



Preparation of indole containing building blocks for the regiospecific construction of indole appended pyrazoles and pyrroles



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ABSTRACT

The preparation of an indole appended vinamidinium salt, an indole appended vinylogous amide and an indole appended chloroenal are described. The subsequent regiospecific conversion of these indole containing building blocks to functionalized pyrazoles and pyrroles is detailed.

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1. Introduction

The indole group has long been considered a privileged structure¹ as it relates to the discovery of new medicinally active substances. The term privileged structure² refers to the ability of 'a single molecular framework able to provide ligands for diverse receptors'. It has been suggested² that 'indoles represent the most important of all structural classes in drug discovery' due to their extremely wide range of pharmacological activity. Some relevant examples of bioactive indole containing substances are presented in Fig. 1.

The range of compounds represented in Fig. 1 include Lycogallic acid³ natural products (**1** and **2**), which have been reported to be biosynthetic precursors to the antitumor agent Staurosporine⁴ (**3**), Chalcone-like antitumor agents⁵ (**4**), Meridianin type kinase inhibitors⁶ (**5**), microtubule inhibitors⁷ (**6**) and COX-2 inhibitors⁸ (**7**). Humphrey and Kuethe¹ have previously reviewed practical methods for the synthesis of indole containing substances and a variety of

useful methodologies are available. Our research group has been interested for some time in the use of vinylogous iminium compounds⁹ and their derivatives for the construction of important bioactive heterocycles and we envisioned using such systems as building blocks for the construction of indole appended heterocyclic motifs. Padwa¹⁰ and co-workers have recently pointed out the advantage of having access to versatile indole containing substances, which could be used for the construction of more highly functionalized compounds. To that end we have studied an indole appended vinamidinium salt (**8**), an indole appended vinylogous amide (**9**) and an indole appended chloroenal (**10**) as building blocks for the regio controlled synthesis of pyrazoles and pyrroles. Since pyrazole¹¹ and pyrrole¹² ring systems are commonly found in medicinal agents as well, we believed it would be of value to develop appropriate synthetic methodology for such a purpose (Fig. 2).

2. Results and discussions

The synthesis of the 2-indolyl appended vinamidinium salt (the perchlorate version of **8**) was reported in 1961 by Arnold¹³ but full characterization of this substance along with a detailed experimental procedure was not provided. We now report full details on

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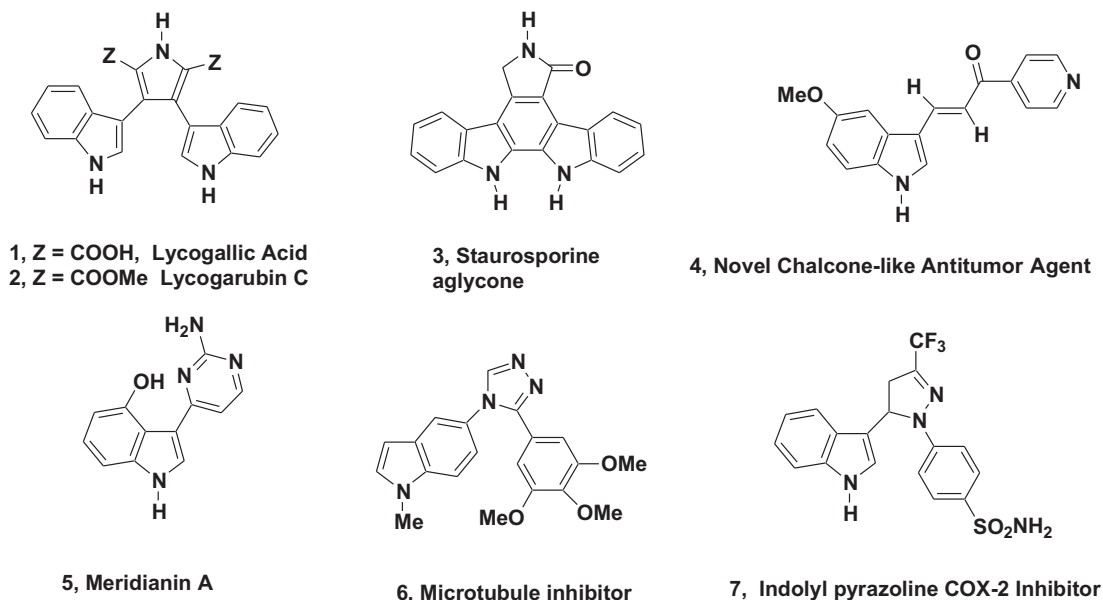


Fig. 1. Biologically active indole derivatives.

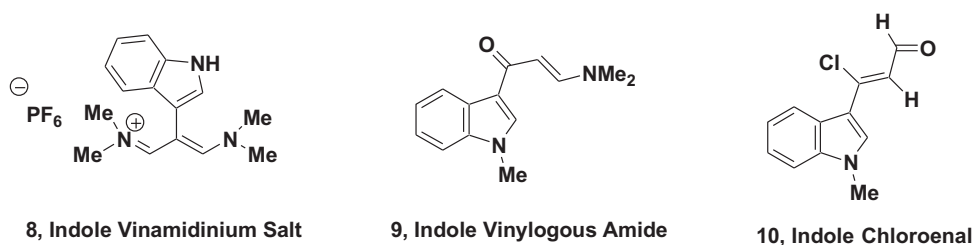
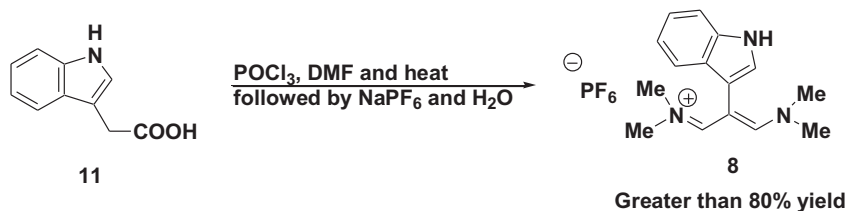


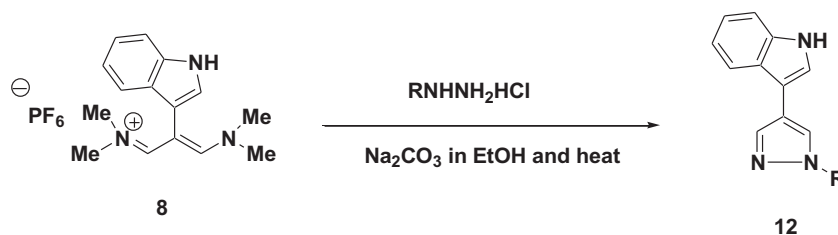
Fig. 2. Indole appended building blocks.

the synthesis and characterization of the 2-indolyl appended vinamidinium hexafluorophosphate (**8**). Indole acetic acid is commercially available and this material is reacted under Vilsmeier–Haack–Arnold conditions (Scheme 1) followed by quenching the reaction mixture with aqueous sodium hexafluorophosphate. The resulting salt (**8**) is somewhat tacky and is usually carefully dried under vacuum prior to being utilized in subsequent reactions.

With this material (**8**) in hand we decided to initially look at its application to pyrazole synthesis (Scheme 2). One of the important aspects of using such a salt (**8**) for synthesis lies in the ability to control regiochemistry in the final product. Since the salt (**8**) is a symmetrically disposed molecule, the indole group would be expected to be located at the central carbon of the pyrazole ring. The following table provides a range of *N*-substituted pyrazoles, which were prepared by the indicated methodology (Table 1).



Scheme 1. Preparation of 2-indole appended vinamidinium salt.



Scheme 2. Synthesis of 4-indole appended pyrazoles.

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