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Synthetic approaches to 5,7-disubstituted imidazo[5,1-*f*][1,2,4]triazin-4-amines

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ABSTRACT

The preparation of 5,7-disubstituted imidazo[5,1-*f*][1,2,4]triazin-4-amines, exemplified by 5-[3-(benzyloxy)phenyl]-7-cyclobutylimidazo[5,1-*f*][1,2,4]triazin-4-amine, was developed through a linear and three convergent synthetic strategies, with the latter providing the greatest flexibility for diversification at the 5-position at the last step of the synthesis.

Kinases represent a class of proteins that serve as important signal regulators for a variety of cellular functions such as differentiation, proliferation, and apoptosis. Efforts within our group directed at identifying inhibitors of such enzymes for use in oncology led to the 5,7-disubstituted imidazo[5,1-*f*][1,2,4]triazin-4-amine scaffold as such a chemotype of interest (Fig. 1).[1] To the best of our knowledge, only a few papers have reported the syntheses of such a heterobicyclic skeleton and a logical synthetic precursor imidazo[5,1-*f*][1,2,4]triazin-4-one,[2] with none being suitable for late-stage diversification at the key 5-position where substitution is known to drive structure–activity relationships (SARs) versus a number of kinase targets.[3] Herein, we describe our initial linear preparation of a proof-of-concept compound **1** starting from methyl amino[3-(benzyloxy)phenyl]acetate **2**, as well as three different convergent synthetic routes which allowed for late-stage analoging at the 5-position via Pd-catalyzed transformations. The synthetic strategy of both linear and convergent routes is shown in Scheme 1.

The details of the linear synthesis are illustrated in Scheme 2. The amino ester **2**[4] was converted to *N*-acyl amino acid **3**, from which the keto-ester **4** was prepared via a Dakin–West reaction[2d] in a modest 16% yield. Attempted cyclization of **4** with formamidrazone [CH(=NH)NHNH$_2$], generated in situ by mixing hydrazine and formamidine in a 1:1 ratio, failed to produce the desired 1,2,4-triazinone **6**.[2d] Therefore, we applied hydrazonoformic hydrazide [CH(=NHNH$_2$)NHNH$_2$], generated in situ by mixing hydrazine and formamidine in a 2:1 ratio, in the cyclization reaction[5] and by using these conditions, compound **5** was successfully obtained in 45% yield. Deamination via the diazonium salt using sodium nitrite in concd HCl afforded **6** in 83% yield.[6] Cyclization of compound **6** with POCl$_3$ provided the desired bicyclic imidazotriazinone **7** in quantitative yield. Installation of a 4-amino group into analogous systems usually requires a two-step sequence: 4-chlorination using POCl$_3$ and subsequent displacement with amines. Although certain 4-chloro imidazotriazine intermediates have been reported to be stable and isolable,[2c] our one-pot procedure using POCl$_3$ and quenching with 1 M NH$_3$ in 2-propanol resulted in no desired product and only recovery of the starting material **7**. However, treatment of compound **7** with POCl$_3$ and 1,2,4-triazole in pyridine and subsequent displacement of the intermediate 1,2,4-triazole adduct[2b] using the above ammonia solution in a one-pot fashion afforded the target compound **1** in 39% yield.[7]

While the synthesis of compound **1** via this linear route was successful, the route was not suitable for the late-stage diversification necessary to further explore the SAR at the 5-position of this new series. Therefore, we undertook the development of a convergent route (I), which would allow for such a late-stage introduction of various substitutions to the 5-position, ideally in the last step of the synthesis.

Our first convergent synthetic route is shown in Scheme 3. Initially we attempted the cyclization of keto-ester **8**[2a] with hydrazonoformic hydrazide prepared in situ, following the same strategy used in the linear synthetic route. Unfortunately, the reaction resulted in a complicated mixture, most likely due to degradation of the phthalimide by the hydrazine component in the reaction mixture. In order to improve this cyclization process, the commercially available thiosemicarbazide was employed, utilizing sulfur as a masked hydrogen at the 2-position.[8] Formation of the hydrazone in EtOH at 80 °C and subsequent treatment with *N*,*N*-diisopropylethylamine successfully afforded the thio-1,2,4-triazinone **9** in 81%

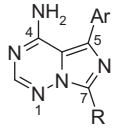

Figure 1. General structure of the imidazo[5,1-*f*][1,2,4]triazine system.

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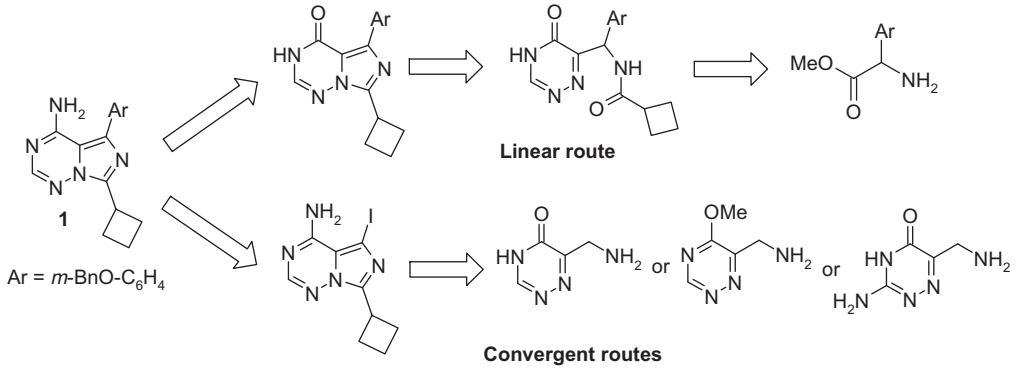
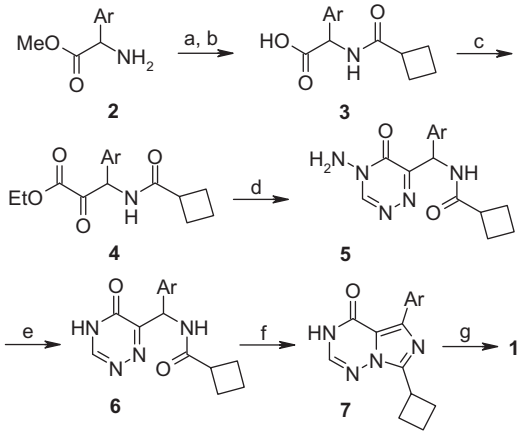
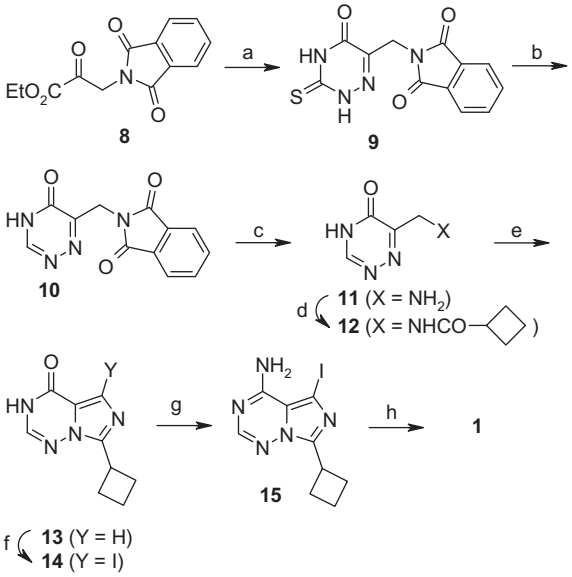


Scheme 1. Synthetic strategy.



Scheme 2. Linear synthetic route. Reagents and conditions: (a) cyclobutanecarbonyl chloride, $NaHCO_3$, THF, 0 °C to rt, 83%; (b) 1 M NaOH, THF/H_2O (1:1), 84%; (c) (i) EtO_2CCOCl, pyridine, DMAP, THF, reflux; (ii) NaOEt, EtOH, reflux, 16%; (d) 1 M N_2H_4 in THF, HC(=NH)NH_2·HCl, EtOH, 0 °C to −20 °C to rt, 45%; (e) $NaNO_2$, concd HCl, EtOH/H_2O, 0 °C to rt, 83%; (f) $POCl_3$, 55 °C, 100%; (g) 1,2,4-triazole, $POCl_3$, pyridine, rt, then 1 M NH_3 in *i*-PrOH, 0 °C to rt, 39%.

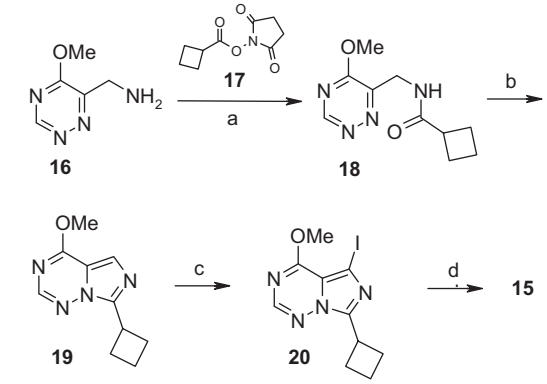


Scheme 3. Convergent route I. Reagents and conditions: (a) thiosemicarbazide, EtOH, 80 °C, 3 h, then DIEA, 40 °C, 16 h, 81%; (b) Raney Ni (10 equiv), EtOH, reflux, 70%; (c) anhydrous hydrazine, DCM/EtOH (1:1), rt; (d) cyclobutanecarbonyl chloride, DIEA, DMF, 0 °C to rt, 57% (two steps from **10**); (e) $POCl_3$, 55 °C, 41%; (f) 5 equiv NIS (5 equiv), DMF, rt to 55 °C, 53%; (g) 1,2,4-triazole, $POCl_3$, pyridine, rt, then 1 M NH_3 in *i*-PrOH, 0 °C to rt, 82%; (h) [3-(benzyloxy)phenyl]boronic acid, $PdCl_2$(dppf), K_2CO_3, dioxane/H_2O (4:1), 100 °C (microwave), 30 min, 72%.

yield. Desulfurization of compound **9** using Raney nickel[9] resulted in compound **10** in 70% yield. Removal of the phthalimide-protecting group with hydrazine provided key intermediate **11**. With compound **11** in hand, various C-5 and C-7 substitutions could be readily installed. Amidation of compound **11** and subsequent treatment with $POCl_3$ yielded the bicyclic compound **13**. Iodination of **13** proceeded with 5 equiv of *N*-iodosuccinimide (NIS) at 55 °C, and the resulting 5-iodoimidazotriazinone **14** was converted to the versatile 4-amino intermediate **15** in 82% yield, using the method described previously for the linear route. From key intermediate **15**, various substitutions could be introduced to the C-5 position by Pd-catalyzed coupling reactions. For example, compound **1** was readily synthesized via Suzuki chemistry with [3-(benzyloxy)phenyl]boronic acid in 72% yield.

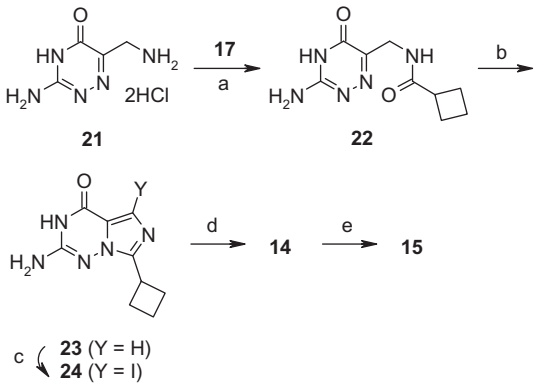
Although route I was effective at providing the desired intermediate **15**, larger scale synthesis proved to be challenging. Firstly, the keto-ester **8** was not easy to synthesize and required a two-step procedure using relatively expensive starting materials.[2a,10] Secondly, the poor solubility of intermediates **9**–**11** and the 1,4-dihydroxyphthalazine byproduct (**10**→**11**) made the scalability and purification challenging. Thirdly, this synthetic route was still considered too lengthy. As a result, we continued exploring other potential routes to prepare the key intermediate **15**.

Our second convergent synthetic route is shown in Scheme 4. Compound **16** was prepared from 6-methyl-4*H*-[1,2,4]triazin-5-one in four steps.[11] Amidation of **16** with the active ester **17** and



Scheme 4. Convergent route II. Reagents and conditions: (a) 10% aq $NaHCO_3$, THF, rt, 72%; (b) $POCl_3$, DMF/MeCN, rt, 55%; (c) NIS, DMF, 55 °C, 68%; (d) 7 N NH_3 in MeOH, rt, 89%.

subsequent $POCl_3$ cyclization gave compound **19** in 40% yield. Iodination of **19** using NIS was realized at 55 °C to give compound



Scheme 5. Convergent route III. Reagents and conditions: (a) 1 M $NaHCO_3$, THF/MeCN (1:1), rt, 83%; (b) $POCl_3$, 1,2-dichloroethane, reflux, 90%; (c) NIS, DMF, rt, 75%; (d) *t*-butylnitrite, 5% DMF/THF (1:5), rt, 91%; (e) 1,2,4-triazole, $POCl_3$, pyridine, rt, then 1 M NH_3 in *i*-PrOH, 0 °C to rt, 82%.

20. The 4-MeO group of **20** was readily displaced by ammonia at rt using 7 N NH_3 in MeOH, providing the intermediate **15**. The NMR spectroscopic data of compound **15** were identical to those obtained when **15** was prepared according to route I (Scheme 3). Of note, there were no solubility issues in this route as was the case in route I.

Our third convergent synthetic route is shown in Scheme 5. Condensation of the inexpensive reagents ethyl bromopyruvate, dibenzylamine, and aminoguanidine bicarbonate, followed by debenzylation via hydrogenation over Pd–C afforded the known 3-amino-6-(aminomethyl)-1,2,4-triazin-5(4*H*)-one dihydrochloride compound **21**.[12a] Selective amidation with the active ester **17** followed by subsequent $POCl_3$ cyclization smoothly afforded compound **23**.[12b] In comparison with the iodination of **13** and **19**, the iodination of **23** was facile using 1.2 equiv of NIS at rt and the isolated yield was improved to 75%. The overall improvement in the reaction is presumed to be due to the electron-donating effect of the 2-NH_2 group activating the 5-position. Removal of the 2-NH_2 group in the imidazotriazinone **24** was the key step in our synthetic design and was realized using 5.0 equiv *t*-butyl nitrite in DMF/THF (1:5, v/v) at rt., affording the desired product **14** in 91% yield.[13] The NMR spectroscopic data of **14** and the subsequent ammonolysis product **15** were identical to those obtained when **15** was prepared according to route I (Scheme 3).

In conclusion, multiple synthetic routes to the novel heterobicyclic scaffold 5,7-disubstituted imidazo[5,1-*f*][1,2,4]triazin-4-amine have been achieved. The linear route, while limited in scope and overall yield, allowed the preparation of an initial proof-of-concept compound **1**, while the three subsequent convergent routes allowed for the rapid and broad exploration of the C-5 and C-7 positions. Of the convergent routes, route III proved the most robust and practical for large-scale synthesis although all of these routes were successfully and extensively used in the medicinal chemistry exploration around this novel core. Based on these chemistries, several oncology-focused novel kinase inhibitors have emerged that are now progressing through the development/clinical stage. Further chemistry exploration based on convergent routes II and III and the biological significance of this chemotype will be discussed in future communications.

Acknowledgments

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7. *Compound* **1**: a white solid, mp 163–165 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 7.89 (s, 1H), 7.46–7.51 (m, 2H), 7.38–7.44 (m, 3H), 7.34 (m, 1H), 7.27 (dd, J = 2.3, 1.5 Hz, 1H), 7.23 (m, 1H), 7.08 (ddd, J = 8.3, 2.5, 0.8 Hz, 1H), 5.17 (s, 2H), 4.04 (quin, J = 8.3 Hz, 1H), 2.42–2.48 (m, 2H), 2.30–2.41 (m, 2H), 2.08 (m, 1H), 1.93 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 158.7, 155.9, 149.1, 145.4, 137.0, 135.7, 133.7, 130.0, 128.4, 127.8, 127.6, 121.2, 115.0, 114.5, 109.9, 69.3, 30.4, 26.7, 18.3; HRMS (ES) calcd for $C_{22}H_{22}N_5O$ [MH$^+$]: 372.1824, found: 372.1819.
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