THE SYNTHESIS OF FUSED HETEROCYCLIC BUILDING BLOCKS AND THEIR APPLICATION AS CORE STRUCTURES OF GPCR LIGANDS

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INTRODUCTION

Heterocyclic chemistry is the most valuable source of compounds exhibitng biological activity mainly because of the ability of heterocyclic molecules to mimic the electronic structure of peptides or signalling molecules and to bind reversibly to proteins.[1] Synthesis of polycyclic frameworks with geometrically well-defined arrangement of "scaffold decorators" (substituents that interact with target's aminoacid residues) is a well recognized way to potent, selective bioactive entities.[2]
Indole is one of the most abundant heterocyclic ring systems in nature. It could be recognized as a scaffold of range of natural products (Fig. 1**A**, **B**, **F**) and indole derivatives are essential compounds in drug-discovery (Fig. 1**C**, **D**, **E**). [3]

Furopyrrole is found across many plant and funghi species as well as in marine organisms (Fig. 2**G**, **H**, **I**). Tensidol A and B isolated from Aspergillus niger potentiate the action of antifungal imidazoles and possess moderate antibacterial properties.[4] Supprisingly, this scaffold is rarely met in medicinal chemistry applications. Concise synthetic protocol developed in our lab may prove its usefullness for synthesis of furopyrroles and other fused heterocycles.

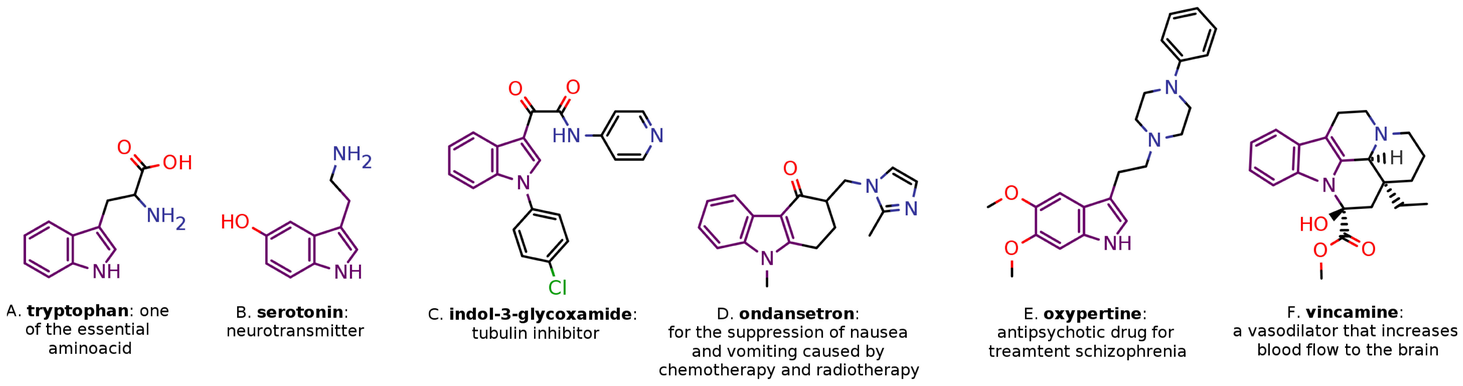

Fig.1 Indole scaffold in natural and synthetic molecules.

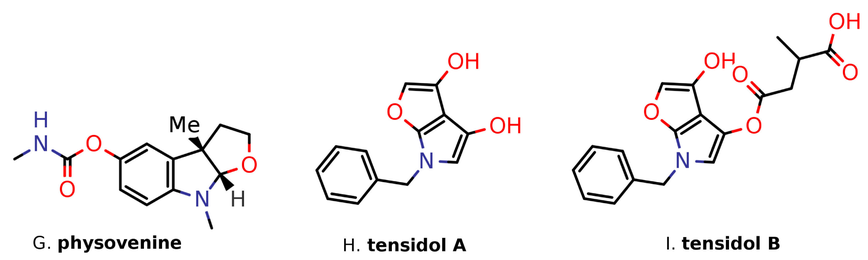

Fig.2 Furopyrrole ring system in natural products.

CHEMISTRY

Our search for selective aminergic GPCR ligands led us to the syntheses of heterocyclic molecules which can serve as substrates for derivatization, e.g. attachment of basic aminergic moiety, ring closure, reactions with various nucleophiles. Our efforts to obtain 2-amino-1-(1H-indol-3-yl)ethan-1-ol (**1**), yielded a straightforward method of synthesis of 3-(3-methyloxiran-2-yl)-1H-indole (**2**) - a very attractive building block for drug discovery which has not been mentioned in literature till date (Fig.4). This epoxide can be readily opened by numerous nucleophiles to yield potential GPCR ligands. Hydrolytic kinetic resolution (HKR) strategy may be employed to separate the demanded diastereoisomer.

We found compounds **3** and **4** of particular interest. For this purpose, we needed a reliable method of making indole-3-acetone (**7**) from readily aviable precursors. Our first attempt was to perform a six step reaction depicted in Fig.3 in one pot. Darzen's condensation and subsequent hydrolysis succeded, however only **12** was obtained, as the decarboxylation step did not proceed. We managed to develop a simple protocol yielding indole-3-acetone (**7**) starting from indole-3-carboaldehyde. (Fig.5) Our trials of direct bromination of indole-3-acetone have failed, consequently yielding tarry polymeric products. The same problem was encountered while using $CuBr_2$. Pyrrolidone hydrotribromide was found the reagent of choice, however only dibromo-derivative (**6**) could be isolated. Despite trials we were not able to reproduce the nonselective bromination−selective debromination strategy demonstrated by Choi and Chi.[5] Our next step was to try brominate *N*-protected indole-3-acetone. We found direct *N*-protection unsuitable due to lack of stability of **8** towards bases - this was solved by acetal protection of the carbonyl group.

To our astonishment, the main product of the reaction of **8** with pyrrolidone hydrotribromide was **5**,with monobromo-derivative existing as a trace ammount detected by LC-MS. In comparison to the known methods of furopyrrole synthesis (Fig.6)[6] our protocol involves the use of mild and inexpensive reagents and conditions.

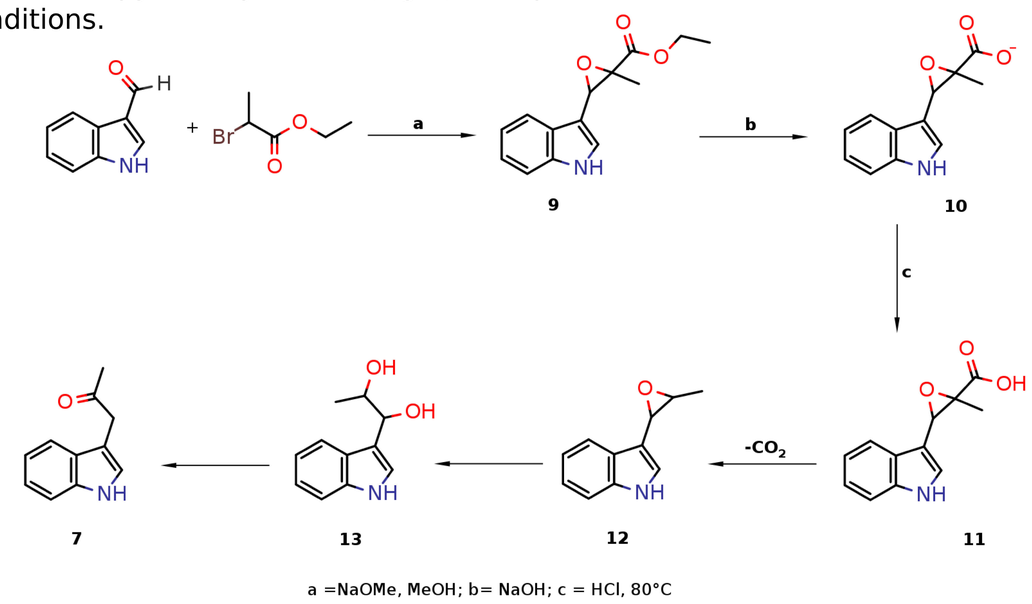

*Fig. 3 One-pot synthesis of indole-3-acetone (**7**).*

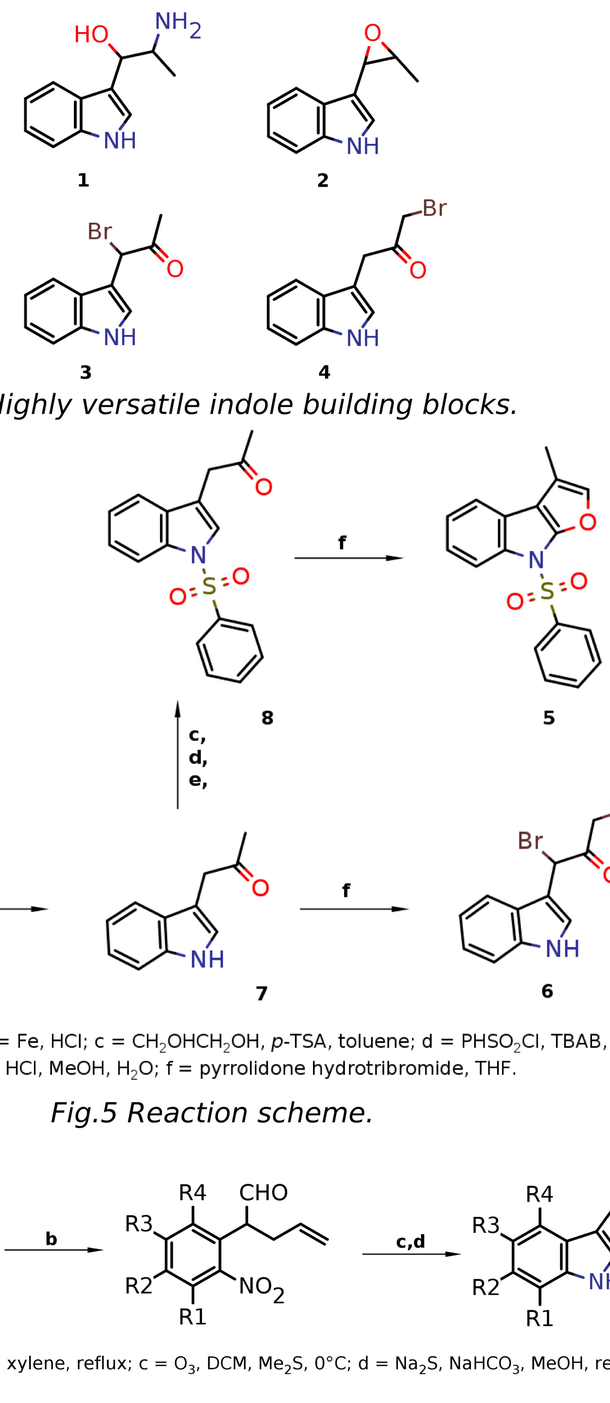

Fig.4 Highly versatile indole building blocks.

Fig.5 Reaction scheme.

Fig.6 Furopyrrole synthesis.

CONCLUSIONS

We have developed a very concise method of synthesis of substituted 8H-furo[2,3-b]indole. It is crucial to determine the possible mechanism of the reaction as we could predict the reaction's scope then. The possible pathways may involve electrophilic attack of bromine on position 2 of indole nucleus, or formation of oxindole derivative.
If we manage to join the Darzen's condensation with all subsequent transformations yielding an aryl-acetone with the freshly discovered ring closure - by far the most straightforward way to furopyrroles will be set.

ACKNOWLEDGEMENTS

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