Tetrahedron 67 (2011) 2110–2117

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Microwave assisted straightforward synthetic method for benzimidazole linked quinoxalinones on soluble polymer support

Cheng-Ting Chou [a], Gorakh S. Yellol [a], Wong-Jin Chang [a], Mei-Lian Sun [b,*], Chung-Ming Sun [a,*]

[a] Department of Applied Chemistry, National Chiao Tung University, Hsinchu 300-10, Taiwan, ROC
[b] General Education Center, National University of Kaohsiung, Kaohsiung 811-48, Taiwan, ROC

ARTICLE INFO

Article history:
Received 19 November 2010
Received in revised form 31 December 2010
Accepted 14 January 2011
Available online 26 January 2011

Keywords:
Benzimidazole
Quinoxalinones
Microwave synthesis
Polymer supported synthesis
Polyethylene glycol
Combinatorial parallel synthesis

ABSTRACT

The simple and efficient method was developed for the synthesis of benzimidazole linked quinoxalinones on soluble polymer support using microwave conditions. The acid catalyzed condensation of 4-fluoro-3-nitrobenzoic acid with polymer immobilized *o*-phenylenediamine, *ipso*-fluoro nucleophilic substitution with various primary amines and cyclization with acetyl chloride are the key steps involved in implemented linear synthesis. In key cyclization step, the regioselective N-acylation at secondary amine with chloroacetyl chloride followed by spontaneous intramolecular ring closure through ortho-amine functionality generate the quinoxaline skeleton under microwave irradiation. The removal of polymer support and exposure of quinoxalines for auto-oxidation finally produce the benzimidazole linked quinoxalinone derivatives with high purity and yields.

1. Introduction

Combinatorial synthetic methodologies provide the main driving force for the preparation of large number of structurally diverse libraries for discovery of lead compounds and high-throughput screening in medicinal chemistry.[1] The rapid development of high-throughput strategies and multidisciplinary synergetic approaches for the generation of arrays of small heterocyclic molecules are high priority programs in modern drug discovery.[2] Various solution phase and solid phase synthetic methods have been developed in combinatorial chemistry. Solid phase synthesis has its advantages and disadvantages over conventional synthetic methods.[3] The use of soluble polymer support is emerging as a leading strategy that combines the advantages of product isolation and purification of solid-phase chemistry with the benefits of traditional solution-phase reactions.[4] The concept of immobilizing the substrate on a soluble support material is now not new; numerous synthesis including multicomponent coupling reactions were developed on soluble polymer support as examples of supported substrate synthetic systems. With an expanding assortment of these soluble polymer supported system, it becomes increasingly viable to construct advanced synthetic routes based on multi-step conversions to generate both combinatorial libraries and more complex molecular architectures. Typically, the substrate can be anchored on the support at the beginning of multistep synthetic sequence. All synthetic steps carried out with no detachment of support by using the advantages of solution phase method for reaction process and reaction monitoring along with the advantages of polymer support for separation and purification of products at every stage. The polymer support could remove at the end of synthetic strategy to liberate the final compounds with molecular complexity and substitutional diversity. The impact of this method has been tremendous in effectively utilizing the chemical space, which is necessary for the diversity oriented organic synthesis.[5]

This combinatorial parallel synthesis has expanded the structural diversity, permitting generation of new molecules required for the lead identification and optimization in the drug discovery process.[1c,e] In general practice of drug optimization that usually develop one active scaffold and expand the extraneous group around it to increase the complexity. Based on privileged structural motifs, new scaffolds synthesized by diversity oriented technique have the ability to address different targets by varying the substitution pattern. The combining two pharmacophore as bi-heterocyclic system and expanding the diversity around it for better bioactivity is the familiar method in drug design and optimization. Bi-heterocyclic compounds offer better binding opportunities with enzyme active site owing to its three dimensional special arrangement.[6] Moreover the activity can be enhanced by changing the substituent around the bi-heterocyclic skeleton. We also used this concept to devise our research. With our interest in

* Corresponding authors. E-mail addresses: lian@nuk.edu.tw (M.-L. Sun), cmsun@mail.nctu.edu.tw (C.-M. Sun).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.01.040

quinoxalinone and benzimidazole moieties,[7] we decided to link quinoxalinone skeleton with benzimidazole moiety and expand the diversity around it with various substitutions for its intended extension of biologically activity.

The last two decades have been growing research in drugs containing quinoxalinone and benzimidazole cores and hence increasing interest in the chemistry of these compounds. Quinoxalinone moiety shows broad spectrum of biological activity, such as anticancer, antimicrobial, antithrombotic, antiallergic, anxiolytic, antispastic, and analgesic activity.[8] Quinoxalinones also shows moderate to good inhibition against HIV-1 and HIV-2 in MT-4 cells **I** (Fig. 1).[9] Some of the quinoxalinone derivatives are strong sodium ion channel inhibitor **II**.[10] Quinoxalinone **III** acts as a PDE5 inhibitor and also inhibited P-glycoprotein activity.[11] The bi-heterocyclic skeleton with quinoxaline (**IV**) is established as PI3 kinase inhibitors.[12] Similarly, benzimidazole is other privileged heterocycles known for a wide range of biological activities.[13] The applications of benzimidazole derivatives are found in diverse therapeutic areas including antiulcer, antihypertensive, antiviral, antifungal, anticancer, antihistaminic, antitubercular, antiallergic, antioxidant, antimicrobial, and in vitro anti Q3 HIV-1 activities.[14] Benzimidazole ring is very useful subunit of the development of biologically promising molecules.[15] More particularly, the installation of benzimidazole moiety on bioactive quinoxalinone skeleton could more promisingly expands its bioactive profile or enhance the activity of present biological portrait. Hence further development of a benzimidazole skeleton linked with quinoxalinones to expand its bioactive profile is warranted.

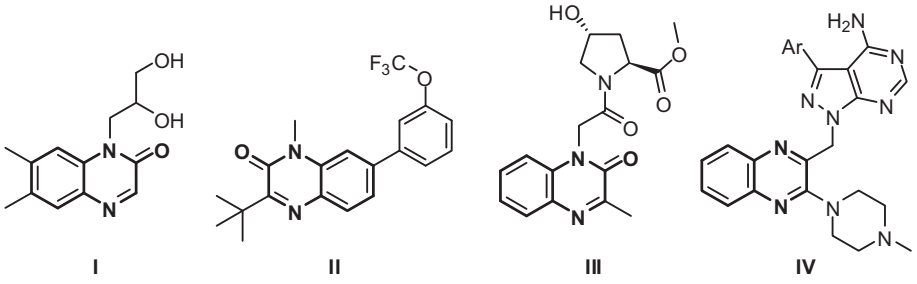


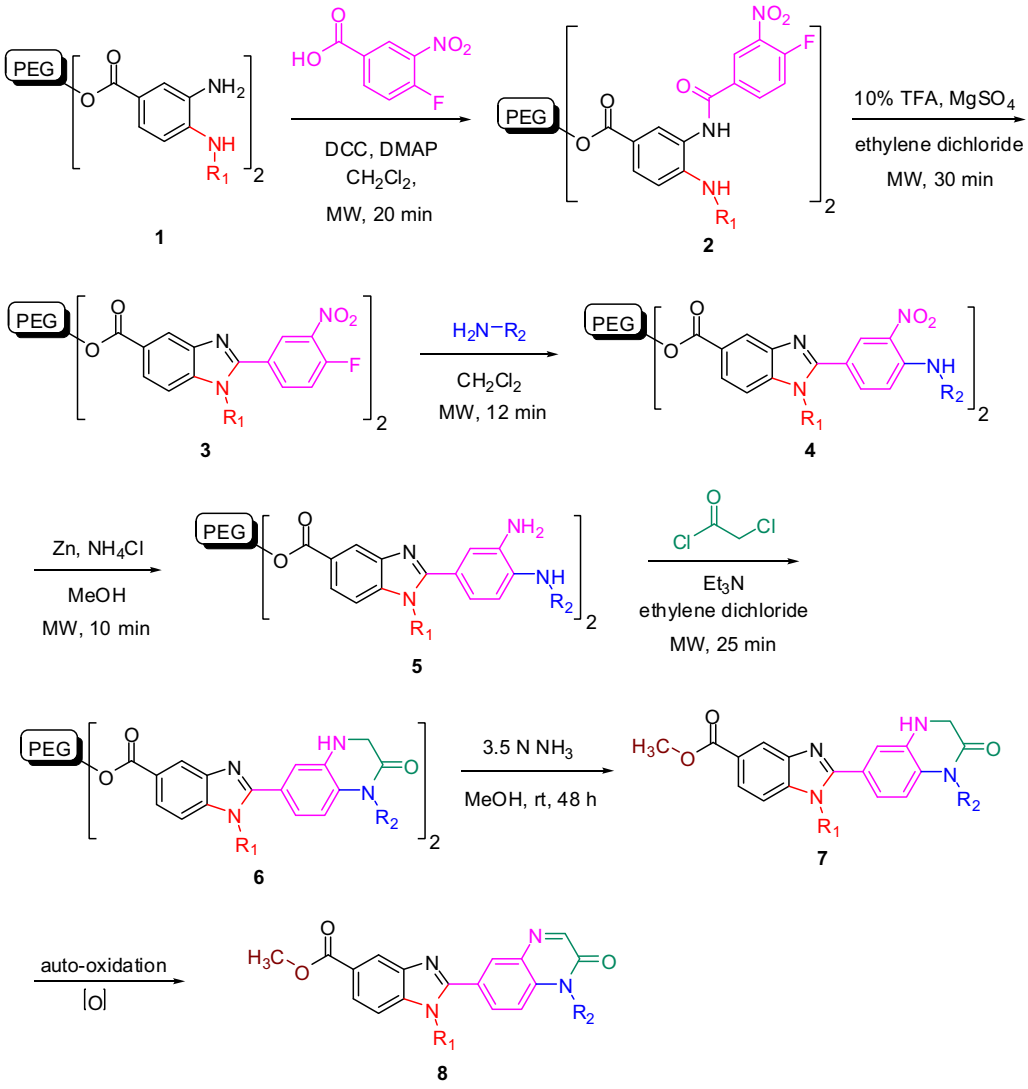
Fig. 1. Related bioactive molecules.

The discovery of more novel biological targets from chemical genetics research creates an immediate need to develop efficient synthetic method for the preparation of small molecular entities.[16] Hence in our continuous effort to develop the expedite and efficient synthetic methods to medicinally important small heterocyclic molecules,[17] here we report the rapid and straightforward synthesis of benzimidazole linked quinoxalinones on soluble polymer support under microwave irradiation.

2. Results and discussion

On our research plan to develop the straightforward method for the synthesis of benzimidazole linked quinoxalinones, we planned the construction of benzimidazole ring with attached fragment, which later can modify into quinoxalinone ring system. The family of long chain polymers link through covalent attachment with a substrate, polyethylene glycol (PEG), is commonly used to synthesize and modify a variety of drug molecules. Here we decided to use PEG 4000 with reactive hydroxyl functionality at both end as a soluble polymer support in our synthetic strategy. Accordingly, the present strategy commenced with the synthesis of polymer immobilized *ortho*-phenylenediamine **1** from 4-fluoro-3-nitrobenzoic acid with built-in structural diversity (R_1) through three step protocol.[18] PEG immobilized diamine **1** was *N*-acylated at the primary amine functionality with 4-fluoro-3-nitrobenzoic acid via DCC activation. Accordingly, anilide conjugates **2** were obtained by the condensation of 4-fluoro-3-nitrobenzoic acid with polymer conjugates **1** through activated ester generated by DCC and DMAP in dichloromethane in 10 min under microwave irradiation (Scheme 1). For the construction of benzimidazole ring, anilide conjugates **2** were subjected to acid catalyzed cyclization in presence of 10% trifluoroacetic acid in 1,2-dichloroethane. The formation of the bi-heterocyclic *o*-fluoronitrobenzene **3** was achieved in 30 min under microwave irradiations. After completion of the reaction, the polymer conjugate was purified by precipitating out the reaction mixtures with excess of cold ether. The PEG supported nitrobenzene **3** was treated with various primary amines to substitute the fluorine atom through *ipso*-fluoro nucleophilic substitution reaction under microwave irradiation. The reaction was carried out in dichloromethane by open vessel microwave conditions in 12 min to obtain the PEG supported nitroamine **4** with good yield. Various aliphatic and aromatic amines were used to create the second diversity in the targeted framework. All PEG supported nitroamines **4** were separated and purified by precipitation in ether solution. The *ipso*-fluoro displacements were confirmed by conventional proton NMR spectrum directly on polymer conjugate **4**. For the reduction of nitro group, compound **4** was treated with zinc and ammonium chloride in methanol. Formation of the amine conjugates **5** was achieved in 3 h at room temperature. However, by the application of microwave irradiation, the desired conjugates **5** were obtained within 10 min. It is noteworthy to say that the metal reduction was proceeded smoothly under microwave condition. The excess zinc and ammonium formate were removed by filtration. Amine conjugates **5** were obtained in pure form by further precipitation in cold ether.

The next critical step was the construction of terminal quinoxaline ring across the amine functionalities on this skeleton. The functionalized PEG diamine conjugates **5** were reacted with chloroacetyl chloride in methanol in the presence of triethyl amine. The cyclization to form new ring across terminal amine functionalities with chloroacetyl chloride resulting into quinoxaline skeleton was achieved in microwave cavity within 25 min. The cyclization occurs through the N-acylation followed by N-alkylation steps. Initially, more reactive secondary amine nitrogen was acylated to form *N*-chloroacetyl conjugate. The primary amine nitrogen in the transient *N*-chloroacetyl conjugate is located in a favorable position to form six member ring through intramolecular cyclization by N-alkylation, which subsequently affords the quinoxaline ring skeleton. It is worthy to note that a facile and high yielding ring closure reaction is quite distinct compared to the regular synthetic approach toward the amino acid functionalized, benzimidazole linked quinoxalines. Finally, removal of PEG support from compound **6** was achieved by 3.5 N ammonia solution in methanol. This is very mild and high yielding method as well as this method replaces the highly toxic KCN reagent required for PEG cleavage and also the reaction is fast than use of NaOMe. The PEG support was smoothly removed by this method at room

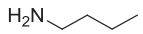
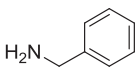
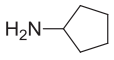
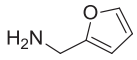
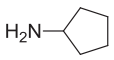
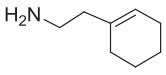
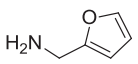
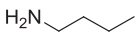
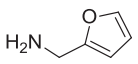
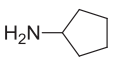


Scheme 1. Synthesis of benzimidazolyl-quinoxalinones on polymer support.

temperature within 48 h. The reaction mixtures were precipitated with ice cold ether and the polymer was removed by filtration. The filtrates were concentrated to furnish benzimidazole linked quinoxaline **7** with good yields, which was subjected to HPLC analysis. Analyzing the spectroscopic data, we observed that the final product is a mixture of two compounds. After careful analysis of spectroscopic data, it was observed that the final product is the mixture of quinoxaline **7** and quinoxalinone **8**. Based on the analysis and spectroscopic data, it was contemplated that quinoxalinone was produced from quinoxaline **7** by auto-oxidation.

Initial study of this particular reaction was carried out with five different substrates and the progress of the reaction was carefully monitored. The results obtained after the cleavage of polymer support step were summarized in Table 1. We observed the similar results with all the substrate, which depict the two peaks in the HPLC analysis of products corresponds to quinoxaline **7** and quinoxalinone **8** (Table 1). The quinoxaline **7** is unstable and is found to be easily air oxidized to furnish the more stable quinoxalinone **8** skeleton resulting into mixture of quinoxaline **7** and quinoxalinone **8**. The beginning of auto-oxidation and the rate of auto-oxidation is depends on the substituents on quinoxaline ring. For detailed study, we recorded the ^{1}H NMR spectrum for compound **7i** immediate after isolation (spectrum A, Fig. 2), which does not show respective auto-oxidized product. However, by keeping the

Table 1
Obtained mixture of quinoxalines **7** and quinoxalinones **8**

Entry	R_1NH_2	R_2NH_2	Yeild[a](%)	HPLC[b]	
				7	**8**
a			78	32	52
b			77	37	59
c			79	29	53
d			92	24	63
e			85	46	37

[a] Total yield of samples (%).
[b] HPLC analysis of crude mixture (%).

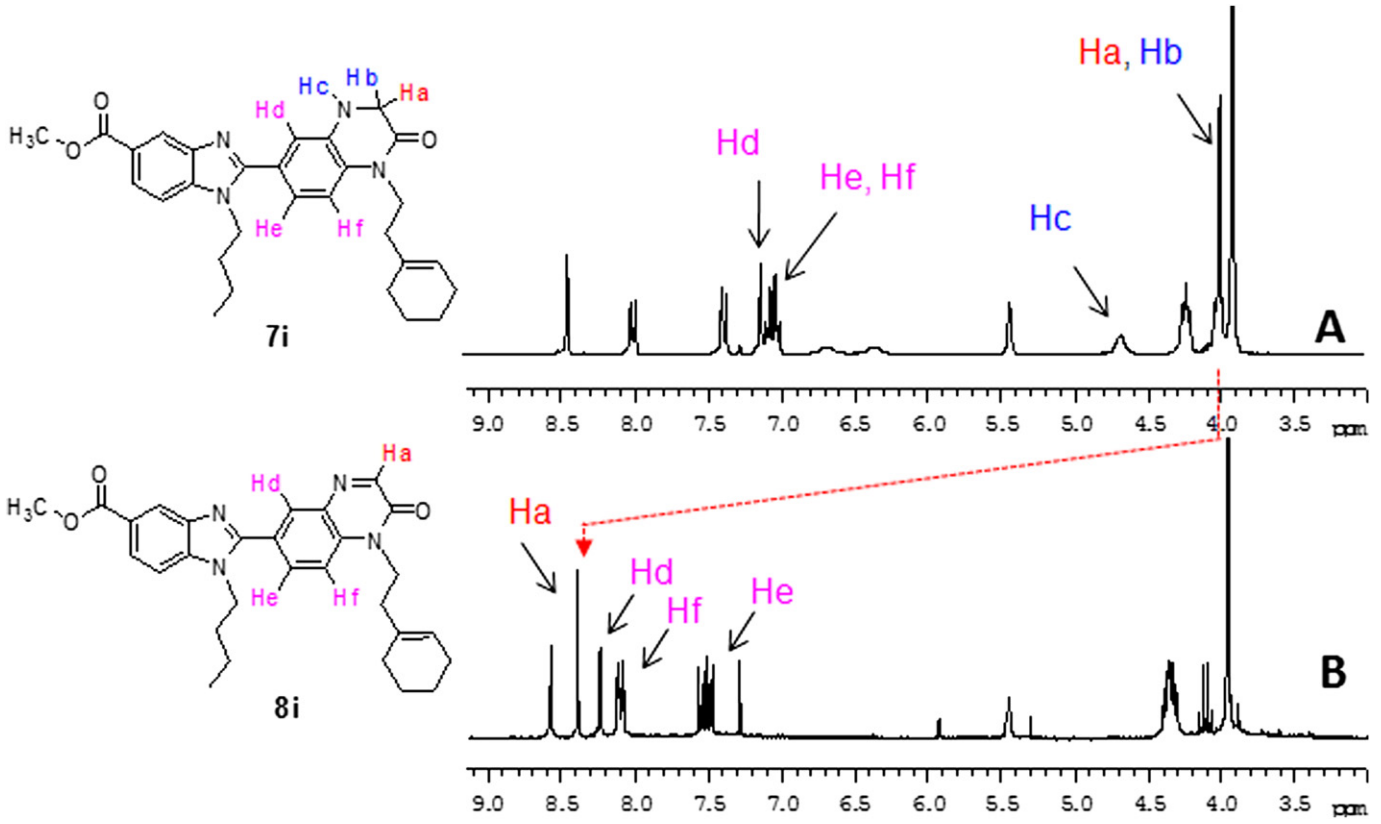


Fig. 2. Comparative proton NMR spectrums of compound **7** and **8**.

samples at room temperature, we monitored the status of compound by proton NMR analysis. Interestingly it is observed that quinoxaline **7i** was auto-oxidized completely into quinoxalinone **8i** in 5 h as seen from ^{1}H NMR spectrums (spectrum B, Fig. 2). The comparative proton NMR analysis was depicted in Fig. 2. The peak for Ha and Hb protons was observed at 4.10 ppm along with N–H proton peak at 4.68 ppm in the spectrum A of compound **7i**. These peaks corresponds to Hb proton and N–H proton disappeared in the spectrum B of compound **8i** while Ha proton peak shifted downfield substantially and appeared at 8.37 ppm. Moreover the peaks corresponds to aromatic protons (Hd, He & Hf) of quinoxaline ring shifted downfield indicates the change of electronic environment of relative rings. These all observations clearly show the auto-oxidation of quinoxaline to quinoxalinone system.

To avoid the critical separation of these products and limited sources to control auto-oxidations, we decided to synthesize pure benzimidazole linked quinoxalinone derivatives. Accordingly, all the above mixture of compounds (7a+8a to 7e+8e) were exposed to auto-oxidation and obtained as a single quinoxalinone compounds (8a to 8e). Additionally, using different mixture of various amines we synthesized PEG supported diamines **5**. These compounds **5** were cyclized with chloroacetyl chloride and subsequently polymer support was cleaved to obtain benzimidazolyl quinoxalines in good yields. The obtained compounds were further exposed for auto-oxidation to afford pure benzmidazolyl-quinoxalinones in good overall yields. Various primary amines were used in combination with each other in the synthetic pathway to generate substitution diversity on benzmidazolyl-quinoxalinones. Gratifyingly, all the reaction work smoothly along with auto-oxidation to furnish various benzmidazolyl-quinoxalinones derivatives. Table 2 depicts the generality of this methodology.

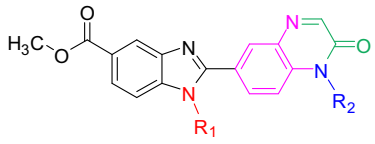
The observed outcome of regioselectivity in cyclization is supported by the results obtained in the reaction and are explained mechanistically. The possible steps involved in regioselective cyclization were depicted in Fig. 3.

The bifunctional diamine compound **5** treated with chloroacetyl chloride, the nucleophilic attack can occur either from the primary amine functionality or from secondary amine functionality of compound **5** on the reactive carbonyl carbon of chloroacetyl chloride. The selectivity depends on the difference in nucleophilicities and steric environments of the two possible sites of nucleophilic attack. The nucleophilic attack by more reactive secondary amine functionality of **5** to chloroacetyl chloride can lead to the intermediate **A** through route 1 with expel of HCl molecule in the form of triethyl amine hydrochloride. Similarly, nucleophilic attack by less hindered primary amine functionality could form intermediate **B** via route 2. Eventually, the possibility of route 2 is discarded on the basis of observed auto-oxidized product. After the cyclization of compound **B** into **C** further auto-oxidation into compound **D** is not possible owing to formation of unstable quaternary ammonium compound. However we observed the complete oxidized product at the end of reaction sequence as seen from HPLC and NMR. This confirms that the nucleophilic attack occurs regioselectivity to produce compound **7** through route 1, which subsequently auto-oxidized into compound **8**.

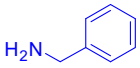
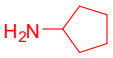
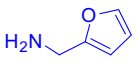
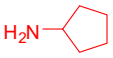
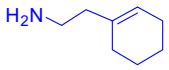
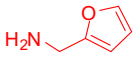
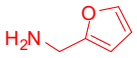
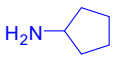
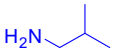
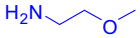
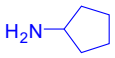
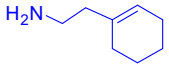
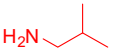
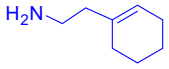
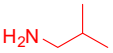
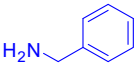
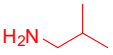
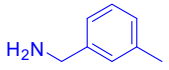
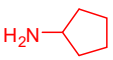
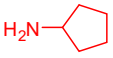
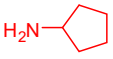
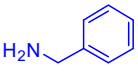
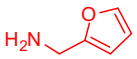
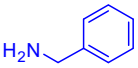
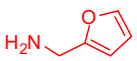
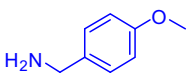
3. Conclusion

The combination of two well established techniques, the use of PEG linkers for facilitating purification and microwave energy for speeding up organic reactions, was effectively used to develop multidisciplinary synergetic approach to speed up the combinatorial parallel synthetic methods. The simple and efficient linear method was developed for the synthesis of biologically interesting bi-heterocyclic benzimidazole linked quinoxalinones on soluble polymer support under microwave conditions. The key cyclization

Table 2
Synthesized Benzimidazole linked quinoxalinone derivatives



8

Entry	R_1NH_2	R_2NH_2	LRMS[a]	Yeild[b](%)	HPLC[c]
8a			466	78	84
8b			468	77	96
8c			496	79	82
8d			456	92	87
8e			468	85	83
8f			423	86	68
8g			418	82	78
8h			444	81	79
8i			484	76	84
8j			484	84	89
8k			466	85	79
8l			484	74	83
8m			430	89	90
8n			466	92	92
8o			478	86	86
8p			490	93	79
8q			520	85	68

[a] LRMS were detected with ESI ionization source.
[b] HPLC purity of unpurified samples.
[c] Yields were determined on the weight of purified samples (%).

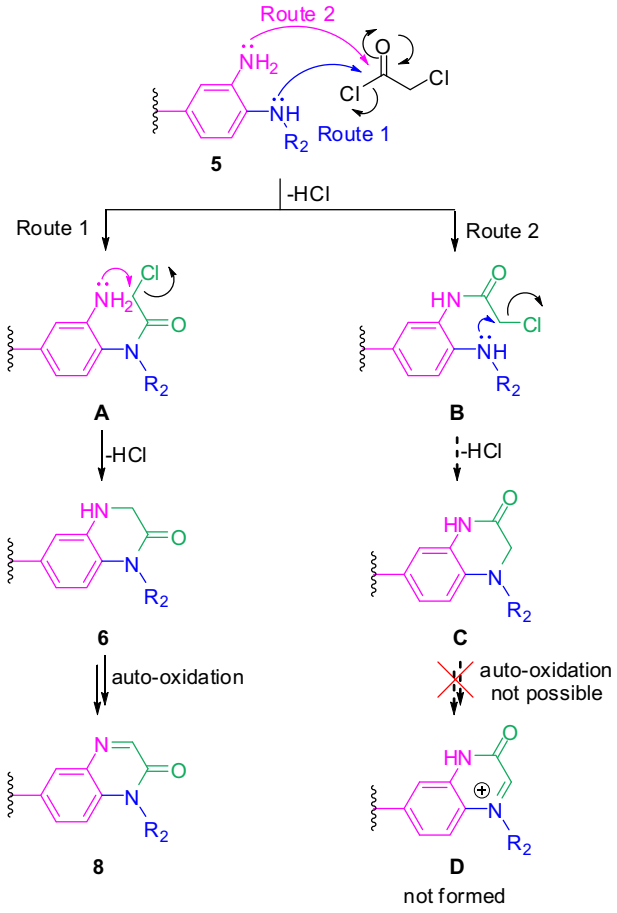


Fig. 3. Possible steps involved in regioselective cyclization.

of PEG supported *o*-phenylenediamine with chloroacetyl chloride in regioselective manner generate the quinoxaline skeleton under microwave irradiation. The exposure of quinoxalines for auto-oxidation finally produces the bi-heterocyclic benzimidazole linked quinoxalinone derivatives. The linear sequence using combination of simple reactions to achieve the synthesis of biologically interesting family of small molecules with two points of diversity is the main feature of this combinatorial parallel synthesis. Short reaction time, easy work up procedure, high yields, pure products, and diversity scope are advantages of this parallel synthetic method. This method dramatically shortens the time required for overall reaction sequence and increases efficiency of the total process. This approach provides a vision to develop combinatorial parallel synthesis by combination of simple reactions with advanced techniques for the rapid synthesis of molecular libraries with high degree of structural diversity.

4. Experimental

4.1. General experimental methods

Dichloroethane and methanol were distilled before use. All reactions were performed under an inert atmosphere with unpurified reagents and dry solvents. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel coated Kiselgel 60 F_{254} plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (Merck, 230–400 mesh). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker DX-300 spectrometer. Chemical shifts are reported in parts per million (ppm) on the scale from an internal standard.

High-resolution mass spectra (HRMS) were recorded on a JEOL TMS-HX 110 mass spectrometer. Normal phase HPLC was performed on a Shimadzu LC-10AT series machine with a Hypersil (250×4.6 mm) analytical column. PEG was purchased from SHOWA. A monomode CEM Discover™ microwave reactor with standard configuration operating at a maximum power of 300 W and equipped with an infrared pyrometer for the control of temperature and compressed air system for cooling was used. All the microwave experiments were performed under optimized reaction conditions of power and temperature in open vessel. To monitor the progression of reaction on a polymer support, a small portion of the reaction mixture was pulled out, compound was precipitated and washed with cold ether, subsequently dried and proton NMR spectrum was recorded.

4.2. General procedure for the preparation of polymer bound3-(4-fluoro-3-nitrobenzamido)-4-(substituted amino) carboxylates 2

Polymer bound o-phenylenediamine **1** (PEG 4000) (1.0 g, 0.25 mmol, 1.0 equiv) dissolved in dichloromethane (5 mL) was added to a solution of 4-fluoro-3-nitrobenzoic acid (0.11 g, 0.60 mmol, 2.4 equiv) in dichloromethane (5 mL) in the presence of N,N′-dicyclohexylcarbodiimide (DCC) (0.144 g, 0.70 mmol, 2.4 equiv) and N,N′-dimethylamino pyridine (DMAP) (3 mg). The reaction mixture was stirred at room temperature and subsequently irradiated under microwave for 20 min to obtain the polymer bound amide conjugates **2**. After completion of the reaction, the suspensible dicyclohexyl urea (DCU) was filtered through filter paper. The reaction mixture was precipitated by slow addition of cold ether and precipitated amide conjugate **2** was filtered through fritted funnel. The crude product was washed successively with ether to remove the undesired impurity and dried for further steps.

4.3. General procedure for the preparation of polymer bound benzimidazole derivatives 3

To a solution of **2** in 1,2-dichloroethane, trifluoroacetic acid (0.5 mL) and $MgSO_4$ (0.5 g) were added and irradiated under microwave conditions for 30 min. After completion of the reaction, $MgSO_4$ was removed by filtration through Celite. The reaction mixtures were precipitated by slow addition of excess of cold ether (100 mL) and filtered through a fritted funnel to obtain the compound **3** in high purity.

4.4. General procedure for the preparation of polymer bound substituted benzimidazole derivatives 4

The polymer bound benzimidazole derivative **3** was treated with various primary amines (5 equiv) in 1,2-dichloroethane (5 mL). The reaction mixtures were irradiated under microwave condition for 12 min to complete S_NAr reaction and the reaction mixtures were washed with cold ether (100 mL), dried to obtain the conjugate **4** in quantitative yields.

4.5. General procedure for the preparation of polymer bound diamine derivatives 5

To a solution of **4** in methanol, Zn (0.5 g, 7.5 mmol, 30 equiv) and ammonium chloride (0.24 g, 3.75 mmol, 15.0 equiv) were added. The reaction mixtures were stirred for 30 min for complete reduction of nitro group, which was evident from color change from yellow to colorless. The reaction mixtures were then subjected to centrifugation for removal of Zn and the supernatant liquid was concentrated by rotary evaporation to remove methanol. Dichloromethane (10 mL) was then added to salt out ammonium formate. The reaction mixture was filtered through filter paper to remove ammonium formate to obtain the PEG conjugate **5**.

4.6. General procedure for the preparation of polymer bound substituted benzimidazolyl-quinoxalinone derivatives 6

To a solution of **5** in dichloroethane (25 mL), chloroacetyl chloride (0.0629 g, 3 equiv) and triethyl amine (0.77 mL, 3 equiv) was added under nitrogen atmosphere. The reaction mixture was irradiated under microwave condition for 25 min to complete coupling and cyclization reaction. After completion of the reaction, insoluble materials were removed by filtration through Celite. The reaction mixtures were precipitated by slow addition of excess of cold ether (100 mL) and filtered through a fritted funnel to obtain the compound **6** in high purity.

4.7. General procedure for the cleavage of polymer to get benzimidazolyl-quinoxalinone derivatives 8

To a solution of conjugates **6** in methanol (10 mL), 3.5 N ammonia solution in methanol (10 mL) was added and stirred for 48 h at room temperature. After completion of the reaction, monitored by TLC, the crude mixture was precipitated with excess of cold ether (100 mL) and the polymer was filtered off and subjected to rotavapor. The residue was dried under vacuum and subjected to crude HPLC analysis and further purified by neutral silica gel column chromatography. The obtained solid was further subjected to air for auto-oxidation and monitored by thin-layer chromatography and proton NMR spectrum. After complete auto-oxidation, the title compounds **8** in good yield and subsequently subjected to spectral analysis.

*4.7.1. 2-(1-Benzyl-2-oxo-1,2-dihydro-quinoxalin-6-yl)-1-butyl-1H-benzoimidazole-5-carboxylic acid methyl ester (**8a**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J=1.0 Hz, 1H), 8.47 (s, 1H), 8.21 (d, J=1.5 Hz, 1H), 8.07 (dd, J=8.5, 1.0 Hz, 1H), 7.94 (dd, J=8.7, 1.5 Hz, 1H), 7.47–7.44 (m, 2H), 7.37–7.29 (m, 5H), 5.54 (s, 2H), 4.31 (t, J=7.5 Hz, 2H), 3.96 (s, 3H), 1.87–1.79 (m, 2H), 1.34–1.25 (m, 2H), 0.88 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.41, 154.97, 151.49, 142.32, 134.54, 133.92, 133.34, 132.23, 130.82, 129.14, 128.20, 128.07, 126.92, 125.17, 124.83, 123.54, 123.38, 122.07,121.89, 115.69, 110.08, 52.21, 45.79, 45.03, 31.89, 19.98, 13.54; MS (EI) m/z 466; HRMS (EI) m/z calcd for $C_{28}H_{26}N_4O_3$ 466.2005, found 466.2012; IR (KBr): 2927, 2854, 1713, 1667, 1440, 1302, 1086, 735 cm^{-1}.

*4.7.2. 1-Cyclopentyl-2-(1-furan-2-ylmethyl-2-oxo-1,2-dihydro-quinoxalin-6-yl)-1H-benzoimidazole-5-carboxylic acid methyl ester (**8b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J=1.0 Hz, 1H), 8.40 (s, 1H), 8.13 (d, J=1.2 Hz, 1H), 8.04 (d, J=8.5, 1.0 Hz, 1H), 8.01 (d, J=8.7, 1.2 Hz, 1H), 7.83 (d, J=8.5 Hz, 1H), 7.57 (d, J=8.7 Hz, 1H), 7.36 (d, J=3.6 Hz, 1H), 6.46 (d, J=4.5 Hz, 1H), 6.35–6.34 (m, 1H), 5.49 (s, 2H), 5.00–4.94 (m, 1H), 3.96 (s, 3H), 2.39–2.30 (m, 2H), 2.20–2.03(m, 4H), 1.80–1.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.45, 154.36, 154.10, 151.27, 148.11, 143.11, 142.72, 136.39, 133.62, 133.08, 132.27, 131.07, 125.92, 124.62, 124.05, 122.55, 115.33, 111.65, 110.75, 109.87, 57.94, 52.13, 38.67, 29.66, 25.24; MS (EI) m/z 468; HRMS (EI) m/z calcd for $C_{27}H_{24}N_4O_4$ 468.1798, found 468.1787; IR (KBr): 2851, 1713, 1673, 1436, 1305, 1224, 1087, 735 cm^{-1}.

*4.7.3. 2-[1-(2-Cyclohex-1-enyl-ethyl)-2-oxo-1,2-dihydro-quinoxalin-6-yl]-1-cyclopentyl-1H-benzoimidazole-5-carboxylic acid methyl ester (**8c**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, J=0.9 Hz, 1H), 8.34 (s, 1H), 8.13 (d, J=1.5 Hz, 1H), 8.02–7.97 (m, 2H), 7.56 (d, J=8.5 Hz, 1H), 7.50 (d, J=8.7 Hz, 1H), 5.44 (s, 1H), 5.06–4.94 (m, 1H), 4.35 (t, J=7.8 Hz, 2H), 3.95 (s, 3H), 2.38–2.28 (m, 4H), 2.18–2.14 (m, 2H), 2.12–2.05 (m, 4H), 2.01–1.87 (m, 2H), 1.77 (m, 2H), 1.69–1.61 (m, 2H), 1.58–1.51(m,

2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.48, 154.50, 154.21, 151.28, 143.35, 136.49, 133.64, 133.57, 133.17, 132.12, 131.25, 125.71, 124.53, 124.29, 123.97, 122.65, 114.66, 111.58, 70.51, 57.94, 52.18, 41.05, 35.21, 30.55, 29.66, 28.49, 25.24, 25.22, 22.76, 22.09; MS (EI) *m*/*z* 496; HRMS (EI) *m*/*z* calcd for $C_{30}H_{32}N_4O_3$ 496.2474, found 496.2468; IR (KBr): 2851, 1713, 1667, 1436, 1304, 1087, 754 cm^{-1}.

*4.7.4. 2-(1-Butyl-2-oxo-1,2-dihydro-quinoxalin-6-yl)-1-furan-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid methyl ester (**8d**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.42 (d, *J*=1.8 Hz, 1H), 8.37 (s, 1H), 8.24 (d, *J*=8.7 Hz, 1H), 8.11 (dd, *J*=8.7, 1.8 Hz, 1H), 7.61–7.55 (m, 2H), 7.45–7.44 (d, *J*=4.3 Hz, 1H), 6.44–6.40 (m, 2H), 5.48 (s, 2H), 4.29 (t, *J*=7.2 Hz, 2H), 3.96 (s, 3H), 1.83–1.72 (quint, *J*=7.4 Hz, 2H), 1.57–1.45 (m, 2H), 1.02 (d, *J*=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.85, 167.43, 154.64, 153.73, 151.33, 148.39, 143.33, 142.48, 139.07, 133.81, 133.31, 132.19, 131.44, 125.19, 124.89, 122.18, 114.71, 110.68, 110.29, 109.19, 52.15, 42.42, 41.97, 29.34, 20.19, 13.73; MS (EI) *m*/*z* 456; HRMS (EI) *m*/*z* calcd for $C_{26}H_{24}N_4O_4$ 456.1798, found 456.1805; IR (KBr): 2853, 1720, 1670, 1617, 1436, 773, 735 cm^{-1}.

*4.7.5. 2-(1-Cyclopentyl-2-oxo-1,2-dihydro-quinoxalin-6-yl)-1-furan-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid methyl ester (**8e**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, *J*=1.0 Hz, 1H), 8.35 (d, *J*=1.8 Hz, 1H), 8.28 (s, 1H), 8.08–8.01 (m, 2H), 7.64 (d, *J*=8.7 Hz, 1H), 7.52 (d, *J*=8.4 Hz, 1H), 7.42–7.41 (d, *J*=4.3 Hz, 1H), 6.38–6.35 (m, 2H), 5.55–5.43 (m, 1H), 5.41 (s, 2H), 3.93 (s, 3H), 2.33–2.23 (m, 2H), 2.14–2.00 (m, 4H), 1.81–1.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.81, 167.42, 155.32, 153.68, 151.76, 148.39, 143.33, 142.39, 139.05, 133.98, 131.73, 131.48, 125.22, 124.92, 124.44, 122.14, 115.51, 110.68, 110.30, 109.19, 55.35, 52.15, 42.42, 41.96, 29.66, 28.03, 25.74; MS (EI) *m*/*z* 468; HRMS (EI) *m*/*z* calcd for $C_{27}H_{24}N_4O_4$ 468.1798, found 468.1791; IR (KBr): 2850, 1651, 1402, 764, 642 cm^{-1}.

*4.7.6. 1-Butyl-2-(1-isobutyl-2-oxo-1,2-dihydro-quinoxalin-6-yl)-1H-indole-5-carboxylic acid methyl ester (**8f**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.38 (s, 1H), 8.20 (d, *J*=1.8 Hz, 1H), 8.09–8.03 (m, 2H), 7.51 (d, *J*=8.7 Hz, 1H), 7.47 (d, *J*=8.7 Hz, 1H), 4.34 (t, *J*=7.2 Hz, 2H), 4.17 (d, *J*=7.5 Hz, 2H), 3.96 (s, 3H), 2.34–2.25 (m, 1H), 1.92–1.81 (quint, *J*=7.2 Hz, 2H), 1.39–1.26 (sext, *J*=7.2 Hz, 2H), 1.04 (d, *J*=6.8 Hz, 6H), 0.90 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.77, 167.53, 155.09, 153.49, 151.43, 142.52, 138.90, 133.94, 133.25, 131.93, 130.84, 125.38, 124.84, 122.27, 115.12, 109.93, 52.13, 48.88, 44.93, 41.97, 31.89, 27.27, 20.10, 13.84; MS (EI) *m*/*z* 432; HRMS (EI) *m*/*z* calcd for $C_{25}H_{28}N_4O_3$ 432.2161, found 432.2146; IR (KBr): 2958, 1715, 1667, 1618, 1301, 771, 753 cm^{-1}.

*4.7.7. 1-Butyl-2-[1-(2-methoxy-ethyl)-2-oxo-1,2-dihydro-quinoxalin-6-yl]-1H-benzoimidazole-5-carboxylic acid methyl ester (**8g**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.38 (s, 1H), 8.19 (d, *J*=2.1 Hz, 1H), 8.10–8.05 (m, 2H), 7.74 (d, *J*=8.7 Hz, 1H), 7.47 (d, *J*=8.7 Hz, 1H), 4.51 (t, *J*=6.4 Hz, 2H), 4.34 (t, *J*=7.4 Hz, 2H), 3.96 (s, 3H), 3.79 (t, *J*=6.4 Hz, 2H), 3.33 (s, 3H), 1.92–1.81 (quint, *J*=7.4 Hz, 2H), 1.36–1.29 (sext, *J*=7.4 Hz, 2H), 0.90 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.20, 154.90, 152.91, 151.37, 144.25, 142.15, 140.75, 134.98, 133.19, 132.20, 130.66, 125.72, 125.25, 121.63, 116.23, 110.28, 69.72, 59.22, 52.31, 45.24, 42.66, 31.87, 20.00, 13.57; MS (EI) *m*/*z* 434; HRMS (EI) *m*/*z* calcd for $C_{24}H_{26}N_4O_4$ 434.1954, found 434.1942; IR (KBr): 2923, 1725, 1666, 1303, 1084, 771 cm^{-1}.

*4.7.8. 1-Butyl-2-(1-cyclopentyl-2-oxo-1,2-dihydro-quinoxalin-6-yl)-1H-indole-5-carboxylic acid methyl ester (**8h**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, *J*=1.8 Hz, 1H), 8.30 (s, 1H), 8.20 (d, *J*=2.1 Hz, 1H), 8.06 (dd, *J*=8.5, 1.8 Hz, 1H), 8.02 (dd, *J*=8.7, 2.1 Hz, 1H), 7.66 (d, *J*=8.7 Hz, 1H), 7.46 (d, *J*=8.5 Hz, 1H), 5.55–5.46 (m, 1H), 4.33 (t, *J*=7.4 Hz, 2H), 3.96 (s, 3H), 2.32–2.26 (m, 2H), 2.16–2.03 (quint, *J*=7.3 Hz, 2H), 1.90–1.80 (m, 4H), 1.38–1.17 (m, 4H), 0.90 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.83, 167.64, 155.01, 142.46, 138.89, 137.96, 130.77, 124.85, 124.56, 124.23, 121.93, 119.90, 119.52, 116.18, 115.88, 109.81, 56.65, 52.09, 48.79, 44.82, 42.05, 31.84, 28.45, 25.52, 19.96, 13.57; MS (EI) *m*/*z* 444; HRMS (EI) *m*/*z* calcd for $C_{26}H_{28}N_4O_3$ 444.2161, found 444.2163; IR (KBr): 2923, 1721, 1666, 1617, 1437, 1224, 771 cm^{-1}.

*4.7.9. 1-Butyl-2-[1-(2-cyclohex-1-enyl-ethyl)-2-oxo-1,2-dihydro-quinoxalin-6-yl]-1H-benzoimidazole-5-carboxylic acid methyl ester (**8i**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, *J*=1.5 Hz, 1H), 8.36 (s, 1H), 8.21 (dd, *J*=8.4, 1.5 Hz, 1H), 8.08–8.04 (m, 2H), 7.53 (d, *J*=8.5 Hz, 1H), 7.47 (d, *J*=8.4 Hz, 1H), 5.45 (s, 1H), 4.40–4.31 (t, *J*=7.4 Hz, 2H), 3.97 (s, 3H), 3.39 (t, *J*=6.8 Hz, 2H), 2.39 (m, 2H), 2.09–1.96 (m, 2H), 1.90–1.80 (m, 4H), 1.70–1.54 (m, 4H), 1.30 (sext, *J*=7.2 Hz, 2H), 0.88 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.51, 164.99, 154.97, 142.25, 138.73, 136.53, 134.21, 129.31, 124.40, 124.10, 123.51, 123.39, 122.8, 121.72, 119.53, 115.21, 114.67, 109.70, 51.98, 47.27, 44.68, 34.92, 31.69, 28.37, 25.17, 22.74, 22.12, 19.82, 13.44; MS (EI) *m*/*z* 484; HRMS (EI) *m*/*z* calcd for $C_{29}H_{32}N_4O_3$ 484.2474, found 484.2460; IR (KBr): 2928, 1723, 1674, 1303, 1086 cm^{-1}.

*4.7.10. 2-[1-(2-Cyclohex-1-enyl-ethyl)-2-oxo-1,2-dihydro-quinoxalin-6-yl]-1-isobutyl-1H-benzoimidazole-5-carboxylic acid methyl ester (**8j**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J*=1.4 Hz, 1H), 8.36 (s, 1H), 8.20 (d, *J*=1.1 Hz, 1H), 8.08–8.02 (m, 2H), 7.53–7.45 (m, 2H), 5.45 (s, 1H), 4.37 (t, *J*=7.6 Hz, 2H), 4.20 (t, *J*=7.5 Hz, 2H), 3.97 (s, 3H), 2.39 (t, *J*=7.5 Hz, 2H), 2.13–2.09 (m, 1H), 1.70–1.62 (m, 4H), 1.59–1.54 (m, 4H), 0.78 (d, *J*=7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.49, 154.57, 153.84, 151.41, 139.06, 133.68, 133.27, 132.19, 131.07, 124.99, 124.63, 124.35, 123.70, 123.43, 122.57, 122.31, 114.79, 110.39, 52.34, 52.18, 41.15, 29.71, 29.07, 28.56, 25.27, 22.81, 22.70, 20.04; MS (EI) *m*/*z* 484; HRMS (EI) *m*/*z* calcd for $C_{29}H_{32}N_4O_3$ 484.2474, found 484.2461; IR (KBr): 3053, 2926, 1713, 1666, 1265, 740, 705 cm^{-1}.

*4.7.11. 2-(1-Benzyl-2-oxo-1,2-dihydro-quinoxalin-6-yl)-1-isobutyl-1H-indole-5-carboxylic acid methyl ester (**8k**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, *J*=1.2 Hz, 1H), 8.47 (s, 1H), 8.21 (d, *J*=1.8 Hz, 1H), 8.04 (dd, *J*=8.5, 1.2 Hz, 1H), 7.90 (dd, *J*=8.7, 1.8 Hz, 1H), 7.46–7.43 (m, 2H), 7.37–7.16 (m, 5H), 5.53 (s, 2H), 4.15 (d, *J*=7.4 Hz, 2H), 3.95 (s, 3H), 2.18–2.09 (m, 1H), 0.77 (d, *J*=7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.59, 158.71, 157.89, 149.61, 144.78, 142.56, 141.98, 141.85, 137.54, 129.68, 128.04, 127.78, 127.45, 127.02, 126.57, 123.54, 123.14, 122.53, 119.85, 112.57, 53.35, 52.19, 48.96, 27.58, 19.04; MS (EI) *m*/*z* 466; HRMS (EI) *m*/*z* calcd for $C_{28}H_{26}N_4O_3$ 466.2005, found 466.2013; IR (KBr): 2825, 1713, 1667, 1620, 1435, 772, 734 cm^{-1}.

*4.7.12. 1-Isobutyl-2-[1-(3-methyl-benzyl)-2-oxo-1,2-dihydro-quinoxalin-6-yl]-1H-benzoimidazole-5-carboxylic acid methyl ester (**8l**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J*=1.2 Hz, 1H), 8.49 (s, 1H), 8.22 (d, *J*=1.8 Hz, 1H), 8.07 (dd, *J*=8.5, 1.2 Hz, 1H), 7.95 (d, *J*=8.5 Hz, 1H), 7.47 (dd, *J*=8.5, 1.8 Hz, 1H), 7.40 (d, *J*=8.5 Hz, 1H), 7.23 (t, *J*=7.8 Hz, 1H), 7.12 (s, 1H), 7.08 (d, *J*=7.8 Hz, 2H), 5.51 (s, 2H), 4.19 (d, *J*=7.5 Hz, 2H), 3.96 (s, 3H), 2.32 (s, 3H), 2.18–2.09 (m, 1H), 0.77 (d, *J*=7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.48, 154.84, 151.40, 142.54, 139.10, 138.93, 134.21, 133.69, 133.28, 132.19, 130.83, 128.92, 128.84, 128.77, 127.20, 126.04, 124.77, 124.47, 123.91, 122.36, 115.57, 110.29, 52.23, 52.15, 45.75, 29.01, 19.98, 19.90; MS (EI) *m*/*z* 480; HRMS (EI) *m*/*z* calcd for $C_{29}H_{28}N_4O_3$ 480.2161, found 480.2148; IR (KBr): 2925, 2359, 1716, 1667, 1302, 1085, 772 cm^{-1}.

*4.7.13. 1-Cyclopentyl-2-(1-isopropyl-2-oxo-1,2-dihydro-quinoxalin-6-yl)-1H-benzoimidazole-5-carboxylic acid methyl ester (**8m**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.29 (s, 1H), 8.13 (d, *J*=1.8 Hz, 1H), 8.03–7.95 (m, 2H), 7.74 (d, *J*=8.7 Hz, 1H), 7.56 (d, *J*=8.7 Hz, 1H), 5.38–5.34 (m, 1H), 5.06–4.94 (m, 1H), 3.96 (s, 3H), 2.39–2.29 (m, 2H), 2.19–2.03 (m, 4H), 1.80–1.74 (m, 2H), 1.69 (d, *J*=7.2 Hz, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.71, 167.51, 155.19, 154.15, 152.05, 143.28, 136.47, 133.76, 131.60, 131.43, 125.50, 124.53, 124.23, 123.98, 122.61, 111.61, 57.93, 52.13, 41.97, 30.54, 29.66, 25.25; MS (EI) *m/z* 430; HRMS (EI) *m/z* calcd for $C_{25}H_{26}N_4O_3$ 430.2005, found 430.1988; IR (KBr): 2852, 1667, 1620, 1436, 1304, 771, 755 cm^{-1}.

*4.7.14. 1-Cyclopentyl-2-[1-(2-methoxy-ethyl)-2-oxo-1,2-dihydro-quinoxalin-6-yl]-1H-benzoimidazole-5-carboxylic acid methyl ester (**8n**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.36 (s, 1H), 8.11 (d, *J*=0.9 Hz, 1H), 8.02–7.94 (m, 2H), 7.73 (d, *J*=8.5 Hz, 1H), 7.55 (d, *J*=8.7 Hz, 1H), 5.05–4.93 (m, 1H), 4.49 (t, *J*=7.2 Hz, 2H), 3.94 (s, 3H), 3.78 (t, *J*=7.2 Hz, 2H), 3.32 (s, 3H), 2.39–2.30 (m, 2H), 2.20–2.03 (m, 4H), 1.80–1.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.46, 154.87, 154.20, 151.08, 143.17, 136.42, 138.38, 133.06, 132.05, 130.89, 125.72, 124.55, 123.98, 122.56, 115.78, 111.61, 69.67, 59.14, 57.93, 52.10, 42.53, 30.53, 25.23; MS (EI) *m/z* 446; HRMS (EI) *m/z* calcd for $C_{25}H_{26}N_4O_4$ 446.1954, found 446.1955; IR (KBr): 2852, 1716, 1667, 1439, 1304, 1225, 974 cm^{-1}.

*4.7.15. 2-(1-Benzyl-2-oxo-1,2-dihydro-quinoxalin-6-yl)-1-cyclopentyl-1H-benzoimidazole-5-carboxylic acid methyl ester (**8o**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, *J*=1.5 Hz, 1H), 8.47 (s, 1H), 8.15 (d, *J*=1.9 Hz, 1H), 8.00 (dd, *J*=8.5, 1.5 Hz, 1H), 7.85 (dd, *J*=8.7, 1.9 Hz, 1H), 7.54 (d, *J*=8.5 Hz, 1H), 7.45 (d, *J*=8.7 Hz, 1H), 7.38–7.26 (m, 5H), 5.54 (s, 2H), 5.01–4.90 (m, 1H), 3.95 (s, 3H), 2.39–2.30 (m, 2H), 2.20–2.03(m, 4H), 1.80–1.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 1.55.0, 154.1, 151.4, 143.1, 136.4, 134.6, 133.8, 133.3, 132.3, 131.2, 129.3, 128.1, 126.9, 125.9, 124.7, 124.1, 122.6, 115.6, 111.7, 58.0, 52.2, 45.8, 30.6, 29.7, 25.3, 23.9; MS (EI) *m/z* 478; HRMS (EI) *m/z* calcd for $C_{29}H_{26}N_4O_3$ 478.2005, found 478.2002; IR (KBr): 2873, 1715, 1667, 1439, 1221, 1087, 734 cm^{-1}.

*4.7.16. 2-(1-Benzyl-2-oxo-1,2-dihydro-quinoxalin-6-yl)-1-furan-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid methyl ester (**8p**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.48 (s, 1H), 8.41 (d, *J*=0.9 Hz, 1H), 8.09–8.04 (m, 2H), 7.55 (d, *J*=8.2 Hz, 1H), 7.48 (d, *J*=8.5 Hz, 1H), 7.43 (d, *J*=3.4 Hz, 1H), 7.38–7.28 (m, 5H), 6.44–6.34 (m, 2H), 5.55 (s, 2H), 5.42 (s, 2H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.17, 154.91, 151.53, 143.50, 138.57, 134.47, 133.36, 132.38, 132.01, 131.51, 129.12, 128.11, 128.06, 127.82, 126.86, 125.32, 124.01, 121.76, 117.76, 115.72, 110.75, 110.51, 109.47, 106.45, 53.39, 45.76, 42.56; MS (EI) *m/z* 490; HRMS (EI) *m/z* calcd for $C_{29}H_{22}N_4O_4$ 490.1641, found 490.1653; IR (KBr): 2851, 1667, 1619, 1436, 1303, 735 cm^{-1}.

*4.7.17. 1-Furan-2-ylmethyl-2-[1-(4-methoxy-benzyl)-2-oxo-1,2-dihydro-quinoxalin-6-yl]-1H-benzoimidazole-5-carboxylic acid methyl ester (**8q**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, *J*=0.9 Hz, 1H), 8.46 (s, 1H), 8.37 (d, *J*=1.0 Hz, 1H), 8.06–8.00 (m, 2H), 7.52 (d, *J*=8.4, 1.0 Hz, 1H), 7.49 (d, *J*=8.6 Hz, 1H), 7.42–7.41 (d, *J*=4.3 Hz, 1H), 7.23 (d, *J*=7.3 Hz, 2H), 6.86 (d, *J*=7.3 Hz, 2H), 6.39–6.34 (m, 2H), 5.47 (s, 2H), 5.39 (s, 2H), 3.95 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.40, 159.31, 154.94, 153.63, 151.43, 148.33, 143.35, 142.40, 139.01, 138.31, 133.91, 133.37, 132.19, 131.38, 128.39, 126.55, 125.24, 124.93, 122.17, 115.53, 114.45, 110.69, 110.30, 109.22, 55.29, 53.40, 45.22, 42.42; MS (EI) *m/z* 520; HRMS (EI) *m/z* calcd for $C_{30}H_{24}N_4O_5$ 520.1747, found 520.1739; IR (KBr): 2851, 1712, 1666, 1620, 1251, 1086, 737 cm^{-1}.

Acknowledgements

We thank the NSC (National Science Council) and the NCTU (National Chiao Tung University) at Taiwan for financial support of this work.

Supplementary data

The ^{1}H NMR spectrums and HPLC spectrums of compounds **9a**–**9q** are available free of charge through Internet. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.01.040.

References and notes

1. (a) Patil, S. A.; Patil, R.; Miller, D. D. *Curr. Med. Chem.* **2009**, *16*, 2531–2565; (b) Gund, P.; Maliski, E.; Brown, F. *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 337–338; (c) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74–84; (d) Nicolaou, K. C.; Hanko, R.; Hartwig, W. *Handbook of Combinatorial Chemistry*; Wiley-VCH: Weinheim, 2002; 1114; (e) Shreiber, S. L. *Science* **2000**, *287*, 1964–1969.
2. (a) Gunawardana, C. G.; Diamandis, E. P. *Cancer Lett.* **2007**, *249*, 110–119; (b) Stromberg, S.; Bjorklund, M. G.; Asplund, C.; Skollermo, A.; Persson, A.; Wester, K.; Kampf, C.; Nilsson, P.; Andersson, A. C.; Uhlen, M.; Kononen, J.; Ponten, F.; Asplund, A. *Proteomics* **2007**, *7*, 2142–2150; (c) Hsiao, Y. S.; Yellol, G. S.; Chen, L. H.; Sun, C. M. *J. Comb. Chem.* **2010**, *12*, 723–732; (d) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. *Chem.—Eur. J.* **1998**, *4*, 1885–1889; (e) Kay, B. K.; Paul, J. I. *Mol. Diversity* **1995**, *1*, 139–140.
3. (a) Nielsen, T. E.; Meldal, M. *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 798–810; (b) Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Science* **2001**, *291*, 1523–1527; (c) Seeberger, P. H.; Danishefsky, S. *Acc. Chem. Res.* **1998**, *31*, 685–695.
4. (a) Chen, R.; Tolbert, T. J. *J. Am. Chem. Soc.* **2010**, *132*, 3211–3216; (b) Zhi, H.; Lue, C.; Zhang, Q.; Luo, J. *Chem. Commun.* **2009**, *20*, 2878–2880; (c) Sun, C. M. In *Combinatorial Chemistry Methods and Protocols*; Bellavance, L., Ed.; The Humana: NJ, 2002; p 345; (d) An, H.; Cook, P. D. *Chem. Rev.* **2000**, *100*, 3311–3340.
5. (a) Weiss, G. A. *Curr. Opin. Biotechnol.* **2007**, *11*, 241–243; (b) Phillipson, D. W.; Milgram, K. E.; Yanovsky, A. I. *J. Comb. Chem.* **2002**, *4*, 591–599; (c) Yang, T. M.; Liu, G. *J. Comb. Chem.* **2007**, *9*, 86–95.
6. (a) Li, X.; Yang, K.; Li, W.; Xu, W. *Drugs Future* **2006**, *31*, 979–989; (b) Carta, A.; Piras, S.; Loriga, G.; Paglietti, G. *Mini-Rev. Med. Chem.* **2006**, *6*, 1179–1200; (c) Zambrowicz, B. P.; Sands, A. T. *Nat. Rev. Drug Discovery* **2003**, *2*, 38–51.
7. (a) Lai, J. J.; Salunke, D. B.; Sun, C. M. *Org. Lett.* **2010**, *12*, 2174–2177; (b) Chanda, K.; Kuo, J.; Chen, C. H.; Sun, C. M. *J. Comb. Chem.* **2009**, *11*, 252–260; (c) Chen, H. Y.; Kulkarni, M. V.; Chen, C. H.; Sun, C. M. *Tetrahedron* **2008**, *64*, 6387–6394; (d) Tung, C. L.; Sun, C. M. *Tetrahedron Lett.* **2004**, *45*, 1159–1162; (e) Chang, W. J.; Yeh, W. B.; Sun, C. M. *Synlett* **2003**, 1688–1692.
8. (a) Jaso, A.; Zarranz, B.; Aldana, I.; Monge, A. *J. Med. Chem.* **2005**, *48*, 2019–2025; (b) Nixey, T.; Tempest, P.; Hulme, C. *Tetrahedron Lett.* **2002**, *43*, 1637–1639; (c) Gris, J.; Glisoni, R.; Fabian, L.; Fernandez, B.; Moglioni, A. G. *Tetrahedron Lett.* **2008**, *49*, 1053–1056.
9. (a) Ali, I. A. I.; Al-Masoudi, I. A.; Aziz, N. M.; Al-Masoudi, N. A. *Nucleosides, Nucleotides Nucleic Acids* **2008**, *27*, 146–156; (b) Ali, I. A. I.; Al-Masoudi, I. A.; Hassan, H. G.; Al-Masoudi, N. A. *Chem. Heterocycl. Compd.* **2007**, *43*, 1052–1061.
10. Koltun, D.; Parkhill, E.; Zablocki, J. Substituted Heterocyclic Compounds, U.S. Patent 20,100,113,461 A1, 2010.
11. Cartaa, A.; Pirasa, S.; Paglietta, G.; Priclb, S.; La Collac, P.; Busonerac, B.; Loddo, R. *Med. Chem.* **2008**, *4*, 194–205.
12. Ren, P.; Liu, Y.; Li, L.; Chan, K.; Wilson, T. E. WO Patent, WO 2010036380A1, 2010.
13. (a) Hasegawa, M.; Nishigaki, N.; Washio, Y.; Kano, K.; Harris, P. A.; Sato, H.; Mori, I.; West, R. I.; Shibahara, M.; Toyoda, H.; Wang, L.; Nolte, R. T.; Veal, J. M.; Cheung, M. *J. Med. Chem.* **2007**, *50*, 4453–4470; (b) Hirashima, S.; Suzuki, T.; Ishida, T.; Noji, S.; Ando, I.; Komatsu, M.; Ikede, S.; Hashimoto, H. *J. Med. Chem.* **2006**, *49*, 4721–4736; (c) Li, Y. F.; Wang, G. F.; He, P. L.; Huang, W. G.; Gao, H. Y.; Tang, W.; Luo, Y.; Feng, C. L.; Shi, L. P.; Ren, Y. D.; Lu, W.; Zuo, J. P. *J. Med. Chem.* **2006**, *49*, 4790–4794; (d) Gravatt, G. L.; Baguley, B. C.; Wilson, W. R. *J. Med. Chem.* **1994**, *37*, 4338–4345.
14. (a) Islam, I.; Skibo, E. B.; Dorr, R. T. *J. Med. Chem.* **1991**, *34*, 2954–2961; (b) Nakano, H.; Inoue, T.; Kawasaki, N. *Chem. Pharm. Bull.* **1999**, *47*, 1573–1578; (c) Kus, C.; Ayhan-Kicigil, G.; Iscan, M. *Arch. Pharmacal Res.* **2004**, *27*, 156–163; (d) Samia, R.; Soda, A.; El-Hesham, M.; Fahmy, T. Y. *Arch. Pharmacal Res.* **2006**, *29*, 826–833.
15. Boyer, P. L.; Hughes, S. H.; Buckheit, R. W. *J. Med. Chem.* **1997**, *40*, 4199.
16. Tolliday, N.; Clemons, P. A.; Ferraiolo, P. .; Koehler, A. N.; Lewis, T. A.; Li, X.; Schreiber, S. L.; Gerhard, D. S.; Eliasof, S. *Cancer Res.* **2006**, *66*, 8935–8942.
17. (a) Chou, L. C.; Chen, C. T.; Lee, J. C.; Way, T. D.; Huang, C. H.; Huang, S. M.; Teng, C. M.; Yamori, T.; Wu, T. S.; Sun, C. M.; Chien, D. S.; Qian, K.; Morris-Natschke, S. L.; Lee, K. H.; Huang, L. J.; Kuo, S. C. *J. Med. Chem.* **2010**, *53*, 1616–1626; (b) Maiti, B.; Chanda, K.; Sun, C. M. *Org. Lett.* **2009**, *11*, 4826–4829; (c) Chen, C. H.; Chien, M. H.; Kuo, M. L.; Chou, C. T.; Lai, J. J.; Lin, S. F.; Thummanagoti, S.; Sun, C. M. *J. Comb. Chem.* **2009**, *11*, 1038–1046.
18. (a) Pan, P. C.; Sun, C. M. *Tetrahedron Lett.* **1999**, *40*, 6443–6446; (b) Yeh, C. M.; Tung, C. L.; Sun, C. M. *J. Comb. Chem.* **2000**, *2*, 341–348.