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Azaindolines: derisking the indoline structural alert

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ABSTRACT

4-Substitued azaindolines, which are isosteres of indolines, are useful synthetic building blocks that reduce the risk of bioactivation induced idiosyncratic toxicity have been prepared. Multigram routes to 2,3-dihydro-1*H*-pyrrolo[2,3-*c*]pyridine-4-triflate **16**, 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-4-carbonitrile **20** and 4-chloro-2,3-dihydro-1*H*-pyrrolo[2,3-*d*]pyridazine **30** are outlined.

Adverse drug reactions (ADR) are particularly worrisome as they are a common cause of drug recalls and labeling changes.[1] When designing new molecules, it is the job of the medicinal chemist to not only design efficacious compounds, but safe compounds that have the greatest chance of becoming medicines without ADRs.

Structural alerts are chemical fragments that are associated with multiple examples of adverse in vivo outcomes and/or ADRs. These outcomes include but are not limited to mutagenicity, direct toxicity, carcinogenicity, DNA intercalation, or idiosyncratic toxicity. Many of these ADRs are caused by bioactivation and can be seen in daily human doses as low as 10 mg.[2] When presented with chemical matter containing structural alerts, a sound philosophy is to remove the offending moiety altogether or modify the structure to remove the risk associated with the alert.

The aniline moiety is a well-known structural alert.[3] Toxicity from anilines is primarily due to two types of bioactivations (Fig. 1): hydroxylation of the aromatic ring leading to reactive iminoquinones **1** and oxidation of the amine which can lead to reactive nitrenium **2** or nitroso **3** derivatives.[4] One of the most straightforward ways to derisk the aniline alert is to place one or more nitrogens in the phenyl ring. These nitrogens reduce the electron density of the phenyl making oxidation to species **1**–**3** less likely. Indoline **4** is an aniline constrained in a five-membered ring. A substructure search of the basic 4-substitued indoline moiety in

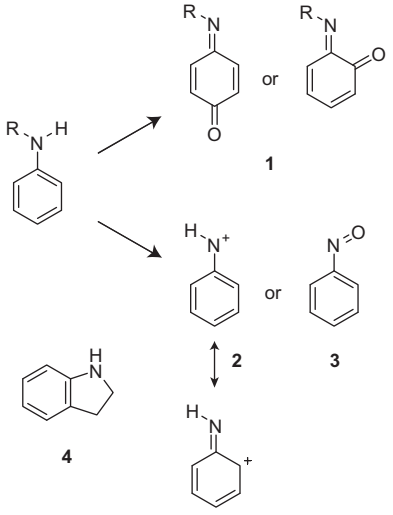

Figure 1. Aniline bioactivation pathways.

SciFinder identifies more than 1300 references where indolines have been described as antibacterials, kinase inhibitors for cancer targets, antidiabetic agents, anti-inflammatory agents, and analgesics. It is therefore surprising that more chemistry does not exist for the preparation of azaindolines which could derisk the aniline structural alert contained within indoline. In the following Letter, we present several routes to functionalized azaindoline

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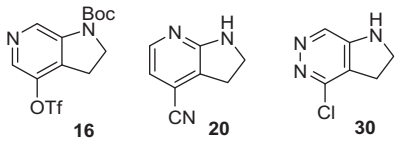


Figure 2. Key indoline synthetic intermediates.

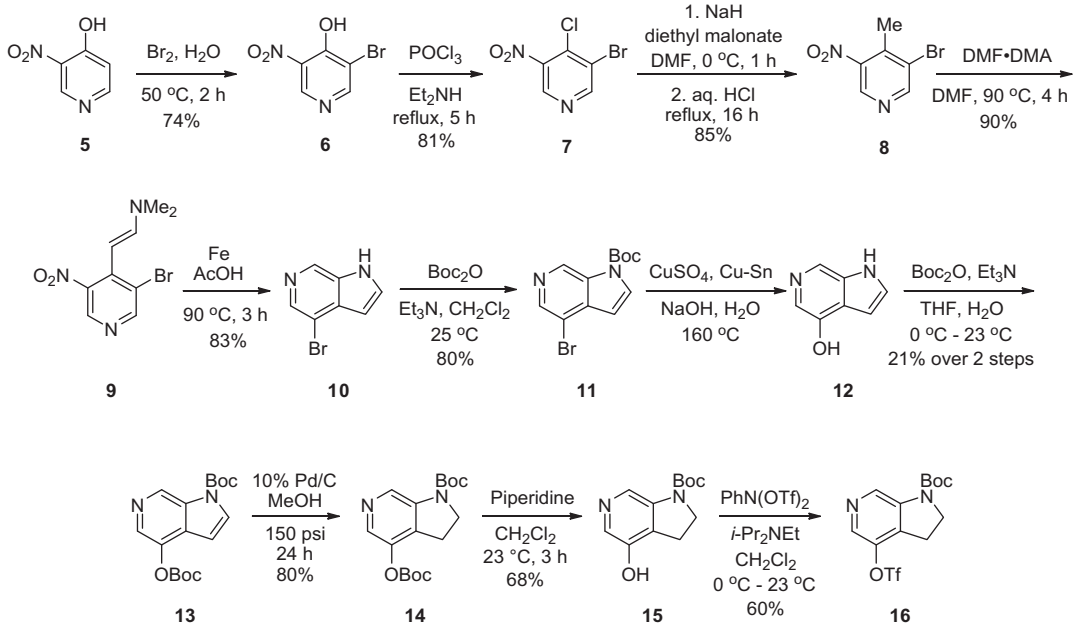
intermediates that could be used as synthetic intermediates **16**, **20,** and **30** (Fig. 2).

The preparation of 2,3-dihydro-1*H*-pyrrolo[2,3-*c*]pyridin-4-yl trifluoromethanesulfonate **16** is presented in Scheme 1. Commercially available 3-nitropyridin-4-ol **5** can be selectively brominated[5] to give 3-bromo-5-nitropyridin-4-ol **6**. Conversion to the corresponding chloride **7** is accomplished by heating with $POCl_3$ and Et_2NH.[6] Replacement of the chlorine in **7** with a Me group is accomplished by a two step procedure where (1) the chlorine was initially displaced with sodium diethylmalonate and (2) the malonylpyridine intermediate is saponified and doubly decarboxylated with aqueous HCl.[7] Elaboration of **8** to enamine **9** is effected with DMF·DMA and the corresponding indole **10** is formed by heating with iron and HOAc.[8] An attempt was made to selectively reduce the enamine double bond in **9** followed by a cyclization to produce azaindoline, but various reaction conditions led to the nitro group reduction without a subsequent cyclization. An alternative synthetic strategy is to selectively reduce the 2,3-indole double bond in **10**, but the reaction with various reducing agents under multiple conditions fails to produce the desired product.[9] Therefore, reduction of the 2,3-indole double bond requires protecting group manipulations and conversion of the 5-bromo to a 5-hydroxy moiety. Thus **10** is *N*-Boc protected under standard conditions to produce **11**. The bromine atom is converted to a hydroxyl moiety with concomitant removal of the *N*-Boc group using an aqueous $CuSO_4$,[10] and the resulting alcohol **12** is *N*-Boc protected again to give **13**. The key reduction step from azaindole **13** to azaindoline **14** was accomplished using hydrogenation over Pd/C. Compound **14** is a useful intermediate in that the N1 and C4 substituents can be differentiated for future chemistry. For example, the C4 *O*-Boc group can be removed using piperdine to give the corresponding alcohol **15** which may then be converted to triflate **16** under standard conditions.[11] Compound **16** could now undergo cross-coupling chemistry at C4 followed by additional N-functionalization after removal of the Boc group at N1.

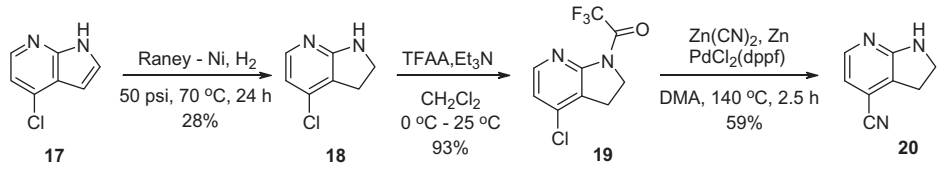
A shorter route to a 4-substitued-7-azaindoline scaffold is presented in Scheme 2. Commercially available 4-chloro-7-azaindole **17** can be directly reduced to the corresponding indoline **18** by hydrogenation over Raney-Ni. It should be mentioned that the same or similar reaction conditions failed to produce the desired product in the case of 6-azaindoline **10**. The C5 and N1 positions are differentially functionalized in that N1 was protected as its trifluoroacetamide **19** using TFAA and the 5-Cl group functionalized to CN using $PdCl_2$(dppf) and $Zn(CN)_2$.[12]

We have also enabled a route to a 4-substituted diazaindoline scaffold which is shown in Scheme 3. Initially 4,5-dichloropyridazin-3(2*H*)-one **21** is protected as its PMB-amide **22**. The 5-Cl group can be selectively displaced with sodium diethylmalonate[13] to give **23** which can be ethyl decarboyxlated on heating in DMSO to give **24**. Reduction of the ethyl ester to alcohol **25** is accomplished with $NaBH_4$, alcohol **26** was converted to mesylate **27**, and displacement with PMB-NH_2 was followed by cyclization to give the *N*-PMB protected 1*H*-pyrrolo[2,3-*d*]pyridazin-4(5*H*)-one **28**. The PMB group can be removed using TFA and aromatization of the pyridazinone ring is accomplished using $POCl_3$ to give the 4-Cl diazaindoline **30**. It should be noted that the need to undertake an extensive protecting group manipulation (PMB) was justified by the unexpected circumstances with this group's deprotection. When the PMB group was carried forward to produce intermediate **31**, its removal on pyridazinone nitrogen could not be achieved under an exhaustive list of conditions. Therefore, we resorted to the sequential deprotection strategy even if it forced us to proceed with unprotected pyridazinone nitrogen going from **26** to **28**.

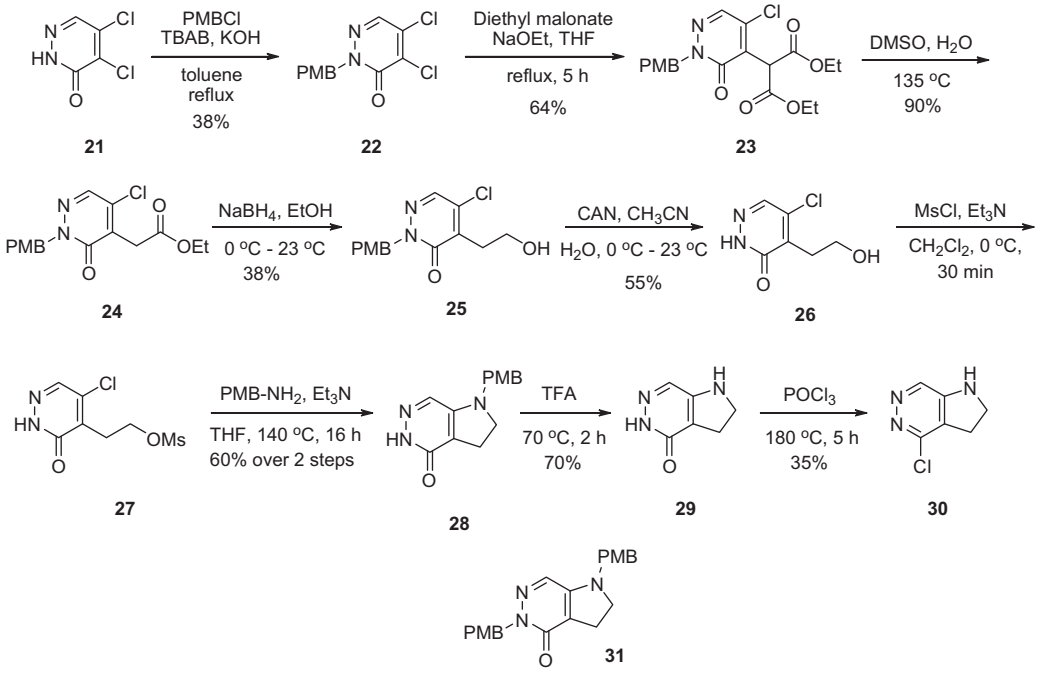
We have highlighted the development of routes to 4-substituted azaindolines. This synthetic effort enables a viable strategy for the replacement of indolines that contain an aniline structural alert. These routes also allow for the preparation of intermediates that can be used in future chemistry by derivatization at the N1 and C5 positions.



Scheme 1. Preparation of 2,3-dihydro-1*H*-pyrrolo[2,3-*c*]pyridine-4-triflate.



Scheme 2. Preparation of 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-4-carbonitrile and intermediate.



Scheme 3. Preparation of 4-chloro-2,3-dihydro-1*H*-pyrrolo[2,3-*d*]pyridazine and intermediates.

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9. Either the starting material **10** or the de-brominated product was observed under the following conditions: (1) $NaBH_4$/AcOH at room temperature for 16 h; (2) $NaCNBH_3$/AcOH at room temperature for 16 h; (3) 10% Pd-C/room temperature/ethanol with H_2/100 psi for 16 h; Raney-Ni/room temperature/ethanol with H_2 for 16 h; (4) BH_3·THF room temperature for 16 h; BH_3·THF reflux for 16 h.
10. A mixture of compound **11** (4 g, 13.5 mmol), NaOH (5.4 g, 135 mmol), $CuSO_4$ (2 g), and Cu–Sn (2 g) in water (15 mL) was taken in steel bomb. The reaction mixture was heated at 160 °C for 16 h. Reaction mixture was cooled to get crude compound **12** in the reaction mixture. This crude reaction mixture was used in the next step without any purification.
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