FACILE SYNTHESIS OF 1,2,3,4-TETRAHYDROBENZO[*b*][1,6]NAPHTHYRIDINES

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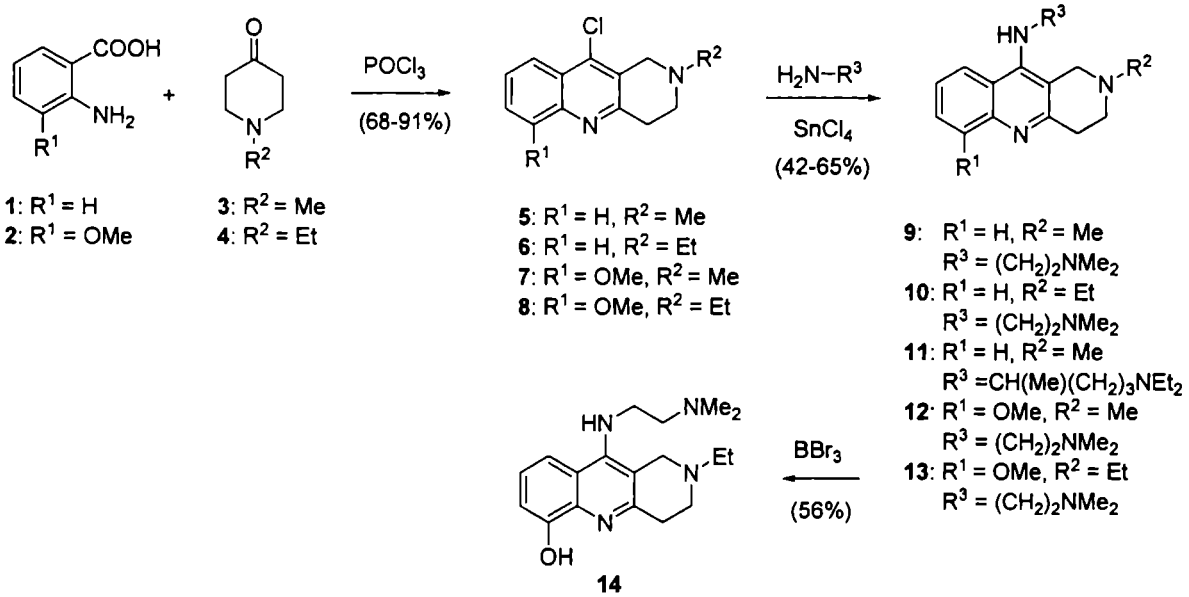
Abstract: Synthesis of analogs of known immunosuppressive quinolines is reported.

Rheumatoid arthritis and systemic lupus erythematosus are autoimmune diseases.[1,2] A number of basic quinolines induce remissions of these diseases. It has also been suggested that such compounds, by temporarily suppressing the immune system, may be useful in the prevention of graft-versus-host disease in bone marrow transplant patients.[3] Our recent research *in vitro* has shown that the basicity of the N1 atom of the quinoline parallels the activity of the immunosuppressive agents and the most active compounds contain additional amino (basic) centers and polar substituents, such as a hydroxy group. Importantly, inhibition of the immunostimulation is observed for relatively small quinolines only.[4,5]

This report pertains to the synthesis of 1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines **9-14** that are analogs of known immunosuppressive agents. The molecules **9-14** are substituted quinolin-4-amines, the N1 atom of which is basic ($pK_a > 7$) due to conjugation of the N^4 atom with the quinoline.[4,5] Additional basic centers are parts of the side chain and the fused aliphatic ring. Derivatives **12-14** contain a polar methoxy or hydroxy group. Biological studies of products **9-14** will be reported in due course.



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The intermediate 9-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines **5-8** were synthesized by condensation of corresponding anthranilic acids **1,2** with *N*-alkyl-4-

piperidones **3,4** in the presence of phosphorus oxychloride.[6,7] Naphthyridine derivate **5** has been reported previously,[6,7] while **6-8** are new compounds. As part of this work it was found that preparation of compounds **5-8** is highly temperature dependent. Thus, heating a mixture of anthranilic acid **1** or **2** (3 mmol), piperidone **3** or **4** (3 mmol), and $POCl_3$ (20 mL) under reflux for 2 h gave a 2-aminobenzoyl chloride and the desired compounds **5-8** as a major and minor product, respectively. By contrast, the reaction conducted at 60 °C for 5 h under otherwise identical conditions gave **5-8** in high yield after quenching of the mixture with aqueous $NaHCO_3$ (*caution: exothermic reaction*) followed by extraction with ethyl acetate.

An attempted nucleophilic displacement of the chlorine substituent in **5-8** by treatment with an amine alone failed to produce the respective products **9-13**, even under forced conditions of temperature and time, and low yield of the product was obtained for the reaction conducted in the presence of phenol. The successful preparation of **9-13** involved heating (120 °C, 10 h, under a nitrogen atmosphere) of **5-8** (1.5 mmol) with an amine (20 mmol) in the presence of a catalytic amount of tin tetrachloride (2 drops). After concentration under reduced pressure, the residue was subjected to silica gel chromatography eluting with AcOEt/MeOH/NEt_3 (17:2:1). The oily products **9-13** were converted to hydrobromide salts by using a general procedure,[8] and the salts were crystallized from 95% ethanol.

The methoxy derivative **13** (0.5 mmol) was demethylated by treatment with boron tribromide (0.5 mL, 5.5 mmol) in dichloromethane (10 mL) at 23 °C for 24 h. After quenching with water (0.3 mL) the mixture was treated with ether (20 mL) and the resultant precipitate of a hydrobromide salt of **14** was crystallized from EtOH/MeOH (1:1).

All new products were characterized by ^{1}H-NMR and ^{13}C-NMR and gave satisfactory results of elemental analysis (C, ± 0.3; H,± 0.2; N, ± 0.2). The composition, yield, and mp: **6**, free base, 91%, 122-123 °C; **7**•2HBr•H_2O, 68%, > 200 °C (dec.); **8**•2HBr•H_2O, 70%, > 230 °C (dec.); **9**•3HBr•1.5H_2O, 42%, 214-215 °C; **10**•3HBr•2H_2O, 67%, 221-222 °C; **11**•2HBr•3.5H_2O, 39%, 222-224 °C; **12**•3HBr•2H_2O, 68%, 203-206 °C (dec.); **13**•3HBr•1.5H_2O, 65%, 245-247 °C; **14**•3HBr•2H_2O, 56%, 262-265 °C (dec.). Selected ^{13}C-NMR spectra (DMSO-d_6): **9**•3HBr•1.5H_2O, δ 24.8, 41.7, 42.1, 42.6, 47.7, 50.4, 55.4, 104.2, 116.3, 119.2, 124.7, 126.2, 133.6, 137.5, 147.3, 154.3; **10**•3HBr•2H_2O, δ 9.2, 24.8, 42.0, 42.8, 45.6, 48.6, 51.2, 55.5, 104.3, 116.2, 119.3, 125.0, 126.5, 134.1, 137.5, 147.2, 154.7; **11**•2HBr•3.5H_2O, δ 8.4, 20.2, 21.2, 24.8, 34.0, 42.2, 45.8, 47.6, 50.2, 50.6, 53.7, 104.1, 116.1, 119.2, 124.7, 126.2, 133.7, 137.6, 146.8, 154.5; **13**•3HBr•1.5H_2O, δ 9.0, 25.0, 41.8, 42.6, 45.5, 48.5, 50.9, 55.3, 56.7, 105.3, 112.7, 115.7, 117.0, 126.4, 129.0, 147.3, 148.6, 154.4; **14**•3HBr•2H_2O, δ 9.1, 25.0, 41.8, 42.8, 45.7, 48.6, 51.1, 55.4, 104.8, 114.3, 115.7, 117.4, 126.7, 128.6, 147.0, 154.5.

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