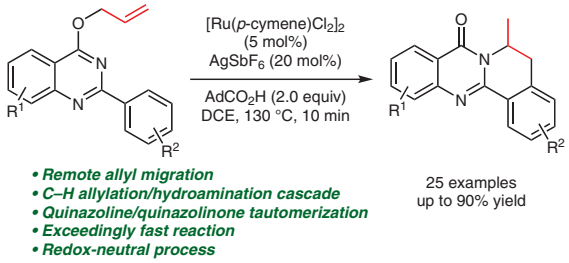
Synthesis G. Bairy et al. Special Topic

Ruthenium(II)-Catalyzed Migratory C–H Allylation/Hydroamination Cascade for the Synthesis of Rutaecarpine Analogues

Gurupada Bairy[a,b]
Arijit Nandi[a]
Kartic Manna[a,b]
Ranjan Jana[*a,b]

[a] Organic and Medicinal Chemistry Division, CSIR-Indian Institute of Chemical Biology, 4 Raja S. C. Mullick Road, Jadavpur, Kolkata 700032, West Bengal, India
rjana@iicb.res.in
[b] Academy of Scientific and Innovative Research (AcSIR), Jadavpur, Kolkata 700032, West Bengal, India

Published as part of the Special Topic *Ruthenium in Organic Synthesis*



Received: 11.03.2019
Accepted after revision: 27.03.2019
Published online:
DOI: 10.1055/s-0037-1611525; Art ID: ss-2019-c0166-st

Abstract An unprecedented allyl migration from a remote position of a quinazoline moiety through a ruthenium(II) shuttle is reported. This present cascade reaction is initiated through the formation of an η^3-ruthenium–allyl complex followed by C–H allylation at the *ortho* position of the 2-aryl moiety. Finally, hydroamination with the quinazolinone -NH group, which is formed through tautomerization of the quinazoline, furnishes the annulation product. This exceedingly fast cascade reaction is complete within 10 minutes to provide rutaecarpine analogues in a single operation.

Key words allyl migration, C–H activation, quinazolinones, ruthenium(II) catalysis, cascade reaction, rutaecarpine scaffold

Quinazolines and quinazolinones represent two important classes of *N*-heterocycles ubiquitously found in numerous natural products, agrochemicals, drugs, and pharmaceutically active ingredients (APIs) (Figure 1).[1] While the quinazoline scaffold is present in several blockbuster anticancer drugs, including terazosin, gefitinib, erlotinib, and lapatinib, the quinazolinones exhibit prominent antimicrobial properties.[2] Hence, significant attention has been paid to the synthesis and manipulation of these two scaffolds[3] in drug discovery programs. Typically, quinazolinones are easily converted into the corresponding quinazolines via chlorination with thionyl chloride.[4] However, the conversion of quinazolines into the corresponding quinazolinones has been less explored, but is in high demand to modify biological properties.

C–H activation[5] is the latest technology added to the organic chemist's toolbox which offers the ability for the rapid construction and late-stage modification of functional molecules. This C–H activation is also emerging as a powerful tool in medicinal chemistry to accelerate hit-to-lead optimization through structure–activity relationship studies.[6]

Our group is actively engaged in the synthesis of biologically active heterocycles through the merger of C–H activation and alkene difunctionalization.[7] This strategy is extremely challenging to execute since most C–H activations proceed through a high energetic pathway at high temperature, whereas deleterious β-hydride elimination is accelerated at this high temperature providing the Fujiwara–Moritani Heck product as a major product.[8] This inherent problem could be circumvented through the judicious choice of the catalyst, ligand, and reaction conditions. In this vein, we have reported a ruthenium(II)-catalyzed divergent synthesis of 2-methylindoles and indolines through a C–H allylation/cyclization cascade.[7c]

Recently, a few strategies have been reported for the annulation of quinazolinones via C–H functionalization. For example, the Xuan group reported a ruthenium-catalyzed synthesis of pyrrolo[2,1-*b*]quinazolin-9(1*H*)-ones via C–H alkenylation with activated alkenes followed by an aza-Michael addition reaction.[9] Mechanistically, the formation of a

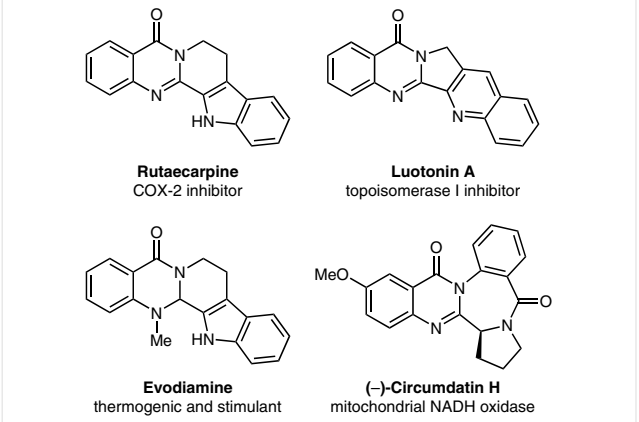
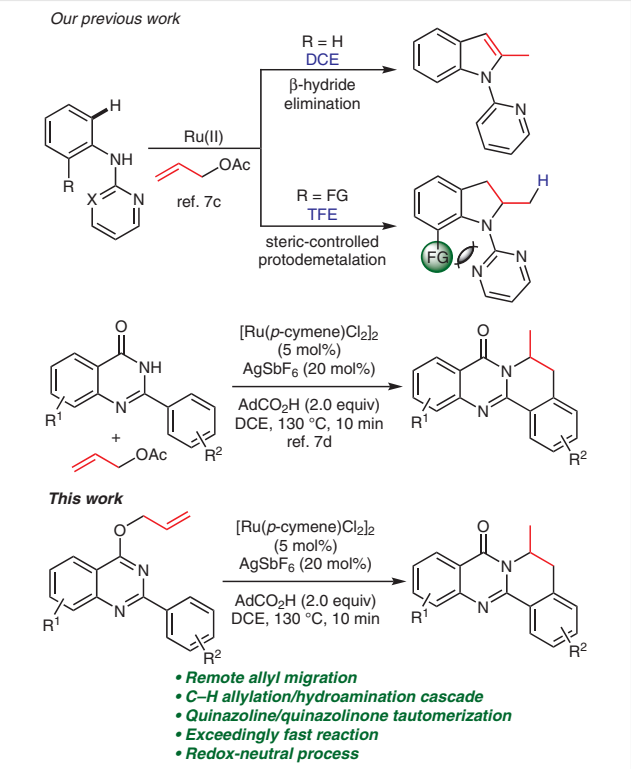


Figure 1 Biologically active, fused quinazolinones



Scheme 1 Annulation through C–H allylation/hydroamination cascades

six-membered ring[10] through metal-mediated cyclization is more challenging than a five-membered ring due to the formation of an energetically disfavorable seven-membered cyclic intermediate and the lack of a proper trajectory.[11] For example, the Peng group obtained a mixture of six-membered and five-membered heterocycles in the rhodium-catalyzed C–H alkylation/cyclization of 2-arylquinazolin-4-ones with vinyl trifluoroacetate.[12]

Xia and Dong reported a ruthenium(II)-catalyzed synthesis of indolo[2,1-*a*]isoquinolines via C–H allylation and oxidative cyclization of 2-phenylindoles;[13] but, selective monoallylation was impossible to achieve. Cui and coworkers reported a palladium-catalyzed synthesis of fused polyheterocycles through sequential [4+2]- and [3+2]-cycloadditions with alkynes.[14] Recently, we have developed a ruthenium(II)-catalyzed, intermolecular C–H allylation/hydroamination cascade for the synthesis of dihydroisoquinolino[1,2-*b*]quinazolinones (Scheme 1).[7d] Taking a cue from this study, we assumed that 2-arylquinazolinones may also provide a suitable platform to study the C–H allylation/hydroamination cascade in an intramolecular fashion. We report herein a mechanistically distinct migratory sp^2 C–H allylation/hydroamination cascade under ruthenium(II) catalysis to provide rutaecarpine derivatives.

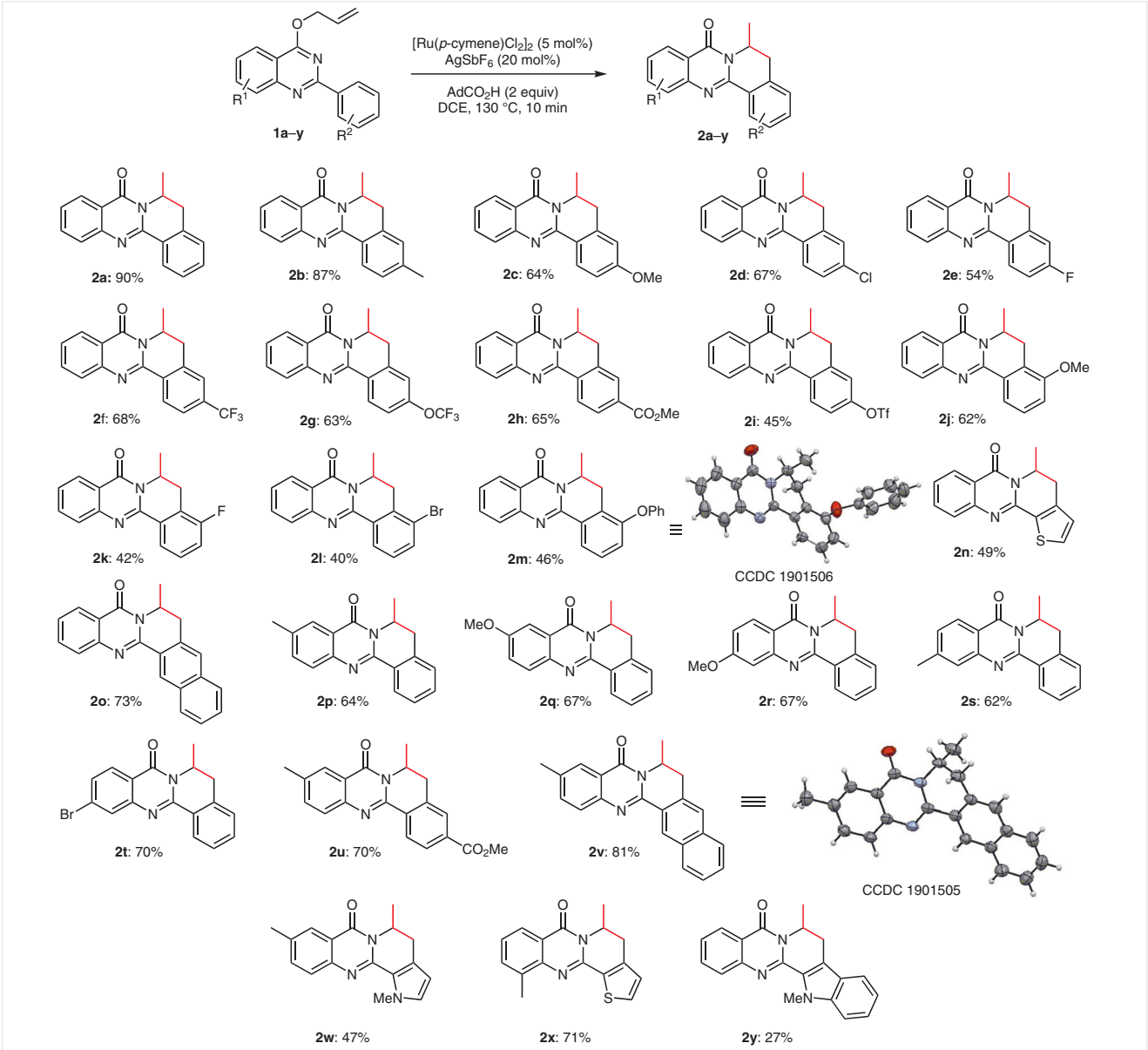
Our hypothesis to initiate the investigation of this intramolecular allyl migration is based on the facile tautomerization of the quinazoline/quinazolinone system, where quinazolinone serves as an excellent leaving group.[15] To examine this, we prepared 4-(allyloxy)-2-phenylquinazoline (**1a**) by treatment of the corresponding quinazolinone with allyl bromide under basic conditions.[16] Interestingly, no *N*-allylation product was formed and the corresponding *O*-allylation product was isolated exclusively. Then, **1a** was subjected to our previously optimized reaction conditions.[7d] Gratifyingly, we observed the formation of the annulation product in excellent yield. From the NMR analysis, we observed that the annulation product was similar to that of our previously reported intermolecular process.[7d] Since any deviation from the reported conditions did not improve the yield further, we decided to proceed to study the substrate scope of this intramolecular annulation strategy.

The scope of the migratory C–H allylation/hydroamination cascade was examined with various substituted 4-(allyloxy)quinazolines **1** which provided the desired dihydroisoquinolino[1,2-*b*]quinazolinones **2** under the standard reaction conditions (Scheme 2). A wide range of functional groups at the *para* position of the 2-phenyl moiety, such as electron-donating methyl or methoxy, or electron-withdrawing chloro, fluoro, trifluoromethyl, trifluoromethoxy, or ester, were compatible under the reaction conditions providing high to excellent yields (**2b–h**, Scheme 2). Remarkably, a *p*-triflate on the 2-phenyl ring remained intact under the standard reaction conditions, furnishing a moderate yield of the desired product **2i**, which indicates the mild nature of the reaction conditions. In our previous report[7d] (see Scheme 1), *meta* substitution at the 2-phenyl ring inhibited the formation of either annulation or C–H allylation product formation. Gratifyingly, in this migratory intramolecular allylation/cyclization cascade reaction, *meta* substitution at the 2-phenyl ring, such as methoxy, fluoro, bromo, or phenoxy, gave effective substrates, providing moderate to good yields (**2j–m**, Scheme 2). Furthermore, 2-heteroaromatic 4-(allyloxy)quinazolines, such as 2-thiophenyl, afforded a moderate yield of the migratory cascade product **2n**. Gratifyingly, 4-(allyloxy)-2-(2-naphthyl)quinazoline provided the corresponding cyclized product **2o** in high yield, whereas the 1-naphthyl derivative did not furnish any cyclized product.

To examine the substitution effect on the aryl ring of 4-(allyloxy)quinazolines, we prepared several substrates with different electron-donating and -withdrawing groups on the fused arene and subjected them to the standard reaction conditions. Gratifyingly, quinazolines derived from benzaldehyde and 5-methylanthranilamide or 5-methoxyanthranilamide afforded the desired cascade products **2p** and **2q** in good yields (Scheme 2). Quinazolines derived from benzaldehyde and 4-methoxyanthranilamide, 4-methylanthranilamide, or 4-bromoanthranilamide afforded the desired cyclization products **2r–t** in good to high yields. In the case of an electron-withdrawing ester group at the *para* position of the 2-phenyl ring, methyl substitution on the quinazoline backbone also furnished the desired prod-

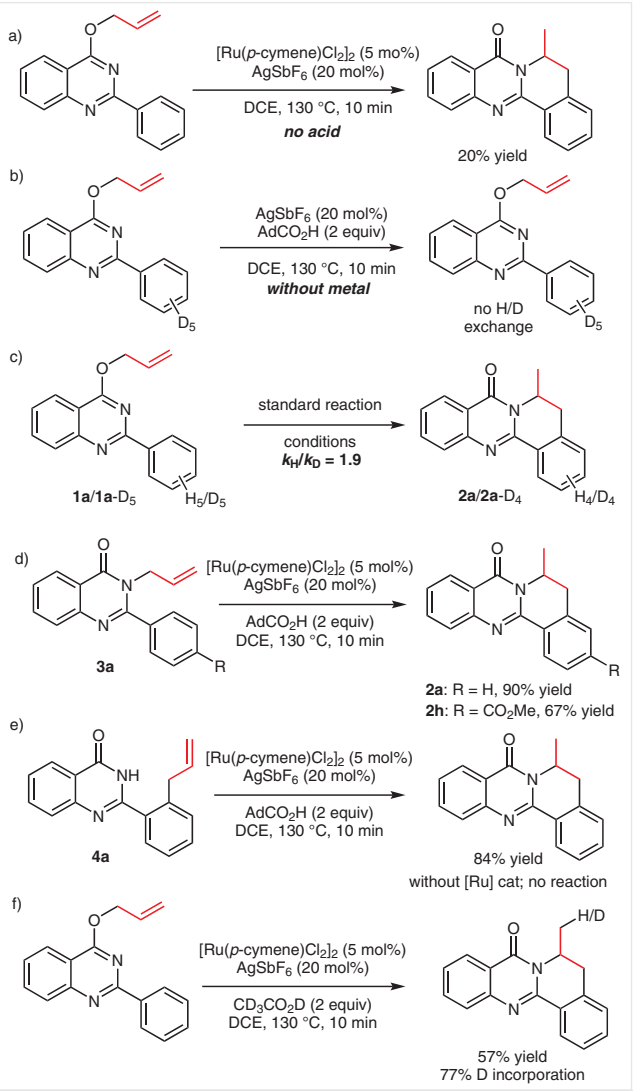
uct **2u** in good yield (70%). 2-Naphthyl substitution at the 2-position and methyl substitution on the quinazoline moiety also provided the desired product **2v** in high yield (Scheme 2). Similarly, 2-heteroaromatics, such as 2-(1-methylpyrrolyl) and 2-thiophenyl, and methyl substitution on the quinazoline backbone provided the corresponding cyclized products **2w** and **2x** in moderate to good yields. In the case of the quinazoline derived from 3-methylanthranilamide and thiophene-2-carboxaldehyde, the desired migratory annulation product **2x** was observed selectively via sp^2 C–H activation, and no sp^3 C–H activation of the methyl group was observed. 4-(Allyloxy)-2-(*N*-methyl-2-indolyl)quinazoline also furnished the corresponding cyclized product **2y** (Scheme 2), albeit in low yield, but this product from the indole derivative resembles the structure of rutaecarpine. The compounds have been well-characterized with representative X-ray crystallographic analysis of compounds **2m** (CCDC 1901506) and **2v** (CCDC 1901505; see the Supporting Information).

To gain mechanistic insight, when 4-(allyloxy)-2-phenylquinazoline (**1a**) was subjected to the standard reaction conditions in the absence of acid additive, the desired annulation product **2a** was obtained in 20% yield along with the corresponding *ortho* C–H allylation product in 50% yield



Scheme 2 Substrate scope of the annulation cascade. All reactions were carried out on a 0.2 mmol scale. Yields refer to the average of isolated yields of at least two experiments.

(Scheme 3a). When deuterated D_5-**1a** was subjected to the reaction conditions without the ruthenium complex, no reaction or deuterium exchange took place (Scheme 3b).

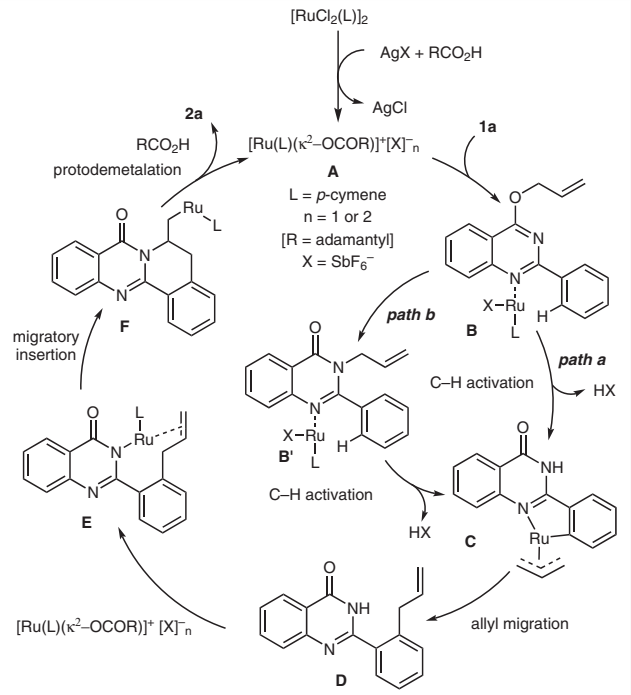


Scheme 3 Control experiments

These experiments suggest that a stoichiometric amount of acid additive is needed for the cyclization product formation and that cationic ruthenium species have a dual role in this migratory cyclization cascade. In the presence of ruthenium catalyst and silver(I) additive, both deallylation of the 4-(allyloxy)quinazoline and metal-catalyzed migratory *ortho* allylation take place in a concerted manner. From a competitive kinetic study between **1a** and the corresponding deuterated substrate D_5-**1a**, the primary kinetic isotope effect (KIE) was determined as k_H/k_D = 1.9, suggesting that the C–H activation step may be involved in the rate-limiting step (Scheme 3c). Mechanistically, an initial 3,3-sigmatropic rearrangement to provide *N*-allylation product[17] followed by *ortho* C–H ruthenation and annulation may provide an isomeric 5-methylated product. However, to our surprise, when the corresponding *N*-allylation product **3a** was prepared separately and subjected to the standard reaction conditions, the same annulation product **2a** was isolated, suggesting the *N*-deallylation pathway (Scheme 3d). Furthermore, when the preformed 2-(*o*-allylphenyl)quinazolinone **4a** was subjected to the reaction conditions, the cyclization product was obtained in 84% yield. This experiment suggests that the reaction may proceed through sp^2 C–H allylation at the *ortho* position of the 2-phenyl ring. Thus, allyl migration to the *ortho* position may take place either through the formation of an η^3-ruthenium–allyl complex directly from *O*-allylated substrate via C–O bond cleavage or via a 3,3-sigmatropic rearrangement to furnish the corresponding *N*-allylation product followed by C–N bond cleavage. However, all our efforts to isolate this *N*-allylated intermediate during the course of the reaction were in vain. When the same reaction was performed in the absence of ruthenium catalyst, no annulation product was obtained from C–H allylation intermediate **4a** suggesting that, although a stoichiometric amount of acid additive is essential for protodemetalation in the hydroamination step, the ruthenium catalyst is involved in both the C–C and C–N bond-formation cascade (Scheme 3e). To probe the protodemetalation step, when **1a** was subjected to the reaction conditions in the presence of 2.0 equivalents of CD_3CO_2D in lieu of adamantylcarboxylic acid ($AdCO_2H$), 57% yield of the cyclized product was observed with 77% deuterium incorporation at the 6-methyl group (Scheme 3f).

Therefore, based on these control experiments and previous reports,[7c,d,18] a plausible mechanism for this cascade reaction is proposed, as depicted in Scheme 4. Both $AgSbF_6$ and $AdCO_2H$ are prerequisite additives for the formation of an electrophilic active ruthenium catalyst **A** where the chloride ion is replaced by the noncoordinating SbF_6^- anion as AgCl precipitation. On the other hand, this active ruthenium species facilitates the deallylation of 4-(allyloxy)quinazolines, presumably via η^3-ruthenium–allyl complex formation. Then, coordination of the nitrogen atom of substrate **1a** to the η^3-ruthenium–allyl complex produces complex **B**, which undergoes sp^2 *ortho* C–H insertion to form five-membered ruthenacycle **C** either in a concerted manner (*path a*) or via a 3,3-sigmatropic rearrangement to furnish the corresponding *N*-allylation product **B′** followed by C–N bond cleavage (*path b*). This coordinately unsaturated ruthenium complex undergoes allyl migration to the *ortho* position of the 2-aryl moiety for C–H allylation to generate intermediate **D**.[7c,d,19] Again, coordination of the ruthenium complex between the amide nitrogen atom and alkene of intermediate **D** produces intermediate **E**. Subsequently, the active ruthenium complex undergoes migratory alkene insertion into the allyl moiety to produce intermediate **F** through intramolecular C–N bond formation. Intermediate **F** undergoes protodemetalation in the presence

of $AdCO_2H$ to produce the desired annulation product **2a**. The active catalyst is regenerated for subsequent runs from the ruthenium hydride species, presumably through the extrusion of hydrogen gas reacting with $AdCO_2H$.[20]



Scheme 4 Plausible mechanism

In conclusion, we have disclosed a ruthenium(II)-catalyzed novel C–H allylation/hydroamination cascade for the annulation of 2-arylquinazolinones. Tautomerization of the quinazoline/quinazolinone moiety offers a suitable platform for the remote allyl migration in a concerted manner. Interestingly, besides C–O bond activation of the allyl moiety, similar products are also obtained from the corresponding *N*-allylquinazolinones through C–N bond activation. A series of rutaecarpine derivatives were synthesized in high yields.

All manipulations with air-sensitive reagents were carried out under a dry nitrogen atmosphere. Unless otherwise stated, all commercial reagents were used without additional purification. Solvents were dried using standard methods and distilled before use. The starting 4-(allyloxy)-2-phenylquinazoline (**1a**) and substituted 4-(allyloxy)-2-phenylquinazolines **1b–y** were prepared using literature methods.[21,22] TLC was performed on silica gel plates (Merck silica gel 60, F_{254}), and the spots were visualized with UV light (254 and 365 nm) or by charring the plate dipped in $KMnO_4$. ^1H NMR spectra were recorded at 300 MHz, 400 MHz, or 600 MHz frequency and ^{13}C NMR spectra were recorded at 75 MHz, 100 MHz, or 150 MHz frequency on Bruker DPX, JEOL JNM-ECZ400S/L1, and Bruker Avance instruments, respectively, in $CDCl_3$ solvent using TMS as the internal standard. Chemical shifts were measured in parts per million (ppm) referenced to 0.0 ppm for TMS. Standard abbreviations are used to denote peak multiplicities. Coupling constants, *J*, are reported in hertz (Hz). HRMS (*m*/*z*) data were measured using ESI techniques on a Q-Tof Micro mass spectrometer.

Isoquinolino[1,2-*b*]quinazolinones 2a–y via a Ruthenium(II)-Catalyzed Migratory C–H Allylation/Hydroamination Cascade; General Procedure

A mixture of the 4-(allyloxy)-2-phenylquinazoline (0.2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (0.01 mmol, 5 mol%), $AgSbF_6$ (0.04 mmol, 20 mol%), and adamantylcarboxylic acid ($AdCO_2H$; 0.4 mmol, 2.0 equiv) was taken into a 15-mL pressure tube. To this reaction mixture, DCE (2.0 mL) was added and the closed reaction mixture was allowed to stir at 130 °C for 10 min. After 10 min, the reaction mixture was cooled to ambient temperature, then diluted with CH_2Cl_2, washed with 1 N NaOH solution to neutralize the excess acid, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain the crude product. Purification by silica gel column chromatography (EtOAc/hexane) afforded the desired isoquinolino[1,2-*b*]quinazolinone product **2a–y**.

6-Methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (2a)

Column chromatography (hexane/EtOAc, 19:1) afforded **2a** as a colorless solid; yield: 47.16 mg (90%); mp 110–112 °C. When the same reaction was performed on a 1.0 mmol scale, the desired product **2a** was obtained in 71% yield.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 7.2 Hz, 1 H), 8.34 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.80–7.75 (m, 2 H), 7.53–7.45 (m, 3 H), 7.30 (d, *J* = 7.2 Hz, 1 H), 5.62–5.57 (m, 1 H), 3.40 (dd, *J* = 15.6, 6.0 Hz, 1 H), 2.92 (dd, *J* = 15.6, 1.2 Hz, 1 H), 1.26 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.3, 148.6, 147.7, 134.8, 134.2, 131.9, 128.9, 128.6, 127.9, 127.54, 127.48, 126.8, 126.5, 120.8, 45.4, 33.5, 18.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{15}N_2O$: 263.1184; found: 263.1181.

3,6-Dimethyl-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (2b)

Column chromatography (hexane/EtOAc, 19:1) afforded **2b** as a white solid; yield: 48.02 mg (87%); mp 116–118 °C.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 8.4 Hz, 1 H), 8.31 (d, *J* = 7.8 Hz, 1 H), 7.75–7.74 (m, 2 H), 7.47–7.43 (m, 1 H), 7.24 (d, *J* = 7.8 Hz, 1 H), 7.08 (s, 1 H), 5.58–5.54 (m, 1 H), 3.34 (dd, *J* = 15.6, 6.0 Hz, 1 H), 2.84 (dd, *J* = 16.2, 1.8 Hz, 1 H), 2.43 (s, 3 H), 1.23 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.4, 148.7, 147.9, 142.5, 134.8, 134.1, 129.2, 128.4, 127.9, 127.4, 126.8, 126.3, 126.2, 120.7, 45.4, 33.5, 21.6, 18.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{17}N_2O$: 277.1341; found: 277.1277.

3-Methoxy-6-methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (2c)

Column chromatography (hexane/EtOAc, 9:1) afforded **2c** as a white solid; yield: 37.38 mg (64%); mp 158–160 °C.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 8.4 Hz, 1 H), 8.30 (d, *J* = 7.8 Hz, 1 H), 7.74 (dd, *J* = 4.8, 1.2 Hz, 2 H), 7.45–7.42 (m, 1 H), 6.97 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.78 (d, *J* = 3.0 Hz, 1 H), 5.59–5.55 (m, 1 H), 3.91 (s, 3 H), 3.36 (dd, *J* = 15.6, 6.0 Hz, 1 H), 2.85 (dd, *J* = 16.2, 1.8 Hz, 1 H), 1.26 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.6, 161.4, 148.6, 148.0, 136.9, 134.1, 130.0, 127.2, 126.8, 126.0, 121.6, 120.5, 113.5, 113.4, 55.4, 45.3, 33.8, 17.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_2$: 293.1290; found: 293.1291.

3-Chloro-6-methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (2d)

Column chromatography (hexane/EtOAc, 19:1) afforded **2d** as a white solid; yield: 39.66 mg (67%); mp 160–162 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 8.4 Hz, 1 H), 8.29 (dt, *J* = 7.6, 1.2 Hz, 1 H), 7.75–7.73 (m, 2 H), 7.47–7.43 (m, 1 H), 7.41–7.38 (m, 1 H), 7.28 (t, *J* = 1.2 Hz, 1 H), 5.59–5.52 (m, 1 H), 3.34 (dd, *J* = 16.0, 6.0 Hz, 1 H), 2.86 (dd, *J* = 16.0, 1.6 Hz, 1 H), 1.23 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 147.8, 147.6, 138.2, 136.6, 134.4, 129.6, 128.7, 128.0, 127.62, 127.58, 127.0, 126.8, 120.9, 45.4, 33.5, 18.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{14}ClN_2O$: 297.0795; found: 297.0797.

3-Fluoro-6-methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (2e)

Column chromatography (hexane/EtOAc, 19:1) afforded **2e** as a white solid; yield: 30.24 mg (54%); mp 120–122 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52–8.48 (m, 1 H), 8.29 (dt, *J* = 8.0, 1.2 Hz, 1 H), 7.74–7.72 (m, 2 H), 7.46–7.42 (m, 1 H), 7.13–7.08 (m, 1 H), 6.98–6.96 (m, 1 H), 5.59–5.52 (m, 1 H), 3.35 (dd, *J* = 16.0, 6.0 Hz, 1 H), 2.86 (dd, *J* = 16.0, 1.6 Hz, 1 H), 1.23 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1 (d, *J* = 252.3 Hz), 161.2, 147.9 (d, *J* = 0.8 Hz), 147.7, 137.7 (d, *J* = 8.9 Hz), 134.4, 130.8 (d, *J* = 9.2 Hz), 127.5, 127.0, 126.6, 125.3 (d, *J* = 3.1 Hz), 120.8, 115.5 (d, *J* = 22.0 Hz), 115.1 (d, *J* = 21.9 Hz), 45.4, 33.7 (d, *J* = 1.4 Hz), 18.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{14}FN_2O$: 281.1090; found: 281.1093.

6-Methyl-3-(trifluoromethyl)-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (2f)

Column chromatography (hexane/EtOAc, 9:1) afforded **2f** as a white solid; yield: 44.88 mg (68%); mp 98–100 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.65 (d, *J* = 8.4 Hz, 1 H), 8.34 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.81–7.77 (m, 2 H), 7.69 (d, *J* = 8.4 Hz, 1 H), 7.57 (s, 1 H), 7.52–7.50 (m, 1 H), 5.64–5.59 (m, 1 H), 3.43 (dd, *J* = 16.2, 6.0 Hz, 1 H), 3.00 (dd, *J* = 16.2, 1.2 Hz, 1 H), 1.26 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.1, 147.4, 147.2, 135.5, 134.4, 133.3 (q, *J* = 21.6 Hz), 132.2, 127.7, 127.1, 127.0 (q, *J* = 273.2 Hz), 126.9, 125.5 (q, *J* = 2.1 Hz), 124.6, 124.3 (q, *J* = 2.4 Hz), 121.0, 45.2, 33.5, 18.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{14}F_3N_2O$: 331.1058; found: 331.1053.

6-Methyl-3-(trifluoromethoxy)-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (2g)

Column chromatography (hexane/EtOAc, 9:1) afforded **2g** as a gray solid; yield: 43.60 mg (63%); mp 84–86 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 8.4 Hz, 1 H), 8.28 (dt, *J* = 8.0, 1.2 Hz, 1 H), 7.73–7.72 (m, 2 H), 7.46–7.42 (m, 1 H), 7.25–7.22 (m, 1 H), 7.10 (s, 1 H), 5.59–5.52 (m, 1 H), 3.36 (dd, *J* = 16.0, 5.6 Hz, 1 H), 2.88 (dd, *J* = 16.4, 1.6 Hz, 1 H), 1.23 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.1, 151.7, 147.6, 147.3, 137.1, 134.3, 130.0, 127.6, 127.5, 126.9, 126.7, 125.5, 120.8, 120.2, 119.6, 45.2, 33.5, 18.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{14}F_3N_2O_2$: 347.1007; found: 347.1010.

Methyl 6-Methyl-8-oxo-6,8-dihydro-5*H*-isoquinolino[1,2-*b*]quinazoline-3-carboxylate (2h)

Column chromatography (hexane/EtOAc, 9:1) afforded **2h** as a white solid; yield: 41.60 mg (65%); mp 200–202 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 7.8 Hz, 1 H), 8.34 (d, *J* = 7.8 Hz, 1 H), 8.10 (d, *J* = 8.4 Hz, 1 H), 7.99 (s, 1 H), 7.81–7.78 (m, 2 H), 7.52–7.50 (m, 1 H), 5.63–5.59 (m, 1 H), 3.98 (s, 3 H), 3.38 (dd, *J* = 15.6, 6.0 Hz, 1 H), 3.01 (dd, *J* = 15.6, 1.8 Hz, 1 H), 1.23 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.4, 161.1, 147.6, 147.5, 134.9, 134.4, 133.0, 132.8, 129.9, 128.5, 128.0, 127.7, 127.0, 126.9, 121.0, 52.5, 45.3, 33.5, 18.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_3$: 321.1239; found: 321.1237.

6-Methyl-8-oxo-6,8-dihydro-5*H*-isoquinolino[1,2-*b*]quinazolin-3-yl Trifluoromethanesulfonate (2i)

Column chromatography (hexane/EtOAc, 19:1) afforded **2i** as a gray solid; yield: 36.90 mg (45%); mp 110–112 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 8.7 Hz, 1 H), 8.35 (d, *J* = 7.8 Hz, 1 H), 7.81–7.75 (m, 2 H), 7.53–7.47 (m, 1 H), 7.34 (dd, *J* = 8.7, 2.4 Hz, 1 H), 7.25 (d, *J* = 6.3 Hz, 1 H), 5.65–5.58 (m, 1 H), 3.42 (dd, *J* = 16.2, 6.0 Hz, 1 H), 2.96 (dd, *J* = 16.2, 1.8 Hz, 1 H), 1.26 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.0, 151.5, 150.8, 147.4, 146.9, 137.6, 134.4, 130.4, 129.3, 127.7, 127.0, 126.9, 121.3, 120.9, 120.5, 45.2, 33.5, 18.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{14}F_3N_2O_4S$: 411.0626; found: 411.0624.

4-Methoxy-6-methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (2j)

Column chromatography (hexane/EtOAc, 9:1) afforded **2j** as a yellowish white solid; yield: 36.21 mg (62%); mp 128–130 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.0 Hz, 1 H), 8.10 (d, *J* = 8.0 Hz, 1 H), 7.76–7.70 (m, 2 H), 7.45–7.41 (m, 1 H), 7.36 (t, *J* = 8.0 Hz, 1 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 5.59–5.53 (m, 1 H), 3.87 (s, 3 H), 3.29 (d, *J* = 16.4 Hz, 1 H), 2.93 (dd, *J* = 16.8, 6.0 Hz, 1 H), 1.21 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.4, 156.9, 148.7, 147.9, 134.2, 130.2, 127.8, 127.6, 126.9, 126.5, 123.9, 121.0, 119.8, 113.1, 55.8, 45.1, 26.5, 18.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_2$: 293.1290; found: 293.1289.

4-Fluoro-6-methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (2k)

Column chromatography (hexane/EtOAc, 19:1) afforded **2k** as a yellowish white solid; yield: 23.52 mg (42%); mp 136–138 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.34–8.31 (m, 2 H), 7.77 (d, *J* = 4.2 Hz, 2 H), 7.51–7.47 (m, 1 H), 7.43–7.40 (m, 1 H), 7.28–7.25 (m, 1 H), 5.66–5.61 (m, 1 H), 3.26 (d, *J* = 16.8 Hz, 1 H), 3.10 (dd, *J* = 16.2, 6.0 Hz, 1 H), 1.26 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.1, 160.2 (d, *J* = 243.9 Hz), 147.51, 147.48, 134.3, 131.1 (d, *J* = 5.0 Hz), 128.3 (d, *J* = 8.1 Hz), 127.6, 126.8 (d, *J* = 11.6 Hz), 123.48, 123.45, 122.1 (d, *J* = 19.6 Hz), 120.9, 118.2 (d, *J* = 21.5 Hz), 44.8, 26.0 (d, *J* = 3.2 Hz), 18.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}FN_2O$: 281.1090; found: 281.1087.

4-Bromo-6-methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (2l)

Column chromatography (hexane/EtOAc, 19:1) afforded **2l** as a white solid; yield: 27.20 mg (40%); mp 158–160 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (d, *J* = 2.0 Hz, 1 H), 8.29 (dt, *J* = 7.6, 1.2 Hz, 1 H), 7.76 (d, *J* = 0.8 Hz, 1 H), 7.75–7.74 (m, 1 H), 7.59 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.48–7.44 (m, 1 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 5.58–5.51 (m, 1 H), 3.28 (dd, *J* = 16.0, 6.0 Hz, 1 H), 2.86 (dd, *J* = 16.0, 1.6 Hz, 1 H), 1.22 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 147.6, 147.2, 134.8, 134.5, 133.7, 131.0, 130.8, 130.4, 127.7, 127.0, 126.9, 121.4, 121.1, 45.4, 33.2, 18.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}BrN_2O$: 341.0290; found: 341.0293.

6-Methyl-4-phenoxy-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (2m)

Column chromatography (hexane/EtOAc, 19:1) afforded **2m** as a yellowish white solid; yield: 32.57 mg (46%); mp 124–126 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34–8.29 (m, 2 H), 7.78 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.75 (td, *J* = 8.4, 1.6 Hz, 1 H), 7.48–7.44 (m, 1 H), 7.39 (td, *J* = 8.0, 1.2 Hz, 1 H), 7.34–7.30 (m, 2 H), 7.13 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.10–7.06 (m, 1 H), 6.94–6.91 (m, 2 H), 5.58–5.51 (m, 1 H), 3.24 (dd, *J* = 16.8, 1.6 Hz, 1 H), 2.99 (dd, *J* = 16.4, 6.0 Hz, 1 H), 1.23 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 157.6, 154.1, 148.3, 147.7, 134.4, 131.1, 129.9, 128.3, 127.7, 127.2, 127.0, 126.8, 123.7, 123.2, 123.0, 121.0, 117.6, 45.1, 27.2, 18.3.

HRMS (ESI): *m*/*z* [M + K]$^+$ calcd for $C_{23}H_{18}N_2O_2K$: 393.1005; found: 393.1011.

5-Methyl-4*H*-thieno[2′,3′:3,4]pyrido[2,1-*b*]quinazolin-7(5*H*)-one (2n)

Column chromatography (hexane/EtOAc, 19:1) afforded **2n** as a yellowish white solid; yield: 26.26 mg (49%); mp 116–118 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 7.8 Hz, 1 H), 7.75–7.66 (m, 2 H), 7.55 (d, *J* = 5.1 Hz, 1 H), 7.44–7.38 (m, 1 H), 6.99 (d, *J* = 5.1 Hz, 1 H), 5.66–5.58 (m, 1 H), 3.25 (dd, *J* = 16.8, 6.6 Hz, 1 H), 2.97 (d, *J* = 16.5 Hz, 1 H), 1.32 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.0, 147.8, 145.8, 140.4, 134.2, 131.7, 130.6, 127.8, 127.0, 126.95, 126.1, 121.0, 46.8, 29.9, 18.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}N_2OS$: 269.0749; found: 269.0743.

7-Methyl-7,8-dihydro-5*H*-benzo[6,7]isoquinolino[1,2-*b*]quinazolin-5-one (2o)

Column chromatography (hexane/EtOAc, 19:1) afforded **2o** as a yellowish white solid; yield: 45.55 mg (73%); mp 218–220 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.06 (s, 1 H), 8.36 (dd, *J* = 8.4, 1.8 Hz, 1 H), 8.05 (d, *J* = 8.4 Hz, 1 H), 7.85 (d, *J* = 8.4 Hz, 2 H), 7.81–7.78 (m, 1 H), 7.74 (s, 1 H), 7.60–7.57 (m, 1 H), 7.55–7.52 (m, 1 H), 7.51–7.48 (m, 1 H), 5.69–5.64 (m, 1 H), 3.51 (dd, *J* = 15.6, 5.4 Hz, 1 H), 3.11 (dd, *J* = 15.6, 1.8 Hz, 1 H), 1.25 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.4, 149.0, 147.9, 135.0 (2C), 134.3, 132.5, 131.1, 129.4, 128.9, 128.1, 127.5, 127.1 (2C), 126.9, 126.5, 126.2, 120.8, 45.7, 34.1, 18.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}N_2O$: 313.1341; found: 313.1333.

6,10-Dimethyl-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (2p)

Column chromatography (hexane/EtOAc, 19:1) afforded **2p** as a yellowish gummy liquid; yield: 35.33 mg (64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (dd, *J* = 7.6, 1.2 Hz, 1 H), 8.08 (d, *J* = 1.2 Hz, 1 H), 7.65 (d, *J* = 8.4 Hz, 1 H), 7.56–7.53 (m, 1 H), 7.45 (td, *J* = 7.2, 1.2 Hz, 1 H), 7.42–7.38 (m, 1 H), 7.25 (d, *J* = 7.2 Hz, 1 H), 5.58–5.52 (m, 1 H), 3.35 (dd, *J* = 16.0, 6.0 Hz, 1 H), 2.87 (dd, *J* = 16.0, 1.6 Hz, 1 H), 2.48 (s, 3 H), 1.21 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 147.9, 145.8, 136.8, 135.8, 134.8, 131.8, 129.2, 128.7, 127.8, 127.6, 127.4, 126.3, 120.7, 45.4, 33.7, 21.5, 18.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O$: 277.1341; found: 277.1342.

10-Methoxy-6-methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (2q)

Column chromatography (hexane/EtOAc, 19:1) afforded **2q** as a white solid; yield: 39.13 mg (67%); mp 126–128 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.70 (d, *J* = 8.8 Hz, 1 H), 7.66 (d, *J* = 3.2 Hz, 1 H), 7.45 (td, *J* = 7.2, 1.6 Hz, 1 H), 7.42–7.38 (m, 1 H), 7.34 (dd, *J* = 8.8, 2.8 Hz, 1 H), 7.24 (d, *J* = 6.4 Hz, 1 H), 5.60–5.53 (m, 1 H), 3.92 (s, 3 H), 3.35 (dd, *J* = 16.0, 5.6 Hz, 1 H), 2.87 (dd, *J* = 16.0, 1.6 Hz, 1 H), 1.22 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 158.4, 146.7, 142.5, 134.6, 131.6, 129.22, 129.16, 128.7, 127.7, 127.6, 124.8, 121.7, 106.2, 55.9, 45.6, 33.7, 18.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_2$: 293.1290; found: 293.1295.

11-Methoxy-6-methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (2r)

Column chromatography (hexane/EtOAc, 19:1) afforded **2r** as a white solid; yield: 39.13 mg (67%); mp 80–82 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 8.0 Hz, 1 H), 8.19 (d, *J* = 8.8 Hz, 1 H), 7.48 (td, *J* = 8.8, 1.2 Hz, 1 H), 7.42 (t, *J* = 8.0 Hz, 1 H), 7.26 (d, *J* = 7.2 Hz, 1 H), 7.15 (d, *J* = 1.6 Hz, 1 H), 7.02 (dd, *J* = 8.8, 2.4 Hz, 1 H), 5.57–5.51 (m, 1 H), 3.93 (s, 3 H), 3.35 (dd, *J* = 15.6, 5.6 Hz, 1 H), 2.87 (dd, *J* = 16.4, 1.6 Hz, 1 H), 1.21 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 160.9, 149.4, 135.1, 132.0, 131.0, 128.7, 128.5, 127.9, 127.6, 117.0, 114.6, 107.9, 100.0, 55.8, 45.2, 33.7, 18.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_2$: 293.1290; found: 293.1292.

6,11-Dimethyl-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (2s)

Column chromatography (hexane/EtOAc, 19:1) afforded **2s** as a gray solid; yield: 34.22 mg (62%); mp 106–108 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.47 (dd, *J* = 7.5, 1.8 Hz, 1 H), 8.20 (d, *J* = 8.1 Hz, 1 H), 7.57 (s, 1 H), 7.52–7.40 (m, 2 H), 7.28 (d, *J* = 8.1 Hz, 2 H), 5.59–5.53 (m, 1 H), 3.37 (dd, *J* = 16.2, 6.0 Hz, 1 H), 2.89 (dd, *J* = 15.9, 1.5 Hz, 1 H), 2.52 (s, 3 H), 1.22 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.2, 148.6, 147.9, 145.1, 134.8, 131.8, 129.1, 128.6, 128.1, 127.8, 127.5, 127.2, 126.6, 118.5, 45.2, 33.6, 21.9, 18.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O$: 277.1341; found: 277.1334.

11-Bromo-6-methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (2t)

Column chromatography (hexane/EtOAc, 19:1) afforded **2t** as a white solid; yield: 47.60 mg (70%); mp 148–150 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 7.8 Hz, 1 H), 8.43 (d, *J* = 1.8 Hz, 1 H), 7.83–7.81 (m, 1 H), 7.63 (d, *J* = 9.0 Hz, 1 H), 7.50 (t, *J* = 7.2 Hz, 1 H), 7.43 (t, *J* = 7.2 Hz, 1 H), 7.28 (d, *J* = 7.2 Hz, 1 H), 5.58–5.53 (m, 1 H), 3.37 (dd, *J* = 16.2, 6.0 Hz, 1 H), 2.90 (d, *J* = 16.2 Hz, 1 H), 1.23 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 160.2, 148.9, 146.6, 137.4, 134.8, 132.1, 129.4, 129.3, 128.68, 128.67, 127.9, 127.6, 122.2, 119.9, 45.6, 33.4, 17.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}BrN_2O$: 341.0290; found: 341.0291.

Methyl 6,10-Dimethyl-8-oxo-6,8-dihydro-5*H*-isoquinolino[1,2-*b*]quinazoline-3-carboxylate (2u)

Column chromatography (hexane/EtOAc, 9:1) afforded **2u** as a white solid; yield: 46.76 mg (70%); mp 158–160 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 8.0 Hz, 1 H), 8.15 (d, *J* = 8.4 Hz, 1 H), 8.02 (dd, *J* = 8.4, 0.8 Hz, 1 H), 7.92 (s, 1 H), 7.53 (s, 1 H), 7.26 (dd, *J* = 8.4, 1.6 Hz, 1 H), 5.58–5.51 (m, 1 H), 3.93 (s, 3 H), 3.36 (dd, *J* = 16.0, 6.0 Hz, 1 H), 2.93 (d, *J* = 16.0 Hz, 1 H), 2.48 (s, 3 H), 1.19 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 161.0, 147.70, 147.68, 145.3, 135.0, 133.2, 132.8, 129.9, 128.7, 128.5, 128.0, 127.5, 126.8, 118.7, 52.5, 45.3, 33.6, 22.0, 18.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}N_2O_3$: 335.1396; found: 335.1394.

3,7-Dimethyl-7,8-dihydro-5*H*-benzo[6,7]isoquinolino[1,2-*b*]quinazolin-5-one (2v)

Column chromatography (hexane/EtOAc, 19:1) afforded **2v** as a yellow solid; yield: 52.81 mg (81%); mp 214–216 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.02 (s, 1 H), 8.13 (s, 1 H), 8.03 (d, *J* = 8.4 Hz, 1 H), 7.84 (d, *J* = 7.8 Hz, 1 H), 7.74 (d, *J* = 8.4 Hz, 1 H), 7.73 (s, 1 H), 7.60 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.58–7.55 (m, 1 H), 7.53–7.50 (m, 1 H), 5.67–5.63 (m, 1 H), 3.50 (dd, *J* = 15.6, 5.4 Hz, 1 H), 3.09 (dd, *J* = 15.6, 1.8 Hz, 1 H), 2.52 (s, 3 H), 1.23 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.3, 148.2, 145.9, 136.7, 135.8, 134.9, 132.5, 131.1, 129.3, 128.6, 127.9, 127.3, 127.2, 127.1, 127.0, 126.3, 126.2, 120.5, 45.7, 34.1, 21.4, 18.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_2O$: 327.1497; found: 327.1646.

1,5,9-Trimethyl-4,5-dihydropyrrolo[2′,3′:3,4]pyrido[2,1-*b*]quinazolin-7(1*H*)-one (2w)

Column chromatography (hexane/EtOAc, 19:1) afforded **2w** as a gray gummy liquid; yield: 26.23 mg (47%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.04 (s, 1 H), 7.50–7.49 (m, 2 H), 6.78 (d, *J* = 2.4 Hz, 1 H), 6.02 (d, *J* = 2.4 Hz, 1 H), 5.59–5.55 (m, 1 H), 4.15 (s, 3 H), 3.15 (dd, *J* = 16.2, 6.0 Hz, 1 H), 2.73 (d, *J* = 15.6 Hz, 1 H), 2.48 (s, 3 H), 1.30 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.5, 145.7, 143.7, 135.4, 135.2, 129.5, 126.5, 126.3, 124.5, 120.9, 120.0, 106.5, 47.1, 37.4, 27.6, 21.3, 18.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_3O$: 280.1450; found: 280.0089.

5,11-Dimethyl-4*H*-thieno[2′,3′:3,4]pyrido[2,1-*b*]quinazolin-7(5*H*)-one (2x)

Column chromatography (hexane/EtOAc, 19:1) afforded **2x** as a white solid; yield: 40.04 mg (71%); mp 150–152 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.4 Hz, 1 H), 7.56 (d, *J* = 7.2 Hz, 1 H), 7.53 (d, *J* = 5.4 Hz, 1 H), 7.30 (t, *J* = 7.8 Hz, 1 H), 6.98 (d, *J* = 5.4 Hz, 1 H), 5.63–5.58 (m, 1 H), 3.24 (dd, *J* = 16.8, 6.6 Hz, 1 H), 2.96 (d, *J* = 16.8 Hz, 1 H), 2.64 (s, 3 H), 1.32 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.3, 146.3, 144.5, 140.1, 135.5, 134.7, 131.4, 131.2, 127.7, 125.7, 124.6, 120.9, 46.7, 29.9, 18.7, 17.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2OS$: 283.0905; found: 283.1031.

7,13-Dimethyl-7,8-dihydroindolo[2′,3′:3,4]pyrido[2,1-*b*]quinazolin-5(13*H*)-one (2y)

Column chromatography (hexane/EtOAc, 9:1) afforded **2y** as a yellow solid; yield: 17.01 mg (27%); mp 194–196 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.33 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.76–7.70 (m, 2 H), 7.65 (d, *J* = 8.4 Hz, 1 H), 7.46–7.43 (m, 2 H), 7.42–7.39 (m, 1 H), 7.22–7.19 (m, 1 H), 5.77–5.72 (m, 1 H), 4.38 (s, 3 H), 3.36 (dd, *J* = 16.8, 6.6 Hz, 1 H), 3.21 (dd, *J* = 16.2, 0.6 Hz, 1 H), 1.38 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.3, 147.3, 144.6, 140.7, 134.1, 127.1, 127.0, 126.22, 126.16, 125.02, 124.98, 120.9, 120.1, 119.9, 116.4, 110.3, 46.8, 32.5, 25.7, 18.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{18}N_3O$: 316.1450; found: 316.1446.

Funding Information

This work was financially supported by the Department of Science and Technology (DST), Science and Engineering Research Board (SERB), Government of India (Ramanujan Fellowship Award No. SR/S2/RJN-97/2012, Extra Mural Research Grant No. EMR/2014/000469). G.B. thanks UGC and K.M. thanks CSIR for their fellowships.

Acknowledgment

We acknowledge S. Jana for X-ray crystal structure analysis.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611525.

References

(1) (a) Lechat, P.; Tesleff, S.; Bownan, W. C. *Aminopyridines and Similarly Acting Drugs*; Pergamon: Oxford, **1982**. (b) Vacher, B.; Bonnaud, B.; Funes, P.; Jubault, N.; Koek, W.; Assie, M. B.; Cosi, C. *J. Med. Chem.* **1998**, *41*, 5070. (c) Andersohn, F.; Konzen, C.; Garbe, E. *Ann. Intern. Med.* **2007**, *146*, 657. (d) Martarelli, D.; Pompei, P.; Baldi, C.; Mazzoni, G. *Cancer Chemother. Pharmacol.* **2008**, *61*, 809. (e) Fang, J.; Ji, H.; Lawton, G. R.; Xue, F.; Roman, L. J.; Silverman, R. B. *J. Med. Chem.* **2009**, *52*, 4533. (f) Hilton, S.; Naud, S.; Caldwell, J.; Boxall, K.; Burns, S.; Anderson, V. E.; Antoni, L.; Allen, C. E.; Pearl, L. H.; Oliver, A. W.; Ahern, G. W.; Garrett, M. D.; Collins, I. *Bioorg. Med. Chem.* **2010**, *18*, 707.

(2) (a) Grover, G. S.; Kini, G. *Eur. J. Med. Chem.* **2006**, *41*, 256. (b) Jatav, V.; Kashaw, S.; Mishra, P. *Med. Chem. Res.* **2008**, *17*, 205. (c) Rohini, R.; Reddy, P. M.; Shanker, K.; Hu, A.; Ravinder, V. *Eur. J. Med. Chem.* **2010**, *45*, 1200. (d) Shallcross, L. J.; Davies, S. C. *J. Antimicrob. Chemother.* **2014**, *69*, 2883. (e) Jafari, E.; Khajouei, M. R.; Hassanzadeh, F.; Hakimelahi, G. H.; Khodarahmi, G. A. *Res. Pharm. Sci.* **2016**, *11*, 1.

(3) (a) Kadi, A. A.; El-Azab, A. S.; Alafeefy, A. M.; Abdel-Hamide, S. G. *Al-Azhar J. Pharm. Sci.* **2006**, *34*, 147. (b) Giri, R. S.; Thaker, H. M.; Giordano, T.; Williams, J.; Rogers, D. *Eur. J. Med. Chem.* **2009**, *44*, 2184. (c) Wang, D.; Gao, F. *Chem. Cent. J.* **2013**, *7*, 95. (d) Bouley, R.; Kumarasiri, M.; Peng, Z.; Otero, L. H.; Song, W. *J. Am. Chem. Soc.* **2015**, *137*, 1738. (e) Jafari, E.; Khajouei, M. R.; Hassanzadeh, F.; Hakimelahi, G. H.; Khodarahmi, G. A. *Res. Pharm. Sci.* **2016**, *11*, 1. (f) Lv, Z.; Wang, B.; Hu, Z.; Zhou, Y.; Yu, W.; Chang, J. *J. Org. Chem.* **2016**, *81*, 9924. (g) Shinde, A. H.; Arepally, S.; Baravkar, M. D.; Sharada, D. S. *J. Org. Chem.* **2017**, *82*, 331. (h) Yao, S.; Zhou, K.; Wang, J.; Cao, H.; Yu, L.; Wu, J.; Qiu, P.; Xu, Q. *Green Chem.* **2017**, *19*, 2945.

(4) (a) Shen, C.; Wang, L.; Wen, M.; Shen, H.; Jin, J.; Zhang, P. *Ind. Eng. Chem. Res.* **2016**, *55*, 3177. (b) Zhang, Q.; Li, Y.; Zhang, B.; Lu, B.; Li, J. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 4885.

(5) For selected reviews on C–H activation, see: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (b) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. *Chem. Rev.* **2017**, *117*, 8754. (c) Xue, X.-S.; Ji, P.; Zhou, B.; Cheng, J.-P. *Chem. Rev.* **2017**, *117*, 8622. (d) Yang, Y.; Lan, J.; You, J. *Chem. Rev.* **2017**, *117*, 8787. (e) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. *Chem. Rev.* **2017**, *117*, 8908. (f) Kim, D.-S.; Park, W.-J.; Jun, C.-H. *Chem. Rev.* **2017**, *117*, 897. (g) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. *Chem. Rev.* **2017**, *117*, 9016. (h) Shang, R.; Ilies, L.; Nakamura, E. *Chem. Rev.* **2017**, *117*, 9086. (i) Hummel, J. R.; Boerth, J. A.; Ellman, J. A. *Chem. Rev.* **2017**, *117*, 9163.

(6) (a) Duncton, M. A. J. *MedChemComm* **2011**, *2*, 1135. (b) Caro-Diaz, E. J. E.; Urbano, M.; Buzard, D. J.; Jones, R. M. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5378.

(7) (a) Manna, M. K.; Hossian, A.; Jana, R. *Org. Lett.* **2015**, *17*, 672. (b) Manna, M. K.; Bhunia, S. K.; Jana, R. *Chem. Commun.* **2017**, *53*, 6906. (c) Manna, M. K.; Bairy, G.; Jana, R. *J. Org. Chem.* **2018**, *83*, 8390. (d) Bairy, G.; Das, S.; Begam, H. M.; Jana, R. *Org. Lett.* **2018**, *20*, 7107.

(8) For reviews on the Fujiwara–Moritani Heck reaction, see: (a) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170. (b) Zhou, L.; Lu, W. *Chem. Eur. J.* **2014**, *20*, 634. For seminal work, see: (c) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119.

(9) Zheng, Y.; Song, W.-B.; Zhang, S.-W.; Xuan, L.-J. *Org. Biomol. Chem.* **2015**, *13*, 6474.

(10) (a) Manikandan, R.; Jeganmohan, M. *Org. Lett.* **2014**, *16*, 3568. (b) Wu, J.; Xiang, S.; Zeng, J.; Leow, M.; Liu, X.-W. *Org. Lett.* **2015**, *17*, 222. (c) Bian, J.; Qian, X.; Wang, N.; Mu, T.; Li, X.; Sun, H.; Zhang, L.; You, Q.; Zhang, X. *Org. Lett.* **2015**, *17*, 3410.

(11) (a) Cui, S.; Zhang, Y.; Wu, Q. *Chem. Sci.* **2013**, *4*, 3421. (b) Cui, S.; Zhang, Y.; Wang, D.; Wu, Q. *Chem. Sci.* **2013**, *4*, 3912. (c) Wu, S.; Zeng, R.; Fu, C.; Yu, Y.; Zhang, X.; Ma, S. *Chem. Sci.* **2015**, *6*, 2275.

(12) Lou, M.; Deng, Z.; Mao, X.; Fu, Y.; Yang, Q.; Peng, Y. *Org. Biomol. Chem.* **2018**, *16*, 1851.

(13) Xia, Y.-Q.; Dong, L. *Org. Lett.* **2017**, *19*, 2258.

(14) Feng, Y.; Tian, N.; Li, Y.; Jia, C.; Li, X.; Wang, L.; Cui, X. *Org. Lett.* **2017**, *19*, 1658.

(15) (a) Bhattacharyya, J.; Pakrashi, S. C. *Heterocycles* **1980**, *14*, 1469. (b) El-Soll, A. M. A. *Global J. Biotechnol. Biochem.* **2011**, *6*, 31.

(16) Palem, J. D.; Alugubelli, G. R.; Bantu, R.; Nagarapu, L.; Polepalli, S.; Jain, S. N.; Bathini, R.; Manga, V. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3014.

(17) Vemula, S. R.; Kumar, D.; Cook, G. R. *ACS Catal.* **2016**, *6*, 5295.

(18) Manoharan, R.; Jeganmohan, M. *Chem. Commun.* **2015**, *51*, 2929.

(19) (a) Huang, L.; Wang, Q.; Qi, J.; Wu, X.; Huang, K.; Jiang, H. *Chem. Sci.* **2013**, *4*, 2665. (b) Wang, H.; Schroder, N.; Glorius, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 5386.

(20) (a) Manikandan, R.; Madasamy, P.; Jeganmohan, M. *ACS Catal.* **2016**, *6*, 230. (b) Manikandan, R.; Tamizmani, M.; Jeganmohan, M. *Org. Lett.* **2017**, *19*, 6678.

(21) (a) Kim, N. Y.; Cheon, C.-H. *Tetrahedron Lett.* **2014**, *55*, 2340. (b) Cheng, R.; Guo, T.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Synthesis* **2013**, *45*, 2998. (c) Hour, M.-J.; Yang, J.-S.; Chen, T.-L.; Chen, K.-T.; Kuo, S.-C.; Chung, J.-G.; Lu, C.-C.; Chen, C.-Y.; Chuang, Y.-H. *Eur. J. Med. Chem.* **2011**, *46*, 2709. (d) Mahiwal, K.; Kumar, P.; Narasimhan, B. *Med. Chem. Res.* **2012**, *21*, 293.

(22) (a) Purandare, A. V.; Gao, A.; Wan, H.; Somerville, J.; Burke, C.; Seachord, C.; Vaccaro, W.; Wityak, J.; Poss, M. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2669. (b) Gellibert, F.; Fouchet, M.-H.; Nguyen, V.-L.; Wang, R.; Krysa, G.; de Gouville, A.-C.; Huet, S.; Dodic, N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2277.