NJC

PAPER

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Cite this: DOI: 10.1039/d0nj00479k

Mn-mediated oxidative radical cyclization of 2-(azidomethyl)phenyl isocyanides with carbazate: access to quinazoline-2-carboxylates†

Mn-TBHP mediated oxidative radical cyclization of 2-(azidomethyl)phenyl isocyanides using methyl carbazate has been described. This procedure is realized through a cascade radical addition and aromatization

process with high atom economy to furnish various heterocyclic C2 diversified guinazoline-2-carboxylate

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Received 28th January 2020, Accepted 29th March 2020

DOI: 10.1039/d0nj00479k

rsc.li/njc

Introduction

Quinazoline derivatives belong to nitrogen-containing heterocycles present in a wide variety of bioactive natural products.¹ Specifically quinazoline and its derivatives represent a medicinally and pharmaceutically important class that is found as the core structural skeleton in a variety of drug molecules such as prazosin² and lapatinib.3 They exhibit a wide range of biological and pharmaceutical activities that include anti-cancer,⁴ anti-viral⁵ and anti-tuberculosis properties.⁶ Quinazolines have also been employed as ligands for benzodiazepine and GABA receptors in the CNS⁷ and also as DNA binders.⁸ This large interest in medicinal chemistry stimulated the development of new variants of quinazoline derivatives by exploring novel synthetic methods. The construction of C2-diversified carboxylate quinazoline derivatives has gained considerable attention in recent years. In this direction, work is underway in our laboratory. There are reports of the classical synthetic approach to construct 2-carboxylate quinazolines. Ferrini developed 2,4-disubstituted quinazolines from 2-aminoacetophenone and ethyl 2-chloro-2-oxoacetate.9a Yuan synthesized 2-carboxylate quinazoline by platinum/iridium alloy-mediated cyclocondensation of 2-(aminomethyl)aniline with ethyl 2-oxoacetates.9b Wenlong reported the condensation of 2-aminobenzamide with diethyl oxalate leading to the synthesis of 2-carboxylate quinazolines.9c Apart from these methods, there are other methods too for 2-carboxylate quinazoline synthesis.¹⁰ However, there are several limiting factors hindering the preparation of 2-carboxylate quinazolines with large molecular diversity. In most of

derivatives.

the previous studies, the work was mainly focused on the functional group, such as an aldehyde, a ketone or an amine, that reacts with an oxalate or oxoacetate, involving two steps. Despite the advances in developing different synthetic strategies, many methods still have drawbacks such as harsh conditions, and use of noble metal alloy catalysts and pre-functional groups. These limitations impede the application of quinazoline derivatives in pharmaceutical synthesis. To overcome this drawback and establish more efficient methods and in continuation of our effort towards the construction of C2 diversified carboxylate quinazoline derivatives for new drug discovery, we hypothesized isocyanides as versatile building blocks as they have been widely applied in the synthesis of numerous nitrogen containing compounds.¹¹ Recently, Ezaki reported the preparation of quinazoline derivatives by using 1-(1-azidomethyl)-2-isocyanoarenes with NaH.12 Li also showed that isocyanides serve not only as nucleophiles but also as efficient radical acceptors to produce imidoyl radical intermediates for subsequent reactions.¹³ In the past few years, elegant advances have been made in the development of use of carbazates as the precursors of alkoxycarbonyl radicals since carbazates (ROCONHNH₂) are usually stable solids and are readily available. In 2016, Gao et al.^{14a} developed an iron-catalyzed oxidative addition of alkoxycarbonyl radicals to heterocyclic rings by using carbazates as the source of ester groups. In 2014, Pan et al.14b reported radical arylalkoxycarbonylation of 2-isocyanobiphenyl with carbazates to give phenanthridine-6-carboxylates. Encouraged by these results, herein, we report a novel and practical method for the synthesis of the second position functionalized quinazoline derivatives by using 1-(1-azidomethyl)-2-isocyanoarenes.

Free radical reactions are a powerful tool in organic synthesis. With their significant potential, this strategy has captured the attention of synthetic chemists. These reactions are applied to a range of organic transformations because of their unique advantages such as excellent reactivity, mild conditions, functional group



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[†] Electronic supplementary information (ESI) available: ¹H and ¹³C NMR spectra of the products and crystallographic information for **3g**. CCDC 1911289. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0nj00479k



Scheme 1 Comparison with previous work.

tolerance, and atom economy. In this paper we report a convenient and an efficient method for the tandem synthesis of 2-quinazoline carboxylates using 2-(azidomethyl)phenyl isocyanides along with carbazates, in the presence of $Mn(OAc)_3 \cdot 2H_2O$ as a promoter and TBHP as a co-oxidant. This procedure is realized through a cascade radical addition and aromatization process with high atom economy and represents the first example of the use of a carbazate as an alkoxycarbonyl radical precursor in isocyanide insertion for direct conversion of 2-(azidomethyl)phenyl isocyanides to quinazoline-2-carboxylate derivatives (Scheme 1).

Results & discussion

We started our studies on the feasibility of the oxidative radical reaction by using 2-(azidomethyl)phenyl isocyanides (1a) (0.63 mmol) with methyl carbazate (2a) (1.26 mmol) in the presence of manganese(III) acetate dihydrate salts (Mn(OAc)₃·2H₂O) (0.63 mmol) as a radical-mediated catalyst and TBHP (1.89 mmol) used as a co-oxidant. The reaction proceeded at 80 $^\circ C$ in toluene for 12 h. The desired C2 diversified carboxylation product of methyl quinazoline-2-carboxylate (3a) was obtained in 45% isolated yield (Table 1, entry 1). To improve the yield, the reaction was carried out by using various oxidants such as TBPB, K₂S₂O₈, TBHP (70% wt) (Table 1, entry 4), Ag_2CO_3 , AgOAc, $(NH_4)_2S_2O_8$, and CH₃COOH (Table 1, entries 2-8). Comparable results were observed for reactions in TBHP (70% wt) (Table 1, entry 4). However, the product yield did not increase with the other oxidants. In order to further improve the reaction yield, we examined the effect of various solvents such as DMF, PhF, CH₃CN, EtOAc and dioxane (Table 1, entries 9-13). We observed

 Table 1
 Optimization studies for manganese-mediated radical cyclization

 of 2-(azidomethyl)phenyl isocyanides (1a) with methyl carbazate (2a)

NC + NH ₂ HN-COOMe conditions				
1a	2a		3a	
Entry	Promoter	Additive	Solvent	Yield (%)
1	Mn(OAc) ₃ ·2H ₂ O	TBHP	Toluene	45
2	$Mn(OAc)_3 \cdot 2H_2O$	TBPB	Toluene	20
3	$Mn(OAc)_3 \cdot 2H_2O$	$K_2S_2O_8$	Toluene	ND
4	$Mn(OAc)_3 \cdot 2H_2O$	TBHP (70 %wt)	Toluene	35
5	$Mn(OAc)_3 \cdot 2H_2O$	Ag_2CO_3	Toluene	ND
6	$Mn(OAc)_3 \cdot 2H_2O$	AgOAc	Toluene	ND
7	$Mn(OAc)_3 \cdot 2H_2O$	$(NH_4)_2S_2O_8$	Toluene	35
8	$Mn(OAc)_3 \cdot 2H_2O$	CH ₃ COOH	Toluene	ND
9	$Mn(OAc)_3 \cdot 2H_2O$	TBHP	DMF	15
10	$Mn(OAc)_3 \cdot 2H_2O$	TBHP	PhF	25
11	$Mn(OAc)_3 \cdot 2H_2O$	TBHP	CH_3CN	55
12	Mn(OAc) ₃ ·2H ₂ O	TBHP	EtOAc	65
13	$Mn(OAc)_3 \cdot 2H_2O$	TBHP	Dioxane	20
14	$Mn(OAc)_3$	TBHP	EtOAc	48
15	$Mn(acac)_3$	TBHP	EtOAc	35
16	$Fe(acac)_2$	TBHP	EtOAc	25
17	FeCl ₃	TBHP	EtOAc	Trace
18	FeCl ₂ ·4H ₂ O	TBHP	EtOAc	Trace
19	$Cu(OAc)_2$	TBHP	EtOAc	ND
20	Oxone	TBHP	EtOAc	ND

Reaction conditions: **1a** (0.63 mmol), **2a** (1.26 mmol), promoter (0.63 mmol), radical initiator (1.89 mmol, 5 M in decane), and solvent (8 mL) under a N_2 atmosphere for 12 h at 80 °C. TBHP (*tert*-butyl hydroperoxide) (5 M in decane), TBHP (entry 4) (70% solution in water). TBPB (*tert*-butyl peroxy benzoate).

that EtOAc was the best solvent as it gave the product in 65% yield (Table 1, entry 12). Further optimization was carried out by testing the efficiencies of various promoters, but the results showed that the reaction yield decreased with Mn(OAc)₃, Mn(acac)₃, Fe(acac)₂, FeCl₃, FeCl₂·4H₂O, Cu(OAc)₂, and oxone (Table 1, entries 14–20). The conditions given in entry 12 of Table 1 are found to be the most suitable as they gave a high yield.

With the optimal reaction conditions in hand, we turned our attention to the scope for the substrates 1-(1-azidomethyl)-2-isocyanoarene compounds for the tandem cyclization and C2-diversified carboxylation (Table 2). Various functional groups such as methoxy, methyl, fluoro, chloro, and bromo were tolerated well under the present oxidative conditions, affording the products in moderate yields. We studied the effects of the substituents at different positions on the aromatic ring with the isocyanide group. As expected, aromatic rings possessing electrondonating groups (3b-3f; Table 2) gave better yields than those possessing electron-withdrawing groups (3h-3m; Table 2). 2-(Azidomethyl)phenyl isocyanides bearing electron-donating groups at the para and meta positions gave better yields (3b, 3c, and 3d; Table 2) than those bearing ortho substituents (3e, 3g, and 3k; Table 2), which is attributed to the steric effect. Notably, the halides were intact and the corresponding products were obtained in moderate yields (3g-3m; Table 2), enabling further derivatizations through metal-catalyzed cross-coupling reactions. We also tested the azidomethane carbon substituent (1-(1-azidoethyl)-2-isocyanobenzene) and noticed that the corresponding product was obtained in 58% yield (3f). Further, when the isocyanide ring bore both

Mn(IV)OH







t-BuO

Scheme 3 Proposed radical pathway for methyl quinazoline-2-carboxylate product formation.

Reaction conditions: 1a (0.63 mmol), 2a (1.26 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (0.63 mmol), TBHP (1.89 mmol, 5 M in decane), and EtOAc (8 mL) for 12 h at 80 °C.

electron donating and electron withdrawing substituents at different positions, the yield of the corresponding product was 55% (**3g**; Table 2).

To have a better understanding of the functionalization of 2-(azidomethyl)phenyl isocyanides, some mechanistic experiments were carried out. The radical inhibitor 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (2.0 equiv.) was added to the reaction mixture; the desired product was not observed and the TEMPO-COOMe (**3aa**) adduct was detected by LCMS (Scheme 2). The radical inhibitor (TEMPO) had a large negative impact on the reaction efficiency with methyl carbazate (**2a**), which provided evidence favoring the free radical mechanism.

Based on the above experimental results, a mechanism is proposed (Scheme 3). Initially, $Mn(OAc)_3 \cdot 2H_2O$ -assisted homolysis of TBHP generates *tert*-butoxy and *tert*-butyl peroxy radicals.^{14c-g} With the aid of Mn(m), the homolysis of TBHP into *tert*-butoxy



Scheme 2 Control experiments for mechanistic studies.

radicals may be accelerated by single-electron transfer along with the formation of Mn(tv) species.¹⁵ The C–N bond cleavage of the methyl carbazate forms an alkoxycarbonyl radical (**I**) with the release of molecular N₂ through stepwise hydrogen abstraction; this radical (**I**) attacks the R–NC bond of 2-(azidomethyl)phenyl isocyanide (**1a**) to form an imidoyl radical intermediate (**II**); this intermediate undergoes intermolecular cyclization with the azido group to give a cyclized aminyl radical (**III**) by nitrogen loss. Finally, hydrogen abstraction of the radical intermediate (**III**) by the *tert*butoxy or *tert*-butyl peroxy radicals leads to the desired product (**3a**). In conclusion, we have developed a novel and practical method for the synthesis of C2 diversified methyl quinazoline-2-carboxylate derivatives from 2-(azidomethyl)phenyl isocyanides (**1a**).

Conclusions

Mn(III) +

t-BuOOH

In summary, a cascade synthesis of methyl quinazoline-2-carboxylates using 2-(azidomethyl)phenyl isocyanides with methyl carbazate has been reported. This protocol provides a novel, general, reliable, straightforward, atom efficient approach to methyl quinazoline-2-carboxylate (**3a**). Furthermore, the utility of this approach can be applied to late-stage functionalization and modification of pharmaceutically and biologically active molecules.

Experimental

General

NMR spectra were recorded on 400 MHz and 500 MHz spectrometers in CDCl₃ or DMSO-d₆. Tetramethylsilane (TMS; δ = 0.00 ppm)

served as an internal standard for ¹H NMR. The corresponding residual nondeuterated solvent signal (DMSO-d₆, δ = 2.4 ppm; $CDCl_3$, $\delta = 7.25$ ppm) served as an internal standard. All the ¹³C NMR experiments were run in CDCl₃ and DMSO-d₆ on 100 MHz and 125 MHz spectrometers. The solvent signal (CDCl₃, δ = 77.01 ppm; DMSO-d₆, δ = 39.55 ppm) was used as an internal standard for ¹³C NMR. Data are reported as follows: chemical shifts in ppm (δ), multiplicity (s = singlet, t = triplet, q = quartet, m = multiplet), and coupling constants (Hz). IR spectra were measured using an FT-IR spectrometer. Mass spectra were obtained for the final compound with an ESI-Q-TOF Mass Spectrometer (HRMS). For all intermediates mass spectra were obtained by LCMS (ESI) m/z. Flash column chromatography was carried out by packing glass columns with commercial silica gel 230-400 mesh (commercial suppliers) and thin-layer chromatography was carried out using silica gel GF-254. All catalysts, reagents, starting materials and coupling partners were procured from commercial suppliers. Solvents were used for the reaction, workup and purification.

General experimental procedure for synthesizing methyl quinazoline-2-carboxylate derivatives

In a 20 mL screw-cap reaction vial 2-(azidomethyl)phenyl isocyanides (1a) (1.0 equiv., 0.63 mmol, 0.1 mg), $Mn(OAc)_3 \cdot 2H_2O$ (1.0 equiv., 0.63 mmol, 0.16 g), $NH_2NHCOOMe$ (2.0 equiv., 1.26 mmol, 0.11 g), and TBHP (5 M in decane) (3 equiv., 1.89 mmol, 0.38 mL) were added followed by the addition of ethyl acetate (8 mL). The vial was capped and placed in a pre-heated (80 °C) metal block for 12 h. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, and diluted with ethyl acetate, which was washed with brine (3 × 20 mL) and water (3 × 20 mL); the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude products were purified by flash column chromatography using ethyl acetate and *n*-hexane to afford the desired products.

Methyl quinazoline-2-carboxylate (3a). Prepared as per the general experimental procedure. White solid (65%, 68 mg). $R_{\rm f}$ (40% ethyl acetate/*n*-hexane) = 0.2. Melting point (°C): 121–123. IR (KBr, cm⁻¹): 3060, 2955, 2100, 1731, 1615, 1557, 1491, 1319, 1153, 977, 803, 781, 746, 647. ¹H NMR (DMSO-d₆, 400 MHz): δ 9.75 (s, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.15–8.11 (m, 2H), 7.90–7.89 (m, 1H), 3.95 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 164.31, 161.21, 152.52, 150.03, 135.13, 130.02, 129.58, 127.19, 125.14, 53.70. HRMS (ESI-TOF) (*m*/*z*): [M + H]⁺ calcd for C₁₀H₈N₂O₂H 189.0664; found 189.0664.

Methyl 6-methoxyquinazoline-2-carboxylate (3b). Prepared as per the general experimental procedure. Brown solid (62%, 62 mg). R_f (40% ethyl acetate/*n*-hexane) = 0.2. Melting point (°C): 158–160. IR (KBr, cm⁻¹): 2954, 2359, 2102, 1727, 1617, 1560, 1490, 1302, 1229, 834, 659. ¹H NMR (DMSO-d₆, 400 MHz): δ 9.59 (s, 1H), 8.07 (d, J = 9.2 Hz, 1H), 7.74 (d, J = 9.2 Hz, 1H), 7.64 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 164.40, 160.29, 159.13, 150.68, 146.23, 131.05, 128.36, 126.57, 103.75, 55.29, 53.52. HRMS (ESI-TOF) (*m*/*z*): [M + H]⁺ calcd for C₁₁H₁₀N₂O₃H 219.0770; found 219.0773. Methyl 5-methoxyquinazoline-2-carboxylate (3c). Prepared as per the general experimental procedure. Brown solid (62%, 62 mg). $R_{\rm f}$ (40% ethyl acetate/*n*-hexane) = 0.2. Melting point (°C): 131–133. IR (KBr, cm⁻¹): 2948, 2359, 2103, 1726, 1607, 1559, 1479, 1381, 1329, 1139, 771, 730. ¹H NMR (CDCl₃, 400 MHz): δ 9.53 (s, 1H), 7.73 (t, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 4.10 (s, 6H). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 164.25, 160.93, 155.37, 151.67, 141.96, 130.61, 126.04, 118.27, 112.59, 56.27, 53.54. HRMS (ESI-TOF) (*m*/*z*): [M + H]⁺ calcd for C₁₁H₁₀N₂O₃H 219.077; found 219.0772.

Methyl 5-methylquinazoline-2-carboxylate (3d). Prepared as per the general experimental procedure. Yellow solid (60%, 61 mg). $R_{\rm f}$ (40% ethyl acetate/*n*-hexane) = 0.2. Melting point (°C): 141–143. IR (KBr, cm⁻¹): 3016, 2095, 1734, 1609, 1565, 1328, 1199, 1148, 799. ¹H NMR (DMSO-d₆, 400 MHz): δ 9.83 (s, 1H), 7.99–7.97 (m, 2H), 7.68 (d, J = 5.2 Hz, 1H), 3.94 (s, 3H), 2.79 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 167.25, 156.37, 140.33, 136.80, 134.29, 129.50, 128.23, 127.81, 118.23, 53.04, 19.59. HRMS (ESI-TOF) (*m*/*z*): [M + H]⁺ calcd for C₁₁H₁₀N₂O₂H 203.0821; found 203.0819.

Methyl 8-methylquinazoline-2-carboxylate (3e). Prepared as per the general experimental procedure. Pale-yellow solid (55%, 58 mg). $R_{\rm f}$ (40% ethyl acetate/*n*-hexane) = 0.2. Melting point (°C): 120–122. IR (KBr, cm⁻¹): 2916, 2100, 1734, 1612, 1566, 1477, 1303, 1140, 804, 771. ¹H NMR (CDCl₃, 400 MHz): δ 9.49 (s, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.67 (t, J = 8.0 Hz, 1H), 4.11 (s, 3H), 2.87 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 164.61, 161.07, 151.88, 149.21, 138.36, 134.81, 129.55, 125.17, 124.81, 53.38, 16.94. HRMS (ESI-TOF) (*m*/*z*): [M + H]⁺ calcd for C₁₁H₁₀N₂O₂H 203.0821; found 203.0819.

Methyl 4-methylquinazoline-2-carboxylate (3f). Prepared as per the general experimental procedure. Brown solid (58%, 57 mg). R_f (40% ethyl acetate/*n*-hexane) = 0.2. Melting point (°C): 98–100. (KBr, cm⁻¹): 2956, 2359, 1730, 1613, 1570, 1254, 1204, 770. ¹H NMR (CDCl₃, 400 MHz): δ 8.25 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.98 (t, *J* = 6.8 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 4.11 (s, 3H), 3.07 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 169.89, 164.67, 151.84, 149.41, 134.47, 130.11, 129.59, 125.06, 124.59, 53.63, 21.98. HRMS (ESI-TOF) (*m*/*z*): [M + H]⁺ calcd for C₁₁H₁₀N₂O₂H 203.0821; found 203.0821.

Methyl 6-fluoro-8-methoxyquinazoline-2-carboxylate (3g). Prepared as per the general experimental procedure. Brown solid (55%, 56 mg). $R_{\rm f}$ (40% ethyl acetate/*n*-hexane) = 0.2. Melting point (°C): 158–160. IR (KBr, cm⁻¹): 3261, 2958, 2106, 1724, 1615, 1561, 1323, 1243, 1192, 1143, 966, 840. ¹H NMR (DMSO-d₆, 400 MHz): δ 9.65 (s, 1H), 7.57–7.52 (m, 2H), 4.04 (s, 3H), 3.93 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 164.13, 161.89, 160.38, 157.74, 151.23, 139.76, 126.53, 104.28, 101.65, 56.86, 53.71. ¹⁹F NMR (376 MHz, CDCl₃): -110.38 to -110.39 (d, 1F). HRMS (ESI-TOF) (*m*/*z*): [M + H]⁺ calcd for C₁₁H₉FN₂O₃H 237.0675; found 237.0674.

Methyl 6-fluoroquinazoline-2-carboxylate (3h). Prepared as per the general experimental procedure. Yellow solid (55%, 56 mg). $R_{\rm f}$ (40% ethyl acetate/*n*-hexane) = 0.2. Melting point (°C): 160–162. IR (KBr, cm⁻¹): 2954, 2105, 1732, 1622, 1560, 1493, 1445, 1296, 1155, 997, 835. ¹H NMR (CDCl₃, 400 MHz):

δ 9.54 (s, 1H), 8.34–8.31 (q, 1H), 7.82–7.78 (m, 1H), 7.65 (d, J = 7.6 Hz, 1H), 4.13 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 164.19, 163.11, 161.07, 160.68, 152.22, 147.30, 132.70, 126.02, 110.61, 53.88. ¹⁹F NMR (376 MHz, CDCl₃): -121.98 to -122.02 (m, 1F). HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₁₀H₇FN₂O₂H 207.057; found 207.0565.

Methyl 5-fluoroquinazoline-2-carboxylate (3i). Prepared as per the general experimental procedure. Pale-yellow solid (55%, 56 mg). $R_{\rm f}$ (40% ethyl acetate/*n*-hexane) = 0.2. Melting point (°C): 177–179. IR (KBr, cm⁻¹): 3279, 2959, 2359, 2103, 1728, 1622, 1568, 1316, 1143, 766, 726. ¹H NMR (CDCl₃, 500 MHz): δ 9.59 (s, 1H), 7.85–7.68 (m, 3H), 4.09 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 164.03, 161.22, 158.57, 156.47, 152.75, 130.35, 126.25, 123.05, 119.45, 53.86. ¹⁹F NMR (376 MHz, DMSO-d₆): –121.10 to –121.12 (d, 1F). HRMS (ESI-TOF) (*m*/*z*): [M + H]⁺ calcd for C₁₀H₇FN₂O₂H 207.057; found 207.0569.

Methyl 5-bromoquinazoline-2-carboxylate (3j). Prepared as per the general experimental procedure. Pale-yellow gummy solid (52%, 53 mg). $R_{\rm f}$ (40% ethyl acetate/*n*-hexane) = 0.2. Melting point (°C): 126–130. IR (cm⁻¹): 2954, 2359, 2096, 1728, 1624, 1550, 1438, 1293, 950, 645. ¹H NMR (CDCl₃, 500 MHz): δ 9.86 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 4.14 (s, 3H). ¹³C {¹H} NMR (CDCl₃, 125 MHz): δ 163.94, 161.26, 153.52, 151.51, 135.47, 133.73, 129.43, 124.46, 121.79, 53.96. HRMS (ESI-TOF) (*m*/*z*): [M + H]⁺ calcd for C₁₀H₇BrN₂O₂H 266.9769; found 268.9821.

Methyl 8-bromoquinazoline-2-carboxylate (3k). Prepared as per the general experimental procedure. Pale-yellow solid (50%, 52 mg). $R_{\rm f}$ (40% ethyl acetate/*n*-hexane) = 0.2. Melting point (°C): 114–116. IR (KBr, cm⁻¹): 3278, 2957, 2359, 1705, 1604, 1537, 1241, 1066, 764. ¹H NMR (DMSO-d₆, 400 MHz): δ 9.78 (s, 1H), 8.21 (t, *J* = 7.2 Hz, 2H), 8.04 (t, *J* = 8.0 Hz, 1H), 3.96 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 163.99, 161.74, 153.41, 147.82, 138.49, 130.38, 126.78, 126.36, 125.08, 53.70. HRMS (ESI-TOF) (*m*/*z*): [M + H]⁺ calcd for C₁₀H₇BrN₂O₂H 266.9769; found 268.9753.

Methyl 7-chloroquinazoline-2-carboxylate (3l). Prepared as per the general experimental procedure. Pale-yellow solid (52%, 53 mg). $R_{\rm f}$ (40% ethyl acetate/*n*-hexane) = 0.2. Melting point (°C): 137–139. IR (KBr, cm⁻¹): 3043, 2946, 2359, 1732, 1610, 1554, 1440, 1298, 1208, 1139, 1068, 651, 619. ¹H NMR (CDCl₃, 400 MHz): δ 9.54 (s, 1H), 8.28 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 4.13 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 163.98, 160.91, 153.44, 150.58, 141.64, 131.23, 128.59, 128.37, 123.46, 53.71. HRMS (ESI-TOF) (*m*/*z*): [M + H]⁺ calcd for C₁₀H₇ClN₂O₂H 223.0274; found 223.0271.

Methyl 5-chloroquinazoline-2-carboxylate (3m). Prepared as per the general experimental procedure. Yellow solid (51%, 50 mg). $R_{\rm f}$ (40% ethyl acetate/*n*-hexane) = 0.2. Melting point (°C): 143–145. IR (KBr, cm⁻¹): 3281, 3051, 2359, 1736, 1605, 1541, 1215, 1141, 720, 685. ¹H NMR (DMSO-d₆, 400 MHz): δ 9.83 (s, 1H), 8.31 (d, *J* = 7.6 Hz, 1H), 8.26 (d, *J* = 7.6 Hz, 1H), 7.87 (t, *J* = 8.0 Hz, 1H), 3.96 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 164.12, 161.76, 153.19, 146.90, 135.03, 134.27, 130.10, 126.45, 126.17, 53.86. HRMS (ESI-TOF) (*m*/*z*): [M + H]⁺ calcd for C₁₀H₇ClN₂O₂H 223.0274; found 223.0271, 225.0374.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank M. Srinivas (SFSL Bangalore) for technical assistance in recording the spectra of the compounds.

Notes and references

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