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A concise synthesis of quinazolinone TGF-β RI inhibitor through one-pot three-component Suzuki–Miyaura/etherification and imidate–amide rearrangement reactions

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This paper is dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday

Abstract—A simple and efficient synthesis of dihydropyrrolopyrazole boronic acid intermediate (**5**) has been developed. Utilization of a three-component Suzuki–Miyaura/etherification with microwave heating led to advanced compound **11** in high yield and with easy purification. Reaction of compound **11** with methanesulfonyl chloride at room temperature furnished the 1,3 *O–N* rearranged product (**12**), which is postulated to proceed via an intramolecular mechanism. The outlined synthesis provides a highly efficient and high-yielding route that is amenable to rapid analog synthesis.

1. Introduction

The serine/threonine kinase TGF-β RI is a member of a large family of growth-factors involved in the regulation of a diverse array of angiogenesis processes. It has been postulated that the TGF-β RI kinase may play an important role in cancer.[1] A number of TGF-β RI kinase inhibitors are known, and some have demonstrated anti-tumor activity in tumor and fibrosis animal models.[2] As a result, the search for potent, selective TGF-β RI inhibitors to be used for the clinical management of cancer and fibrosis remains an active area of research.

Our search for novel TGF-β RI inhibitors has been aided by the availability of high-resolution X-ray crystal structure data showing that a hydrogen bond forms between the quinoline nitrogen of compound **1** (LY364947, Fig. 1) and a hinge-region proton (N–H, His-283), and well as a hydrogen bond interaction of the pyridine nitrogen with a water molecule.[2b,3] Using this information, we became interested in quinazoline and quinazolinone rings as heterocyclic replacements for quinoline (Fig. 1). Our efforts led to the preparation of structure **3** in a highly concise manner through a set of one-pot, three-component Suzuki/etherification and imidate ester–amide rearrangement reactions.

2. Results and discussion

Previously we have reported a synthesis of dihydropyrrolopyrazole TGF-β kinase inhibitors where lepidine was reacted with an appropriate picolinic ester followed by condensation of the resulting ketone with 1-amino-2-pyrrolidinone.[2e] However, this route was neither synthetically flexible nor durable enough for some of the envisioned analogs, including quinazoline and quinazolinone derivatives.

As shown in the retrosynthetic analysis (Fig. 2), we envisioned access to the flexible boronic acid intermediate (**5**) as deriving from the corresponding bromide. The bromide is readily derived from the carboxylic acid, which is available via 6-methyl-pyridine-2-carboxylic acid methyl ester and ethyl acetate.

The synthesis of boronic acid **5** is outlined in Scheme 1. Picolinate **6**[4] and 1-aminopyrrolidin-2-one hydrochloride[5] were synthesized according to the reported literature procedures.[2h–j] A Claisen condensation of ester **6** with ethyl

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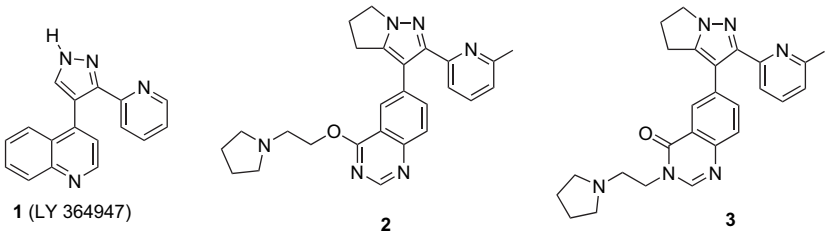
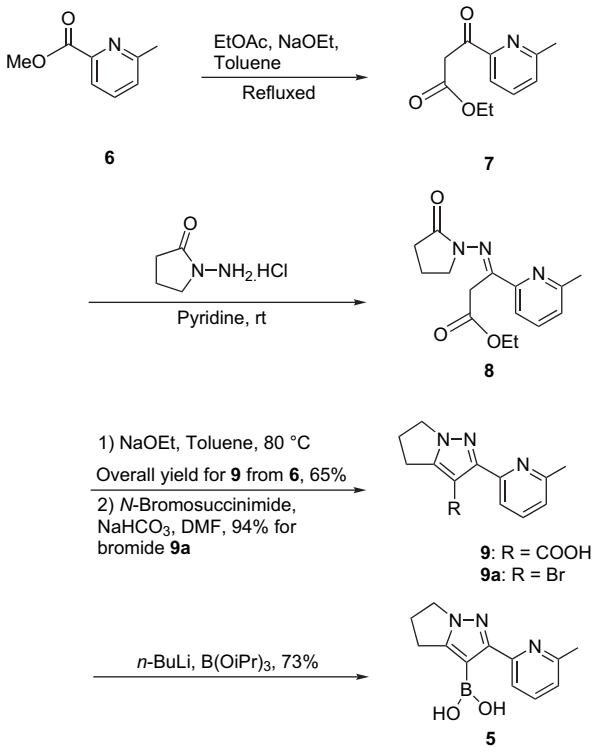


Figure 1.

acetate under refluxing conditions gave β-keto ester **7**. The purity of compound **7** after a simple extraction was 86% based on HPLC analysis. Without further purification, β-keto ester **7** was condensed with 1-amino-2-pyrrolidinone hydrochloride in pyridine to provide the corresponding acyl hydrazone **8**. On reaction with NaOEt, the crude hydrazone **8** underwent cyclization and hydrolysis to give carboxylic acid **9**, which was purified by slurring in MTBE. The overall yield of **9** from **6** was 65%. The conversion of acid **9** to bromide **9a** was accomplished in 94% yield by treatment with NBS at room temperature.[6] The boronic acid was then prepared by lithium–bromide exchange and in situ quench with triisopropyl borate.[7] At this stage, purification by silica gel chromatography gave compound **5** in 73% yield.[2h–j]



Scheme 1.

Our initial exploration of the Suzuki–Miyaura reaction of boronic acid **5** with quinazoline **10** under several standard reaction conditions[8] was not very encouraging. Besides an undesired Suzuki reaction (10–20%) that occurred at the 2-chloro of the quinazoline, we observed a 10–40% reduction of the boronic acid as well (among the catalysts, $Pd(PPh_3)_4$ gave the least reduction of compound **5**, while in contrast, $PdCl_2$(dppf) gave the most). Also separation of the desired product from multiple undesired products was not synthetically practical and resulted in impure product. Using ethylene glycol as a solvent with microwave heating, we discovered that we could react ethylene glycol to the 2-chloro-position under the Suzuki–Miyaura reaction conditions and prevent side reactions at the same time.[9] As shown in Scheme 2, the three-component Suzuki–Miyaura/etherification reaction occurs in one-pot to produce advanced compound **11**. Although undesired products from dimerization and boronic acid reduction were still identified, purification of polar alcohol **11** was straightforward and the overall yield was good (72%).

The structure of compound **11** was confirmed by HMBC (Table 1).[10] The clear HMBC cross-peaks between C-9 (δ_C 112.6) of the pyrazole and H-6′ (δ_H 8.30) and H8′ (δ_H 7.90) of the quinazoline determined that the Suzuki–Miyaura reaction occurred at the 7′-position of the quinazoline ring. Furthermore, the clear HMBC cross-peak between C-4′ (δ_C 165.7) of the quinazoline and H_2-11′ (δ_H 4.55) of the side chain confirmed that alkylation occurred at the 4-position of quinazoline.

To understand what reagents/factors are necessary for affecting the C–O bond formation, quinazoline **10** was subjected to the reaction conditions which were used for the Suzuki–Miyaura/etherification one-pot reaction (Scheme 3, Method 1), as well as similar conditions except without palladium catalyst and ligand (Scheme 3, Method 2), and further

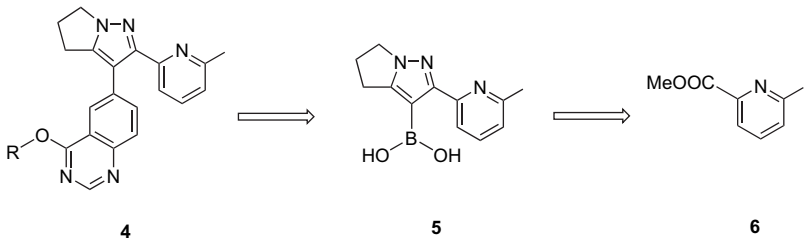
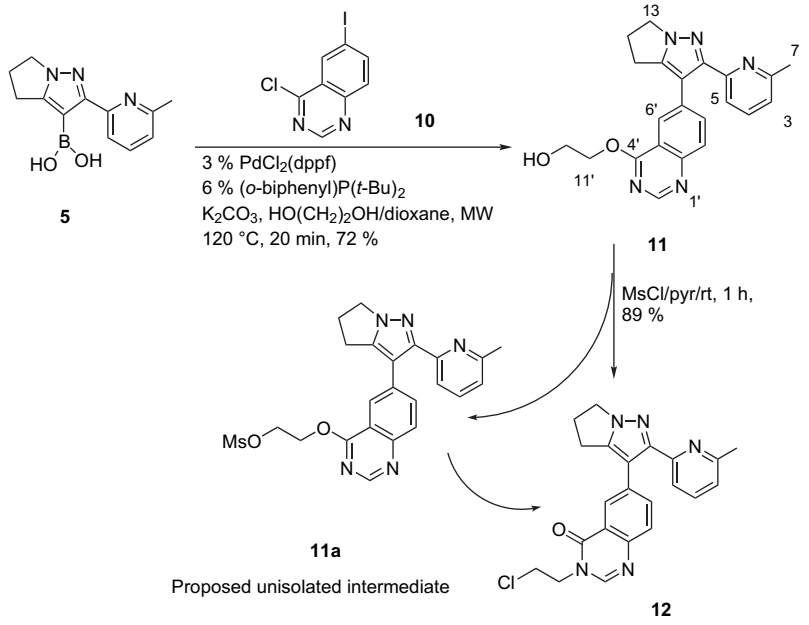


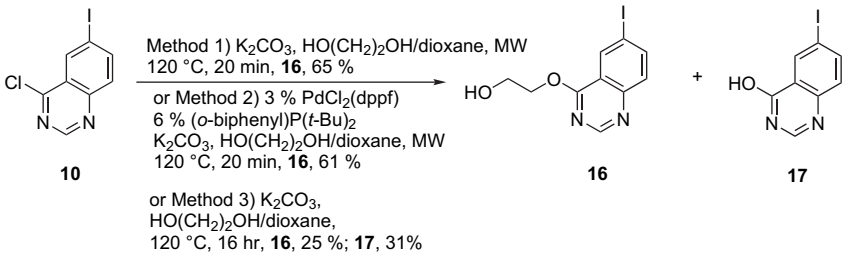
Figure 2. Retrosynthetic analysis.



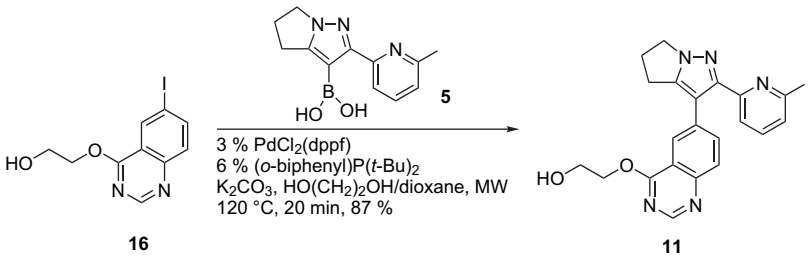
Scheme 2.

Table 1. ^{13}C (125 MHz) and ^{1}H (500 MHz) NMR spectral data for compounds **11**, **12**, and **3** in DMSO-d_6

No.	δ_C **11**	δ_H **11** (J in Hz)	δ_C **12**	δ_H **12** (J in Hz)	δ_C **3**	δ_H **3** (J in Hz)
2	156.6		156.6		156.6	
3	121.5	7.15 (d, 7.6)	121.4	7.15 (d, 7.6)	121.4	7.15 (d, 7.6)
4	136.6	7.69 (t, 7.7)	136.5	7.69 (t, 7.7)	136.5	7.68 (t, 7.7)
5	118.6	7.56 (d, 7.2)	118.7	7.53 (d, 7.5)	118.7	7.53 (d, 7.5)
6	152.2		152.2		152.2	
7	23.4	2.28 (s)	23.4	2.31 (s)	23.4	2.31 (s)
8	150.9		150.9		150.8	
9	112.6		112.4		112.5	
10	146.1		145.9		145.7	
11	22.7	3.06 (t, 6.8)	22.8	3.05 (t, 6.8)	22.8	3.04 (t, 6.9)
12	25.3	2.64 (m)	25.4	2.63 (m)	25.3	2.63 (m)
13	47.5	4.22 (t, 7.2)	47.4	4.21 (t, 7.2)	47.5	4.20 (t, 7.3)
2′	153.2	8.72 (s)	147.2	8.33 (s)	147.4	8.27 (s)
4′	165.7		159.9		159.8	
5′	115.3		120.7		120.8	
6′	121.8	8.30 (dd, 2.1, 0.5)	124.9	8.31 (dd, 2.1, 0.5)	125.0	8.29 (dd, 2.1, 0.5)
7′	132.9		132.6		132.3	
8′	135.4	7.90 (dd, 8.7, 2.1)	134.9	7.81 (dd, 8.5, 2.1)	134.6	7.78 (dd, 8.4, 2.1)
9′	125.8	7.80 (d, 8.8)	126.0	7.60 (d, 8.4)	125.9	7.57 (d, 8.4)
10′	148.7		145.6		145.6	
11′	68.2	4.55 (t, 5.0)	47.2	4.32 (t, 6.0)	44.4	4.07 (t, 6.1)
12′	58.8	3.80 (dd, 10.2, 5.4)	41.9	3.98 (t, 5.9)	53.6	2.72 (t, 6.1)
12′-OH		4.94 (t, 5.8)				
14′/17′					53.3	2.50 (m)
15′/16′					22.9	1.65 (m)



Scheme 3.



Scheme 4.

without microwave heating (Scheme 3, Method 3). Although the conversion of 4-chloroquinazolines to 4-alkoxyquinazoline is generally done using a strong base (alkoxide or hydride), the etherification with a relatively weaker base K_2CO_3 proceeded nicely under the first two conditions (Methods 1 and 2) with microwave heating to give compound **16** with comparable yields of 65% and 61%, respectively. Apparently, the presence of a palladium catalyst did not show a positive impact on this reaction. However, the conditions using conventional heating at 120 °C (Method 3) for 16 h afforded two isolated products with similar yields (~30%). This result indicated that conventional heating with a weaker base was insufficient for the imidate formation. Interestingly, it is likely that microwave heating accelerated the favored etherification more than hydrolysis, which resulted in the low selectivity of the reaction.

To test that the one-pot protocol was superior to the two-step sequence, compound **16** was reacted with boronic acid **5** using the conditions used for the one-pot reaction (Scheme 4). The overall yield from two reactions and two purifications, including etherification was 56%, in comparison with 72% yield from one reaction and one purification.

For the preparation of our potential target compound **2** (Fig. 1), compound **11** was treated with methanesulfonyl chloride in pyridine at room temperature, which unexpectedly led to a chlorinated product instead of our desired key intermediate, mesylate **11a** (Scheme 2). The structure of the undesired product was determined to be the arranged product **12** by the combination of HMBC, ROESY,[11] and HSQC[12] spectra.

As shown in Figure 3, the HMBC connection from H_2-11′ (δ_H 4.32) to C-2′ (δ_C 156.6) and C-4′ (δ_C 136.5) indicates that the 11′-CH_2 is attached to a nitrogen atom N-3′. The NOE between H-2′ (δ_H 8.33) and H_2-11′ (δ_H 4.32) further confirmed this conclusion. In addition, the structures of *N*-alkylated compound **12** and *O*-alkylated compound **11** could

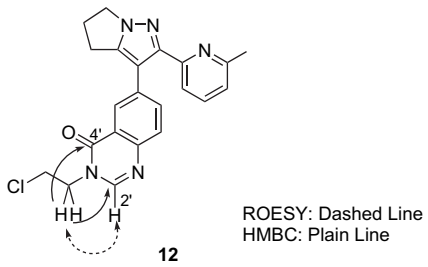


Figure 3. Selected HMBC and ROESY correlations for compound **12**.

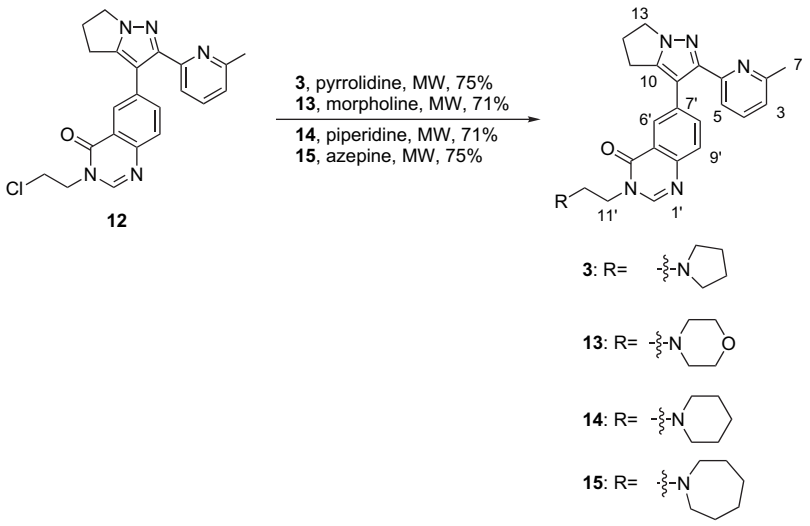
be distinguished conclusively by the ^1H and ^{13}C NMR chemical shifts. The N–CH_2 peak (δ_C 47.2) in compound **12** is much more upfield compared to the corresponding peak (δ_C 68.2) of the *O*–CH_2 in compound **11**.

A survey of the literature indicates that aryl, alkyl, or allyl groups of imidates are known to migrate from oxygen to nitrogen.[13] The uncatalyzed thermal rearrangement of aryl imidates via a 1,3 *O–N* shift requires harsh conditions of over 200 °C for several days.[13a,d,e] Even if the alkyl 1,3 *O–N* rearrangement is catalyzed by chloride, the energy for rearrangement still requires refluxing in an organic solvent for many hours.[13c] This 1,3 rearrangement has also been reported with the quinazoline system by refluxing in MeCN for 24 h.[13f] Although a closely related alkyl 1,3 *O–N* rearrangement with a tosylate as the leaving group was reported to occur (TsCl/triethylamine/CH_2Cl_2) at probably low temperature, the detailed information was not disclosed.[13g] In our case, the quantitative 1,3 rearrangement took place in just 30 min at room temperature, which is likely consistent with the observation in Ref. 13g. It appears that mesylate is a better leaving group and speeds up the rate of rearrangement. Evidently, the complete migration observed at such a low temperature further ascertains that the mechanism probably proceeds via intra- rather than intermolecular rearrangement of the alkyl group.[13d]

Consequently, the final products bearing a solublizing group (**3**, **13**–**15**) were synthesized by the amination of compound **12** under microwave heating conditions (Scheme 5).

3. Conclusion

In summary, by utilizing the synthetic route outlined in Scheme 1, a dihydropyrrolopyrazole boronic acid intermediate was synthesized, which should allow rapid preparation of diverse heterocyclic analogs of the quinazoline group of **2** and **3**. Furthermore, the three-component Suzuki–Miyaura/etherification procedure allows for access to advanced compound **11** and proved to be more facile than the two-step sequence. Finally, the 1,3 *O–N* rearrangement at room temperature is postulated to proceed via an intramolecular mechanism and provides a practical approach for the synthesis of substituted quinazolinone analogs. Compounds **3**, **13**–**15** were potent at inhibiting the TGF-β RI kinase domain with enzymatic IC_{50} values of 93, 95, 123, and 192 nM, respectively, and were comparable in activity to a previously reported TGF-β RI inhibitor having an enzymatic IC_{50} of 68 nM.[2b,g]



Scheme 5.

4. Experimental section

4.1. General

All reagents and solvents were used without further purification or drying. All reagents were purchased from Sigma–Aldrich, unless otherwise specified. Commercial grade anhydrous solvents were purchased from EMD chemicals or Mallinckrodt. All reactions were performed under nitrogen, unless otherwise specified. Flash column chromatography was carried out using prepacked silica gel columns from Isco. ^{1}H NMR spectra were collected on Varian 400 MHz or 500 MHz instrument. Mass spectra were obtained on a Micromass QTOF-II, a Finnigan LCQ Duo Ion Trap or a PESciex API 150EX mass spectrometer, using electrospray ionization (ES) or atmospheric pressure chemical ionization (APCI). Analytical HPLC (system A) was conducted on LC column of Xterra C_{18} 2.1×50 mm, 3.5 μM with flow rate of 1 mL/min, using the following gradient: 5–100% MeCN with 0.2% NH_4OH in 7.0 min, then held at 100% MeCN for 1.0 min. Analytical HPLC (system B) was conducted on LC column of YMC C_{18} 2.0×50 mm, 3 μM with flow rate of 1 mL/min, using the following gradient: 5–100% 1:1 MeCN/H_2O with 0.2% ammonium formate in 7.0 min, then held at 100% 1:1 acetonitrile/water for 1.0 min.

4.1.1. 3-(6-Methyl-pyridin-2-yl)-3-oxo-propionic acid ethyl ester (7). To a mixture of sodium ethoxide (90 g, 1.32 mol) and toluene (0.5 L) in a 2 L flask equipped with reflux condenser, mechanical stirrer, and nitrogen inlet was added ethyl acetate (0.2 L, 1.98 mol). After stirring for 1 h, was added 6-methyl-pyridine-2-carboxylic acid methyl ester (**6**, 100 g, 0.66 mol). Upon heating the mixture at reflux (92 °C) for 20 h, the mixture was cooled to rt and acidified with glacial acetic acid to pH 6. The mixture was then diluted with water (0.5 L) and extracted with toluene (0.5 L). The organic layer was dried with sodium sulfate, filtered, and concentrated in vacuo to yield the title product (154 g, 96%) as dark oil in 86% purity by HPLC analysis. MS ES$^+$ *m/z* 208 (M+1)$^+$. ^{1}H NMR (300 MHz, toluene-d_8) tautomer-1 (major ~87%) δ 7.90 (7.90, *J*=7.7 Hz, 1H), 7.78 (d, *J*=7.8 Hz, 1H), 7.53 (d, *J*=7.7 Hz, 1H), 4.09 (s, 2H), 4.08 (q, *J*=7.1 Hz, 2H), 2.53 (s, 3H), 1.13 (t, *J*=7.1 Hz, 3H), tautomer-2 (minor ~13%) δ 12.20 (s, 1H), 7.84 (t, *J*=7.7 Hz, 1H), 7.70 (d, *J*=7.8 Hz, 1H), 7.41 (d, *J*=7.7 Hz, 1H), 6.22 (s, 1H), 4.22 (q, *J*=7.1 Hz, 2H), 4.09 (s, 2H), 2.51 (s, 3H), 1.26 (t, *J*=7.1 Hz, 3H).

4.1.2. 3-(6-Methyl-pyridin-2-yl)-3-(2-oxo-pyrrolidin-1-ylimino)-propionic acid ethyl ester (8). To a mixture of 1-aminopyrrolidin-2-one hydrochloride (99.4 g, 0.73 mol) and compound **7** (154 g, 0.66 mol) in a 3 L flask equipped with mechanical stirrer and nitrogen inlet was added pyridine (280 mL). After stirring at rt for 20 h, the resulting mixture was diluted with water (200 mL) and extracted with toluene (2×250 mL). The organic layer was combined, filtered, and concentrated in vacuo to yield the title product (201 g, 94%) as dark oil. MS ES$^+$ *m/z* 290 (M+1)$^+$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.89 (t, *J*=7.5 Hz, 1H), 7.79 (t, *J*=7.5 Hz, 1H), 7.55 (d, *J*=7.5 Hz, 1H), 4.10 (s, 2H), 4.05 (q, *J*=7.0 Hz, 2H), 2.53 (s, 3H), 1.14 (t, *J*=7.0 Hz, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 195.1, 168.4, 158.2, 151.6, 138.3, 128.1, 119.3, 60.9, 44.9, 24.3, 14.4.

4.1.3. 2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole-3-carboxylic acid (9). To a solution of sodium ethoxide (657 g, 9.26 mol) and toluene (12 L) in a 22 L flask equipped with a mechanical stirrer, nitrogen inlet, and a reflux condenser was added compound **8** (1.24 kg, 4.63 mol). The resulting mixture was heated at 100 °C for 24 h and then cooled to rt. After the content was diluted with water (6 L) and the pH adjusted to 4 with concentrated hydrochloric acid, compound was extracted with 10% isopropyl alcohol in chloroform (3×8.5 L) and washed with water. The organic fraction was combined and dried with sodium sulfate, filtered, and concentrated in vacuo, reslurried in MTBE (1.2 L), filtered and dried to yield the title product (743 g, 86% yield) as a light yellow solid in 98% purity by HPLC analysis. MS ES$^+$ *m/z* 244.11 (M+1)$^+$, MS ES$^-$ *m/z* 242.19 (M−1)$^-$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.03 (d, *J*=7.0 Hz, 1H), 7.99 (t, *J*=7.5 Hz, 1H), 7.10 (d, *J*=7.5 Hz, 1H), 4.21 (t, *J*=7.5 Hz, 2H), 3.08 (t, *J*=7.0 Hz, 2H), 2.59 (m, 2H), 2.56 (s, 3H). ^{13}C NMR (125 MHz,

CD_2Cl_2) δ 163.5, 155.5, 154.9, 149.9, 149.1, 140.8, 124.5, 118.6, 108.9, 48.7, 25.5, 24.9, 22.3.

4.1.4. 3-Bromo-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole (9a). To a solution of compound **9** (1.4 g, 5.8 mmol) in *N*,*N*-dimethylformamide (20 mL) was added *N*-bromosuccinamide (1 g, 5.6 mmol). After the resulting mixture was stirred at rt for 16 h, compound was extracted with ethyl acetate and washed three times with water, once with brine. The organic layer was dried with sodium sulfate, filtered, and concentrated in vacuo to yield the title compound, (1.5 g, 94%), as light yellow solid. MS ES$^+$ *m*/*z* 278 (M+1)$^+$. HRMS (AP$^+$): *m*/*z* calcd for $C_{12}H_{12}B_3N_3$ 278.0293, found 278.0283. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.67 (d, *J*=8.0 Hz, 1H), 7.62 (t, *J*=7.6 Hz, 1H), 7.10 (d, *J*=7.6 Hz, 1H), 4.21 (t, *J*=7.6 Hz, 2H), 2.91 (t, *J*=6.8 Hz, 2H), 2.62 (m, 2H), 2.58 (s, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 157.9, 151.5, 151.3, 146.7, 136.3, 121.8, 118.8, 85.4, 49.0, 25.4, 24.2, 22.8.

4.1.5. 2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole-3-boronic acid (5). To a solution of compound **9a** (1.44 g, 5.18 mmol) in tetrahydrofuran (28.0 mL) in a 100 mL round-bottom flask equipped with a temperature probe, a magnetic stirrer, and a septum and put under a nitrogen atmosphere was added triisopropyl borate (3.10 mL, 13.5 mmol). Upon cooling the mixture to −78 °C using a dry ice/acetone bath, 1.4 M *n*-butyllithium in hexanes (8.80 mL, 12.4 mmol) was added dropwise via a syringe pump over 10 min keeping the temperature below −40 °C. After removing the dry ice/acetone bath, the reaction mixture was warmed to room temperature. The saturated aqueous ammonium chloride (10 mL) was added and extracted with chloroform (2×100 mL). The organic layers were combined, dried over solid sodium sulfate, and the solvent was removed under reduced pressure to afford oil. The oil was purified with normal phase flash chromatography (120 g Biotage KP-Sil 40L: 100% ethyl acetate in hexanes for 25 min, 0–10% methanol in ethyl acetate in ramp over 15 min, then 10% methanol in ethyl acetate) to yield the title compound (910 mg, 73%). MS ES$^+$ *m*/*z* 244 (M+1)$^+$. HRMS (AP$^+$): *m*/*z* calcd for $C_{12}H_{14}BN_3O_2$ 243.1293, found 243.1312. ^{1}H NMR (400 MHz, 10% $CDOD_3$/CD_2Cl_2) δ 7.95 (d, *J*=8.4 Hz, 1H), 7.70 (t, *J*=7.2 Hz, 1H), 7.12 (d, *J*=7.2 Hz, 1H), 4.13 (t, *J*=7.6 Hz, 2H), 3.01 (t, *J*=6.8 Hz, 2H), 2.59 (m, 2H), 2.59 (s, 3H). ^{13}C NMR (100 MHz, 10% $CDOD_3$/CD_2Cl_2) δ 158.2, 156.3, 156.1, 152.6, 138.1, 122.2, 117.9, 47.6, 25.6, 24.2, 22.7.

4.1.6. 2-[2-(6-Methyl-pyridin-2-yl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-quinazolin-4-yloxy]-ethanol (11). To a solution of compound **5** (70 mg, 0.3 mmol), 4-chloro-6-iodo-quinazoline (130 mg, 0.45 mmol), and 2 M potassium carbonate (1 mL) in 2:1 dioxane/ethylene glycol (6 mL) in a 10 mL glass tube was added Pd(dppf)$_2$Cl$_2$ (7 mg, 3% mol) and (*o*-biphenyl)P(*t*-Bu)$_2$ (3 mg, 6% mol). The tube was then sealed with a septum and placed in a microwave reactor. After the mixture was irradiated at 120 °C (100 W) for 20 min, 3:1 $CHCl_3$/*i*-PrOH was added and washed with brine. The organic layer was dried, filtered through Na_2SO_4, and concentrated in vacuo to give a viscous mixture. Finally, the mixture was subjected to silica gel flash chromatography eluting gradually from CH_2Cl_2 to 10% MeOH/CH_2Cl_2 to give the desired product (80 mg, 72%). HRMS (AP$^+$): *m*/*z* calcd for $C_{22}H_{21}N_5O_2$ 388.1773, found 388.1799. HPLC (system A), 98%.

4.1.7. 3-(2-Chloro-ethyl)-6-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl]-3*H*-quinazolin-4-one (12). To a solution of compound **11** (300 mg, 0.8 mmol) in dry pyridine (5 mL) at −20 °C was added methanesulfonyl chloride (1 mL, 12.67 mmol). The resulting mixture was stirred at −20 °C for 10 min and then at room temperature for 30 min. After the reaction was quenched with adding 3:1 $CHCl_3$/*i*-PrOH, the organic layer was washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to silica gel chromatography eluting gradually from CH_2Cl_2 to 10% MeOH/CH_2Cl_2 to give the targeted compound (280 mg, 89%). MS ES$^+$ *m*/*z* 405.1 (M+1)$^+$. HRMS (AP$^+$): *m*/*z* calcd for $C_{22}H_{20}ClN_5O$ 406.1435, found 406.1450. For NMR data, see Table 1.

4.1.8. 6-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl]-3-(2-pyrrolidin-1-yl-ethyl)-3*H*-quinazolin-4-one (3). Compound **12** (30 mg, 0.07 mmol) in pyrrolidine (1 mL) was sealed in a pressure tube (10 mL) and placed in a microwave reactor. After the reaction mixture was irradiated at 140 °C for 1 h, the crude reaction mixture was subjected to silica gel chromatography eluting gradually from CH_2Cl_2 to 10% MeOH/CH_2Cl_2 to give the targeted compound (25 mg, 75%). MS ES$^+$ *m*/*z* 457.5 (M+1)$^+$. HRMS (AP$^+$): *m*/*z* calcd for $C_{26}H_{28}N_6O$ 441.2403, found 441.2394. For NMR data, see Table 1. HPLC (system A), >99%; HPLC (system B), >99%.

4.1.9. 6-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*] pyrazol-3-yl]-3-(2-morpholin-4-yl-ethyl)-3*H*-quinazolin-4-one (13). Prepared using the same procedure as for **3**, but employing morpholine as the amine resource (25 mg, 75% yield). MS ES$^+$ *m*/*z* 457.5 (M+1)$^+$. HRMS (AP$^+$): *m*/*z* calcd for $C_{26}H_{28}N_6O$ 457.2347, found 457.2347. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.29 (d, *J*=2.0 Hz, 1H), 8.01 (s, 1H), 7.74 (dd, *J*=8.0, 2.0 Hz, 1H), 7.57 (t, *J*=7.6 Hz, 1H), 7.56 (d, *J*=8.4 Hz, 1H), 7.46 (d, *J*=7.6 Hz, 1H), 7.07 (d, *J*=8.0 Hz, 1H), 4.25 (t, *J*=7.2 Hz, 2H), 4.07 (t, *J*=5.6 Hz, 2H), 3.65 (t, *J*=4.4 Hz, 4H), 3.10 (t, *J*=6.8 Hz, 2H), 2.70 (m, 4H), 2.51 (t, *J*=4.4 Hz, 4H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, 10% $CDOD_3$/CD_2Cl_2) δ 161.5, 155.9, 148.6, 147.3, 146.6, 142.2, 135.1, 135.1, 131.9, 127.7, 125.6, 124.4, 122.1, 121.7, 114.4, 63.9, 55.4, 52.6, 48.5, 41.1, 25.9, 23.1, 21.4. HPLC (system A), >99%; HPLC (system B), >99%.

4.1.10. 6-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl]-3-(2-piperidin-1-yl-ethyl)-3*H*-quinazolin-4-one (14). Prepared using the same procedure as for **3**, but employing piperidine as the amine resource (136 mg, 71% yield). LRMS (ES$^+$) *m*/*z* 455.2 (M+1)$^+$. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.28 (d, *J*=2.4 Hz, 1H), 8.02 (s, 1H), 7.71 (dd, *J*=8.4, 2.4 Hz, 1H), 7.56 (t, *J*=7.6 Hz, 1H), 7.55 (d, *J*=8.4 Hz, 1H), 7.46 (d, *J*=7.6 Hz, 1H), 7.07 (d, *J*=7.6 Hz, 1H), 4.25 (t, *J*=7.2 Hz, 2H), 4.04 (t, *J*=5.6 Hz, 2H), 3.10 (t, *J*=6.8 Hz, 4H), 2.70 (m, 2H), 2.63 (t, *J*=6.4 Hz, 2H), 2.44 (m, 4H), 2.42 (s, 3H), 1.59 (m, 4H), 1.45 (m, 2H). HPLC (system A), >99%; HPLC (system B), >99%.

4.1.11. 3-(2-Azepan-1-yl-ethyl)-6-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl]-3*H*-quinazolin-4-one (15). Prepared using the same procedure as for **3**, but employing azepane as the amine resource (136 mg, 71% yield). LRMS (ES^+) *m/z* 469.2 $(M+1)^+$. ^1H NMR (400 MHz, CD_2Cl_2) δ 8.28 (d, J=2.0 Hz, 1H), 8.04 (s, 1H), 7.71 (dd, J=8.4, 2.0 Hz, 1H), 7.56 (t, J=7.6 Hz, 1H), 7.55 (d, J=8.4 Hz, 1H), 7.45 (d, J=7.6 Hz, 1H), 7.06 (d, J=7.6 Hz, 1H), 4.25 (t, J=7.2 Hz, 2H), 4.04 (t, J=5.6 Hz, 2H), 3.14 (d, J=6.0 Hz, 2H), 3.10 (t, J=7.6 Hz, 2H), 2.83 (m, 2H), 2.69 (m, 4H), 2.42 (s, 3H), 1.59 (m, 8H). HPLC (system A), >99%; HPLC (system B), >99%.

4.1.12. 3-(2-Azepan-1-yl-ethyl)-6-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl]-3*H*-quinazolin-4-one (16). *Method 1*. To a solution of 4-chloro-6-iodo-quinazoline (292 mg, 1.0 mmol) in 2:1 dioxane/ethylene glycol (6 mL) in a 10 mL glass tube was added 2 M potassium carbonate (1 mL). The tube was then sealed with a septum and placed in a microwave reactor. After that, the mixture was irradiated at 120 °C for 20 min and was monitored by LCMS, which indicated the completion of reaction. The reaction was then quenched with 3:1 $CHCl_3$/*i*-PrOH and washed with brine. The organic layer was dried, filtered through Na_2SO_4, and concentrated in vacuo to give a viscous mixture. Finally, the mixture was subjected to silica gel flash chromatography eluting gradually from CH_2Cl_2 to 10% MeOH/CH_2Cl_2 to give the desired product (205 mg, 65%). LRMS (ES^+) *m/z* 317.0 $(M+1)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.57 (d, J=2.4 Hz, 1H), 8.17 (dd, J=8.8, 2.4 Hz, 1H), 7.66 (d, J=8.8 Hz, 1H), 4.52 (t, J=4.8 Hz, 2H), 3.81 (t, J=5.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.4, 155.0, 149.9, 142.8, 132.4, 129.8, 117.9, 93.4, 69.6, 59.3. HPLC (system A), >99%.

Method 2. To a solution of 4-chloro-6-iodo-quinazoline (292 mg, 1.0 mmol) and 2 M potassium carbonate (1 mL) in 2:1 dioxane/ethylene glycol (6 mL) in a 10 mL glass tube were added $Pd(dppf)_2Cl_2$ (23 mg, 3% mol) and (*o*-biphenyl)P(*t*-Bu)$_2$ (10 mg, 6% mol). The tube was then sealed with a septum and placed in a microwave reactor. After the mixture was irradiated at 120 °C for 20 min, the reaction was monitored by LCMS, which indicated the completion of reaction. The reaction was quenched ($CHCl_3$/*i*-PrOH) and washed with brine. The organic layer was dried, filtered through Na_2SO_4, and concentrated in vacuo to give a viscous mixture. Finally, the mixture was subjected to silica gel flash chromatography eluting gradually from CH_2Cl_2 to 10% MeOH/CH_2Cl_2 to give the desired product (192 mg, 61%).

Method 3. To a solution of 4-chloro-6-iodo-quinazoline (292 mg, 1.0 mmol) in 2:1 dioxane/ethylene glycol (6 mL) in a 10 mL glass tube was added 2 M potassium carbonate (1 mL). The tube was then sealed with a septum and placed in a microwave reactor. After that, the mixture was heated at 120 °C and the reaction was monitored by LCMS until the reaction was completed after 16 h (starting material disappeared). The reaction was then quenched with 3:1 $CHCl_3$/*i*-PrOH and washed with brine. The organic layer was dried, filtered through Na_2SO_4, and concentrated in vacuo to give a viscous mixture. Finally, the mixture was subjected to silica gel flash chromatography eluting gradually from CH_2Cl_2 to 10% MeOH/CH_2Cl_2 to give the desired product **16** (78 mg, 25%) and **17** (85 mg, 31%). Compound **17**: LRMS (ES^+) *m/z* 273.0 $(M+1)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.4 (s, 1H), 8.35 (d, J=2.0 Hz, 1H), 8.10 (s, 1H), 8.05 (dd, J=8.8, 2.0 Hz, 1H), 7.41 (d, J=8.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.8, 148.5, 146.6, 143.1, 134.6, 129.8, 124.9, 92.2. HPLC (system A), ~86.0%.

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Supplementary data

NMR spectra of compounds **11**, **12**, and **3**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.08.069.

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