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Synthesis of benzimidazole based JNK inhibitors

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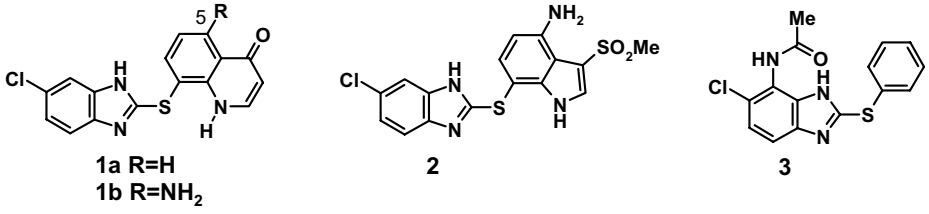
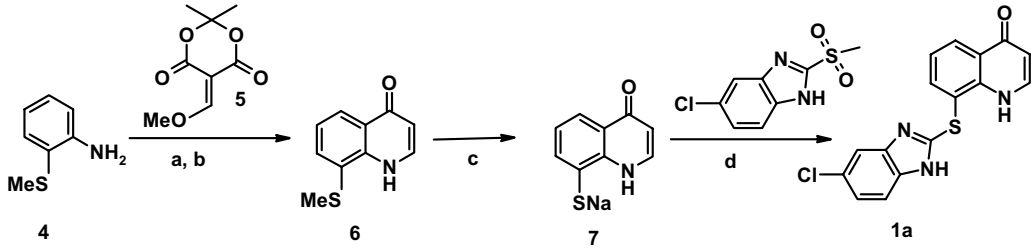
Abstract—Substituted benzimidazoles were synthesised using a number of novel reactions, including displacement of a 2-sulfone group, preparation of 4-diazo benzimidazole derivatives and lithiation of benzimidazoles in the 4-position.

The synthesis of JNK kinase inhibitors is an ongoing activity within the pharmaceutical industry.[1] Screening of the AstraZeneca compound collection identified a number of ATP-site binding inhibitors including the 2-thioaryl benzimidazole inhibitor **1a**, R = H (Scheme 1). Subsequent SAR studies necessitated synthesis of the aminoquinolone **1b**, R = NH_2, indole sulfone **2** and 4-substituted benzimidazole **3**.

The known synthesis of **1a** was very lengthy[2] and a more expeditious route was required. The quinolinone **6** (Scheme 2) was formed from the commercially available aniline **4** by thermolysis with the Meldrum's acid derivative **5**.[3] Deprotection to the required thiol **7** was achieved in high yield using sodium dissolved in liquid ammonia. Initially nucleophilic displacement of a group at the 2-position of 5-chlorobenzimidazole proved



Scheme 1.



Scheme 2. Reagents, conditions and yields: (a) **5**, MeCN, rt, 20 h, 98%; (b) Ph_2O, 250 °C, 98%;[4] (c) Na, NH_3 (l), −30 °C, then **6**, THF, 86%; (d) benzimidazole-2-sulfone, AcOH, IPA, reflux 20 h, 10%.

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problematical. For instance, a 2-chloro substituent failed to be displaced by thiol **7** under a range of conditions. This may be the result of competing deprotonation of the 1*H*-benzimidazole. However displacement of a 2-methylsulfone moiety proceeded smoothly to give the required compound **1a** in acceptable yield.

The quinolinone **1a** had unacceptable solubility in the aqueous buffers used for biological testing. Compounds were required incorporating a solubilising group in the 5-position of the quinolinone, necessitating the synthesis of **1b** (Scheme 1). The functionalisation of this position also enabled an alternative disconnection of the thioether linkage to be employed involving nucleophilic attack of a 2-thiobenzimidazole at the 8-position of the quinolinone.

The required quinolinone **9** (Scheme 3) was synthesised by annulation of the aniline **8** with **5**. This formally electrophilic cyclisation was surprisingly still effective when carried out upon the very electron deficient aniline **8**. Displacement of the fluoro group to give **10** using the benzimidazole thiolate gave the required product even though deprotonation of the acidic 1*H*-quinolone might have been anticipated. Reduction of the nitro group gave **1b** which was reductively aminated with a variety of polar aldehydes to introduce solubilising substituents.

Replacements for the quinolinone moiety were required including indole **2** (Scheme 1).

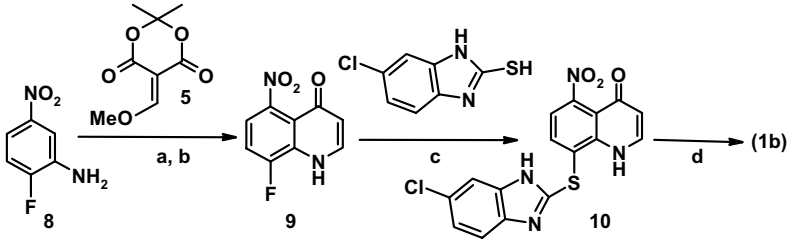
The Gassman indole synthesis[5] (Scheme 4) when carried out upon the fluoro-nitroaniline **8** gave the required oxindole **11** even though intramolecular displacement of the fluoro group by the ylide to give an alternative oxindole is plausible. The oxindole **11** could be reduced to a separable mixture of hydroxy derivatives **12** and **13**. These reacted in differing ways. The *syn*-disposition of the H-3 and the 2-hydroxyl resulted in imine formation and reduction to give the 3-methanesulfanyl-dihydroindole **14**. *anti*-Disposition resulted in the elimination of water to give the vinyl sulfide **15**.

Oxidation of **15** gave the required vinyl sulfone **16** (Scheme 5). Displacement of the fluoro group by the 2-thiobenzimidazole and reduction of the nitro group completed the required synthesis of **2**.

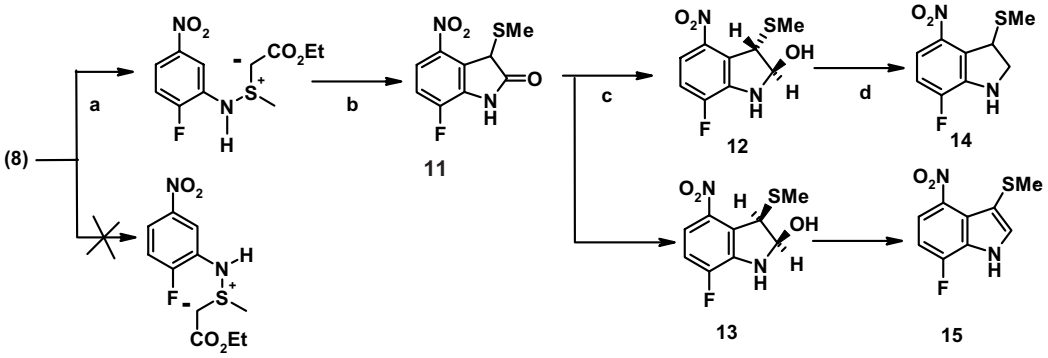
Incorporation of a 4-substituent on the benzimidazole was anticipated to be acceptable from knowledge of the binding orientation of these compounds relative to that of ATP. This was based upon X-ray crystallography of the compounds complexed with the target protein. The group in the 4-position utilises the space occupied by the ribose unit of ATP. However, the methodologies available to elaborate 4-substituted 2-thiobenzimidazoles were limited.

The required 4-nitrobenzimidazole **18** (Scheme 6) was prepared using the known regio-selective nitration of the seleno-protected dianiline **17**.[7]

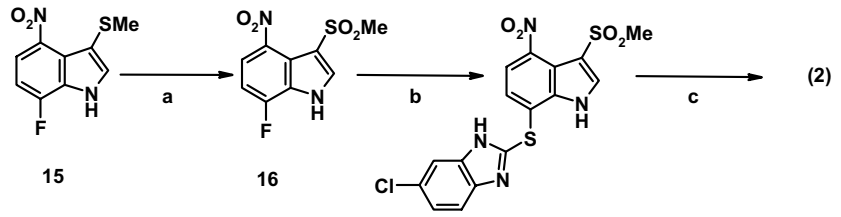
Reduction and diazotisation gave the iodide **19** (Scheme 7). This is the first reported synthesis of a 4-diazo-benzimidazole. The iodide underwent Heck type reactions.



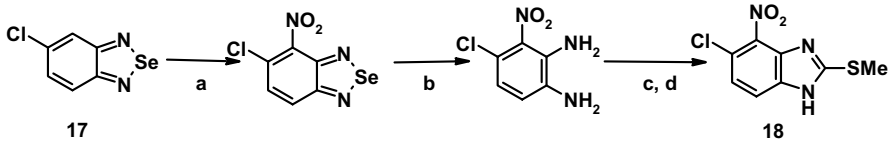
Scheme 3. Reagents, conditions and yields: (a) **5**, MeCN, rt, 20 h, 100%; (b) Ph_2O, 61%;[4] (c) 2-thiobenzimidazole, 10 M NaOH, EtOH, 100 °C, 20 h, 40%; (d) H_2, 10%Pd/C, AcOH, 5 bar, 8 days, 77%.



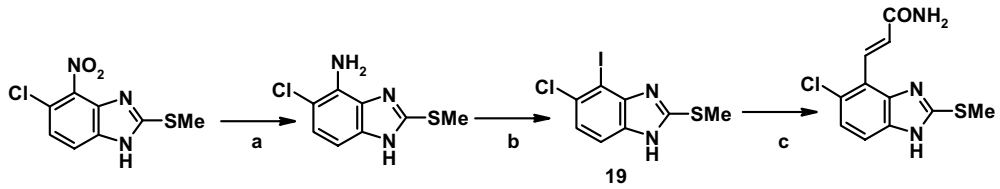
Scheme 4. Reagents, conditions and yields: (a) $MeSCH_2CO_2Et$, SO_2Cl_2, Proton-Sponge, DCM;[6] (b) Et_3N, −70 °C, 1 h then rt, 20 h, 70% over two steps; (c) 1 M BH_3, THF, 0 °C, 15 min; (d) rt, 20 h, 77% (41% **14**, 37% **15**).



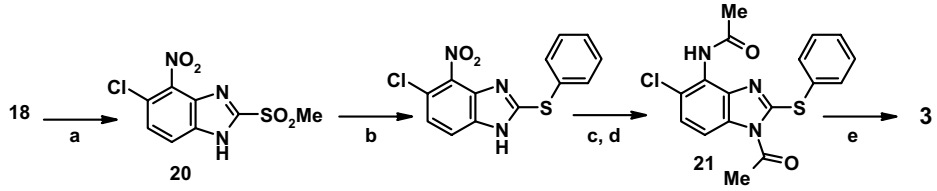
Scheme 5. Reagents, conditions and yields: (a) Oxone, MeOH, H_2O, rt, 30 h, 84%; (b) 2-thiobenzimidazole, *n*PrOH, KOH, reflux, 30 min, then **16**, reflux, 20 h, 42%; (c) $SnCl_2$, EtOH, reflux 7 h, 72%.



Scheme 6. Reagents, conditions and yields: (a) $cHNO_3$, cH_2SO_4, <10 °C, 3 h, 51%; (b) cHCl, 48% HI, rt, 2 h, 93%; (c) CS_2, DMF, rt, 5 days, 84%; (d) MeI, K_2CO_3, Me_2CO, rt, 20 h, 84%.



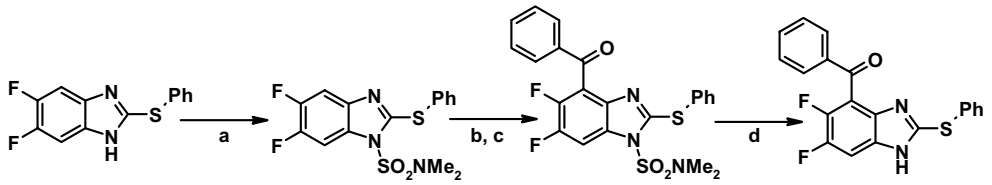
Scheme 7. Reagents, conditions and yields: (a) Fe, $EtOH/H_2O/AcOH/HCO_2H$ (70/22/7/1), reflux, 2 h, 86%; (b) $NaNO_2$, 2 N HCl, 3 °C, 1.5 h, then KI, rt, 20 h, 40%; (c) $CH_2CHCONH_2$, $Pd(OAc)_2$, (*o*-tolyl)$_3$P, Et_3N, MeCN, 80 °C, 20 h, 75%.



Scheme 8. Reagents, conditions and yields: (a) Oxone, MeOH, H_2O, rt, 20 h, 96%; (b) PhSH, IPA, reflux, 3 h, 82%; (c) Fe, $EtOH/H_2O/AcOH/HCO_2H$ (70/22/7/1), reflux, 4 h, 81%; (d) AcCl, Et_3N, DCM, rt, 20 h; (e) $NaHCO_3$, MeOH, rt, 20 h, 60% (two steps).

Oxidation of **18** gave the nitrosulfone **20** (Scheme 8), which surprisingly, but pleasingly, underwent regioselective displacement of the 2-sulfone rather than the 5-chloro group, to give the required 2-aryl thiobenzimidazole. This could be reduced to the aniline, then bis-acylated to give **21**. Mono deacylation then gave the required 4-*N*-acylated derivative **3**.

Finally, in a rare example of the use of 4-lithiobenzimidazoles, 5,6-difluoro-2-*S*-phenyl benzimidazole could be protected, lithiated and quenched at the 4-position with electrophiles (Scheme 9) to give the required 4-benzimidazole compounds. Similar chemistry with one or both of the fluoro-substituents replaced by chloro-groups failed to lithiate or gave unacceptable mixtures of products.



Scheme 9. Reagents, conditions and yields: (a) NaH, $ClSO_2NMe_2$, DMF, rt, 20 h, 50%; (b) LDA, THF, −78 °C, 20 min; (c) PhCOCl, THF, rt, 20 h, 95%; (d) 2 N HCl, IPA, 100 °C, 1 h, 95%.

The powerful inductive effect of fluorine substituents makes them very effective directors of *ortho*-metallation.[8]

The methods outlined above enabled a range of structurally diverse benzimidazoles to be synthesised and their biological properties to be examined.

References and notes

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3. Nakahara, S.; Kubo, A. *Heterocycles* **2003**, *60*, 2017–2018.
4. A typical experimental is as follows: 2,2-dimethyl-5-[2-(methylsulfanyl)anilino]-methylene-1,3-dioxane-4,6-dione (7 g) was added portionwise to stirred diphenyl ether (60 g) at reflux. After addition was complete, heating was continued for 15 min and then the mixture cooled with ice to 50 °C. The resulting solution was poured into stirred isohexane (800 ml) and the dark brown precipitate was collected by filtration (4.99 g).
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6. A typical experimental is as follows: A stirred solution of ethyl(methylthio)acetate (28.5 ml) in DCM (600 ml) at −70 °C was treated dropwise with sulfuryl chloride (16.5 ml) and stirred for 30 min. A solution of 2-fluoro-5-nitroaniline (28 g) and Proton-Sponge (46.2 g) in DCM (450 ml) was added dropwise at −70 °C and the mixture was stirred for 2 h. Et_3N (29.8 ml) was added at −70 °C and after 1 h the cooling bath was removed and the reaction stirred at 25 °C for 20 h. After aqueous work-up the resulting red oil was taken up in AcOH and stirred for 1 h before evaporation to dryness. Trituration with 2 N HCl followed by filtration and further trituration with Et_2O gave the required indole (30.6 g).
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