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Solid-phase synthesis of quinoxaline derivatives using 6-amino-2,3-dichloroquinoxaline loaded on AMEBA resin

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Abstract—The solid-phase synthesis of quinoxaline derivatives **1** was accomplished through successive introduction of building blocks such as amines, methoxide, acid chlorides, and isocyanates into 6-amino-2,3-dichloroquinoxaline **2** loaded on AMEBA resin **3**. The method made it possible to obtain the compound **1** in 63–100% purities and 36–89% isolated yields.

Combinatorial chemistry along with high-throughput screening has emerged as a powerful tool for efficient drug discovery process.[1] The synthesis of combinatorial libraries based on the so-called privileged structures has attracted particular attention because single scaffolds are able to provide potent and selective ligands for a range of different biological targets across and within different target families through modification of functional groups.[2] From this point of view, the quinoxaline scaffold is of particular interest for us in that its derivatives exhibit various biological activities. A review of the biological activity of quinoxaline derivatives up to 1987 was published.[3a] Apart from those described in the review, they were reported to have a variety of activities such as tranquilizing,[3b] antimycobacterial,[3c,d] cardiotonic,[3e] antidepressant,[3f] and antitumor[3g,h] activities depending on the substitution pattern on the scaffold. In addition, they were shown to be 5-HT_3 receptor antagonist,[3i] NMDA receptor antagonist,[3j] PDGF–RTK inhibitor,[3k,l,m] IL-8 receptor antagonist,[3n] and CCR1 antagonist[3o] in the same manner.

In connection with a project for exploring the novel potent RTK inhibitors, we have designed some target compounds for quinoxaline-based library construction taking into account the structural features of the previously reported diverse drug-like small molecule inhibitors identified through high-throughput screening efforts.[4] For such RTK-directed library construction, we needed to develop a versatile method for the solid-phase synthesis of quinoxaline derivatives. Recent reports described the utilization of 4-fluoro-3-nitrobenzoic acid attached to SynPhase™ Rink Lanterns,[5a] polymer-bound 1,2-diaza-1,3-butadienes,[5b,c] PAL resin-bound amines,[5d] and polymer-linked 2-nitrophenylcarbamates[5e] to obtain the quinoxalines. Herein, we wish to present the solid-phase synthesis of quinoxaline derivatives **1** through successive introduction of the building blocks into 6-amino-2,3-dichloroquinoxaline **2**[6] loaded on AMEBA resin **3**[7] (Scheme 1). The method would enable us to achieve diverse amino-related functionality at 6 position as well as diversification at 2 and 3 position of quinoxaline scaffold.

First of all it was needed to determine the order in which the substituents should be combined into the (2,3-dichloroquinoxalin-6-yl)amino resin **4**. The model study in solution by use of piperidine as an amine (Scheme 2) confirmed that it was optimal to introduce the building blocks in the order (**4** → **5** → **6** → **7**) shown in Scheme 1. When compound **13** was subjected to excess NaOMe in DMF at rt, methoxylation was followed by debenzoylation to give **11** as the final product. The treatment of benzoylated dichloroquinoxaline **14** with excess piperidine in DMF at rt afforded the bisaminated product **15**. The sequence **9** → **10** → **11** → **12** did not bring about any undesirable reaction. The reaction of 2,3-dichloro-6-(2,4-dimethoxybenzylamino)quinoxaline **9**, prepared from the reductive amination of **2** with 2,4-dimethoxybenzaldehyde under the standard condition in 75% yield, with excess piperidine in DMF at rt gave

Keywords: Solid-phase synthesis; Quinoxaline; AMEBA resin.
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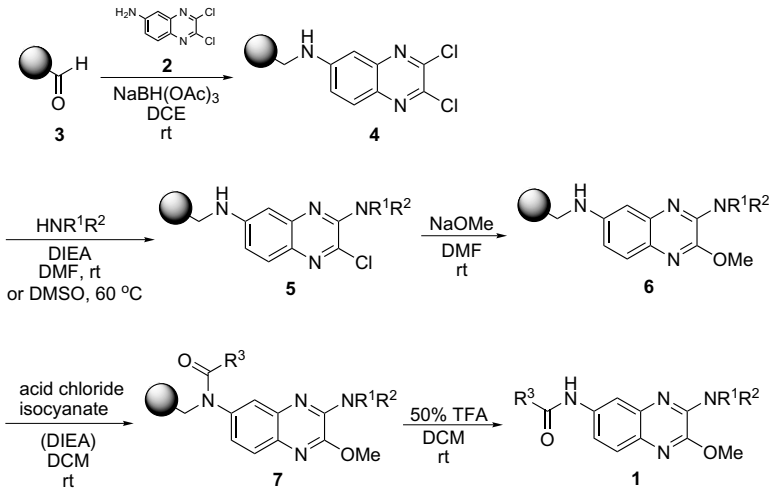
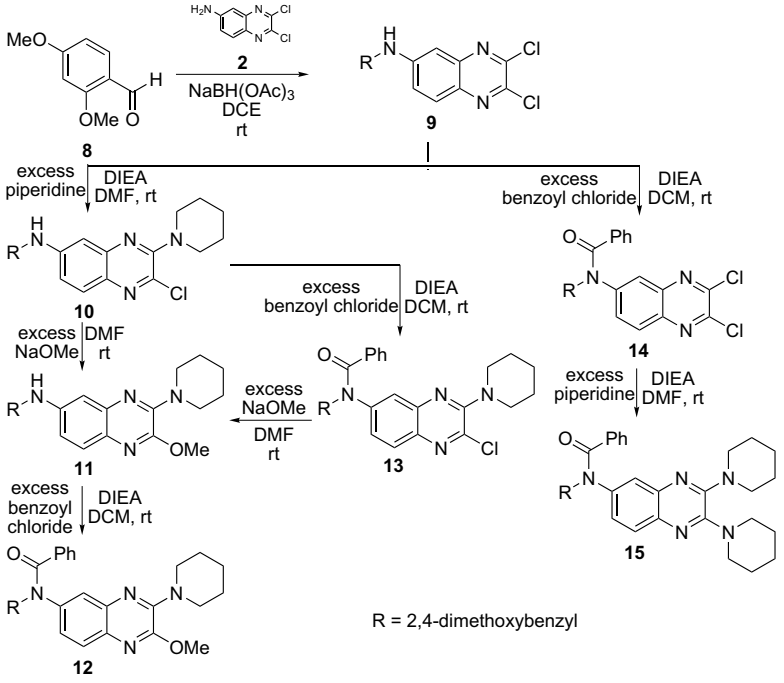


Scheme 1.



Scheme 2.

3-piperidino derivative **10** as single regioisomer in 96%. The subsequent methoxylation and benzoylation proceeded successfully to form **11** and **12** in 91% and 84%, respectively. The regiochemistry of the product **10** in the first step was assigned on the analogy of the previous result obtained from the reaction of 6-amino-2,3-dichloroquinoxaline **2** with amines.[6a]

According to the results obtained from the solution-phase model study, the solid-phase synthesis of quinoxaline derivatives **1** was performed as shown in Scheme 1. Compound **2** was prepared from the reduction of 2,3-dichloro-6-nitroquinoxaline[6a] in THF in the presence of 10% Pd/C and a few drops of concd HCl under H_2 atmosphere (~40 psi) at 50 °C in 83% yield and AMEBA resin **3** was obtained from Merrifield resin by the literature method.[7c] The loading of **2** on AMEBA resin **3** was accomplished by reductive amination in DCE in the presence of $NaBH(OAc)_3$ at rt. The completion of the reaction was confirmed by the disappearance of the aldehyde carbonyl band (1677 cm^{-1}) of AMEBA resin **3** and the appearance of amino band (3414 cm^{-1}) on single bead ATR-FTIR spectrum. The polymer-bound 6-amino-2,3-dichloroquinoxaline **4** was treated with amines in the presence of DIEA to give the aminated resins **5**. The amination step was performed in DMF at rt for secondary cyclic amines and in DMSO at 60 °C for primary and secondary acyclic amines. In the case of primary amines, the use of DMF as solvent gave the corresponding dimethylamino derivative as a

Table 1. Purities and yields of the compounds **1**

Compound	R^1R^2N	R^3	Purity[a] (%)	Yield (%[b]/%[c])
1aa[d]	*n*-PrNH	C_6H_5	93	69/41
1ab[d]	*n*-PrNH	C_6H_5NH	92	71/40
1ba[d]	*i*-PrNH	C_6H_5	98	80/55
1bb[d]	*i*-PrNH	C_6H_5NH	89	87/63
1ca[d]	BnNH	C_6H_5	88	100/87
1cb[d]	BnNH	C_6H_5NH	85	84/65
1da[e]	Et_2N	C_6H_5	97	82/67
1db[e]	Et_2N	C_6H_5NH	94	90/73
1ea	Piperidino	C_6H_5	95	100/88
1eb	Piperidino	4-$MeOC_6H_4$	93	92/79
1ec	Piperidino	4-PhC_6H_4	95	85/70
1ed	Piperidino	2-ClC_6H_4	77	66/36
1ee	Piperidino	4-BrC_6H_4	97	87/75
1ef	Piperidino	4-NCC_6H_4	77	84/67
1eg	Piperidino	4-$O_2NC_6H_4$	91	80/71
1eh	Piperidino	BnNH	92	85/71
1ei	Piperidino	EtO_2CCH_2NH	100	80/65
1ej	Piperidino	4-$MeOC_6H_4NH$	90	94/66
1ek	Piperidino	Me	86	77/64
1el	Piperidino	Cyclopropyl	93	85/62
1fa	Pyrrolidino	$MeOCH_2$	89	100/68
1fb	Pyrrolidino	Cyclohexyl	86	99/60
1fc	Pyrrolidino	2-Furyl	90	97/73
1fd	Pyrrolidino	4-*t*-BuC_6H_4NH	88	81/69
1ga	Morpholino	2-Thienyl	92	97/80
1gb	Morpholino	4-*t*-BuC_6H_4	90	100/83
1gc	Morpholino	2-FC_6H_4NH	85	95/70
1gd	Morpholino	2-ClC_6H_4NH	85	70/59
1ge	Morpholino	2-BrC_6H_4NH	63	82/42
1gf	Morpholino	*t*-$BuCH_2$	85	94/75
1ha	4-Methylpiperazino	2-FC_6H_4	89	90/75
1hb	4-Methylpiperazino	4-ClC_6H_4	90	98/72
1hc	4-Methylpiperazino	2-$MeOC_6H_4NH$	85	99/68
1hd	4-Methylpiperazino	4-FC_6H_4NH	91	97/89

[a] Determined on the basis of LC–MS spectrum of crude product after cleavage from the resin **7**.
[b] Yield of crude product after cleavage from the resin **7** (six-step overall yield from Merrifield resin).
[c] Yield after column chromatography of crude product (six-step overall yield from Merrifield resin).
[d] The product was compound formed from benzoylation or phenyl isocyanate addition with amino group at 6 position, not with that at 3 position.
[e] Sterically hindered secondary acyclic amines such as diisopropylamine and dibenzylamine gave the corresponding 2,3-dimethoxy derivatives as major products.

byproduct and the reaction proceeded much faster in DMSO than in DMF for secondary acyclic amines. Subsequent methoxylation of the (2-chloro-3-alkylamino and 3-dialkylaminoquinoxalin-6-yl)amino resins **5** with excess NaOMe in DMF at rt afforded the (3-alkylamino- and 3-dialkylamino-2-methoxyquinoxalin-6-yl)-amino resins **6**, which were treated with acid chlorides in the presence of DIEA or isocyanates alone in DCM at rt. The fully derivatized resins **7** showed the corresponding carbonyl bands on single bead ATR-FTIR spectra. Finally, the desired quinoxaline derivatives **1** were obtained in good purities and yields by the cleavage from the resins **7** under the conditions of 50% TFA/DCM at rt.[8] The results are summarized in Table 1. The structures of compounds **1aa**–**hd** were assigned on the basis of ^{1}H NMR and MS spectral data.

In brief, the quinoxaline derivatives **1** were prepared using 6-amino-2,3-dichloroquinoxaline loaded on AMEBA resin. The simple and efficient method for solid-phase synthesis of quinoxaline derivatives will make it possible to construct desired library with a larger size using a variety of amines, alkoxides, acid chlorides, and isocyanates. On the other hand, investigation into a versatile method for the quinoxaline derivatives regioisomeric with **1** is in progress.

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Supplementary data

^{1}H NMR and MS spectral data of compounds **1aa**–**hd**, single bead ATR-FTIR spectra of resins **4**, **5ea**, **6ea**, and **7ea**, LC–MS and ^{1}H NMR spectra of compound **1ea**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.05.096.

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8. *Representative procedure*: (a) Preparation of 6-amino-2,3-dichloroquinoxaline **2**. To a solution of 2,3-dichloro-6-nitroquinoxaline (2.00 g, 8.20 mmol) in THF (200 mL) were added 10% Pd/C (200 mg) and a few drops of concd HCl. The mixture was agitated under H_2 atmosphere (~40 psi) at 50 °C for 40 h, filtered over Celite and magnesium sulfate, and evaporated in vacuo. The residue was chromatographed on a silica gel column and elution with methylene chloride gave the compound **2** (1.46 g, 83%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.45 (br s, 2H), 6.85 (d, J = 2.2 Hz, 1H), 7.30 (dd, J = 9.2 and 2.2 Hz), 7.73 (d, J = 9.2 Hz, 1H); (b) Preparation of AMEBA resin **3**.[7c] A mixture of Merrifield resin (1.6 mmol/g, 5.00 g, 8.0 mmol), 2-methoxy-4-hydroxybenzaldehyde (2.44 g, 16.0 mmol), potassium carbonate (2.22 g, 16.1 mmol), and potassium iodide (40 mg, 0.24 mmol) in DMF (50 mL) was stirred at 55 °C for 16 h. The resin was filtered, washed several times with DMF, toluene/H_2O, MeOH, and DCM, and dried in a vacuum oven to give **3** (5.81 g, 98%): Single bead ATR-FTIR 3024, 2923, 2851, 1677 (C=O), 1598, 1578, 1492, 1464, 1452, 1422, 1292, 1259, 1197, 1162, 1113, 1102, 1027, 1016, 815, 757, 697 cm^{-1}; (c) Preparation of (2,3-dichloroquinoxalin-6-yl)amino resin **4**. To a suspension of AMEBA resin **3** (6.10 g, theoretically 8.2 mmol) in DCE (50 mL) at rt was added 6-amino-2,3-dichloroquinoxaline **2** (2.64 g, 12.3 mmol) and sodium triacetoxyborohydride (2.62 g, 12.4 mmol). The mixture was stirred at rt for 20 h and the resin was filtered, washed several times with DCM, DMF, MeOH, and DCM, and dried in a vacuum oven to give **4** (7.48 g, 97%): Single bead ATR-FTIR 3414 (NH), 3025, 2922, 2850, 1614, 1588, 1504, 1493, 1463, 1451, 1420, 1286, 1257, 1235, 1196, 1155, 1128, 1030, 1017, 995, 821, 758, 735, 698 cm^{-1}; (d) Preparation of (2-chloro-3-piperidin-1-ylquinoxalin-6-yl)amino resin **5ea** (NR_2 = piperidin-1-yl). A mixture of the resin **4** (2.00 g, theoretically 2.1 mmol), piperidine (914 mg, 10.7 mmol), and diisopropylethylamine (2.77 g, 21.4 mmol) in DMF (20 mL) was stirred at rt for 48 h. The resin was filtered, washed several times with DMF, MeOH, and DCM, and dried in a vacuum oven to give **5ea** (2.07 g, 100%): Single bead ATR-FTIR 3410 (NH), 3024, 2920, 2848, 1613, 1588, 1530, 1504, 1493, 1463, 1451, 1283, 1195, 1157, 1130, 1114, 1029, 1013, 817, 757, 698 cm^{-1}; (e) Preparation of (2-methoxy-3-piperidin-1-ylquinoxalin-6-yl)amino resin **6ea** (NR_2 = piperidin-1-yl). To a suspension of the resin **5ea** (2.07 g, theoretically 2.1 mmol) in DMF (20 mL) at rt was added 25 wt. % NaOMe in MeOH (3.81 g, 17.6 mmol) and the mixture was stirred at rt for 20 h. The resin was filtered, washed several times with DMF, MeOH, and DCM, and dried in a vacuum oven to give **6ea** (2.05 g, 99%): Single bead ATR-FTIR 3412 (NH), 3025, 2922, 2850, 1612, 1589, 1504, 1492, 1451, 1415, 1301, 1256, 1196, 1157, 1129, 1027, 1017, 817, 736, 698 cm^{-1}; (f) Preparation of *N*-benzoyl-(2-methoxy-3-piperidin-1-ylquinoxalin-6-yl)amino resin **7ea** (NR_2 = piperidin-1-yl, R^1 = Ph). To a mixture of the resin **6ea** (50 mg, theoretically 0.051 mmol) and diisopropylethylamine (65 mg, 0.50 mmol) in DCM (2 mL) at rt was added benzoyl chloride (21 mg, 0.15 mmol) and the mixture was stirred overnight at rt. The resin was filtered, washed several times with DCM, DMF, MeOH, and DCM, and dried in a vacuum oven to give **7ea** (53 mg, 96%): Single bead ATR-FTIR 3025, 2923, 2852, 1649 (C=O), 1611, 1504, 1492, 1451, 1415, 1377, 1257, 1197, 1157, 1116, 1027, 927, 822, 758, 697 cm^{-1}; (g) Preparation of 6-benzamido-2-methoxy-3-piperidin-1-ylquinoxaline **1ea** (NR_2 = piperidin-1-yl, R^1 = Ph). The resin **7ea** (51 mg, theoretically 0.047 mmol) in 50% TFA/DCM (2 mL) was stirred at rt

for 1 h. The resin was filtered and washed with DCM. The filtrate was evaporated in vacuo and the residue was dissolved in acetone and passed through SAX resin. The solvent was removed in vacuo to give the crude product (17 mg, 100%) with 95% purity on the basis of LC–MS. The crude product was further purified by a silica gel column chromatography (5:1 mixture of methylene chloride and ethyl acetate) to afford the pure compound **1ea** (15 mg, 88%): ^{1}H NMR (500 MHz, acetone-d_6): δ 1.57 (m, 6H), 3.53 (m, 4H), 3.93 (s, 3H), 7.40 (m, 2H), 7.46 (t, J = 7.3 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.65 (dd, J = 8.8 and 2.4 Hz, 1H), 7.90 (d, J = 7.1 Hz, 2H), 8.23 (d, J = 2.4 Hz, 1H), 9.50 (br s, 1H); MS (ESI) m/z 363 ($[M+H]^+$).