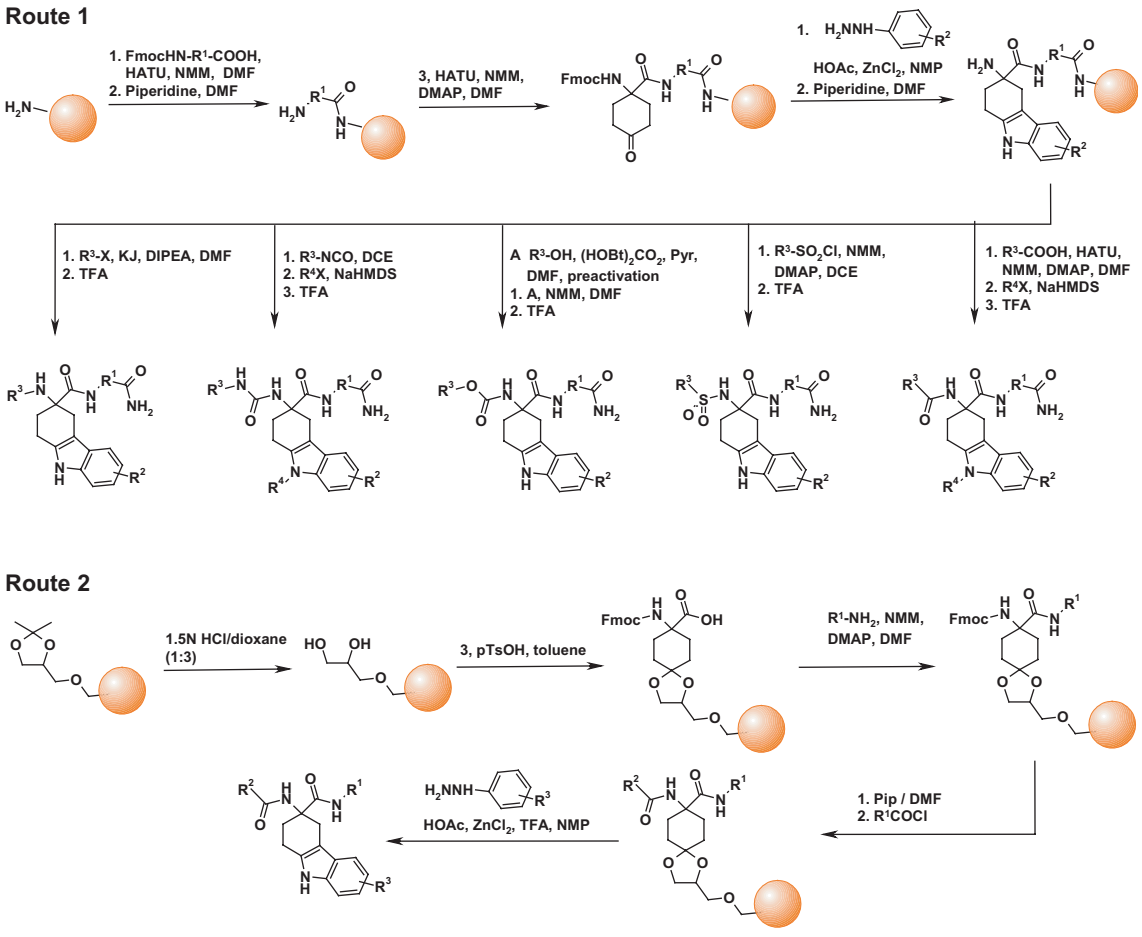
Fmoc protection of the amino functionality and acid-catalyzed hydrolysis of the ketal. Since results of biological assays had shown that C-terminal carboxamides are advantageous for activity, Rink amide resin was chosen as solid support and the envisaged synthesis route was designed to allow the introduction of all four diversity elements on the solid phase.

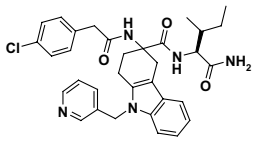
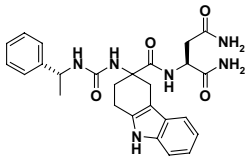
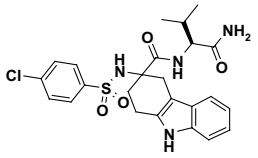
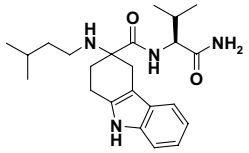
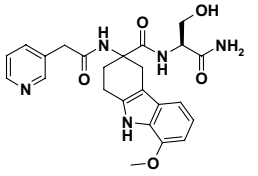
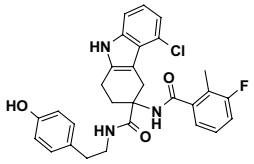
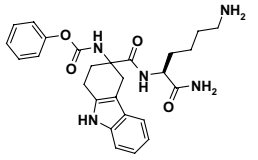
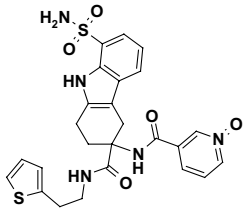
The synthesis starts out by coupling one or more Fmoc-protected amino carboxylic acids to Rink amide resin using standard protocols (cf. Scheme 1, route 1).

The central building block exhibits reduced reactivity at the amino and carboxy functionality due to steric hindrance caused by the α-branch. We therefore used 2×2 equiv of this building block with HATU/DIPEA/cat DMAP activation for coupling to amino groups. Establishment of the tetrahydrocarbazole scaffold is then achieved related to the procedure in solution using Fischer indolization. Various procedures for indole formation on solid support have been described to date,[3] some of which rely on Fischer-type cyclizations.[4] Similar to Britten and Lockwood[1] and also Hutchins and Chapman[4a] we found $ZnCl_2$ to be advantageous for the indole cyclization step. In our optimized procedure we used 5–10 equiv of 0.5 M hydrazine derivative/$ZnCl_2$ in 30% DMF/HOAc. We found that the two possible α-carbon stereoisomers are generated in about equal amounts also for the diastereo case and that the diastereomers usually can be readily separated on RP-HPLC. Equally, when using meta substituted phenyl hydrazines, no significant stereoselection could be observed. We would like to point out, that indolization is also possible after other stages of the synthesis, for example, prior to cleavage from the resin. Derivatization at the amino group can be achieved in many ways, although some of usually successful procedures did not work due to steric hindrance. For N-alkylation, nucleophilic substitutions are superior to reductive amination procedures.[5,6] We found 5 equiv of halide, catalytic KI and DIPEA in DMF at elevated temperatures to be optimal. Except for MeI we did not observe any bisalkylation products. Formation of ureas was achieved in good to excellent yields with isocyanates[7] at room temperature with prolonged reaction times. Attempts to preactivate the amino group with *p*-nitrophenylchloroformate and subsequently substitute with amines were not satisfactory in this case.[8,9] For carbamate synthesis, we followed a procedure outlined by Warrass et al.[10] utilizing dibenzotriazolycarbonate for preactivation of alcohols. Sulfonamide derivatization is possible with sulfonyl chlorides when reaction times are extended and excess of reagent is used. Amide formation with carboxylic acids is best achieved by HATU activation as



Scheme 1. Solid-phase synthesis routes 1 and 2 for the production of tetrahydrocarbazole-based libraries.

Table 1. Product examples of solid-phase routes 1 and 2

Route	Compound	Yield (%)	Route	Compound	Yield (%)
1		A: 10.3 B: 12.5	1		A: 22.8 B: 23.3
1		A: 13.3 B: 13.3	1		A: 10.5 B: 9.2
1		A: 30.7 B: 28.8	2		39.2
1		A: 18.1 21.2	2		48.6

described above for coupling of **3**. Deprotonation of the indole nitrogen is possible with strong bases, thereby allowing nucleophilic substitutions of alkyl halides. While solid sodium hydride as base yielded good results, it proved to be incompatible for handling on our synthesizer. We found NaHMDS in THF almost equipotent for automated synthesis applications. It should be noted, however, that sometimes overalkylation or hydantoin formation as side reactions can occur.

To further expand the scope of accessible structures, we next focused our attention on routes, which would allow to install amines at the 3-carboxy function without mandatory carboxy function for resin anchoring (cf. Scheme 1, route 2). However, neither coupling of **3** to amino-modified formyl resin, nor reductive amination of formyl resin (4-formyl-3,5-dimethoxyphenoxy linker) with amino ester or attachment of **3** to Kenner's safety catch linker were successful due to steric hindrance. We therefore decided to attach **3** via ketal linkage to diol resin, commercially available as 1-(2,3-isopropylidene)glycerol polystyrene resin. Resin loading is easily achieved after deprotection with HCl/dioxane 1:3 by refluxing **3** with catalytic *p*-toluenesulfonic acid and resin in toluene under azetropic water removal with a Dean–Stark trap. This does not require salts like Na_2SO_4.[11,12] Reaction with amines under HATU activation again yields carboxamido-modified derivatives, subsequent Fmoc deprotection and derivatization with procedures like above (here amide bond formation) allows modifications at the 3-amino moiety. Tetrahydrocarbazole formation is performed in the last step by cyclizative cleavage with excess phenyl hydrazines/$ZnCl_2$ in TFA/HOAc/NMP 3:4:3. Excess hydrazines are easily removed during purification by HPLC. Representative product examples for the described procedures, together with yields after preparative RP-HPLC, are given in Table 1. Both routes were used to synthesize libraries of about 1000 members each on a 0.2 mmol scale. The obtained purities range between 30–95%, while the average yield after preparative HPLC is about 35%.

In conclusion, we have developed two related solid-phase synthesis allowing the production of highly diverse tetrahydrocarbazole libraries.

Supplementary data

The file contains experimental procedures as well as physicochemical data of selected compounds. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tetlet.2004.12.058.

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