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Chemically enabled synthesis of 2-amino-4-heteroarylpyrimidines

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ABSTRACT

2-Amino-4-heteroarylpyrimidines were initially synthesized by microwave-induced S_NAr reactions of primary alkyl amines and 2-methylsulfonylpyrimidines or 2-chloropyrimidines. Following this methodology, pendant piperidine functionality was elaborated utilizing silica-bound reagents in microwave-assisted reductive amination and amide bond formation protocols. These methods proved to be versatile, efficient, and amenable to parallel synthesis.

c-Jun N-terminal kinase-1 (JNK1), a member of the mitogen-activated protein kinase (MAPK) family, has recently emerged as an attractive target for diabetes therapy, since JNK1 is believed to play a key role in linking obesity and insulin resistance.[1]

As part of an ongoing JNK1 drug discovery program in our laboratories, compounds **1** and **2** were identified from high-throughput screening (HTS) and possessed promising potency as well as attractive structural features amenable to optimization by rapid parallel synthesis (Fig. 1).

Unfortunately, **1** was highly cleared in vitro (human hepatocytes and liver microsomes). Metabolite ID studies revealed that metabolism was occurring exclusively on the alkylamino portion of the molecule. Our strategy was thus to dramatically reduce the lipophilicity (*E*LogD = 4.42) of this hit, whilst maintaining or improving the ligand efficiency (LE = 0.44).[2] More specifically, we wished to expediently and efficiently vary the alkylamino portion of the molecule.

The initial route to these targets was via the 2-methylsulfonylpyrimidine intermediate **7**. This intermediate was accessed in a straightforward fashion following the four-step protocol below (Scheme 1).[3] 2-Mercapto-4-methyl pyrimidine **3** was alkylated with iodomethane to afford 2-mercapto-4-methyl pyrimidine **4**.[4] Deprotonation and reaction of the anion of **4** with methyl 4-chlorobenzoate **5** gave ketone **6** in good yield.[4] Ketone **6** was initially treated with dimethylformamide dimethylacetal followed by hydrazine hydrate yielding the required pyrazole.[5] Oxidation of the methylsulfide intermediate to the required methylsulfonylpyrimidine **7** was achieved in a straightforward fashion.[6]

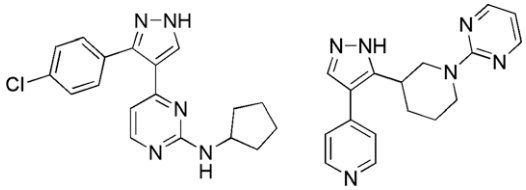

Figure 1. Initial hits from high-throughput screening.

The final S_NAr step was optimized under a variety of conditions, utilizing cyclopentylamine as our partner of choice.[7] Initially, it was found that performing this reaction in dioxane under microwave irradiation (137 °C, 10 min) afforded the required product (**8**, where R = cyclopentyl) in a 77% yield.[8] Unfortunately, when using this protocol with a small test set of amines and amine hydrochlorides, it was immediately apparent that the heterogeneity hindered the reaction progress in some instances. Further optimization showed that this reaction could be performed in 2-propanol (175 °C, 10 min) with no diminution in yield. Due to the reagents enhanced solubility and the higher reaction temperature, this optimized protocol showed greater generality over a more diverse set of amine monomers. For example, utilizing isopropylamine afforded the required product (R = ^{i}Pr) in 42% yield, 2-fluoroethylamine hydrochloride gave **8** (R = CH_2CH_2F) in 49% yield, and cyclobutylamine afforded **8** (R = cyclobutyl) in 56% yield.

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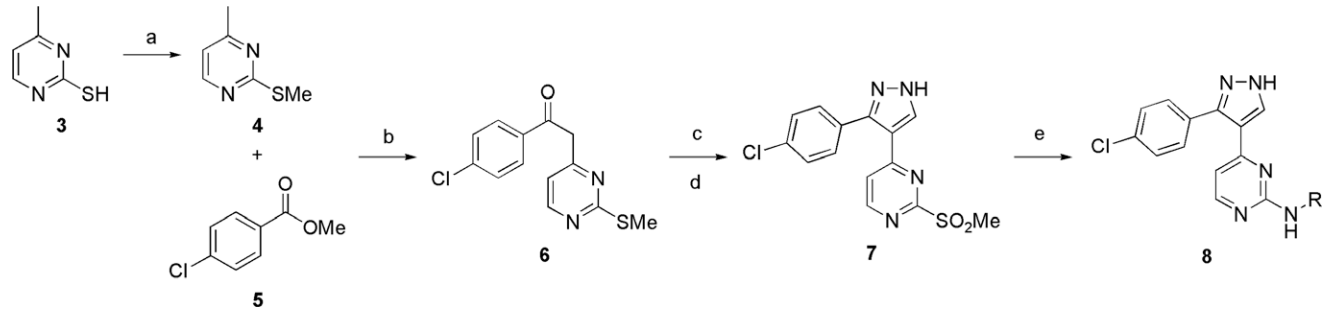


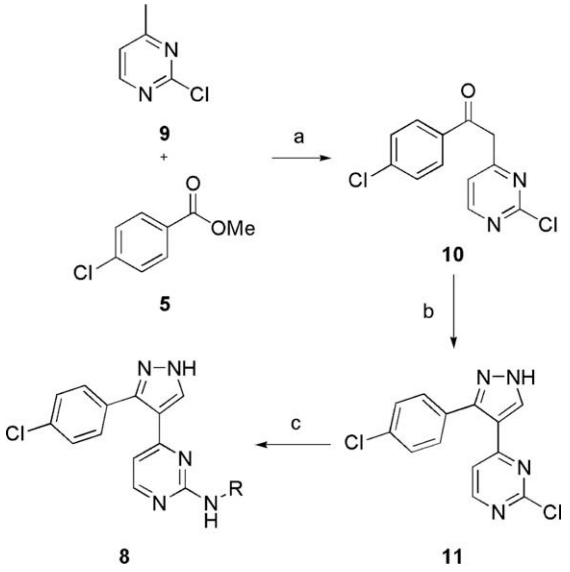
Scheme 1. Reagents and conditions: (a) NaOH, H_2O, EtOH, MeI, rt, 16 h, 95%; (b) LiHMDS, THF, 0 °C, 2 h, 89%; (c) $(MeO)_2CHNMe_2$, PhMe, reflux, 16 h then $H_2NNH_2{\cdot}H_2O$, EtOH, rt, 2 h, 84%; (d) *m*CPBA, CH_2Cl_2, rt, 16 h, 84%; (e) RNH_2, ^{i}PrOH, μW, 175 °C, 30 min.

Unfortunately, a number of amine monomers failed to give any pure final target, due to either their lack of reactivity (presumably due to steric hindrance and/or unfavorable electronics) or instability under the reaction conditions. For example, *tert*-butylamine, 1-methyl-1-phenylpropylamine, and benzhydrylamine all resulted in no isolable products. We therefore attempted to increase the reactivity of the pyrimidine electrophile by choosing to access these final targets via the 2-chloropyrimidine intermediate **11** (Scheme 2). The initial step of this synthetic route required slow addition (via syringe pump over 30 min) of chloropyrimidine **9** to LDA at −78 °C, followed by the addition of methyl 4-chlorobenzoate **5** to give ketone **10** in moderate yield.[5] The moderate yield was primarily due to competing addition of diisopropylamine to the chloropyrimidine moiety and hydrolysis of the reactive chloropyrimidine moiety to afford the polar pyrimidinone by-product. Ketone **10** was converted to pyrazole **11** as before, but this time in moderate yield.[5] Brief optimization of the final S_NAr step showed that the reaction could once again be performed in 2-propanol under microwave irradiation (160 °C, 60 min), but this time with added base and longer reaction times (most likely due to the unreactive nature of the chosen amines).[9] For example, utilizing *cis*-2-amino-1-cyclopentanecarboxamide afforded the required product in 29% yield, L-alaninamide hydrochloride gave **8** in 44% yield, and (*S*)-β-homoalanine hydrochloride afforded **8** in 41% yield.

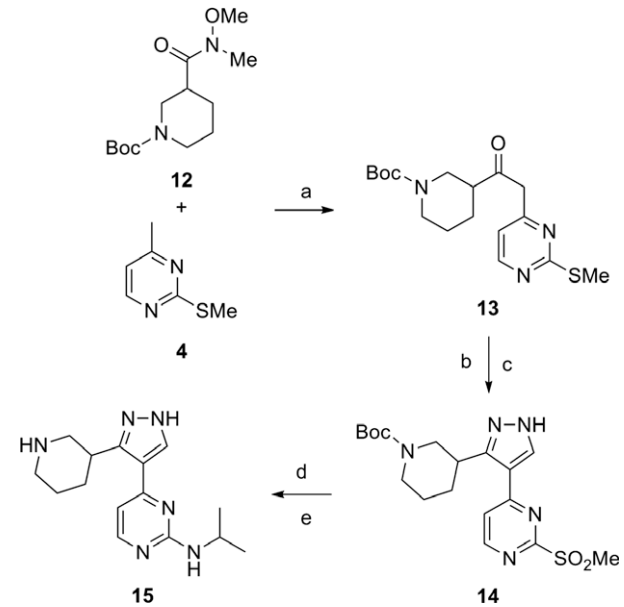
Our primary strategy for HTS hit **2** was to remove the 4-pyridyl moiety, so we decided to replace it with the 2-aminopyrimidine motif found in compound **1**. The synthetic scheme to access these molecules needed to be flexible enough to vary both the 2-aminopyrimidine moiety and the piperidine substitution in an efficient and expedient manner, in order to rapidly explore the SAR of this chemical series (Scheme 3).

The initial route to these targets was via the key piperidine intermediate **15**. Weinreb amide **12** was obtained via the method described by Barton et al.[10] 2-Mercapto-4-methyl pyrimidine **4** was then coupled with Weinreb amide **12**, at low temperature, to afford ketone **13** in good yield.[4] Compound **13** was then converted into the pyrazole and the sulfide was oxidized to sulfone **14** in short order.[5,6] Finally, sulfone **14** underwent S_NAr reaction with isopropylamine, followed by Boc deprotection to yield piperidine **15**. This synthetic route could be performed on large scale, with only the penultimate S_NAr reaction limiting the throughput of material.

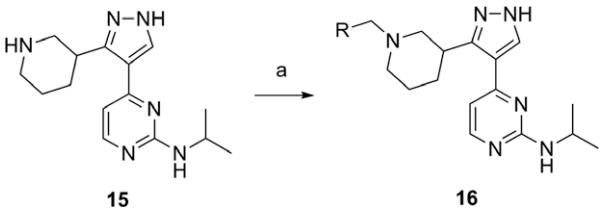
In an effort to functionalize intermediate amine **15**, we decided to explore the use of silica-bound cyanoborohydride-mediated reductive aminations (Scheme 4).[11] Specifically, amine **15** was irradiated with a variety of aldehydes in the presence of Silia*Bond*-cyanoborohydride at 150 °C for 5 min. The crude reaction mixture was then subjected to an SPE 'catch and release' work-up with SCX cartridges.[12] This allowed for the products **16** to be isolated in pure



Scheme 2. Reagents and conditions: (a) LDA, THF, −78 °C, 16 h, 35%; (b) $(MeO)_2CHNMe_2$, PhMe, reflux, 16 h then $H_2NNH_2{\cdot}H_2O$, EtOH, rt, 2 h, 45%; (c) RNH_2, ^{i}PrOH, ^{i}Pr$_2$NEt, μW, 160 °C, 60 min.

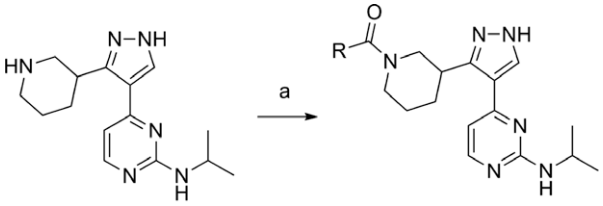


Scheme 3. Reagents and conditions: (a) LiHMDS, THF, 0 °C, 2 h, 84%; (b) $(MeO)_2CHNMe_2$, PhMe, reflux, 16 h then $H_2NNH_2{\cdot}H_2O$, EtOH, rt, 2 h, 63%; (c) *m*CPBA, CH_2Cl_2, rt, 16 h, 77%; (d) ^{i}PrNH$_2$, dioxane, 110 °C, sealed tube, 4 h; (e) HCl, ^{i}PrOH, reflux, 2 h, 34% (two steps).



15 16

Scheme 4. Reagents and conditions: (a) RCHO, Silia*Bond*-cyanoborohydride, AcOH, DMF, μW, 150 °C, 5 min.



15 17

Scheme 5. Reagents and conditions: (a) RCO_2H, Silia*Bond*-carbodiimide, CH_2Cl_2, μW, 150 °C, 5 min.

form, free from any residual DMF solvent. For example, utilizing acetaldehyde afforded the required product (R = Me) in 91% yield, benzaldehyde gave **8** (R = Ph) in 97% yield, and cyclopropanecarboxaldehyde afforded **8** (R = cyclopropane) in 94% yield.

Exploration into the use of silica-bound carbodiimide-mediated amide bond formations was also deemed of interest (Scheme 5).[11] Specifically, amine **15** was irradiated with a variety of carboxylic acids in the presence of Silia*Bond*-carbodiimide at 150 °C for 5 min to afford amides **17**. For example, utilizing isobutyric acid afforded the required product (R = ^{i}Pr) in 98% yield, benzoic acid gave **8** (R = Ph) in 94% yield, and cyclohexanecarboxylic acid afforded **8** (R = cyclohexane) in 97% yield.

In summary, we have successfully developed a number of efficient and versatile routes to 2-amino-4-heteroarylpyrimidines. Efforts on hit compound **1** required target compounds to be synthesized by microwave-induced S_NAr reactions of primary alkyl amines and 2-methylsulfonylpyrimidines or 2-chloropyrimidines. Hit-to-lead efforts on hit **2** allowed for pendant piperidine functionality to be elaborated utilizing silica-bound reagents in microwave-assisted reductive amination and amide bond formation protocols.

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