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FULL-LENGTH PAPER

Ionic liquid-supported synthesis of dihydroquinazolines and tetrahydroquinazolines under microwave irradiation

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Abstract An efficient microwave-assisted and water-soluble ionic liquid (IL)-supported synthesis of medicinally important dihydro- and tetrahydroquinazolines has been developed. The protocol involves the S_N2 substitution reaction of IL-bound 4-bromomethyl-3-nitrobenzoic acid with various primary amines to provide IL-bound 4-((alkylamino) methyl)-3-nitrobenzoate under microwave irradiation. Further elaboration followed by sequential cyclization with various isothiocyanates and aldehydes furnished IL-bound target compounds. Cleavage of the IL support by methanolysis gave dihydro- and tetrahydroquinazolines with high purity and excellent yields. The new protocol has the advantages of shorter reaction time, easy workup process, excellent yields, reduced environmental impact, wide substrate scope, and convenient procedure.

Keywords Tetrahydroquinazolines · Ionic liquid support · Microwave-assisted synthesis · Green chemistry

Introduction

Quinazoline-based heterocycles have a significant impact on the drug discovery process due to their essential roles in all levels of biology such as cell growth, signaling, proliferation, and sensing, and such frameworks are pervasive in both pharmaceutical industry and academic research [1,2]. Dihydro- and tetrahydroquinazolines, congeners of quinazoline, serve as an essential core structure for a wide range for natural products and are important pharmacophore of synthetic drugs demonstrating anti-inflammatory, antiviral, anticancer agents, anticonvulsants, antimalarial, antibacterial analgesic, and anti-Alzheimer properties [3–5]. Moreover, they have been employed as potent inhibitors against tyrosine kinases and cellular phosphorylation [6–8]. Recently, it has been found that 3,4-dihydroquinazoline derivatives such as **I** and **II** act as potent T-type Ca^{2+} channel blockers (Fig. 1), particularly against two isoforms of T-type Ca^{2+} channel [9–12]. Moreover, the quinazoline skeleton in the natural product-like vasicine and deoxypeganine **III** shows bronchodialatory, thrombopoietic, and antihistamine activity [13]. Commercialized drug compounds Gefitinib (**IV**) and Erlotinib (**V**) both feature a quinazoline framework that is active toward epidermal growth factor receptor for the treatment of lung cancer [14,15].

Access to these bioactive heterocycles with desired complexity by an efficient synthetic sequence remains a challenge in synthetic chemistry. A phase-tagged strategy aiming for the rapid construction of pharmacologically promising compounds to meet the demand of high-throughput screening has been developed. However, polymer-supported solid-phase synthesis suffers from serious drawbacks, such as heterogeneous reaction conditions, nonlinear kinetics, excess reagents as well as inability to characterize intermediates without the use of destructive compound cleavage methods for their analysis [16].

In contrast to biphasic reaction media raising from solid-phase chemistry, soluble polymer support technologies such as polyethylene glycol (PEG) was developed as an alternative carrier to provide homogeneous reaction media and facilitate the characterization of intermediates by conventional analytical methods. However, low loading support capacity and recovery rate of product limit their implementation for

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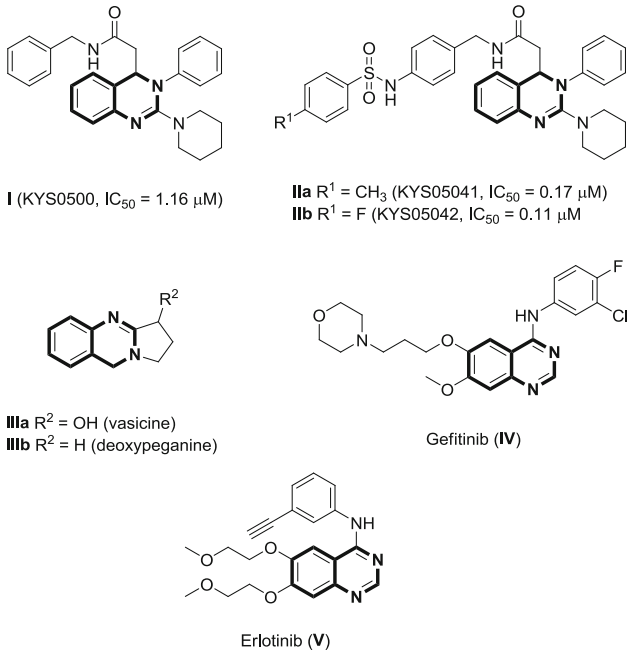


Fig. 1 Representative examples of biologically active quinazoline derivatives

molecular library construction [17–20]. The use of "fluorous phase" in organic synthesis has gained acceptance due to its broad application potential. Fluorous phase technology has been successfully applied in the synthesis of oligopeptides, oligosaccharide, and small molecules [21–24].

The development of cleaner, safer, and more economical synthetic methods is a central goal for chemists. Ionic liquids (IL) featuring zero vapor pressure, high thermal and superb chemical stability, recyclability, and nonflammability were originally used as reaction media to replace conventional organic solvents in organic synthesis [25]. In general, IL-tagged molecules are purified by simply washing the reaction mixture with a solvent in which the IL-anchored product is immiscible [26–32]. These features dramatically reduced the usage of organic solvents during synthetic exercises.

Microwave-assisted organic synthesis (MAOS) has had a great impact in the area of synthetic organic chemistry with the introduction of precision controlled microwave reactors [33–43]. Just as other well-documented phase tag protocols, IL-supported technology is compatible with microwave-assisted conditions so that reaction times and efficiency can be dramatically enhanced in comparison with conventional reflux conditions.

In line with our efforts to establish more facile approaches to synthesize structurally diverse small molecules, IL-supported technology has been introduced as a platform to explore a novel protocol to access desired heterocycles. Herein, we report the IL-supported synthesis of quinazoline-based heterocycles using microwave-assisted conditions.

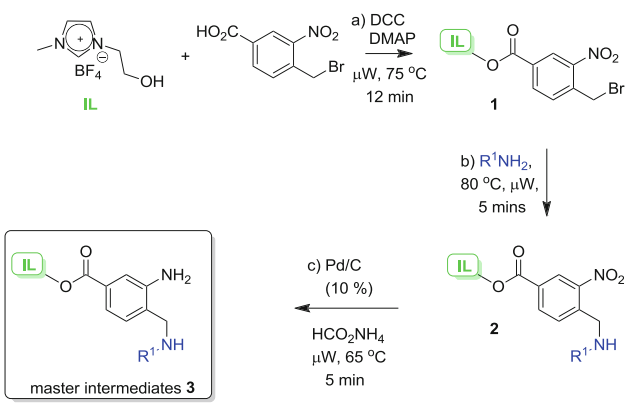
Results and discussion

Commercially available 4-bromomethyl-3-nitrobenzoic acid was employed as a pilot precursor in order to plot the scope of the IL-supported synthesis, while the tagged conjugate serves as the key intermediate to be further elaborated into the desired dihydro- and tetrahydroquinazoline derivatives. Condensation of 4-bromomethyl-3-nitrobenzoic acid with IL via *N,N′*-dicyclohexylcarbodiimide (DCC) coupling reaction [44–47] generates the IL conjugate **1** (Scheme 1). After reaction completion, the insoluble dicyclohexyl urea (DCU) was filtered off and the IL conjugate **1** was purified by precipitating out the product from the reaction mixture with excess of cold ether. IL conjugate **1** was then derivatized by reacting it with primary amines via nucleophilic substitution in acetonitrile under microwave irradiation for 5 min to give IL-tagged nitroamines **2** with satisfactory yields.

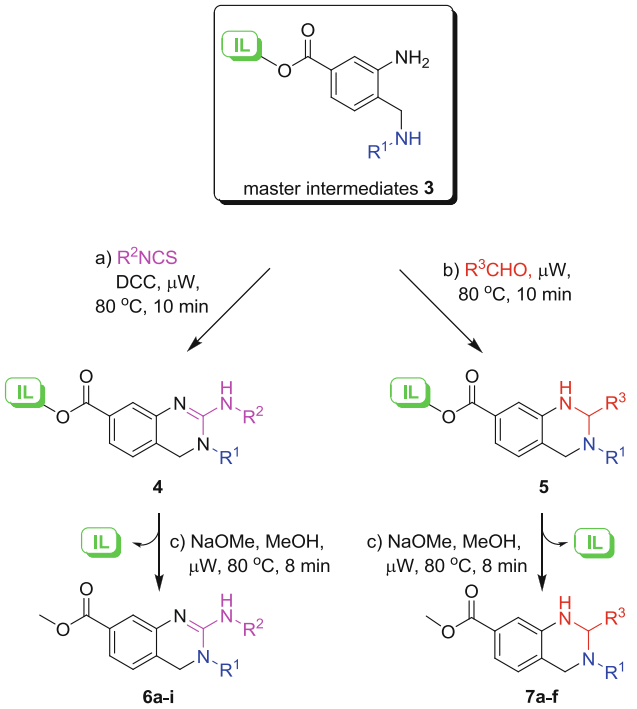
Then, IL-tagged nitroamines **2** were successfully reduced using Pd/C and ammonium formate under microwave irradiation conditions for 5 min followed by precipitation giving the master intermediates **3** (Scheme 1).

To construct the quinazoline framework with extended molecular diversity, the elaboration of the master intermediates **3** to the desired heterocyclic skeleton requires a one-carbon electrophile. Therefore, a divergent synthetic design involving isothiocyanates or aldehydes serving as the one-carbon synthon to rapidly access toward the desired target dihydro- and tetrahydroquinazolines has been delineated (Scheme 2).

Treatment of IL conjugates **3** with isothiocyanates in the presence of DCC as an activating agent in anhydrous acetonitrile under microwave irradiation at 80 °C furnished dihydroquinazoline IL conjugates **4**, whereas condensation of IL conjugates **3** with aldehydes resulted in tetrahydroquinazoline IL conjugates **5**. Cleavage of the IL tag from conjugates **4** and **5** under basic methanolysis conditions liberated heterocycles **6** and **7** with diverse molecular complexity (Table 1).



Scheme 1 Synthesis of IL-conjugated master intermediates **3**



Scheme 2 Rapid diversification of master IL conjugates **3** toward the target heterocyclic frameworks **6** and **7**

Most of the chemical manipulations in our research were complete with short reaction times (ca. 10–15 min) under microwave irradiation versus the required 2 h (or longer) when using conventional heating/refluxing conditions.

The formation of the IL-conjugated dihydroquinazolines **6** involves the nucleophilic addition of the secondary amine group of IL conjugates **3** into isothiocyanates forming intermediate "**a**". The use of a coupling agent further activates the thiocarbonyl moiety of intermediate "**a**" which after an intramolecular cyclization followed by a rearrangement generates the target compounds **6** as anticipated (Scheme 3).

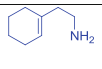
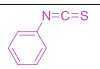
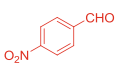
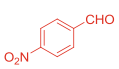
It is worth mentioning that the main advantage of the IL support is that a reaction can be monitored by thin-layer chromatography (TLC), MS, and/or ^{1}H NMR analysis. The final product obtained post IL-tag cleavage is highly pure.

Figure 2 shows a clear ^{1}H NMR comparison of IL species indicating how convenient IL-based synthesis can be monitored avoiding the use of sample-destructive analytical methods.

Conclusion

In conclusion, an efficient IL-supported microwave irradiation synthesis strategy for dihydro- and tetrahydroquinazoline derivatives has been developed. Room temperature IL (RTIL)-supported synthesis offers the advantages of uniform reaction conditions, easier monitoring of reaction progress in contrast to other phase-supported chemistry. This method provides minimum chromatographic purification exercises in general, with a better loading capacity than that of using soluble PEG or resins as carriers in organic synthesis. Currently, more IL-tagging strategies to access more diverse heterocyclic frameworks are under investigation and will be reported in due course.

Table 1 IL-supported synthesis of quinazoline derivatives under microwave irradiation

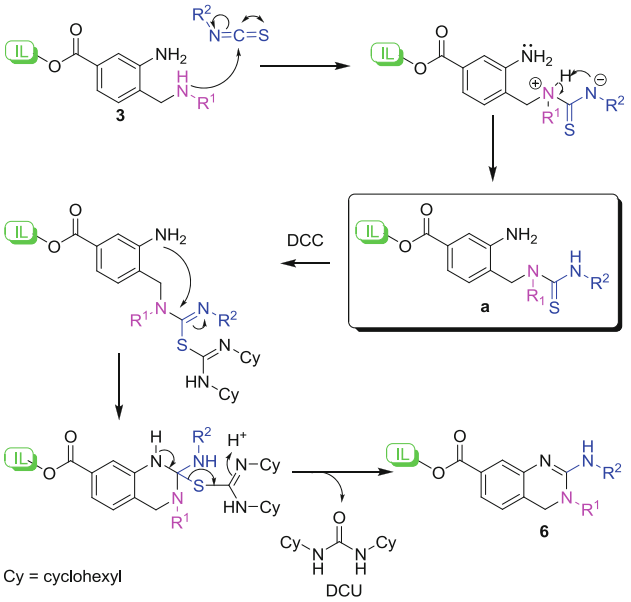
Entry	R^1	R^2/R^3	product	Yield (%)[a]
1			**6a**	70
2			**6b**	71
3			**6c**	85
4			**6d**	82
5			**6e**	70
6	^{i}BuNH$_2$		**6f**	80
7	^{i}BuNH$_2$		**6g**	84
8	^{i}BuNH$_2$		**6h**	70
9	^{i}PrNH$_2$		**6i**	85
10	^{i}PrNH$_2$		**7a**	82
11	^{i}BuNH$_2$		**7b**	74
12			**7c**	78
13			**7d**	91
14			**7e**	81
15			**7f**	81

[a] Isolated overall yields

Experimental section

General directions

Acetonitrile was distilled from calcium hydride before use. All reactions were performed under inert atmosphere with unpurified reagents and dry solvents. Analytical TLC was performed using 0.25-mm silica gel-coated 60-F plates with



Scheme 3 Proposed mechanism for the formation of dihydroquinazolines

a fluorescent indicator. Flash chromatography was performed using the indicated solvent and silica gel 60 (230–400 mesh). All the microwave heating experiments were conducted under optimized reaction conditions of power and temperature in a closed vessel in a Biotage initiator model no: Initiator US, 355286, 10429-22T, using IR sensor as internal probe for temperature control and compressed air system for cooling. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale from an internal standard. Low-resolution and high-resolution mass spectra were recorded on either a VG platform II or VG AutoSpec spectrometers with only molecular ions (M^+, MH^+ or MNH_4^+) were quoted. High-resolution mass spectra (HRMS) were recorded using positive mode electron spray ionization (ESI) and measurements are valid to ±5 ppm. Analytical HPLC analyses were performed using an Agilent 1100 Series HPLC system with UV detection at λ = 254 nm (column: Sphereclone 5μ Si (250 × 4.6 mm).

General procedure for the synthesis of IL-bound 4-bromomethyl-3-nitrobenzene carboxylate **1**

4-Bromomethyl-3-nitrobenzoic acid (0.63 g, 2.43 mmol), 1-methyl-3-ethyl imidazolium tetrafluoroborate (IL) (0.40 g, 1.87 mmol), and *N,N′*-dimethylamino pyridine (DMAP) (0.005 g) are placed in a dry, nitrogen-purged, pressure-sustaining microwave reaction vessel charged with dry CH_3CN (15 mL). DCC (0.54 g, 2.62 mmol) dissolved in dry CH_2Cl_2 (5 mL) was added dropwise to the reaction mixture for a period of 5 min. The reaction mixture was stirred for another 15 min at room temperature. Then, this vessel was exposed to microwave radiation to 75 °C for 12 min. After reaction completion, the reaction mixture was allowed to settle, and the insoluble DCU was filtered off and washed with CH_3CN (50 mL × 3). The solvent was evaporated, and the residue was crystallized in cold ether, filtered through a fritted funnel, and dried under vacuo to give *IL conjugate* **1** as pale white solid.

General procedure for the preparation IL-bound 4-((substituted amino) methyl)-3-nitrobenzene carboxylates **2**

IL-bound 4-bromomethyl-3-nitrobenzene carboxylate **1** (1.0 g, 2.19 mmol) in acetonitrile (15 mL) was treated with various primary amines (1.5 equiv). The reaction mixtures were irradiated with microwaves at 80 °C, 1 bar for 5 min to complete the reactions followed by evaporation of the solvent and washing the residue with cold ether (75 mL), dried over oven (50 °C) to obtain the ionic *IL conjugates* **2** as pale red solids.

General procedure for the preparation IL-bound 3-amino-4-((substituted amino) methyl) benzene carboxylates **3**

To a suspension solution of IL conjugate **2** in acetonitrile (15 mL), 10% Pd/C (5 equiv) and ammonium formate (7 equiv) were added. The crude mixture was irradiated with microwaves at 65 °C for 12 min to completely reduce the nitro group. The reaction mixture was filtered through a Celite plug to obtain the master intermediate *IL conjugate* **3**.

*General procedure for the preparation IL-bound dihydro-(**4**) and tetrahydroquinazoline derivatives* **5**

To a stirred solution of **3** in dry CH_3CN (20 mL), DCC (2.0 equiv) and isothiocyanates (2.0 equiv) were added. The reaction mixture was sealed and exposed to microwave irradiation at 80 °C, 1 bar for 10 min. Upon completion of the irradiation time, the insoluble DCU was allowed to settle, and the reaction mixture was filtered and washed with CH_3CN (50 mL × 3). The crude product was purified by precipitation with cold ether and dried in an oven (50 °C) to obtain the *IL conjugates* **4** in high purity.

In the case of tetrahydroquinazoline derivatives, various aldehydes (3 equiv) were added to the stirred solution of IL conjugates **5** in dry CH_3CN (20 mL). The reaction mixture was irradiated with microwaves at 80 °C, 1 bar for 10 min. Upon completion of the irradiation time, the crude product

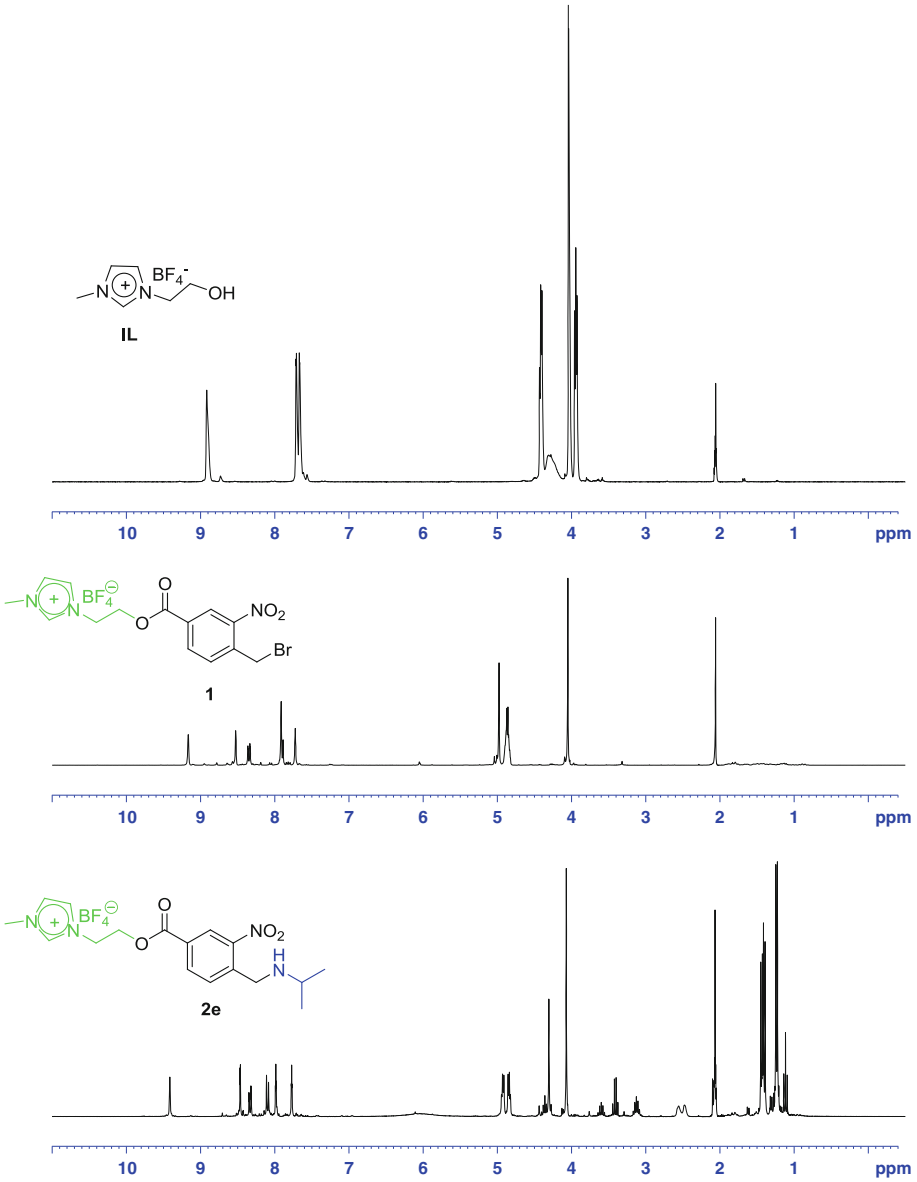


Fig. 2 Representative ^{1}H NMR spectra of IL-tagged intermediates

was purified by precipitation with cold ether and dried to obtain the *IL conjugates* **5** in high purity.

*General procedure for the cleavage of IL-bound substituted leading dihydro- (**6**) and tetrahydroquinazoline derivatives* **7**

To a solution of conjugates **4** and **5** in methanol (20 mL), NaOMe (100 mg) was added. The reaction mixture was exposed to microwave radiation at 80 °C for 8 min. After reaction completion, the crude product was precipitated with excess of cold ether (100 mL), the IL was filtered off from the organic mixture. The filtration liquid was dried over $MgSO_4$. The organic liquid was dried under vacuo, and subjected to crude HPLC analysis with UV detection at 254 nm (column: Sphereclone 5μ Si (250 × 4.6 mm); gradient: 35% ethyl acetate in hexane; flow rate: 1 mL/min). The residue was dissolved in dichloromethane (5 mL) and the solvent was again removed using a rotavapor. The slurry obtained was loaded on a silica gel column and eluted with a mixture of ethyl acetate and hexane (1:4) to get title compounds **6** and **7** in good yields.

*Methyl 3-[2-(cyclohex-1-en-1-yl)ethyl]-2-(phenylamino)-3, 4-dihydroquinazoline-7-carboxylate (**6a**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (s, 1H), 7.37 (dd, J = 6.1, 1.7 Hz, 1H), 7.35–7.32 (m, 3H), 7.31 (d, J = 1.7 Hz, 1H), 7.23 (m, 1H), 7.14 (d, J = 6.1 Hz, 1H), 5.48 (m, 1H), 4.62 (brs, 1H), 3.89 (s, 3H), 3.57 (t, J = 7.4 Hz, 2H), 2.18 (t,

J = 7.4 Hz, 2H), 1.98–1.88 (m, 4H), 1.88–1.80 (m, 2H), 1.62–1.48 (m, 4H);^{13}C NMR (75 MHz, $CDCl_3$): δ 181.9, 167.6, 146.6, 140.0, 134.8, 131.5, 131.3, 129.2, 126.5, 126.4, 125.0, 124.5, 118.9, 116.8, 53.9, 52.5, 48.2, 35.5, 29.0, 25.6, 23.1, 22.5; MS (ESI): m/z 390 (MH^+); HRMS (ESI) calcd for $C_{24}H_{28}N_3O_2$: m/z 390.2181, found 390.2184; IR (KBr): 3322, 2925, 1707, 1600, 1533, 1448 cm^{-1}.

*Methyl 3-[2-(cyclohex-1-en-1-yl)ethyl]-2-[(2-methylpropyl) amino]-3,4-dihydroquinazoline-7-carboxylate (***6b***)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.28 (m, 2H), 7.09 (d, J = 7.7 Hz, 1H), 5.67 (t, J = 4.8 Hz, 1H), 5.41 (brs, 1H), 3.88 (s, 3H), 3.52 (t, J = 6.3 Hz, 2H), 3.38 (t, J = 7.7 Hz, 2H), 2.04 (t, J = 7.7 Hz, 2H), 1.97–1.88 (m, 3H), 1.89–1.83(m, 3H), 1.63–1.49 (m, 5H), 0.95 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.4, 167.6, 146.6, 134.7, 131.4, 131.3, 124.9, 124.6, 118.7, 116.6, 54.3, 54.0, 52.5, 47.3, 35.3, 28.9, 28.6, 25.6, 23.1, 22.4, 20.7; MS (ESI): m/z 370 (MH^+). HRMS (ESI) calcd for $C_{22}H_{32}N_3O_2$: m/z 370.2494, found 370.2496; IR (KBr): 3324, 2925, 1710, 1631, 1529, 1438 cm^{-1}.

*Methyl 3-cyclopentyl-2-[(furan-2-ylmethyl)amino]-3, 4-dihydroquinazoline-7-carboxylate (***6c***)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (dd, J = 7.9, 1.4 Hz, 1H), 7.35 (d, J = 1.4 Hz, 1H), 7.27 (m, 1H), 7.04 (d, J = 7.9 Hz, 1H), 6.27 (dd, J = 3.1, 1.8 Hz, 1H), 6.17 (d, J = 3.1 Hz, 1H), 5.74 (t, J = 4.4 Hz, 1H), 5.29 (t, J = 8.5 Hz, 1H), 4.83 (d, J = 4.8 Hz, 2H), 4.62 (s, 2H), 3.95(brs, 1H), 3.88 (s, 3H), 1.99–1.93 (m, 2H), 1.69–1.55 (m, 4H), 1.48–1.41 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.7, 167.4, 151.3, 144.1, 142.5, 130.7, 127.7, 125.8, 120.4, 117.5, 110.8, 108.0, 61.7, 52.5, 47.2, 43.6, 29.3, 24.2; MS (ESI) m/z 354 (MH^+); HRMS (ESI) calcd for $C_{20}H_{24}N_3O_3$: m/z 354.1818, found 354.1815; IR (KBr): 3365, 2952, 1708, 1631, 1529, 1436 cm^{-1}.

*Methyl 3-cyclopentyl-2-(prop-2-en-1-ylamino)-3, 4-dihydroquinazoline-7-carboxylate (***6d***)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (dd, J = 7.9, 1.4 Hz 1H), 7.41 (d, J = 1.4 Hz, 1H), 7.10 (d, J = 7.9 Hz, 1H), 5.84 (m, 1H), 5.44 (t, J = 5.3 Hz, 2H), 5.38 (m, 1H), 5.10–5.02 (m, 2H), 4.61 (s, 2H), 4.30 (t, J = 5.3 Hz, 2H), 3.89 (s, 3H), 2.03–1.95 (m, 2H), 1.69–1.55 (m, 3H), 1.48–1.41 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.9, 167.4, 144.0, 134.2, 130.8, 127.6, 125.7, 120.4, 117.5, 117.0, 61.8, 52.6, 49.0, 47.0, 29.3, 24.2; MS (ESI) m/z 314 (MH^+); HRMS (ESI) calcd for $C_{18}H_{24}N_3O_2$: m/z 314.1868, found 314.1866; IR (KBr): 3370, 2954, 1710, 1631, 1577, 1444 cm^{-1}.

*Methyl3-(2-methoxyethyl)-2-[(2-methylpropyl)amino] -3, 4-dihydroquinazoline-7-carboxylate (***6e***)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (t, J = 8.1, Hz 1H), 7.32–7.28 (m, 1H), 7.05 (d, J = 8.1 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 2H), 3.52 (t, J = 8.4 Hz, 2H), 3.45 (t, J = 5.7 Hz, 2H), 3.30 (t+s, 5H), 1.97–1.88 (m, 2H), 0.87 (d, J = 8.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.2, 167.6, 146.8, 131.6, 131.4, 125.1, 118.6, 116.5, 72.1, 59.6, 54.9, 54.5, 52.5, 49.7, 28.4, 20.7; MS (ESI) m/z 320 (MH^+); HRMS (ESI) calcd for $C_{17}H_{26}N_3O_3$: m/z 320.1974, found 320.1977. IR (KBr): 3338, 2952, 1728, 1629, 1579, 1240 cm^{-1}.

*Methyl 3-(2-methylpropyl)-2-[(2-methylpropyl)amino]- 3,4-dihydroquinazoline-7-carboxylate (***6f***)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (dd, J = 7.8, 1.5 Hz 1H), 7.29 (d, J = 1.5 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 5.70 (m, 2H), 4.80–4.55 (brs, 1H), 3.87 (s, 3H), 3.51 (t, J = 6.8 Hz, 2H), 3.16 (d, J = 7.6 Hz, 2H), 2.06 (m, 1H), 1.93 (m, 1H), 0.91 (t, 6.8 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.1, 167.5, 146.5, 131.3, 131.2, 124.9, 118.9, 116.8, 55.1, 54.4, 54.3, 52.5, 28.5, 27.6, 20.9, 20.7; MS (ESI) m/z 318 (MH^+); HRMS (ESI) calcd for $C_{18}H_{28}N_3O_2$: m/z 318.2181, found 318.2179; IR (KBr): 3370, 2954, 1710, 1631, 1577, 1444 cm^{-1}.

*Methyl 2-[(furan-2-ylmethyl)amino]-3-(2-methylpropyl) -3, 4-dihydroquinazoline-7-carboxylate (***6g***)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.28 (m, 3H), 7.04 (d, J = 7.8 Hz, 1H), 6.32 (dd, J = 3.2, 2.0 Hz, 1H), 6.27 (d, J = 3.2, 1H), 5.94 (t, J = 4.6 Hz, 2H), 4.88 (d, J = 4.6 Hz, 2H), 3.90 (s, 3H), 3.15 (d, J = 7.6 Hz, 2H), 2.05–1.99 (m, 1H) 0.86 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.9, 167.6, 151.2, 146.4, 142.6, 131.3, 131.2, 124.8, 118.9, 116.8, 110.9, 108.3, 55.0, 54.5, 52.5, 43.8, 27.5, 20.8; MS (ESI) m/z 342 (MH^+); HRMS (ESI) calcd for $C_{19}H_{24}N_3O_3$: m/z 342.1818, found 342.1817; IR (KBr): 3446, 2927, 1704, 1531, 1438 cm^{-1}.

*Methyl 3-(2-methylpropyl)-2-(prop-2-en-1-ylamino)-3, 4-dihydroquinazoline-7-carboxylate (***6h***)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (dd, J = 7.7, 1.6 Hz 1H), 7.28 (d, J = 1.6 Hz, 1H), 7.03 (d, J = 7.7 Hz, 1H), 5.90 (m, 1H), 5.73 (t, J = 5.1 Hz, 1H), 5.19 (s, 2H), 5.15–5.11 (m, 1H), 4.34–4.30 (m, 2H), 3.85 (s, 3H), 3.16 (d, J = 7.7 Hz, 2H), 2.06 (m, 1H), 0.83 (d, J = 7.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.1, 167.6, 146.4, 134.3, 131.2, 130.8, 124.9, 118.9, 117.3, 116.8, 55.0, 54.4, 52.5, 49.2, 27.5, 20.8; MS (ESI) m/z 302 (MH^+); HRMS (ESI)

calcd for $C_{17}H_{24}N_3O_2$: m/z 302.1868, found 302.1867; IR (KBr): 3370, 2954, 1710, 1631, 1577, 1444 cm^{-1}.

*Methyl 3-(propan-2-yl)-2-(prop-2-en-1-ylamino)-3, 4-dihydroquinazoline-7-carboxylate (**6i**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, J = 8.3, 1.4 Hz, 1H), 7.42 (d, J = 3.3 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 5.80 (m, 1H), 5.46–5.37 (m, 2H), 5.07–4.99 (m, 2H), 4.60 (s, 2H), 4.31–4.26 (m, 2H), 3.89 (s, 3H), 1.21 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.1,166.9, 143.7, 133.8, 130.5, 127.5, 125.1, 119.9, 117.1, 116.5, 52.1, 51.5, 48.5, 45.3, 19.9; MS (ESI) m/z 288 (MH^+); HRMS (ESI) calcd for $C_{16}H_{22}N_3O_2$: m/z 288.1712, found 288.1710; IR (KBr): 3376, 2954, 1712, 1629, 1577, 1444 cm^{-1}.

*Methyl 3-(propan-2-yl)-2-(pyridin-3-yl)-1,2,3,4-tetrahydroquinazoline-7-carboxylate (**7a**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.70 (s, 1H), 8.51 (dd, J = 4.8 Hz, 1H), 7.76 (dt, J = 6.8, 1.5 Hz, 1H), 7.34–7.22 (m, 3H), 6.93 (d, J = 7.6 Hz, 1H), 5.38 (s, 1H), 4.64 (brs, NH), 3.88 (s, 3H), 3.78 (d, J = 16.8 Hz, 1H), 3.65 (d, J = 16.8 Hz, 1H), 2.97–2.87 (m, 1H), 1.18 (d, J = 6.2 Hz, 3H), 1.08 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 149.2, 149.0, 142.2, 138.3, 135.0, 129.2, 127.0, 125.3, 123.7, 119.0, 114.9, 68.6, 52.4, 49.9, 44.3, 22.2, 20.4. MS (ESI) m/z 311 (M^+) HRMS (EI) calcd for $C_{18}H_{21}N_3O_2$: m/z 311.1634, found 311.1639; IR (KBr): 3394, 1706, 1297 cm^{-1}.

*Methyl 3-isobutyl-2-phenyl-1,2,3,4-tetrahydro-7-quinazolinecarboxylate (**7b**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65–7.43 (m, 2H), 7.38–7.28 (m, 5H), 6.94 (d, J = 7.8 Hz, 1H), 5.10 (s, 1H), 4.52 (brs, 1H), 3.91 (s, 3H), 3.76 (d, J = 16.7 Hz, 1H), 3.56 (d, J = 16.7 Hz, 1H), 2.41 (dd, J = 16.7, 7.8 Hz, 1H), 2.24 (dd, J = 16.7, 7.8 Hz, 1H), 1.84 (m, 1H), 0.93 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 142.7, 129.1, 128.9, 128.5, 127.8, 127.7, 127.2, 126.9, 125.2, 118.3, 114.2, 72.5, 60.0, 52.0, 49.9, 26.0, 19.0; MS (EI): m/z 324 (M^+); HRMS (ESI) calcd for $C_{19}H_{24}N_2O_2$: m/z 324.1838, found: 324.1833; IR (KBr): 3386, 1706, 1502, 1295 cm^{-1}.

*Methyl 2-phenyl-3-(thiophen-2-ylmethyl)-1,2,3, 4-tetrahydroquinazoline-7-carboxylate (**7c**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53–7.50 (m, 2H), 7.38–7.26 (m, 6H), 6.98–6.92 (m, 3H), 5.21 (s, 1H), 4.55 (brs, 1H), 4.02 (d, J = 16.8 Hz, 1H), 3.89 (s, 3H), 3.85-3.80 (m, 2H), 3.65 (d, J = 16.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ167.8, 143.3, 142.4, 142.3, 129.8, 128.9, 128.3, 128.1, 127.4, 126.9, 126.2, 125.7, 124.0, 119.0, 115.0, 71.2, 52.4, 51.7, 48.8; $MS(EI)$: m/z 364 (M^{+1}). HRMS (ESI) calcd for $C_{21}H_{20}N_2O_2S$: m/z 364.1245, found 364.1243; IR (KBr): 3380, 1705, 1616, 1505 cm^{-1}.

*Methyl 2-(4-nitrophenyl)-3-(thiophen-2-ylmethyl)- 1,2,3, 4-tetrahydroquinazoline-7-carboxylate(**7d**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (dd, J = 6.9, 2.1 Hz, 1H), 7.69(d, J = 8.7 Hz, 2H), 7.43 (d, J = 1.5 Hz, 1H), 7.39 (d, J = 1.5 Hz, 1H), 7.30 (dd, J = 7.5, 1.5 Hz, 1H), 6.98–6.91 (m, 4H), 5.23 (s, 1H) 4.63 (brs, 1H), 4.06 (d, J = 16.4 Hz, 1H), 3.91 (s, 3H), 3.80–3.70 (m, 2H), 3.58 (d, J = 16.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 147.6, 140.8, 130.5, 129.8, 128.1, 127.8, 126.7, 126.4, 125.7, 124.3, 124.1, 123.7, 119.3, 115.0, 70.5, 69.3, 52.1, 51.7; MS (ESI) m/z 410 (MH^{+1}); HRMS (ESI) calcd for $C_{21}H_{20}N_3O_4S$: m/z 410.1174, found 410.1176; IR (KBr): 2931, 1708, 1600, 1505 cm^{-1}.

*Methyl 2-(phenyl)-3-[2-(pyridin-2-yl)ethyl]-1,2,3, 4-tetrahydroquinazoline- 7-carboxylate (**7e**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (d, J = 4.8 Hz, 1H), 8.09 (dd, J = 9.3, 1.8 Hz, 1H), 7.60 (td, J = 7.5, 1.8 Hz, 1H), 7.35–7.31 (m, 3H), 7.18–7.11 (m, 4H), 6.91 (d, J = 7.5 Hz, 1H), 5.27 (s, 1H), 4.78 (brs, 1H), 3.87 (s, 3H), 3.65 (s, 2H), 3.15-3.00 (m, 2H), 2.95–2.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 159.6, 149.6, 148.5, 147.4, 141.2, 137.0, 129.6, 128.1, 127.7, 123.7, 123.6, 121.6, 119.1, 115.2, 71.3, 52.3, 52.0, 48.1, 36.7; MS (ESI) m/z 419 (MH_{+1}); HRMS (ESI) calcd for $C_{23}H_{23}N_4O_2$: m/z 419.1719, found 419.1717; IR (KBr): 2925, 1712, 1294 cm^{-1}.

*Methyl 2-(2-fluorophenyl)-3-[2-(pyridin-2-yl)ethyl]-1,2,3, 4-tetrahydroquinazoline-7-carboxylate (**7f**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.45 (dd, J = 4.2, 0.9 Hz, 1H), 7.56 (td, J = 4.2, 1.8 Hz, 1H), 7.35–7.17 (m, 4H), 7.16 (d, J = 8.4 Hz, 1H), 7.06–6.95 (m, 4H), 5.58 (s, 1H), 4.54 (brs, 1H), 3.90 (s, 3H), 3.76 (d, J = 16.7 Hz, 1H), 3.56 (d, J = 16.7 Hz, 1H), 3.15–3.00 (m, 2H), 2.95–2.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 159.9, 149.0, 142.3, 136.4, 129.7, 129.1, 128.4, 128.3, 127.4, 123.7, 123.4, 121.2, 118.6, 115.8, 115.5, 114.4, 66.7, 53.4, 52.0, 49.0, 36.9; MS (ESI) m/z 392 (MH^+); HRMS (ESI) calcd for $C_{23}H_{23}N_3O_2$: m/z 392.1774, found 392.1772; IR (KBr): 2933, 2854, 1706, 1228 cm^{-1}.

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