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Convenient preparation of *N*-8-quinolinyl benzenesultams as novel NF-κB inhibitors

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Abstract

An efficient synthesis of a series of *N*-8-quinolinyl benzenesultams as novel NF-κB inhibitors was described via diazotization-induced cyclization of easily accessible *N*-8-quinolinyl-2-aminobenzenesulfonamides.

Keywords: Benzenesultam; NF-κB; Diazotization; Cyclization

Nuclear factor kappaB (NF-κB) is a pivotal transcription factor that regulates gene expression involved in inflammation and immune responses. The NF-κB pathway has provided a favorable target for pharmacological intervention of chronic inflammation, neurodegenerative diseases, and certain types of cancer, where the pathway is often constitutively or excessively active. Peptides, siRNA, natural products, and small molecules that target one or multiple steps of NF-κB signaling are under investigation as potential therapeutics.[2] Our NIH Molecular Libraries Screening Centers Network (MLSCN) recently identified sultam **1** (Fig. 1) as a novel NF-κB inhibitor in cell-based high throughput screening assays.

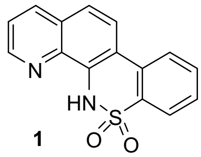

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Fig. 1. The structure of NF-κB inhibitor **1**.

NF-κB is normally sequestered in the cytoplasm through an association with its inhibitory protein IκB. Upon stimulation of the NF-κB pathway, IκB is rapidly phosphorylated, ubiqutinated, and then degraded by proteasomes. Freed from its inhibition, NF-κB translocates to the nucleus where it binds to DNA regulatory sites and activates specific gene expression.[1] Preliminary results[3] show that compound **1** stabilizes IκB and prevents NF-κB translocation in different types of cells with sub-micromolar IC_{50}s. In contrast to existing blockers of NF-κB translocation, compound **1** did not appear to inhibit IκB kinases (IKKs) and proteasomes, the major components of the IκB degradation machinery, and thus likely represents a structurally and pharmacologically new class of modulators of the NF-κB pathway. For structure–activity relationship studies and further biological investigation, we sought an easy synthetic access to the original hit **1** and its analogs.

The tetracyclic target **1** consists of a structurally constrained cyclic sulfonamide with the sultam bridging quinolinyl and phenyl moieties. This unique scaffold has rarely been studied and lacks a general synthetic method. In this Letter, we describe an efficient synthesis of this class of compounds that allows a diverse substitution pattern.

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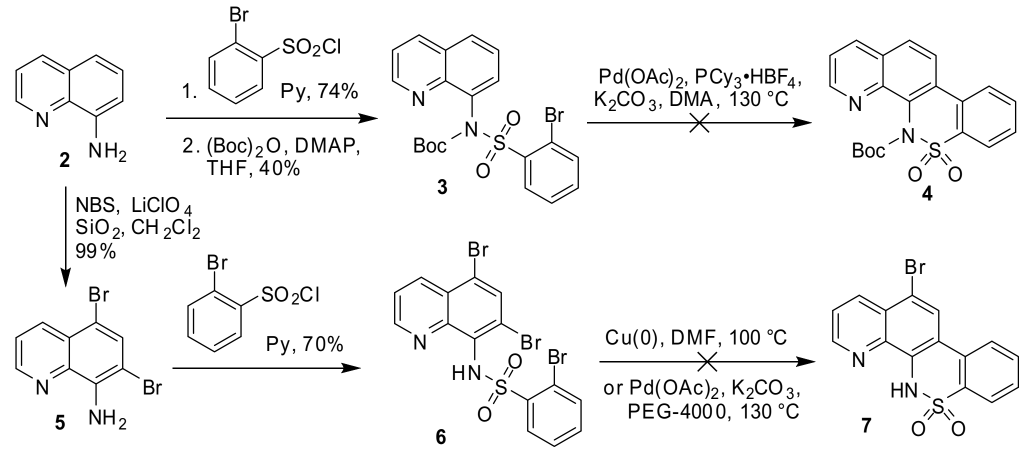


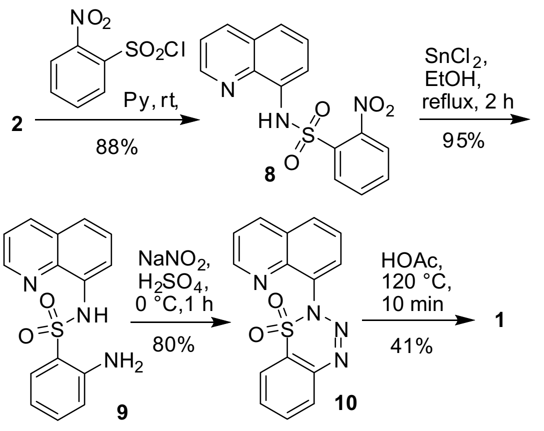
Scheme 1. The attempts of intermolecular arylation.

Our synthetic strategy was to construct the sultam skeleton through the cyclization of easily accessible *N*-8-quinolinyl benzenesulfonamides. We first attempted metal-mediated intermolecular arylation. As shown in Scheme 1, 8-aminoquinoline **2** was treated with 2-bromobenzenesulfonyl chloride in pyridine followed by the protection of the nitrogen on sulfonamide with Boc_2O to give precursor **3**. Unfortunately, palladium-catalyzed direct intramolecular arylation[4] of bromide **3** failed to effect cyclization. Bromination of 8-aminoquinoline **2** provided dibromide,[5] and subsequent sulfonamidation yielded tribromide **6**. However, neither Ullmann reaction nor palladium-catalyzed intramolecular coupling[6] of aryl bromide **6** afforded the desired product **7**.

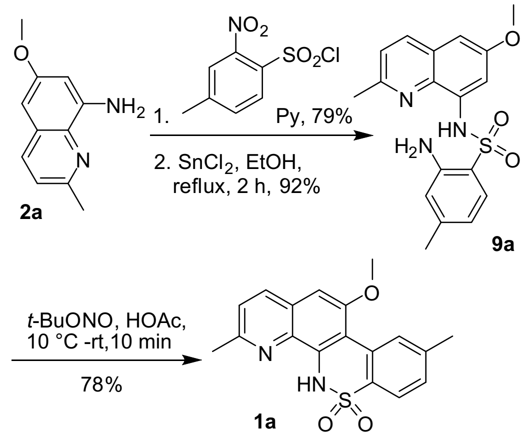
Ultimately, diazotization-induced cyclization was employed to synthesize the target compound (Scheme 2). Sulfonamide **8** was prepared, as above, from 2-nitrobenzenesulfonyl chloride and 8-aminoquinoline **2** in pyridine. The nitro group was reduced with $SnCl_2$ to provide amine **9**, and subsequent diazotization afforded triazine **10** in good yield. A literature procedure employing Cu(0) and NaOH[7] failed to yield the desired product, but we found that thermolysis in a variety of solvents (EtOH, H_2O, DMSO, or HOAc) or neat afforded product **1** in moderately poor yield. The best result (41% yield) was obtained by heating in glacial acetic acid at 120 °C for 10 min. Beyond low yield, thermolysis in acid generated large amounts of intractable tar and required multiple rounds of chromatography on silica gel.

In the course of improving the synthesis of the triazine intermediates, we attempted a mild non-aqueous diazotization-induced by *tert*-butyl nitrite (*t*-BuONO). This led to our discovery of a convenient one-pot synthesis of *N*-8-quinolinyl benzenesultams from *N*-8-quinolinyl-2-aminobenzenesulfonamides. In a typical reaction, as shown in Scheme 3, 2-aminobenzenesulfonamide **9a** prepared from 6-methoxy-2-methylquinolin-8-amine **2a**[8] was dissolved in HOAc and treated with 1.5 equiv of *t*-BuONO at 10 °C. The reaction was allowed to warm to room temperature over 10 min and smoothly afforded sultam **1a** in good yield (78%) without the isolation of the triazine intermediate.[9]

To investigate the scope of this one-pot protocol, a selection of *N*-8-quinolinyl-2-aminobenzenesulfonamides (**9a–p**) was prepared and subsequently cyclized in one-pot reactions to give sultams (**1a–p**). In each case, the



Scheme 2. Synthesis of sultam **1** via triazine intermediate.



Scheme 3. The one-pot synthesis of compound **1a**.