Ramchandra Jedhe, Vijaykumar Paike and Chung-Ming Sun*

# Rapid synthesis of novel isoindolo[1,2-a]quinazoline on ionic liquid support under microwave irradiation

**Abstract:** An efficient ionic liquid-supported (ILs) strategy is applied for the synthesis of substituted isoindolo[1,2-a]quinazoline under microwave irradiation. The ILs enhances the coupling capability of microwave flash heating in green organic synthesis. The acid-catalyzed heterocyclization of ionic liquid bounded 3-amino-4-[(alkylamino) methyl]benzoate was carried out with $\alpha$-ketobenzoic acids or $\gamma$-ketoaliphatic acid to synthesize five and six member fused N-heterocycles. The one-pot heterocyclization proceeded *via* amidation between primary amines and 2-acylbenzoic acids or $\gamma$-ketoaliphatic acid, followed by the intramolecular dehydrocyclization with the keto group under microwave heating. The significant advantages in green synthesis by using ILs synthesis under controlled microwave dielectric heating are the dramatic reduction in reaction time, improved energy utilization, simple purification, and increasing the productivity of desired compounds.

**Keywords:** ionic liquid support; isoindolo[1,2-a]quinazoline; microwave chemistry; *N*-heterocyclic.

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## 1 Introduction

Room temperature ionic liquids (RTILs) have received a significant interest as green solvents in organic synthesis, owing to their task-specific properties [1–4]. RTIL has been used as soluble support in liquid phase synthesis and represents a new approach for parallel synthesis of medicinal scaffolds with a high productivity [5–7]. Hence, the significant advantages of ionic liquid support (ILs) synthesis are a high loading capacity, nature of homogeneous reaction mixture, simple purification, and easy monitoring reaction progress [5, 8–13].

Quinazoline heterocycles are widely found in many bioactive compounds, which are useful as building blocks in the synthesis of many natural products and in pharmacological active molecules [14–17]. Quinazoline integrates with other heterocyclic templates, such as the isoindole, to obtain isoindolo[1,2-a]quinazoline (Figure 1), which exhibits pharmacological activities such as anticancer, antifungal, and antitrypanosomal [18–23]. Batracylin (I) is structurally related to isoindoloquinazoline, which has activity against colon carcinomas, as well as cisplatin and doxorubicin resistant tumors. Some isoindoloquinazoline analogous found in alkaloids, such as vasicine (II), act *in vitro* on validated targets of the malaria parasite *Plasmodium falciparum*. Tryptanthrin (III) is available for the chemotherapy of sleeping sickness *Trypanosoma brucei*, and luotonin A (IV) is cytotoxic towards murine leukemia P-388 cells [21]. Recently, a microwave-assisted green protocol was used to construct heterocyclic compounds by either solid or ionic liquid support, due to their important biological applications [24–28].

The use of IL-immobilized synthesis under a microwave flash heating technique, increases the power of microwave absorbance, and makes the reaction faster for the rapid synthesis of bioactive molecules in drug discovery programs [29–34]. In view of this, a remarkable scope and demand for such types of ecologically and economically safe systems in green processing and organic synthesis are envisaged. Nevertheless, there are rare reports available on the general synthesis of isoindolo[1,2-a]quinazoline fused compounds [35–39]. Kumar and coworkers synthesized isoindolo[2,1-a] quinazoline by a multicomponent reaction of isatoic anhydride, aniline, and 2-formylbenzoic acid, using montmorillonite K-10 as a solid catalyst [35]. Martınez-Viturro and Dominguez proposed the Mitsunobu reaction, followed by spontaneous cyclization, for the synthesis of isoindolo[1,2-b]quinazolin-12-ones from aminoacetophenones or aminobenzophenones, with phthalimide [36]. Condensation of phthalic anhydride with 2,5-diaminobenzylamine produced isoindoloquinazolines in heated dioxane [37]. Reaction of a 1,4-phenylenedicarbamate with N-(hydroxymethyl) phthalimide to deliver batracylin (I, Figure 1) under acidic conditions was reported by Dzierzbicka et al. [38]. Kurihara reported the synthesis of isoindolo[1,2-a]quinazoline by the condensation of anthranilamide with phthalic anhydride at 160°C, and intramolecular acyl rearrangement afforded isoindolo[1,2-b]quinazoline from isoindolo[1,2-a]quinazoline [39]. Strong interest still remains in the design of a cost

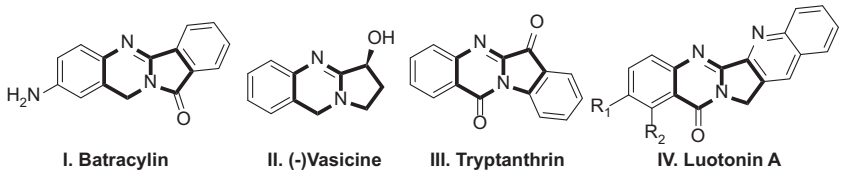



**Figure 1** Biologically active isoindoloquinazolines and their analogous.

effective, environmentally benign and metal-free chemical strategy for the synthesis of these biologically interesting molecules. Recently, we synthesized new nitrogen polyheterocyclic molecules on soluble polymer support, under microwave irradiation [40, 41]. Within this background, we investigated, in the present study, the impact of ILs synthesis under microwave dielectric heating for the synthesis of the pharmaceutically important isoindolo[1,2-a]quinazoline.

# 2 Experimental

## 2.1 General

All reactions were carried out in oven-dried glassware using standard syringes, cannulae, septa and other apparatus (Pyrex lab glasses, Japan). Solvents were dried with calcium hydride or sodium/benzophenone and distilled before use. For the microwave reactions, a microwave reactor Panasonic NNS565 (Panasonic Twain Co., Ltd., Taiwan) home microwave was used. The $^{1}$H NMR and $^{13}$C NMR spectra were recorded with a Bruker DRX-300 and 400 NMR (Bruker AXS Pte Ltd., Singapore) in acetone-$d_6$ ($C_3D_6O$) and methanol-$d_4$ ($CD_3OD$). Infrared spectra were recorded (neat samples) on a HORIBA FT-720 Fourier transform infrared spectrophotometer (HORIBA Ltd., Hsinchu, Taiwan) and the characteristic IR absorption frequencies are reported in cm$^{-1}$. Unless otherwise noted, reagents were purchased from commercial sources (Sigma Aldrich Chemical Co., Taipei, Taiwan) and used without further purification.

## 2.2 Typical synthetic procedures for methyl 6-pentyl-6a-methyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-a]quinazoline-2-carboxylate (8a)

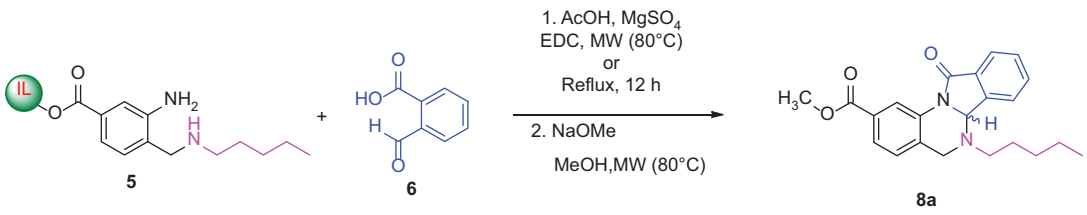
IL-bound methyl 3-amino-4-[(hexylamino)methyl]benzoate [42] **5** (0.328 g, 0.091 mmol, 1 equiv) was dissolved in ethylene dichloride (DCE, 4 ml) followed by addition of 2-fomylbenzoic acid **6** (0.164 g, 0.109 mmol, 1.2 equiv) and $MgSO_4$ with slow addition of acetic acid (0.273 g, 0.456 mmol, 5 equiv) in a microwave vial at room temperature. The resultant reaction mixture was microwave irradiated at 80°C for 10 min. After the reaction was complete, the solvent was diluted by the addition of cold ether, to precipitate ILs isoindolo[2,1-a]quinazoline **7**. Cleavage of the IL-support from **7** (0.406 g, 0.085 mmol, 1 equiv) was performed with sodium methoxide (0.047 g, 0.085 mmol, 1 equiv) in methanol (4 ml). The mixture was heated under microwave (80°C, 10 min) until the complete release of support to compound **8**. The mixture was filtered, washed with excess ether and the resulting crude residue was purified by silica column chromatography (eluent: 10% ethyl acetate in hexane) to obtain the corresponding methyl 6-pentyl-6a-methyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-a]quinazoline-2-carboxylate **8a** (84%). The general synthetic approach illustrated in Scheme 1. This general procedure was used for the synthesis of all isoindolo[2,1-a]quinazoline **8** derivatives.

## 2.3 Methyl-11-oxo-6-pentyl-5,6,6a,11-tetrahydroisoindolo[2,1-a]quinazoline-2-carboxylate (8a)

$^{1}$H NMR (300 MHz, acetone-$d_6$) δ 9.26 (s, 1H), 7.86 (d, $J$=7.2 Hz, 1H), 7.79–7.64 (m, 4H), 7.39 (d, $J$=7.8 Hz, 1H), 6.04 (s, 1H), 4.59 (d, $J$=17.2 Hz, 1H), 4.59 (d, $J$=17.2 Hz, 1H), 3.91 (s, 3H), 2.00–1.93 (m, 2H), 1.42–1.13 (m, 6H), 0.80 (t, $J$=6.6 Hz, 3H); $^{13}$C NMR (75 MHz, acetone-$d_6$) δ 168.5, 164.6, 141.1, 136.5, 133.4, 132.6, 129.8, 129.3, 128.0, 127.5, 124.1, 123.6, 123.4, 118.8, 77.0, 52.0, 51.5, 44.5, 27.3, 22.1, 13.3; IR (cm$^{-1}$, neat) 2950, 1720, 1697; MS (EI-MS) *m/z:* 365 $[M+1]^+$; HRMS: Calculated for $C_{22}H_{24}N_2NaO_3$: 387.1685; found: 387.1683 $[M+Na]^+$ *m/z*.

## 2.4 Methyl-6-cyclopentyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-a]quinazoline-2-carboxylate (8b)

$^{1}$H NMR (300 MHz, acetone-$d_6$) δ 9.23 (s, 1H), 7.87 (d, $J$=7.5 Hz, 1H), 7.99–7.67 (m, 4H), 7.39 (d, $J$=7.8 Hz, 1H), 6.15 (s, 1H),




**Scheme 1** Synthesis of methyl 6-pentyl-6a-methyl-11-oxo-5,6,6a, 11-tetrahydroisoindolo-[2,1-a]quinazoline-2-carboxylate (8a).

4.62 (d, *J*=17.5 Hz, 1H), 4.37 (d, *J*=17.5 Hz, 1H), 3.92 (s, 3H), 3.23 (m, 1H), 1.43–1.12 (m, 8H); $^{13}$C NMR (75 MHz, acetone-$d_6$): δ 166.2, 164.7, 141.2, 137.1, 133.1, 132.4, 130.3, 129.7, 128.9, 126.6, 124.2, 123.4, 118.9, 76.7, 58.2, 51.5, 49.8, 31.4, 23.1, 22.0; IR (cm$^{-1}$, neat) 2948, 1720, 1695; MS (EI-MS) *m/z*: 363 [M+1]$^+$; HRMS: Calculated for $C_{22}H_{22}N_2NaO_3$: 385.1528; found: 385.1530 [M+Na]$^+$ *m/z*.

## 2.5 Methyl-6-(1,2-diphenylethyl)-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-a] quinazoline-2-carboxylate (8c)

$^1$H NMR (300 MHz, acetone-$d_6$) δ 8.79 (s, 1H), 7.89 (d, *J*=7.2 Hz, 1H), 7.65 (t, *J*=7.3 Hz, 1H), 7.60 (t, *J*=7.3 Hz, 1H), 7.49 (dd, *J*=1.6, 7.9 Hz, 1H), 7.34–7.24 (m, 3H), 7.18–7.11 (m, 3H), 6.78–6.76 (m, 6H), 6.10 (s, 1H), 4.90 (d, *J*=18.1 Hz, 1H), 4.69 (d, *J*=18.1 Hz, 1H), 3.87–3.83 (m, 4H), 3.44 (dd, *J*=6.1, 13.4 Hz, 1H), 2.86 (dd, *J*=5.1, 13.5 Hz, 1H); $^{13}$C NMR (75 MHz, acetone-$d_6$): δ 166.2, 164.1, 140.2, 140.1, 139.8, 136.9, 134.0, 132.3, 129.9, 129.9, 129.6, 128.2, 128.0, 127.9, 127.2, 126.9, 125.9, 125.9, 124.0, 123.5, 123.4, 118.4, 76.5, 62.1, 51.3, 47.8, 40.0; IR (cm$^{-1}$, neat) 2948, 1716, 1697; MS (EI-MS) *m/z*: 475 [M+1]$^+$. HRMS: Calculated for $C_{31}H_{26}N_2NaO_3$: 497.1841; found: 497.1843 [M+Na]$^+$ *m/z*.

## 2.6 Methyl-11-oxo-6-phenethyl-5,6,6a,11-tetrahydroisoindolo[2,1-a]quinazoline-2-carboxylate (8d)

$^1$H NMR (300 MHz, acetone-$d_6$) δ 9.25 (s, 1H), 7.88–7.80 (m, 1H), 7.72 (d, *J*=7.8 Hz, 1H), 7.62–7.53 (m, 2H), 7.38 (d, *J*=7.8 Hz, 1H), 7.26–7.16 (m, 4H), 6.99 (d, *J*=8.7 Hz, 2H), 5.98 (s, 1H), 4.60 (d, *J*=17.4 Hz, 1H), 4.35 (d, *J*=17.4 Hz, 1H), 3.89 (s, 3H), 2.69–2.67 (m, 2H), 2.30 (m, 1H), 2.17 (m, 1H); $^{13}$C NMR (75 MHz, acetone-$d_6$) δ 166.2, 165.1, 140.7, 140.1, 136.6, 133.3, 132.5, 129.7, 129.4, 128.8, 128.0, 128.0, 127.5, 125.8, 124.2, 123.6, 123.3, 118.8, 76.7, 52.2, 51.5, 46.9, 34.4; IR (cm$^{-1}$, neat) 2946, 1718, 1693; MS (EI-MS) *m/z*: 399 [M+1]$^+$; HRMS: Calculated for $C_{25}H_{22}N_2NaO_3$: 421.1528; found: 421.1525 [M+Na]$^+$ *m/z*.

## 2.7 Methyl-11-oxo-6-(thiophen-2-ylmethyl)-5,6,6a,11-tetrahydroisoindolo[2,1-a] quinazoline-2-carboxylate (8e)

$^1$H NMR (300 MHz, acetone-$d_6$) δ 9.32 (s, 1H), 7.90 (d, *J*=6.3 Hz, 1H), 7.82–7.69 (m, 4H), 7.38–7.35 (m, 2H), 6.91–6.81 (m, 2H), 6.22 (s, 1H), 4.60 (d, *J*=12.2 Hz, 1H), 4.08 (d, *J*=12.2 Hz, 1H), 3.86 (s, 3H), 3.48 (d, *J*=9.5 Hz, 1H), 3.33 (d, *J*=9.6 Hz, 1H); $^{13}$C NMR (75 MHz, acetone-$d_6$) δ 166.5, 164.9, 158.7, 142.0, 140.2, 136.3, 133.3, 132.9, 130.1, 129.5, 128.1, 126.9, 126.6, 125.9, 125.4, 124.5, 123.7, 123.5, 118.9, 76.2, 51.5, 44.4; IR (cm$^{-1}$, neat) 2948, 1718, 1698; MS (EI-MS) *m/z*: 391 [M+1]$^+$; HRMS: Calculated for $C_{22}H_{18}N_2NaO_3S$: 413.0936; found: 413.0933 [M+Na]$^+$ *m/z*.

## 2.8 Methyl-6-(3-methylbutan-2-yl)-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-a] quinazoline-2-carboxylate (8f)

$^1$H NMR (300 MHz, $CD_3OD$) δ 9.07 (s, 1H), 7.90 (d, *J*=7.2 Hz, 1H), 7.75 (t, *J*=7.2 Hz, 2H), 7.68–7.63 (m, 2H), 7.35 (d, *J*=7.5 Hz, 1H), 6.15 (s, 1H), 4.59 (d, *J*=18.6 Hz, 1H), 4.29 (d, *J*=18.6 Hz, 1H), 3.94 (s, 3H), 2.24 (m, 1H), 1.69 (m, 1H), 1.05 (d, *J*=6.6 Hz, 3H), 0.75 (d, *J*=6.0 Hz, 3H), 0.55 (d, *J*=6.6 Hz, 3H); $^{13}$C NMR (75 MHz, acetone-$d_6$) δ 166.2, 164.3, 140.3, 137.3, 133.6, 132.4, 131.6, 129.7, 128.8, 125.9, 124.4, 124.3, 123.7, 119.2, 76.7, 57.7, 51.4, 47.1, 32.8, 20.5, 19.3, 15.3; IR (cm$^{-1}$, neat) 2952, 1720, 1695; MS (EI-MS) *m/z*: 365 [M+1]$^+$; HRMS: Calculated for $C_{22}H_{24}N_2NaO_3$: 387.1685; found: 387.1682 [M+Na]$^+$ *m/z*.

## 2.9 Methyl-3a-methyl-1-oxo-4-propyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a] quinazoline-8-carboxylate (8g)

$^1$H NMR (300 MHz, acetone-$d_6$) δ 9.28 (s, 1H), 7.69 (d, *J*=7.6 Hz, 1H), 7.32 (d, *J*=7 Hz, 1H), 4.19 (d, *J*=17.2 Hz, 1H), 3.88 (s, 3H), 3.74 (d, *J*=17.2 Hz, 1H), 2.74–2.67 (m, 2H), 2.51–2.42 (m, 2H), 2.29–2.23 (m, 2H), 1.61–1.52 (m, 2H), 1.25 (s, 3H), 0.93 (t, *J*=7.1 Hz, 3H); $^{13}$C NMR (100 MHz, acetone-$d_6$) δ 172.3, 167.1,

135.4, 129.9, 129.7, 127.7, 124.5, 120.9, 120.8, 78.8, 52.2, 49.9, 33.1, 31.2, 21.9, 15.5, 11.9; IR ($cm^{-1}$, neat) 2962, 1720, 1695; MS (EI-MS) *m/z*: 303 $[M+1]^+$; HRMS: Calculated for $C_{17}H_{22}N_2NaO_3$: 325.1528; found: 325.1526 $[M+Na]^+$ *m/z*.

### 2.10 Methyl-6-isobutyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-a]quinazoline-2-carboxylate (8h)

$^1H$ NMR (300 MHz, acetone-$d_6$) δ 9.23 (s, 1H), 7.87 (d, *J*=7.5 Hz, 1H), 7.80–7.65 (m, 4H), 7.39 (d, *J*=7.8 Hz, 1H), 6.06 (s, 1H), 4.63 (d, *J*=17.4 Hz, 1H), 4.23 (d, *J*=17.4 Hz, 1H), 3.92 (s, 3H), 1.98 (dd, *J*=3.7, 11.7 Hz, 1H), 1.77 (m, 1H), 1.56 (t, *J*=11.2 Hz, 1H), 0.88 (d, *J*=6.3 Hz, 3H), 0.66 (d, *J*=6.3 Hz, 3H); $^{13}C$ NMR (75 MHz, acetone-$d_6$) δ 166.3, 165.3, 141.3, 136.5, 133.5, 132.6, 129.9, 129.3, 128.0, 127.5, 124.2, 123.9, 123.4, 118.8, 76.9, 52.8, 52. 7, 51.5, 26.2, 20.1, 19.9; IR ($cm^{-1}$, neat) 2942, 1720, 1695; MS (EI-MS) *m/z*: 351 $[M+1]^+$; HRMS: Calculated for $C_{21}H_{22}N_2NaO_3$: 373.1528; found: 373.1526 $[M+Na]^+$ *m/z*.

### 2.11 Methyl-6-cyclopropyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-a]quinazoline-2-carboxylate (8i)

$^1H$ NMR (300 MHz, acetone-$d_6$) δ 9.26 (s, 1H), 7.87 (d, *J*=6.6 Hz, 1H), 7.74–7.65 (m, 4H), 7.40 (d, *J*=7.2 Hz, 1H), 6.08 (s, 1H), 4.66 (d, *J*=17.1 Hz, 1H), 4.26 (d, *J*=17.1 Hz, 1H), 3.93 (s, 3H), 1.70 (m, 1H), 0.41–0.29 (m, 3H), 0.10 (m, 1H); $^{13}C$ NMR (75 MHz, acetone-$d_6$) δ 166.3, 165.6, 141.0, 136.2, 133.0, 131.9, 129.5, 129.2, 128.0, 127.4, 124.9, 124.4, 123.3, 119.2, 76.5, 55.3, 51.5, 9.6, 3.8; IR ($cm^{-1}$, neat) 2950, 1716, 1697; MS (EI-MS) *m/z*: 335 $[M+1]^+$; HRMS: Calculated for $C_{20}H_{18}N_2NaO_3$: 357.1215; found: 357.1216 $[M+Na]^+$ *m/z*.

### 2.12 Methyl-4-(4-methoxybenzyl)-3a-methyl-1-oxo-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline-8-carboxylate (8j)

$^1H$ NMR (300 MHz, acetone-$d_6$) δ 9.29 (d, *J*=1.5 Hz, 1H), 7.65 (dd, *J*=1.5, 7.9 Hz, 1H), 7.32 (d, *J*=8.7 Hz, 2H), 7.21 (d, *J*=7.8 Hz, 1H), 6.90 (d, *J*=8.7 Hz, 2H), 4.03 (d, *J*=13.2 Hz, 1H), 3.86 (s, 3H), 3.79–3.77 (m, 4H), 3.29 (d, *J*=13.2 Hz, 1H), 2.83–2.74 (m, 2H), 2.58–2.49 (m, 3H), 1.38 (s, 3H); $^{13}C$ NMR (100 MHz, acetone-$d_6$) δ 172.3, 167.0, 159.9, 135.4, 131.2, 130.6, 130.5, 129.8, 129.6, 127.7, 124.6, 120.9, 120.8, 114.5, 78.8, 55.4, 53.9, 52.2, 49.6, 33.3, 31.3, 15.7; IR ($cm^{-1}$, neat) 2950, 1718, 1691; MS (EI-MS) *m/z*: 381 $[M+1]^+$; HRMS: Calculated for $C_{22}H_{24}N_2NaO_4$: 403.1634; found: 403.1636 $[M+Na]^+$ *m/z*.

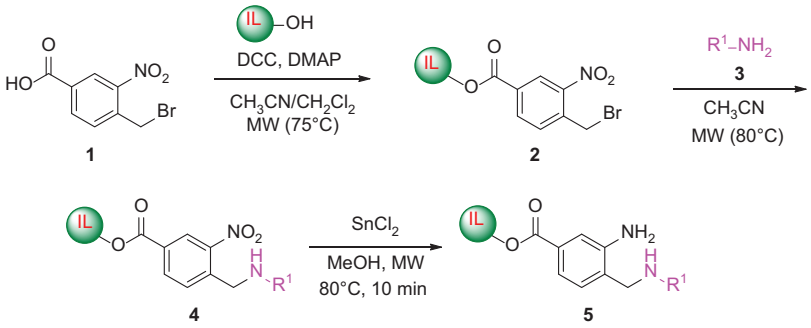
## 3 Results and discussion

ILs 4-(bromomethyl)-3-nitrobenzoate **2** was obtained by esterification of 4-(bromomethyl)-3-nitrobenzoic acid with 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate [(hydemim)[$BF_4$]] (IL) under microwave irradiation (75°C, 12 min). IL-bound nitrobenzoate **2** was reacted with primary amines **3** *via* nucleophilic bromo displacements in acetonitrile under microwave irradiation for 5 min at 80°C, to give nitroamines **4**. Then, IL-tagged nitroamines **4** were successfully reduced by tin(II) chloride in methanol under microwave heating for 10 min, followed by precipitation to give the main intermediates **5** (Scheme 2) [42].

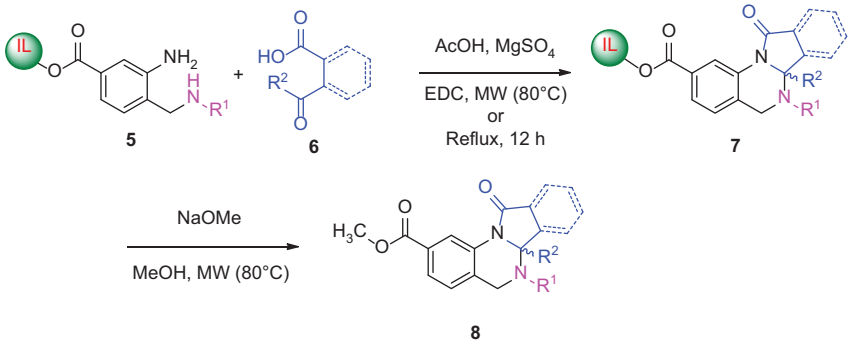
One of the major challenges and aim of the present work is the intramolecular one-pot dehydrocyclization to the construction of bi-heterocycles in the presence of reactive primary and secondary amino groups, with $\alpha$-ketobenzoic acids or $\gamma$-ketoaliphatic acid. The reaction of **5** and **6** was first investigated as the model reaction and optimization of catalysts was under microwave and conventional heating (Scheme 3).

To our delight, treatment of diamine **5** with $\alpha$-ketobenzoic acids or $\gamma$-ketoaliphatic acid in the presence of trifluoacetic acid (TFA) and magnesium sulfate under microwave irradiation (80°C) for 15 min leds to the isoindole fused quinazolines **7** with inferior yields (50–55%). The cyclization reaction was found to deliver isoindolo[1,2-a]quinazoles **7** in higher yields (80–85%) in the presence of acetic acid. After the completion of the reaction, the final product was precipitated out and washed with the cold ether to yield the IL bound isoindoloquinazoline **7;** final structures were confirmed by proton, carbon NMR, and mass spectroscopy (MS). However, the same one pot reaction took 12 h to completion under reflux conditions. The reaction is presumed to precede condensation of ketoacid **6** with primary amine **5** through amide bond formation, followed by intramolecular dehydrocyclization to furnish IL-support isoindoloquinazoline **7**.

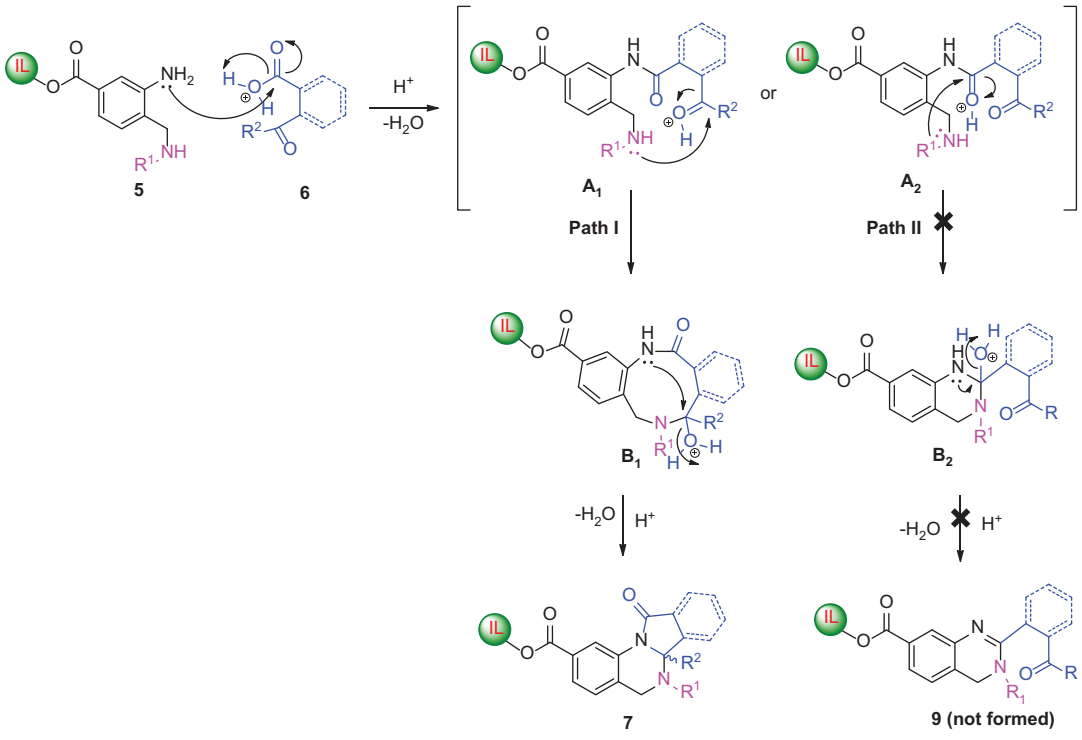
In a subsequent step, removal of the ILs **7** was achieved *via* trans-esterification by sodium methoxide in methanol, to obtain methyl ester isoindoloquinazoline **8** in good yields (75–85%) (Scheme 3). The ILs was removed by precipitation too. The final product **8** was confirmed by proton NMR, where the -$OCH_3$ singlet was recorded at 3.8 ppm. The best outcomes obtained when the microwave irradiation used for the synthesis of **8**, the efficiency of




**Scheme 2** Synthetic route for IL-bounded diamine **5**.

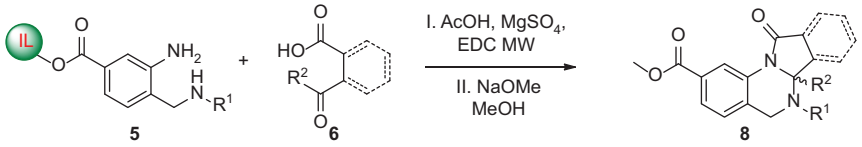


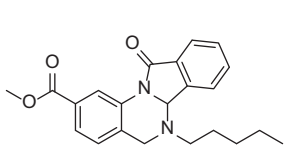

**Scheme 3** Acid catalyzed synthesis of isoindoloquinazoline **8**.

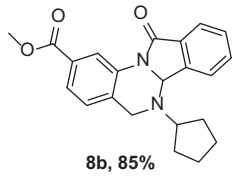


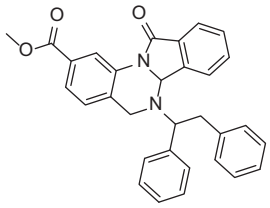

**Scheme 4** Plausible mechanism for isoindoloquinazoline **7**.

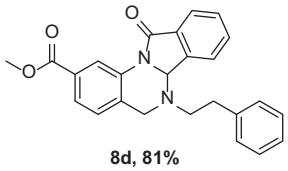
**Table 1** Substrate scope of heterocyclization under microwave irradiation.[a]

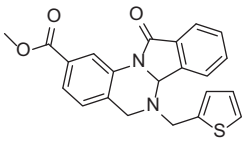


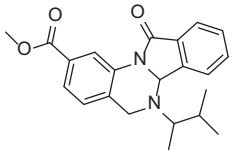


8a, 84%

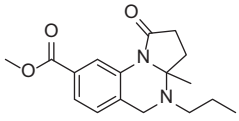

8b, 85%

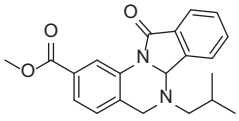

8c, 80%

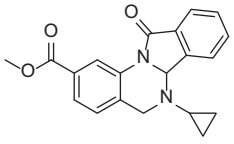

8d, 81%

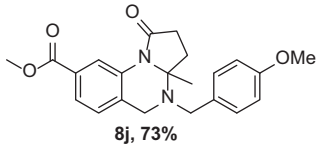

8e, 78%


8f, 77%


8g, 75%


8h, 88%


8i, 85%



8j, 73%

[a]All reactions were performed under microwave (80°C, 10 min) in acetic acid with ethylene dichloride. Isolated yield after column purification.

microwave flash heating in reduced reaction times with enhanced rate of reactions. This cleavage reaction was performed under microwave heating for 10–15 min, vs. 6 h or more of conventional heating conditions.

The plausible mechanistic pathway for the formation of **7** was proposed in acidic conditions, illustrated in Scheme 4. The ionic liquid conjugated primary amines **5** react with the carbonyl electrophiles of the acidic functional group of compound **6** and form the amide intermediates $\mathbf{A}_1$ by the exclusion of water. It is possible that intermediates $\mathbf{A}_1$ may undergo intramolecular dehydrocyclization in two fashions. In path I, intermediates $\mathbf{A}_1$ undergo the cyclization reaction by the activated keto group, to construct nine membered (diazonan-6-one) cyclic rings $\mathbf{B}_1$, followed by a secondary amine to attack the carbon of a tertiary hydroxyl group to form C-N bonds, and construct the bi-heterocyclic isoindoloquinazoline **7**. In path II, the amide group activation of intermediates $\mathbf{A}_2$ did not undergo intramolecular cyclization to form other molecular frameworks of dihydroquinazolines **9** *via* the formation of $\mathbf{B}_2$ (tetrahydroquinazoline-2-ol) ring intermediate.

The same convenient procedure could be utilized to synthesize a variety of isoindoloquinazolines (**8a–j**) in good yields (Table 1). Heterocyclization reactions proceeded well with aliphatic amino substitution (Table 1, entry **8a,b** and **8f–i**). $\gamma$-Ketoaliphatic acid gave slightly lower yields (73–75%) of the final products (Table 1, entry **8g** and **8j**).

In summary, we have successfully developed the rapid and one-pot synthesis of bi-heterocyclic fused isoindolo[1,2-a]quinazoline with the introduction of ionic liquid as a soluble support and microwave as a greener energy source. Postulation of a pathway for the construction isoindolo[1,2-a]quinazoline is proceeded through amide formation, followed by intramolecular cyclization. Notably, the immobilized intermediates and final products were purified by simple precipitation in all steps.

A green microwave assisted protocol displayed a short reaction time compared to conventional heating, an easy separation process, and least by-product, with high yields of desired products; further application of the strategy for synthesis of novel heterocycles is in progress in our laboratory.

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