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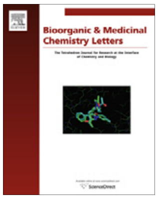

Proline isosteres in a series of 2,4-disubstituted pyrrolo[1,2-*f*][1,2,4]triazine inhibitors of IGF-1R kinase and IR kinase

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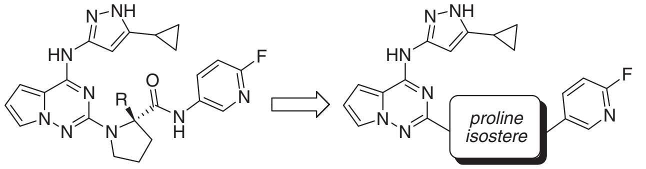
ABSTRACT

Pyrrolidine, pyrrolidinone, carbocyclic, and acyclic groups were used as isosteric proline replacements in a series of insulin-like growth factor I receptor kinase/insulin receptor kinase inhibitors. Examples that were similar in potency to proline-containing reference compounds were shown to project a key fluoropyridine amide into a common space, while less potent compounds were not able to do so for reasons of stereochemistry or structural rigidity.

We have previously described the discovery of the clinical development candidate **1a**,[1] a potent and selective inhibitor of insulin-like growth factor I receptor kinase (IGF-1R), an important emerging oncology target,[2] and insulin receptor kinase. Both **1a** and related compound **1b** feature a carbon–nitrogen bond connecting the ring nitrogen of a proline to the pyrrolo[1,2-*f*][1,2,4]triazine core. The early SAR exploration that led to the discovery of these compounds focused on the synthesis of heterocyclic proline amides. Retaining the fluoropyridine amide of **1a** and **1b** as an optimal substituent, recent efforts shifted toward a series of analogs (**2**) that replaced the nitrogen-linked proline moiety with an isostere that featured a carbon–carbon bond to the pyrrolotriazine core (Fig. 1). This carbon–carbon linkage was unprecedented in our research program at the time, and provided an opportunity to introduce diversity while monitoring for changes in the SAR compared to the carbon–nitrogen-linked analogs. Specifically, we focused on four categories of carbon-linked proline isosteres; pyrrolidine, pyrrolidinone, carbocyclic, and acyclic. Herein, we describe the IGF-1R potency of these analogs.

The syntheses of two enantiomeric carbon-linked pyrrolidine analogs were conducted separately. The EDC-mediated condensation of 1-amino-1*H*-pyrrole-2-carboxamide[3] **3** with (*S*)- or (*R*)-*N*-Boc proline, respectively, provided **4**, which was cyclized to **5** in hot aqueous KOH (Scheme 1). The protecting group was then switched from Boc to Cbz in a one-pot procedure to give **6** because a single protecting group compatible with all synthetic steps was not found. Although the Cbz-protected analog of **4** underwent cyclization with hot aqueous KOH, the Cbz was partially removed[4] and provided a lower overall yield. The Boc group was found to be unstable to later steps, necessitating the switch to the Cbz group. Activation of **6** with BOP[5] followed by exposure to 5-cyclopropyl-1*H*-pyrazol-3-amine produced mostly the undesired ring-nitrogen addition product **7** with only a minor amount of the desired isomer **8**.[6,7] Alternatively, **6** was converted to the heteroaryl chloride with $POCl_3$. The addition of the 5-cyclopropyl-1*H*-pyrazol-3-amine to a preheated (>70 °C) solution of this intermediate gave a ~3:1 ratio of **8** to **7**.



1a, R = Me
1b, R = H

2

Figure 1.

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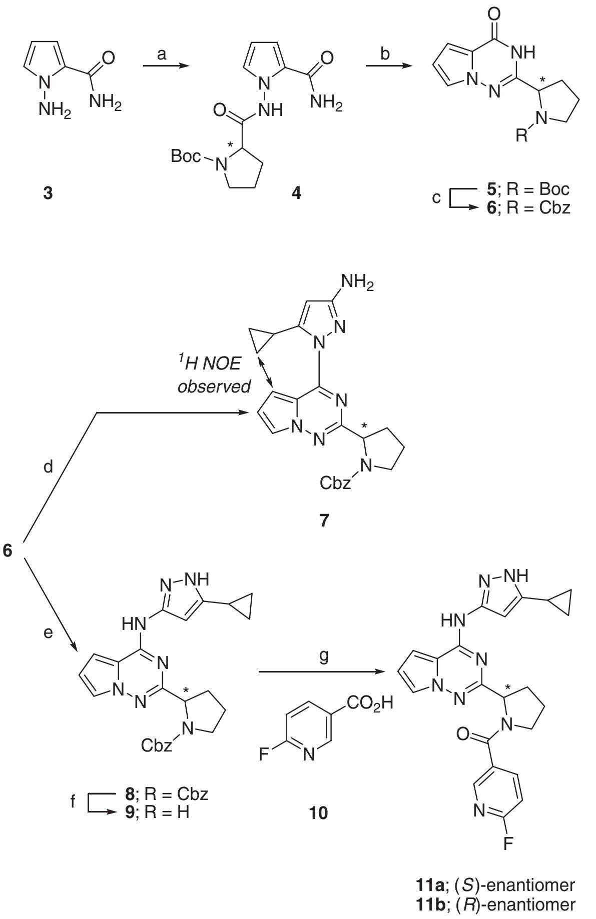
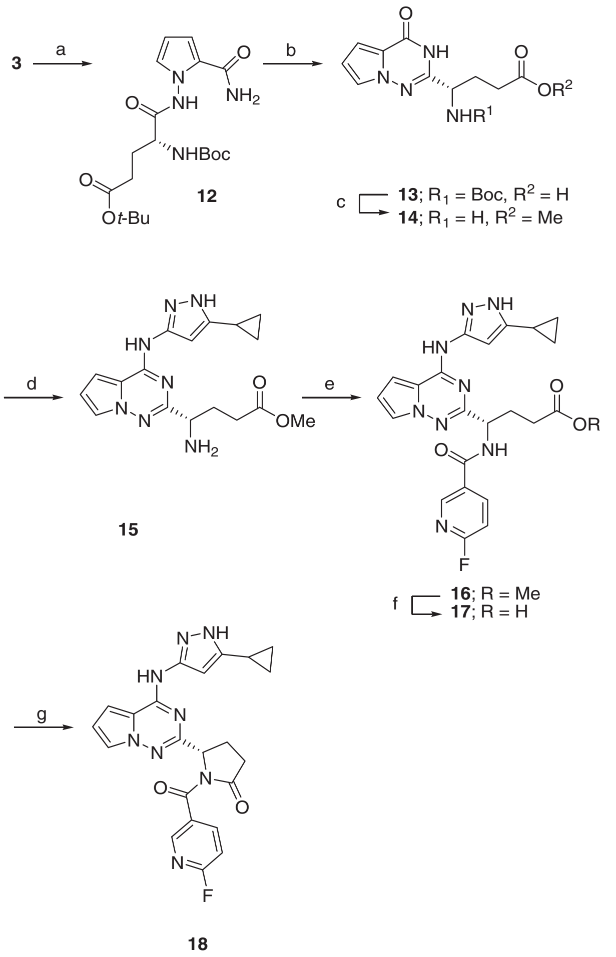
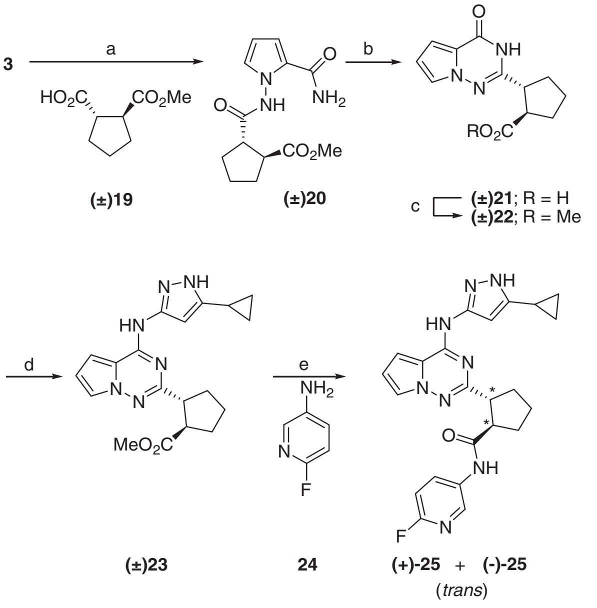


Scheme 1. Reagents and conditions: (a) (*R*)- or (*S*)-*N*-Boc-Pro, EDC, THF, 81%; (b) aq KOH, reflux, 3 days, 62%; (c) i—TFA, DCM; ii—Cbz-Cl, aq $NaHCO_3$, 89%; (d) i—BOP, MeCN, DBU, rt, 10 min; ii—5-cyclopropyl-1*H*-pyrazol-3-amine, DIPEA, NMP, 70 °C, 50%; (e) i—$POCl_3$, 80 °C, 1 h; ii—5-cyclopropyl-1*H*-pyrazol-3-amine, DIPEA, NMP, 70 °C, 45%; (f) 10% Pd/C, MeOH, HCO_2H, rt, 20 min, 89%; (g) HATU, DIPEA, NMP, 39%.



Scheme 2. Reagents and conditions: (a) Boc-Asp-O*t*-Bu, EDC, THF, 85%; (b) aq KOH, EtOH, 90%; (c) MeOH, acetyl chloride, 80%; (d) i—$POCl_3$, 80 °C; ii—5-cyclopropyl-1*H*-pyrazol-3-amine, NMP, 80 °C, 55%; (e) **10**, HATU, DIPEA, NMP, 40%; (f) aq LiOH, THF, 89%; (g) i—pentafluorophenol trifluoroacetate, pyridine, THF; ii—0.1 M $NaHCO_3$, THF, MeCN, 67%.



Scheme 3. Reagents and conditions: (a) **3**, EDC, THF, 72%; (b) aq KOH, EtOH, reflux, 90%; (c) MeOH, acetyl chloride, 84%; (d) i—$POCl_3$, 85 °C; ii—5-cyclopropyl-1*H*-pyrazol-3-amine, NMP, 85 °C, 50%; (e) i—MeMgBr, **24**, Et_2O, THF, 69%; ii—chiral separation.

Addition at lower temperatures, even with subsequent heating, still favored the formation of **7**. This pattern of reactivity was observed with subsequent analogs, which typically afforded similar ratios of isomers under the same conditions. With **8** in hand, removal of the Cbz protecting group via transfer hydrogenation cleanly afforded **9**, which was then acylated with **10** to give either **11a** or **11b**.

Using a modified approach, a pyrrolidinone analog was constructed beginning with the condensation of **3** and Boc-Asp-O*t*-Bu to give **12** (Scheme 2). Cyclization was effected to afford **13**, which was then exposed to in situ generated HCl in methanol. This simultaneously removed the Boc protecting group while protecting the carboxylic acid as its methyl ester (**14**). Conversion to the heteroaryl chloride intermediate followed by high temperature addition of 5-cyclopropyl-1*H*-pyrazol-3-amine led to mostly **16**, with a minor amount of an undesired ring-nitrogen addition isomer. Hydrolysis gave the free carboxylic acid **17**, which was converted to pyrrolidinone **18** via conversion to its pentafluorophenol ester followed by cyclization with mild aqueous base.

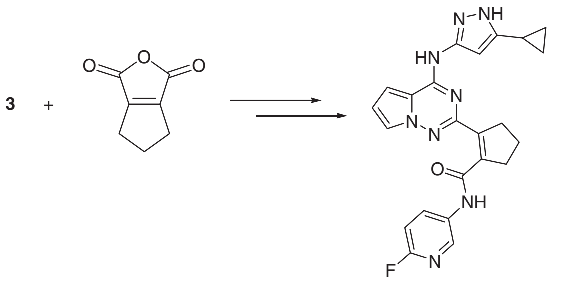
Two cyclopentane-based analogs were synthesized starting with *trans*-1,2-cyclopentanedicarboxylic acid monomethyl ester [(±)**19**] (Scheme 3).[8b] Condensation with **3** afforded (±)**20**, which was cyclized to (±)**21** in high yield. These conditions also removed the methyl ester, which was reintroduced under Fischer conditions to give (±)**22**. Activation with $POCl_3$ and addition of 5-cyclopropyl-1*H*-pyrazol-3-amine produced (±)**23**, again with only a minor amount of an undesired ring-nitrogen addition isomer. The addition of the magnesium salt of 6-fluoropyridin-3-amine (**24**) to (±)**23** followed by chiral separation gave (+)-**25** and (−)-**25**.[9] The achiral cyclopentene analog **27** was constructed in a similar manner, starting with the commercially available anhydride **26** (Scheme 4).

The synthesis of a simple acyclic analog began with the condensation of *N*-Boc glycine with **3** to give **28**, which was smoothly cyclized to **29** (Scheme 5). A switch of the protecting group from Boc to phthalate gave **30** in high yield. This was necessary because the phthalate-protected analog of **28** failed to cyclize under a variety of conditions, while the Boc-protected compound **29** was not stable to the POCl$_3$ used in the following step to convert **30** to the heteroaryl chloride intermediate **31**. High-temperature addition of 5-cyclopropyl-1*H*-pyrazol-3-amine to **31** gave mostly **32** with a minor amount of an undesired ring-nitrogen addition isomer. Removal of the phthalate protecting group with hydrazine afforded **33**, which was then acylated with **10** to produce **34**.

Table 1
SAR of proline-replacement analogs

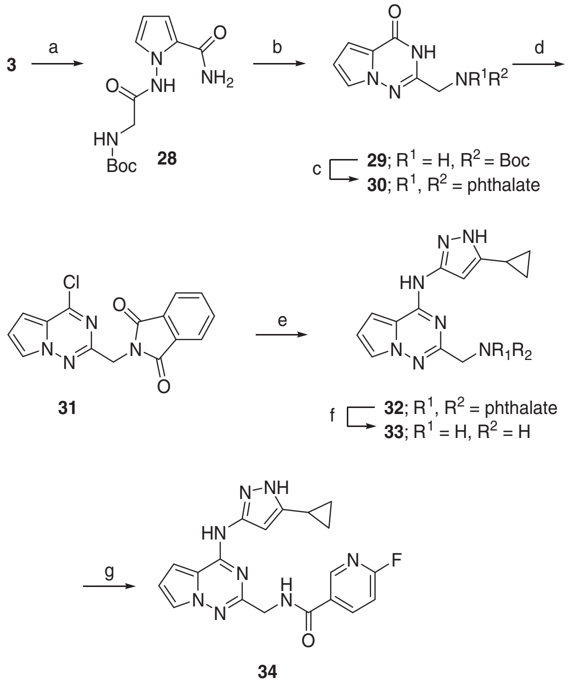
Compound	IGF-1R IC$_{50}$ (nM)	IGF-Sal IC$_{50}$ (nM)	PAMPA (nm/s)
1a	8.4	2.1	634
1b	2.7	1.0	770
11a	7.0	162	721
11b	8400	n/a	935
18	11	508	600
(+)-**25**	9.7	206	509
(−)-**25**	190	389	854
27	32	237	822
34	5.3	40	525

Table 1 shows the IGF-1R kinase potencies for the new analogs in comparison to **1a** and **1b** as well as IGF-Sal cellular potencies and PAMPA permeability. All analogs exhibited no selectivity versus IR.



26 **27**

Scheme 4.



Scheme 5. (a) *N*-Boc Gly, EDC, THF, 82%; (b) EtOH, aq KOH, 100 °C, 86%; (c) i—HCl, dioxane, 100%; ii—phthalic anhydride, DMF, 98%; (d) POCl$_3$, 100 °C, 64%; (e) 5-cyclopropyl-1*H*-pyrazol-3-amine, DIPEA, NMP, 80 °C; (f) hydrazine hydrate, EtOH, 40 °C, 55%; (g) **10**, HATU, DIPEA, NMP.

Structural differences between **11a** and **11b** compared to **1a** include the number of connecting atoms between the fluoropyridine and the pyrrolotriazine core, the secondary versus tertiary nature of the amide, and the direction of the amide connectivity. Despite these differences, IGF-1R potency of **11a** was comparable to that of **1a** and **1b**. The (*R*)-enantiomer (**11b**) showed a 1200-fold decrease in kinase potency versus **11a**, which led us to suspect a suboptimal placement of the fluoropyridine amide.

Pyrrolidinone analog **18** showed only a small reduction of IGF-1R potency. Because of the dramatic loss of potency demonstrated by **11b** compared to **11a**, the (*R*)-enantiomer of **18** was not made.

Carbocycles have previously been used as proline isosteres.[8] One of the cyclopentane analogs, (+)-**25**, showed comparable potency to **1a**, while (−)-**25** was approximately 20-fold less potent. Cyclopentene analog **27** suffered a moderate loss of IGF-1R potency.

The acyclic analog **34** was considered experimentally equipotent to **11a**,[10] demonstrating that a cyclic proline isostere was not necessary for kinase potency.

Individual X-ray structures of **1a**, **11a**, **11b**, and **34** co-crystallized with IGF-1R were obtained.[11] All four compounds exhibit the hydrogen bond donor–acceptor–donor triad across the aminopyrazole substituent to the hinge binding region of IGF-1R

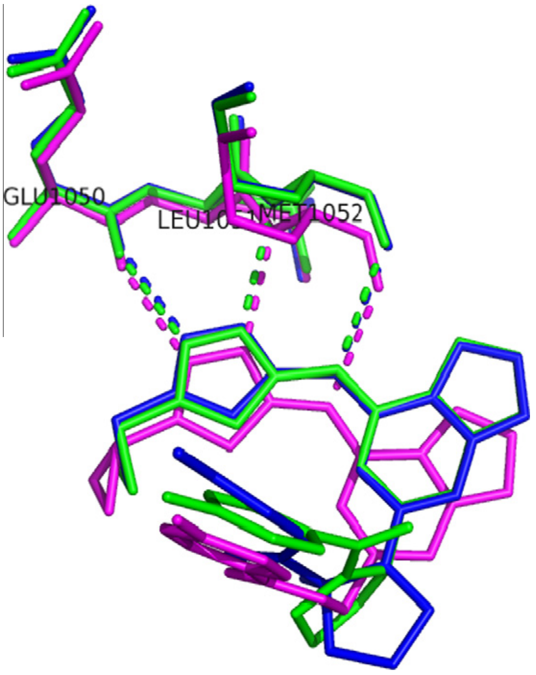


Figure 2. Overlay of the X-ray co-crystal structures of IGF-1R with **1a** (blue), **11a** (green), and **34** (magenta).

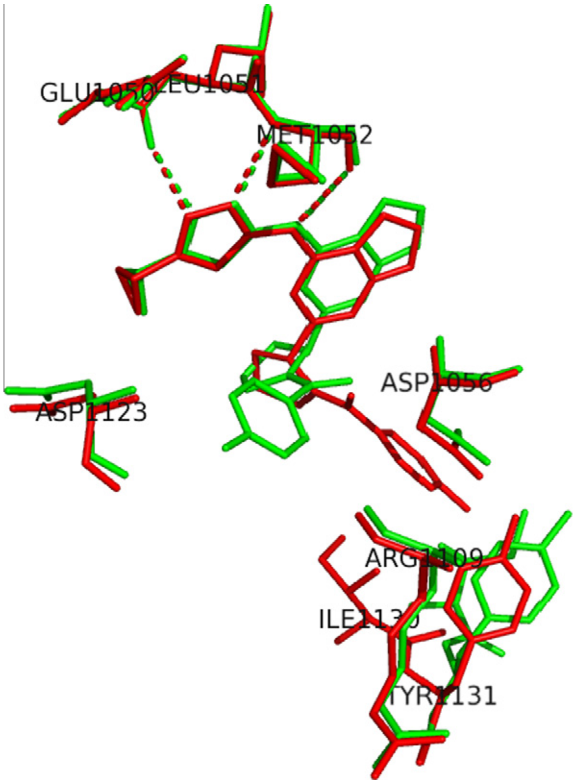


Figure 3. Overlay of the X-ray co-crystal structures of IGF-1R with **11a** (green) and **11b** (red).

(Glu1050, Leu1051, and Met1052). Despite the structural differences in the groups linking the fluoropyridine amide to the pyrrolotriazine core, **1a**, **11a**, and **34** occupy much the same space in the regions critical for IGF-1R potency (Fig. 2). In contrast, **11b** was shown to display the fluoropyridine into a space that brings it into steric conflict with Asp1056, explaining its sharp loss of potency versus its enantiomer **11a** (Fig. 3). The additional carbonyl present in **18** did not substantially affect IGF-1R potency, implying that the placement of the fluoropyridine was not significantly changed compared to **11a**. Although the difference in potency between (+)-**25** and (−)-**25** is not as dramatic as that of **11a** and **11b**, a similar situation could reasonably be envisioned whereby one enantiomer has a clear stereochemical advantage over the other in the context of IGF-1R binding. Finally, the moderate decrease in potency of **27** could be explained by the rigid double bond of the cyclopentene ring at least partially preventing what appears to be the need for a slight turn or bend necessary for optimal placement of the fluoropyridine moiety.

For reasons which were not clear, none of the new analogs demonstrated potency in the IGF-Sal cellular assay.[12] Passive permeability as measured in the PAMPA assay indicated the compounds were permeable, and the IGF-Sal cell line does not have a functional efflux mechanism. Nevertheless, in this case PAMPA was not predictive of cellular potency despite the comparable kinase potencies of some of the new analogs compared to **1a** and **1b**.

In summary, this series of analogs demonstrate that a variety of groups could replace the proline of **1a** or **1b** and retain IGF-1R kinase potency provided the key fluoropyridine amide in each was able to be positioned into a similar space. As evidenced by X-ray co-crystal structures with IGF-1R, both cyclic and acyclic proline isosteres demonstrated this ability. Analogs that had reduced IGF-1R potency were shown or presumed to place the fluoropyridine into a suboptimal space, due to stereochemical factors or structural rigidity.

Acknowledgments

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10. Experimental variability is typically 2×. See Ref. 1 and citations therein for a more complete description of both the IGF-1R kinase and IGF-Sal cellular assays.
11. The atomic coordinates have been deposited in the RSCB Protein Data Bank as entries 3I81 (**1a**), 3NW5 (**11b**), 3NW6 (**11a**), and 3NW7 (**34**).
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