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# Synthesis and biological evaluation of 4-quinazolinones as Rho kinase inhibitors

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ABSTRACT

Rho kinase (ROCK) is an attractive therapeutic target for various diseases including glaucoma, hypertension, and spinal cord injury. Herein, we report the development of a series of ROCK-II inhibitors based on 4-quinazolinone and quinazoline scaffolds. SAR studies at three positions of the quinazoline core led to the identification of analogs with high potency against ROCK-II and good selectivity over protein kinase A (PKA).



The Rho-associated coiled-coil containing protein kinase, also known as ROCK, is an integral component of the Rho signaling pathway. Two isoforms of ROCK, ROCK-I and ROCK-II, have been identified to date. These isoforms share 65% overall sequence identity with 92% homology in the kinase domain.[1] By phosphorylating various substrates including myosin light chain (MLC), MLC phosphatase (MLCP), ezrin/radixin/moexin (ERM), and LIM kinases, ROCK controls actin cytoskeleton assembly and cell contraction.[2] Inhibition of ROCK was demonstrated to contribute to effects such as smooth muscle relaxation[3] and alteration of intercellular junctions in the trabecular meshwork of the eye.[4] Therefore, inhibitors of ROCK may have beneficial implications for the treatment of diseases including hypertension[5] and glaucoma.[6]

Over the past 5 years, several groups have reported the development of potent ROCK inhibitors.[7–9] We previously reported the identification of chroman-containing inhibitors with high affinity and selectivity for ROCK[10,11] and disclosed the effects of several analogs in reducing intraocular pressure (IOP).[12–14] In our continued efforts in this area, we identified benzodioxane-substituted quinazolinone **1** (Fig. 1), a compound with high affinity for ROCK-II ($IC_{50}$ = 1 nM).[15] This compound was potent in our cell-based myosin light chain bis-phosphorylation (ppMLC) assay[16] ($IC_{50}$ = 10 nM), and displayed an excellent pharmacokinetic (PK) profile in Sprague–Dawley rats, including high oral bioavailability ($F$ = 79%).[17] No selectivity was observed against the highly homologous protein kinase A (PKA), chosen to gauge the potential for broad selectivity over other kinases. Hence, we aimed to improve the PKA selectivity of this class while maintaining potent inhibition of ROCK-II and favorable PK properties.

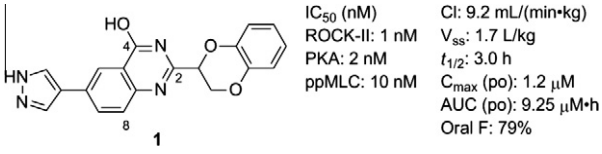


**Figure 1.** Structure and biological properties of quinazolinone **1**.

Our strategy to optimize 4-quinazolinone **1** was set in two stages. The first stage involved the modification of the benzodioxane portion of inhibitor **1**. Based on our experience in ROCK inhibitor design, we observed that various alterations on the benzodioxane group were well tolerated for ROCK inhibition. In general, such substitutions include an aromatic group to generate hydrophobic interactions with the glycine-rich phosphate-binding loop (P-loop) region of ROCK.[18] The second stage was aimed to introduce functionalities at either the 4- or 8-position of the quinazoline core to identify functionalities that could confer favorable potency and selectivity.

The synthesis of quinazolines and related C-4-substituted quinazolines with no substitution at the 8-position (Scheme 1, $R^2$ = H) began with the coupling of aniline **3**[19] with acid **2** via either acid chloride formation or HATU-mediated conditions. Subsequent Suzuki heteroarylation and dehydration were achieved in one step

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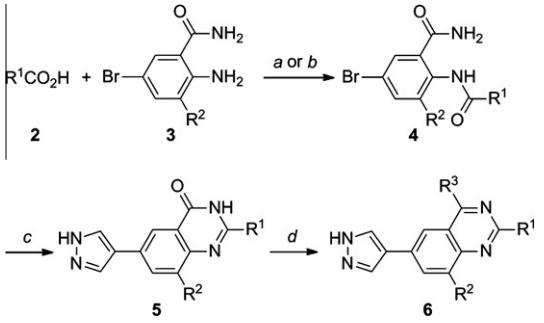
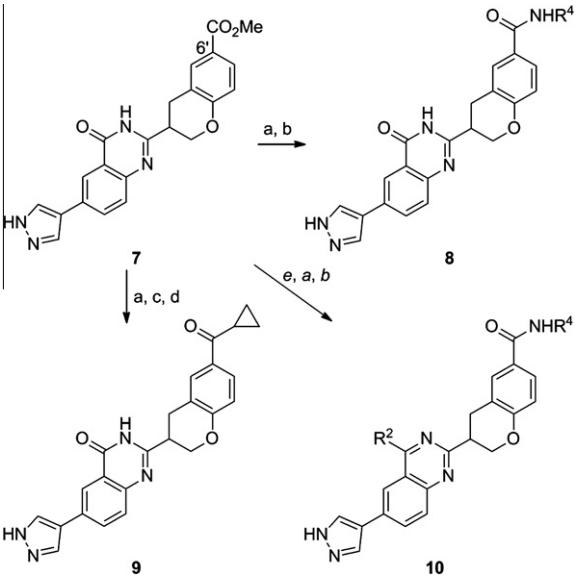


**Scheme 1.** Reagents and conditions: (a) $(COCl)_2$, pyridine, $CH_2Cl_2$, 2 h; (b) HATU, *N*-methylmorpholine, DMF, 36 h; (c) 1*H*-pyrazole-4-boronic acid pinacol ester, $Pd(PPh_3)_4$, $K_2CO_3$, toluene, ethanol, $H_2O$, 1 h, 135 °C, μW; (d) $R^3XH$, BOP, DBU, DMF, 2 h.

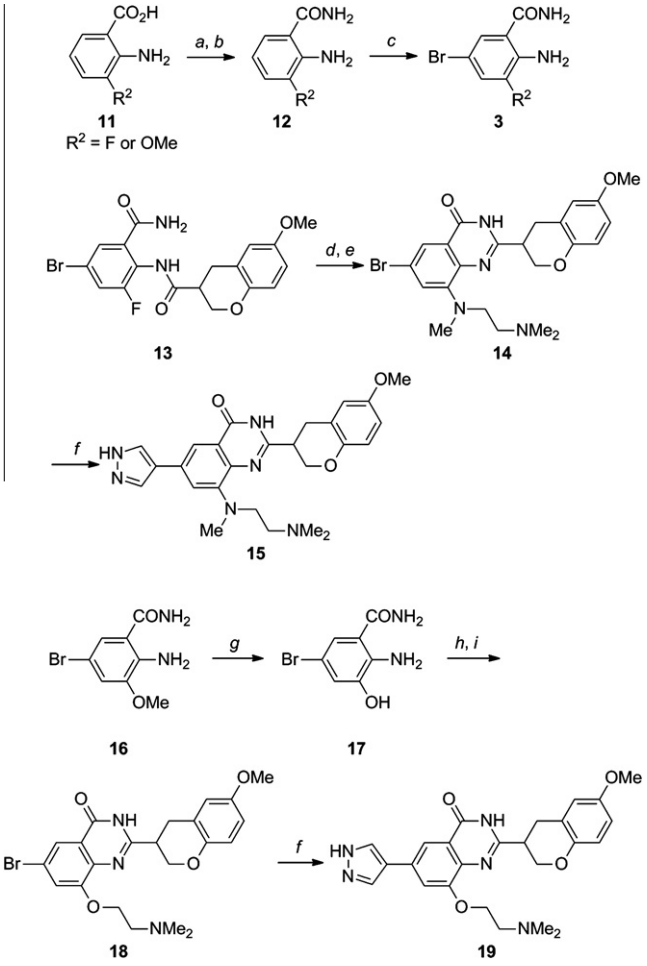
under microwave conditions from amide **4** to obtain quinazolinone **5**. Further substitution at C-4 was achieved by BOP-mediated coupling[20] with an amine or thiol nucleophile ($R^3XH$, X = N or S) to afford quinazoline **6**.

The construction of inhibitors with an amide or ketone at the 6′-position of the chroman ring is described in Scheme 2. Ester **7**, which was synthesized according to Scheme 1 with the appropriate chroman-3-carboxylic acid, was saponified and coupled with an amine to obtain amide **8**. Ketone **9** was prepared by hydrolysis of ester **7**, followed by formation of a Weinreb amide,[21] and treatment of cyclopropylmagnesium bromide. For the preparation of quinazoline **10**, coupling at the quinazoline C-4 was performed first, followed by ester hydrolysis and amide formation.

To access quinazolinones with substituent $R^2$ at C-8, aniline **3** with either a fluoro or methoxy group at the appropriate location was prepared by carboxamide formation, followed by bromination (Scheme 3). Compound **15**, which contains a dimethylaminoethylmethyl amine group, was obtained in three steps involving condensation, nucleophilic substitution, and finally Suzuki coupling under microwave conditions. The dimethylaminoethoxy analog (**19**) was synthesized from bromide **16** in four steps. Demethylation with $BBr_3$, amide formation via an acid chloride intermediate, and nucleophilic substitution of 2-dimethylaminoethyl chloride



**Scheme 2.** Reagents and conditions: (a) LiOH, dioxane, $H_2O$, 3 h; (b) $R^4NH_2$, HATU, $Et_3N$, DMF, 1 h; (c) *N*,*O*-dimethylhydroxylamine, HATU, $Et_3N$, DMF, 1 h; (d) cyclopropylmagnesium bromide, THF, 16 h, 0 °C; (e) $R^3XH$, BOP, DBU, DMF, 2 h.

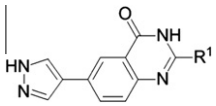


**Scheme 3.** Reagents and conditions: (a) $SOCl_2$, DMF, 2 h, 75 °C; (b) $NH_4OH$, $CH_2Cl_2$, 1 h; (c) *N*-bromosuccinimide, DMF, 8 h; (d) $K_2CO_3$, dioxane, $H_2O$, 1 h, 140 °C, μW; (e) *N*,*N*,*N*′-trimethylethylenediamine, 1 h, 165 °C, μW; (f) 1*H*-pyrazole-4-boronic acid pinacol ester, $Pd(PPh_3)_4$, $K_2CO_3$, dioxane, $H_2O$, 1 h, 140 °C, μW; (g) $BBr_3$, $CH_2Cl_2$, 1 h, −78 °C; (h) 6-methoxychroman-3-carboxylic acid, $(COCl)_2$, DIEA, $CH_2Cl_2$, cat. DMF, 1 h; (i) 2-dimethylaminoethyl chloride, $NaHCO_3$, DMF, 6 h, 60 °C.

gave bromide **18**. Finally, Suzuki heteroarylation gave the desired product, **19**.[22]

In agreement with earlier studies, a chroman functional group could readily replace the benzodioxane moiety of quinazolinone **1** (Table 1).[10,11] The inhibition of ROCK-II was assessed by HTRF methods.[12,23] With the exception of chromene **20** and chroman **24**, these compounds were highly effective inhibitors of ROCK, with $IC_{50}$ values less than 50 nM. Chromans **21** and **22** have similar affinity for ROCK-II as benzodioxane **1**, with at least 10-fold improvement in selectivity over PKA and higher stability to human liver microsomes. Selectivity was further enhanced with 6′-methoxychroman **25**, which displayed an $IC_{50}$ value of 2 nM for ROCK-II and 380-fold selectivity against PKA. Consistent with our previous studies, chroman regioisomers with 5′- or 8′-methoxy groups (**23** and **24**, respectively) were less effective.[24] The asymmetric synthesis of chroman-3-amide-based inhibitors was recently disclosed and we observed that the chirality of these compounds contributes to inhibition of ROCK-II.[23] Thus, the enantiomers of quinazoline **25** were prepared with slightly modified conditions[25] and the enantiomeric purity was verified by chiral reverse-phase HPLC (Chiralpak AD-RH). The (*R*)-enantiomer of chroman **25** was the eutomer, with $IC_{50}$ values of <1 nM against ROCK-II and at the lowest limits of detection (4 nM) in the cell-based ppMLC assay.[16] In comparison, the (*S*)-enantiomer was a modest inhibitor

**Table 1**
Kinase inhibition and stability of 2-substituted quinazolinones



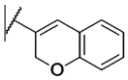
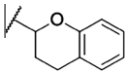
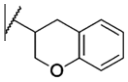
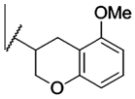
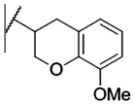
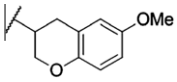
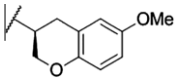
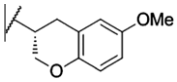
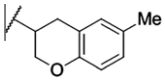
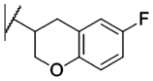
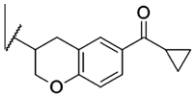
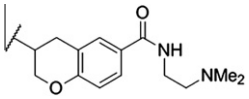
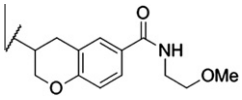
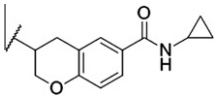
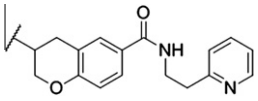
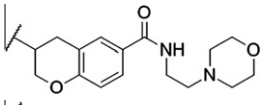
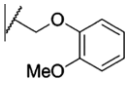
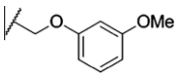
| Compd | $R^1$ | $IC_{50}$[a] (nM) | | $t_{1/2}$[b] (min) HLM |
|---|---|---|---|---|
| | | ROCK-II | PKA | |
| **20** |  | >5000 | >20,000 | 438 |
| **21** |  | 2 | 47 | 62 |
| **22** |  | <1 | 34 | 66 |
| **23** |  | 31 | 591 | 51 |
| **24** |  | 423 | >5000 | nd[c] |
| **25** |  | 2 | 760 | 17 |
| (*R*)-**25** |  | <1 | 144 | 62 |
| (*S*)-**25** |  | 87 | >20,000 | 2 |
| **26** |  | 6 | 702 | 31 |
| **27** |  | 3 | 326 | 143 |
| **9** |  | 18 | >20,000 | 218 |
| **28** |  | <1 | 32 | 31 |
| **29** |  | <1 | 29 | 42 |
| **30** |  | 1 | 67 | 107 |
| **31** |  | <1 | 102 | 102 |
| **32** |  | <1 | 269 | 18 |
| **33** |  | 188 | 257 | nd[c] |

**Table 1** (*continued*)

| Compd | $R^1$ | $IC_{50}$[a] (nM) | | $t_{1/2}$[b] (min) HLM |
|---|---|---|---|---|
| | | ROCK-II | PKA | |
| **34** |  | 33 | 876 | 17 |
| **35** |  | 123 | 2830 | 330 |

[a] Average of two or more measurements with error within ±30% of the mean.
[b] 1 mg/mL human liver microsomes were used in stability studies.
[c] Not determined.

of ROCK-II ($IC_{50}$ = 87 nM) with no detectable activity in the ppMLC assay even at 2.7 μM. This difference in ROCK-II affinity was likely attributed to more favorable interactions between the (*R*)-chroman group and the glycine-rich P-loop. Interestingly, chroman (*R*)-**25** was also more stable than its stereoisomer in the microsome assay.

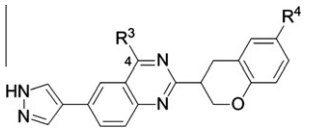
Since substituents at the 6′-position of the chroman ring were best tolerated, other small functional groups were introduced at this position (chromans **26**, **27**, and **9**). These analogs were similarly potent ROCK-II inhibitors with high stability to human liver microsomes. In particular, cyclopropylketone **9** showed the highest level of stability (>3.5 h) and selectivity over PKA (>1000-fold) in this series. In our earlier work on benzimidazole-based ROCK inhibitors, we observed that the installation of amides usually containing a polar group on the chroman C-6′ could enhance potency and selectivity.[24] Inspired by these results, several analogs were synthesized and evaluated (**28**–**32**). These inhibitors were indeed highly potent inhibitors of ROCK-II, with most $IC_{50}$ values in the subnanomolar range. Compounds **30** and **31** possessed high microsomal stability and moderate levels of PKA selectivity, and morpholine **32** demonstrated the best PKA selectivity in this carboxamide series.

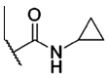
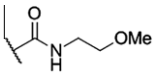
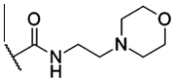
We also investigated the effect of using non-chroman groups, including phenoxymethyl analogs **33** and **34**, and the cyclopropyl analog, **35**. These compounds were moderate inhibitors of ROCK-II with up to 25-fold selectivity over PKA. The modest ROCK affinity of cyclopropyl **35** suggested that while a chroman or a similar aromatic group may assist in improving affinity to the enzyme, it was less important for binding than the quinazolinone scaffold.

Based on our experience in the development of Rho kinase inhibitors using other scaffolds, we believed that the addition of a side chain at an appropriate location could enhance favorable properties such as kinase selectivity.[11,13,14] To this end, we first introduced a side chain at the C-4 position of the quinazoline scaffold, which was synthetically accessible as depicted in Scheme 1. Compared to chroman **25**, mercapto analog **36** showed a slight decrease in inhibition of ROCK-II while retaining the same level of PKA selectivity and having higher microsomal stability (Table 2). Since the other C-4 substituents studied conferred less favorable properties (**37**–**39**), we turned our attention to analogs of thioether **36**. Inhibitors **40**–**42** had similar affinity for ROCK-II as quinazoline **36** and improved selectivity over PKA compared to their 4-hydroxy counterparts. In particular, more than 1000-fold selectivity was observed for morpholine **42** and methoxy ether **41** was as potent as benzodioxane **1** in the cell-based ppMLC assay.

We next examined the effects of substituents on the C-8 site of the quinazolinone core (Table 3), accessed as shown in Scheme 3. Incorporation of a methoxy group (**43**) maintained a similar level of affinity for ROCK-II inhibition and vastly improved PKA selectivity to 7000-fold. In contrast, fluoro substitution was not tolerated at this position. Installation of basic chains (**15** and **19**) slightly

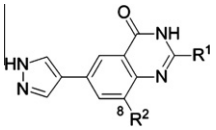
**Table 2**
Effects of quinazoline C-4 substitution on kinase inhibition, cell-based potency, and half-life in human liver microsomes

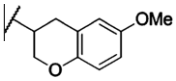
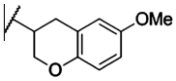
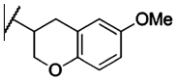
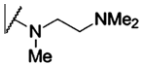
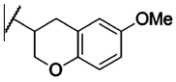
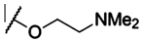
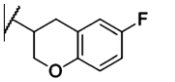
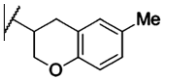
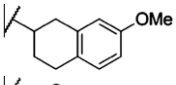
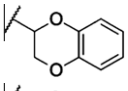
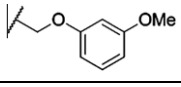


| Compound | $R^3$ | $R^4$ | $IC_{50}$[a] (nM) | | $IC_{50}$[a] (nM) ppMLC | $t_{1/2}$[b] (min) HLM |
|---|---|---|---|---|---|---|
| | | | ROCK-II | PKA | | |
| **36** | $S(CH_2)_2NMe_2$ | OMe | 6 | 2600 | nd[c] | 37 |
| **37** | $N(Me)(CH_2)_2OH$ | OMe | 22 | 1870 | 55 | 14 |
| **38** | $N(Me)(CH_2)_2NMe_2$ | OMe | 358 | nd[c] | nd[c] | nd[c] |
| **39** | $NHCH_2$(2-pyridine) | OMe | >5000 | >5000 | nd[c] | nd[c] |
| **40** | $S(CH_2)_2NMe_2$ |  | 6 | 1680 | 50 | 19 |
| **41** | $S(CH_2)_2NMe_2$ |  | 3 | 1850 | 10 | 13 |
| **42** | $S(CH_2)_2NMe_2$ |  | 3 | 4450 | 81 | 9 |

[a] Average of two or more measurements with error within ±30% of the mean.
[b] 1 mg/mL human liver microsomes were used in stability studies.
[c] Not determined.

**Table 3**
Effects of quinazolinone C-8 substitution on kinase inhibition, cell-based potency, and stability



| Compound | $R^1$ | $R^2$ | $IC_{50}$[a] (nM) | | $IC_{50}$[a] (nM) ppMLC | $t_{1/2}$[b] (min) HLM |
|---|---|---|---|---|---|---|
| | | | ROCK-II | PKA | | |
| **43** |  | OMe | 2 | 14,200 | 12 | 77 |
| **44** |  | F | 104 | 4120 | nd[c] | nd[c] |
| **15** |  |  | 21 | 805 | 1700 | nd[c] |
| **19** |  |  | 16 | >20,000 | 370 | 64 |
| **45** |  | OMe | 1 | 1020 | 11 | 124 |
| **46** |  | OMe | 5 | 12,500 | 28 | 94 |
| **47** |  | OMe | 11 | >20,000 | 2700 | 73 |
| **48** |  | OMe | 2 | 111 | 39 | 22 |
| **49** |  | OMe | 1 | 197 | 33 | 39 |

[a] Average of two or more measurements with error within ±30% of the mean.
[b] 1 mg/mL human liver microsomes were used in stability studies.
[c] Not determined.

**Table 4**
Pharmacokinetic profile for ROCK-II inhibitors in rats[a]

| Compd | Cl (mL/min/kg) | $V_{ss}$ (L/kg) | $t_{1/2}$ (h) | $C_{max}$ po (μM) | AUC po (μM·h) | Oral *F* (%) |
|---|---|---|---|---|---|---|
| **25** | 1.4 | 0.27 | 2.7 | 8.00 | 43.4 | 66 |
| (*R*)-**25** | 0.66 | 0.14 | 2.7 | 2.85 | 63.2 | 46 |
| (*S*)-**25** | 4.7 | 0.49 | 1.7 | 0.58 | 2.36 | 13 |
| **43** | 0.25 | 0.10 | 5.0 | 4.60 | 87.9 | 26 |
| **19** | 16 | 1.3 | 1.5 | 0.05 | 0.15 | 3 |
| **49** | 1.4 | 0.22 | 2.6 | 0.66 | 9.63 | 15 |

[a] Data was generated from three determinations. Formulated and dosed as described in Ref. 17.

reduced inhibition of ROCK-II, and more than 1200-fold selectivity over PKA was observed for ether **19**. Thus, other compounds containing the C-8 methoxy group were synthesized and evaluated. In general, these compounds displayed 10- to 50-fold improvement in selectivity for ROCK-II compared to their counterparts with no C-8 substituent. Chromans **45** and **46** demonstrated 1000- and 2500-fold greater affinity for ROCK-II over PKA, respectively. The selectivity of benzodioxane **48** was significantly enhanced compared to quinazolinone **1**, and compound **49** had a 30-fold increase from quinazolinone **34** in ROCK-II inhibition. ppMLC assays were performed on these compounds and chromans **43** and **45** were equipotent in cells as benzodioxane **1**. Several other inhibitors also had $IC_{50}$ values less than 50 nM in the cell-based assay. A notable exception is tetrahydronaphthalene **47**, which showed no inhibition at 2.7 μM despite good potency in the enzyme assay. We concluded that both the 6′-substituted chroman moiety and the 8-methoxyquinazolinone group contributed to improved PKA selectivity with high ROCK affinity, and the combination of these two factors (chroman **43**) led to a particularly desirable profile. Based upon the higher ROCK affinity of (*R*)-**25** versus its (*S*)-enantiomer, the corresponding (*R*)-enantiomer of quinazolinone **43** is expected to be preferred.

The PK data of selected compounds in Sprague–Dawley rats was next determined (Table 4). Quinazolinones **25** and **43** showed low clearance, low volume of distribution, high AUC, and high oral $C_{max}$. Compound **49** also displayed low clearance and volume of distribution, but with lower oral absorption. Comparing the pharmacokinetic properties of the enantiomer of inhibitor **25**, the eutomer, (*R*)-**25** was more favorable for systemic applications. Less desirable systemic PK properties were observed for quinazolinone **19**, which was likely ascribed to its dimethylaminoethoxy group.

In conclusion, we have described a series of quinazoline and 4-quinazolinone pyrazoles as potent ROCK inhibitors. SAR studies at the C-2, C-4 and C-8 positions of the quinazoline scaffold led to the identification of several chroman analogs with excellent affinity for ROCK and selectivity over PKA. In addition, compounds **25** and **43** possessed oral exposure levels favorable for systemic applications. Future studies to be reported in due course include more extensive target selectivity profiling of these potent ROCK inhibitors[26] as well as in vivo pharmacological studies to assess their efficacy as therapeutic agents for hypertension or glaucoma.

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25. Synthesis of quinazolines (*S*)-**25** and (*R*)-**25** involved modifications of the reactions described in Scheme 1. In brief, the carboxylic acid (prepared in Ref. 20) and aniline were coupled with EDC and HOAt in dichloromethane without the presence of base. The following Suzuki heteroarylation was then performed with sodium bicarbonate in place of potassium carbonate as the base.
26. Compounds **9** and **25** were also screened against three other kinases, MRCKα, JNK3, and p38 and no inhibition was observed at 20 μM concentration.