Tetrahedron 68 (2012) 3532–3540

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Traceless polymer-supported divergent synthesis of quinoxalinones by microwave irradiation

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ARTICLE INFO

Article history:
Received 7 August 2011
Received in revised form 4 March 2012
Accepted 6 March 2012
Available online 13 March 2012

ABSTRACT

A novel protocol for rapid assemble of quinoxalinones framework has been demonstrated. This method incorporated with soluble polymer support provides a convenient approach for diversification of heterocyclic compounds and for easy purification via facile precipitation from reaction matrix. The key transformation of this study involves in situ reduction of aromatic nitro compound, tandem lactamization concomitant with traceless cleavage of the polymer support under microwave irradiation in a one-pot fashion. Moreover, forward synthetic routes were introduced to maximize complexity of the master intermediate on which further chemical elaboration was applied. The strategy is envisaged to apply for establishment of drug-like small-molecule libraries for high-throughput screening.

1. Introduction

Heterocyclic compounds are pervasive in both academic and pharmaceutical industry mainly focused on small-molecule drug discovery due to their highly structural diversity.[1] Quinoxalinones are such the paradigm of framework exhibiting wide spectra of bioactivities. The scaffold of quinoxalinones demonstrates on antimicrobial, antithrombotic, anti-tumor, and deconditioning activities.[2] Ambident hydrogen bonding donor–acceptor system and salt bridge acceptors (quaternized nitrogen atoms) may contribute to the versatile pharmaceutical activity portfolio of quinoxalinones.

This privileged pharmacophore is highly visible in structure–activity relationship (SARs)-based drug design approaches for developing chemotherapeutics (Fig. 1). For instance, inhibition of quinoxalinone peptidomimetic analogue (**I**) on matrix metalloproteinases (MMPs) is potential lead for anticancer drug development.[3] Macrocyclic quinoxalinone (**II**) shows highly potent cyclin-dependent kinases (Cdks) antagonism (nanomolar magnitude) offering an attractive target for cancer research.[4] A class-B calcium-channel blocker, a marketing drug named caroverine (**III**), designed to enhance antispasmodic activity and tinnitus treatments has also been found effective in scavenging of hydroxy free radical.[5] Moreover, tricyclic imidazoquinoxalinone (**IV**) reveals activity against testis-specific serine/threonine kinase 1.[6] These functional molecules are potent drug leads in pharmaceutical chemistry.

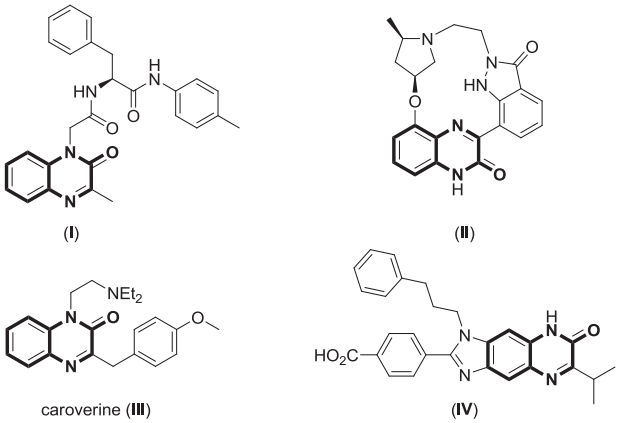

Fig. 1. Representative molecules of bioactive quinoxalinones.

Rapidly obtaining quinoxalinone core with diversified functionality is essential for their bioactivity evaluation. Combinatorial synthetic strategies offer great opportunities to generate sufficient number of molecular libraries in a time efficient and parallel fashion to fulfill demand of compounds for high-throughput screening in medicinal chemistry.[7] Although batch-wise linear synthetic operations are still performed sporadically,[8] protocols involving the combinatorial concept using solid-phase organic synthesis (SPOS) to furnish quinoxalinone scaffolds are more predominated and popular in nowadays strategy.[9] Nevertheless, fundamental issues (e.g., prolonged reaction time, difficult to characterize of intermediates, and limited reaction monitoring

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0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2012.03.015

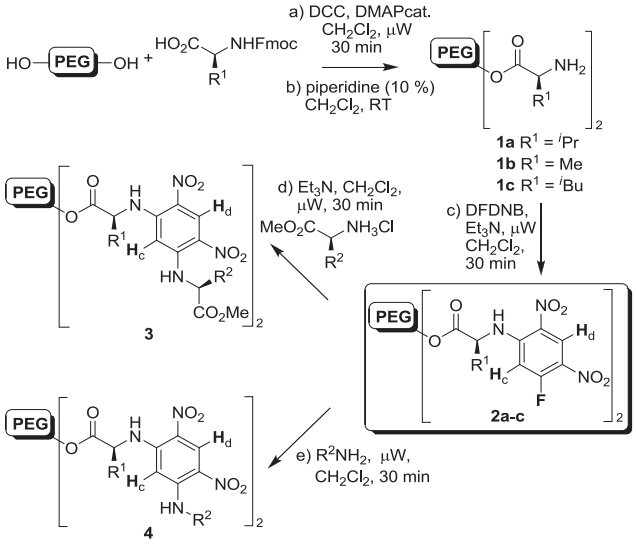
method) encompass in solid-phase chemistry. The major inadequacy of SPOS in routine operational exercise attributes to biphasic reaction media but this property is the advantage for ease of purification of intermediates and the target molecules. In contrast to biphasic reaction matrix used in SPOS system, homogenous phase-tagged synthesis has been developed as an alternative strategy in combinatorial chemistry aiming for easy reaction monitoring and intermediates characterization by conventional analytical methods (e.g., TLC, NMR, MS, and HPLC), meanwhile remaining with advantageous aspects for parallel organic synthesis.[10] Soluble polymer-supported synthesis has been demonstrated as a powerful platform in elaborating molecular complexity under more familiar and convenient to operate environment in solution, and the purification tasks are simply performed by recrystallization at ambient temperature.[11] Reaction parameters used in solution phase are readily to be applied on the liquid phase soluble polymer-support synthesis with non- or minimum-optimization, which minimizes unexpected outcomes and offers a user-friendly interface.

The concept of soluble polymer-supported organic synthesis is achieved by soluble macromolecule serving as a phase tag anchored with small molecules for chemical manipulations. Among soluble polymer supports, polyethylene glycols (PEGs) with molecular weight 2000–20,000 are well documented and widely used in combinatorial organic synthesis.[12] PEGs with lower molecular weight have higher loading capacities but exhibit less crystalline propensity than that of higher molecular weight. PEG_{4000} and PEG_{6000} are the most popular soluble polymer supports representing of molecular weight 4000 and 6000 with loading capacities 0.5 and 0.33 mmol g^{-1}, respectively. PEG_{4000} composing two hydroxy groups can be introduced onto small molecules as a protecting group or a traceless phase tag. This homopolymer features in a wide range of solubility toward organic solvents in synthetic tasks and aqueous media but precipitates in hexane, Et_2O, and ^{t}BuOMe at room temperature or below due to the helical backbone of the polymer.[13] As a result, the soluble PEG-tagged intermediates can be easily isolated by simple precipitation/recrystallization procedure from the reaction matrix and examined by general analytical methods. This liquid phase PEG-tagged methodology is compatible with microwave-assisted organic synthesis (MAOS) to promote chemical transformations. Microwave technology has well pronounced in chemistry synthesis in the past two decades and automated parameters are established to fulfill nowadays demanding of compound libraries. By irradiating reaction mixture with microwave energy under controlled conditions, heating efficiency is more superior to that of by a traditional oil bath heating. Reaction rate and yields are significantly enhanced by microwave irradiation contributed synergically from microwave dielectric heating and thermolytic effects.[14] The versatile portfolio of MAOS is rapidly adopted by medicinal chemists to facilitate synthesis of molecular libraries in a combinatorial fashion within short period for biological evaluation on drug discovery.[15]

The quinoxalinone framework is typically afforded through a synthetic sequence commencing from coupling of amines with 1,5-difluoro-2,4-dinitrobenzene (DFDNB) through a sequential aromatic nucleophilic substitution (S_NAr) manner followed by reductive cyclization. However, in solution phase operation, a critical issue on this *ipso*-fluorous replacement process is often concomitant with bis-substituted side product, which has adverse effects on both separation tasks and reaction yields. Recently, our group has demonstrated convenient approaches for synthesis of diversified quinoxalinone scaffold using soluble polymer support technology.[16] Further study in this research field results in new discovery on elaboration of novel quinoxalinone derivatives. Herein, we report our latest achievement in developing of an efficient soluble PEG-tagged traceless synthesis of new class quinoxalinone analogues facilitated by microwave irradiation for molecular library construction. Our strategy leading to the target heterocycles is based on PEG-tagged master cores of which molecular complexity is maximized. This concept of divergent synthesis is envisaged to accumulate sufficient molecular databases within a short time course for bioassay screening and to telescope drug discovery process.

2. Results and discussion

PEG_{6000} (HO-PEG_{6000}-OH; abbreviated as PEG thereafter in this article) was chosen as a soluble polymer support in this study. The synthetic efforts commenced on anchoring of Fmoc–L-amino acids onto the polymer to furnish the PEG-tagged Fmoc–L-amino acids by treatment of *N*,*N*′-dicyclohexylcarbodiimide (DCC) as a coupling reagent in the presence of DMAP as a catalyst in CH_2Cl_2 under microwave irradiation for 30 min. It is worthy to mention that this reaction proceeded sluggishly (8 h) without engagement of microwave reaction. The transformation was well monitored by TLC and the desired PEG-tagged Fmoc–L-amino acids were obtained in a pure form by crystallization from cold Et_2O followed by filtration and flushing the filter cake with Et_2O. The easy removal of excess reagents and residues has well demonstrated in this approach because these chemicals (i.e., DCC and *N*,*N*′-dicyclohexylurea) are particularly troublesome for purification tasks performed in tag-free chemistry. Upon incubation of the PEG-tagged Fmoc–L-amino acids in a 10% solution of piperidine in CH_2Cl_2 at room temperature for 1 h, free PEG-tagged L-amino acids **1** were librated to which the essential aromatic core of the target heterocyclic compounds was integrated with this soluble polymer platform through an S_NAr reaction manner. According to the procedure adopted by our group,[16b] the PEG-tagged master scaffolds **2a**–**c** were prepared by treatment of the PEG–L-amino acid tags **1a**–**c** with 1,5-difluoro-2,4-dinitrobenzen and Et_3N in CH_2Cl_2 under microwave heating conditions for 30 min. Sequential chemical manipulations were achieved by a second S_NAr reaction by subjection of PEG-tags **2** with amino acid methyl ester HCl salts and aliphatic amines individually under the microwave heating conditions aforementioned. Privileged molecular platforms, PEG-tags **3** and **4**, were obtained after standard recrystallization/filtration exercises employed on soluble polymer support chemistry (Scheme 1).



Scheme 1. Preparation of PEG-tagged master scaffold **2** and PEG-tagged molecular platforms **3**–**4**.Reagents and conditions: (a) DCC (1.2 equiv), DMAP (5 mol %), CH_2Cl_2, μW (270 W), 30 min; (b) piperidine (10% in CH_2Cl_2, v/v), rt, 1 h; (c) DFDNB (2.5 equiv), Et_3N (5.0 equiv), CH_2Cl_2, μW (270 W), 30 min; (d) amino acid methyl ester·HCl (2.5 equiv), Et_3N (5.0 equiv), CH_2Cl_2, μW (270 W), 30 min; (e) R^2NH_2 (5.0 equiv), CH_2Cl_2, μW (270 W), 30 min.

Examining the PEG-tagged master scaffolds in the case of **2a** (R^1=^{i}Pr) by conventional ^{1}H NMR spectroscopy revealed expected coupling systems at aromatic region at which the coupling patterns of $^3J_{F-Hc}$ and $^4J_{F-Hd}$ indicating that only one fluorous atom on DFDNB was replaced by each amino acid nucleophile anchored on the PEG-tag **1** (Fig. 2). No cross- or higher-order substitution reactions were concomitant with the desired transformation owning to PEG-tag **2** as a unified form. This excellent mono-*ipso*-fluorous substitution is probably beneficial from sterically hindered PEG backbone at the reaction terminuses so that the multiple fluorous replacement side-reactions are efficiently suppressed.

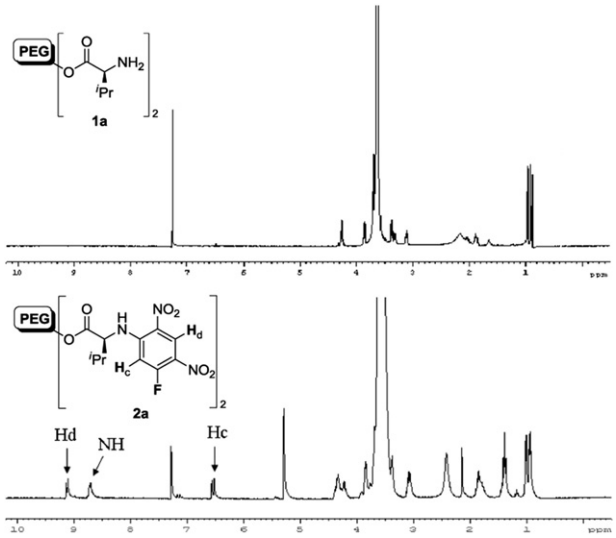


Fig. 2. ^{1}H NMR spectra of PEG-tagged L-amino acid **1a** and master scaffold **2a**.

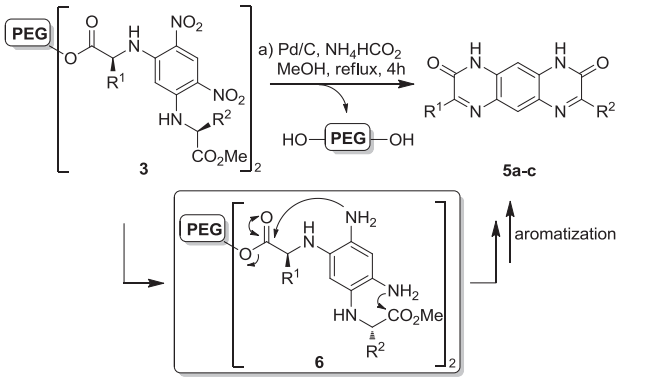
With successfully secured essential portfolios, our strategy to reach quinoxalinone core required full reduction of the aromatic nitro groups, cyclization, and cleavage off the PEG vehicle. Inspired by our previous investigation in this aspect, the latter two transformations occur simultaneously upon anilines are formed. To fulfill our original orchestration by this 'one-pot' setting, PEG-tags **3** were employed as test ground to test this reductive cyclization. Gratifyingly, pyrazino[2,3-*g*]quinoxalindiones **5** were obtained by subjection of PEG-tags **3** with catalytic amount of Pd/C and ammonium formate under MeOH refluxing for 4 h (Table 1).

As expected, the tandem cyclization process took place upon the aromatic nitro groups on PEG-tag **3** were reduced to the corresponding bis-aniline **6** followed by lactam formation and aromatization process. In addition, this reductive lactamization also facilitates cleavage of the PEG carrier to liberate the soluble polymer support so that the tag-free quinoxalinones were recruited from liquid media after removal of PEG by crystallization and filtration. Encouraged by the promising results, PEG-tags **4** were subjected to the same reduction conditions to furnish diamines **7**, which will serve as repertoire building blocks to access elaborated heterocycles. Privileged frameworks such as imidazoquinoxalinones **8**–**10** are envisaged to be diversified from diamines **7** through tractable synthetic exercises (Scheme 2).

Analysis of the crude diamines, **7a** as an example (R^1=R^2=^{i}Pr), obtained from filtration liquid and the retrieved PEG support by ^{1}H NMR spectroscopy revealed a clean and efficient transformation as designed. No heterocyclic compound was contaminated with the PEG residue nor incomplete cleavage occurred, which augurs well to apply this strategy to the preparation of molecular libraries in an exquisite manner (Fig. 3).

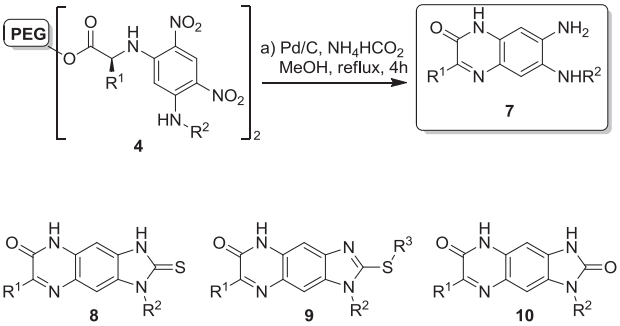
With secure of the front end precursors, forward synthetic approaches on diamines **7** were accomplished by late stage chemical

Table 1
One-pot traceless reductive cyclization toward pyrazino[2,3-*g*]quinoxalindiones **5**. Reagents and conditions: (a) Pd/C (10 wt %), NH_4HCO_2 (20 equiv), MeOH, reflux, 4 h



Entry	R^1	R^2	Product	Yield[a] (%)
1	^{i}Pr	^{i}Pr	**5a**	71
2	^{i}Pr	^{i}Bu	**5b**	73
3	Me	^{i}Pr	**5c**	66

[a] Isolated yields.



Scheme 2. One-pot traceless reductive lactamization to access diamines **7**. Reagents and conditions: (a) Pd/C (10 wt%), NH_4HCO_2 (20 equiv), MeOH, reflux, 4 h.

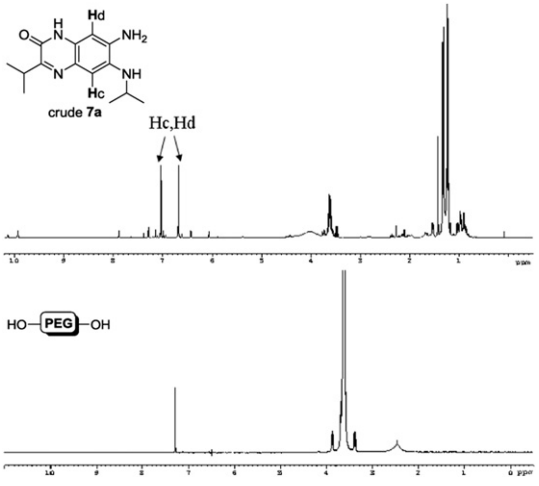
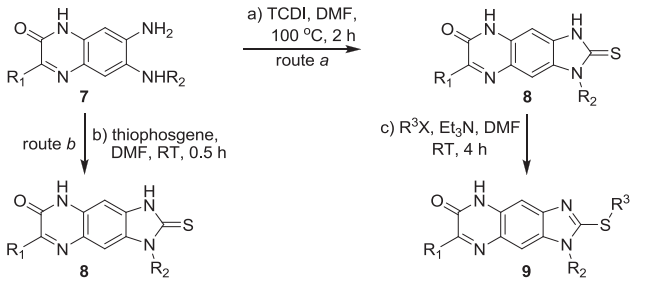


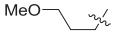
Fig. 3. ^{1}H NMR spectra of crude diamine **7a** and retrieved PEG support.

manipulations on the diamino functionality. Treatment of diamines **7** with 1,1′-thiocarbonyldiimidazole (TCDI) in DMF at 100 °C for 2 h gave thioxoimidazo[4,5-*g*]quinoxalinones **8** as a privileged core. Due to poor solubility of the diamines **7** in most organic solvents

resulting inferior outcomes, polar aprotic solvent DMF is required. Besides, although milder and more facile reaction conditions (route b) were found by employing thiophosgene, safety concerns rising from highly toxic and volatile thiophosgene confine its application on a routine basis. As a consequence, a variety of thioxoimidazo [4,5-*g*]quinoxalinones **8** were synthesized by the original conditions (route a, Table 2).

Table 2
Diversification of diamines **7** leading thioxoimidazo[4,5-*g*]quinoxalinones **8**. Reagents and conditions: (a) TCDI (1.5 equiv), DMF, 100 °C, 4 h; (b) Cl_2CS (1.5 equiv), DMF, 0 °C, 0.5 h; (c) R^3X (2.0 equiv), Et_3N (5.0 equiv), DMF, rt, 4 h

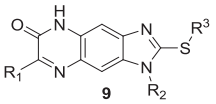


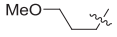
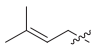
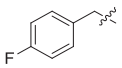
Entry	R^1	R^2	Product	Yield[a] (%)
1	^{i}Bu		**8a**	80
2	^{i}Bu		**8b**	79
3	^{i}Bu	^{i}Bu	**8c**	82
4	^{i}Bu	^{i}Pr	**8d**	75
5	^{i}Bu		**8e**	74
6	^{i}Pr	^{i}Pr	**8f**	72
7	Me		**8g**	70

[a] Isolated yields.

Further nucleophilic alkylation of imidazothione motif on quinoxalinones **8** by organic halides realized alkylthioimidazo[4,5-*g*] quinoxalinones **9** on which the alkyl spacer could enhance their biological activity exerted by secondary interaction with the target proteins (Table 3).

Table 3
Nucleophilic alkylation of thioxoimidazo[4,5-*g*]quinoxalinones **8** owning to imidazoquinoxalinones **9**

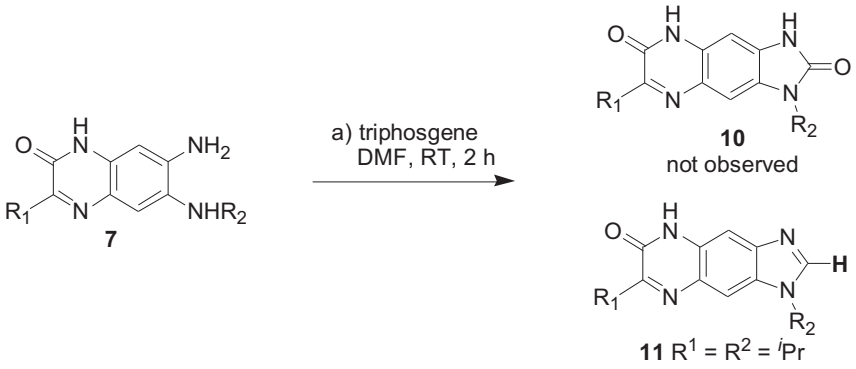


Entry	R^1	R^2	R^3	Product	Yield[a] (%)
1	^{i}Bu	^{n}Bu		**9a**	91
2	^{i}Bu		Me	**9b**	80
3	^{i}Bu			**9c**	90
4	^{i}Bu	^{i}Pr		**9d**	88
5	^{i}Bu			**9e**	81
6	^{i}Pr	^{i}Pr		**9f**	73
7	Me			**9g**	88

[a] Isolated yields.

Applying similar analogy on formation of imidazolone subunit on quinoxalinones **8** by using triphosgene as a carbonylation agent gave unanticipated outcomes and no imidazoquinoxalinedione was observed under the reaction arrangements. Careful examination of resulting product by means of NMR and mass spectrometry revealed an imidazole fragment fused with the core skeleton owning imidazoquinoxalinone **11**. Because a methine group is required along with the two amino groups to form imidazole unit, we prospect that DMF has participated in this transformation serving as a congener of methine equivalence. The reaction mechanism was proposed and delineated (Scheme 3).

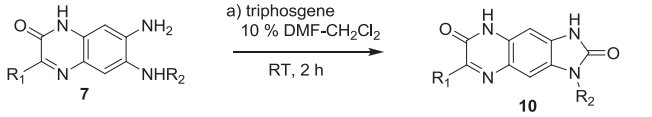
Highly reactive Vilsmeier reagent (*N*-chloromethylene-*N*,*N*′-dimethyl ammonium chloride) is generated in situ from DMF and triphosgene[17] to react with diamine **7** to give iminium ion on which the adjacent amino group undergoes cyclization spontaneously via 5-*exo*-*trig* pathway to afford intermediate. Imidazoquinoxalinone **11** was formed after elimination of a molecule of dimethylamine driving by nature of aromaticity. A minor modified reaction condition using DMF/CH_2Cl_2 (1:9, v/v) as a co-solvent was applied to

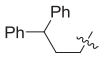


Scheme 3. Reaction toward the formation of imidazoquinoxalinone **11**. Reagents and conditions: (a) triphosgene (1.5 equiv), DMF, rt, 2 h.

circumvent this unexpected reaction pathway. To our delight, the target heterocycles were finally obtained in good yields under such reaction media (Table 4). Imidazo[4,5-*g*]quinoxalinediones **10** were rapidly prepared by this revised arrangement of which DMF-participated side reaction was suppressed while homogeneous reaction media remained. These representative examples indicate capability of diversification the highly versatile diamines **7** to intricate heterocyclic compounds.

Table 4
Diversification of diamines **7** leading to imidazo[4,5-*g*]quinoxalinediones **10**. Reagents and conditions: (a) triphosgene (1.5 equiv), DMF/CH_2Cl_2 (1:10, v/v), rt, 2 h



Entry	R^1	R^2	Product	Yield[a] (%)
1	Bn		**10a**	73
2	Bn	^{i}Bu	**10b**	78
3	Bn		**10c**	70
4	H		**10d**	68

[a] Isolated yields.

3. Conclusion

In conclusion, a divergent synthetic strategy to access a series of privileged pharmacophores consisting of quinoxalinone framework from a master scaffold was established. In corporation with the well-documented soluble polymer support phase-tagged technology with our synthetic approach provides alternative purification tactics, easy reaction monitoring, and intermediate characterization by conventional methods. It is envisaged that this concept delivers an elegant and general approach to be adopted for preparing intricate polycyclic compounds by simple operations in a parallel manner. Further elaboration of substrate scope and applying this concept to synthesize drug-like small molecules are currently under investigation in our group.

4. Experimental section

4.1. General directions

All reactions were performed under anhydrous conditions and an atmosphere of nitrogen in flame-dried glassware. PEG_{6000} polymer support was commercially supplied from Fluka. *Solvents and reagents:* All solvents were distilled before use. Commercial grade solvents used for chromatography were distilled before use. Anhydrous THF and Et_2O were distilled from sodium/benzophenone ketyl under nitrogen immediately prior to use. Anhydrous CH_2Cl_2 was distilled from CaH_2 immediately prior to use. All reagents were used as commercially supplied and used without further purification. *Chromatography*: Flash chromatography (FC) was always performed on silica gel (Merck Kieselgel 60 F_{254} 230–400 mesh) according to the method of W.C. Still.[18] Thin layer chromatography (TLC) was performed on Merck aluminum-backed plates pre-coated with silica (0.2 mm, 60 F_{254}), which were visualized either by quenching of ultraviolet fluorescence (λ_{max}=254 and 366 nm) or by charring with 10% $KMnO_4$ in 1 M H_2SO_4 or by charring with 10% $Ce(SO_4)_2$ and 15% H_2SO_4. *Microwave-assisted reaction*: All reactions involved microwave irradiation were performed by a domestic microwave oven (max output: 270 W). *Infrared spectra*: These were recorded as thin films, on a Perkin–Elmer Paragon 1000 Fourier transform spectrometer. Only selected absorbances (ν_{max}) are reported. *^{1}H NMR spectra*: These were recorded at either 300 MHz on a Bruker DRX-300 instrument. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak. Coupling constants (*J*) are reported to the nearest 0.5 Hz. *^{13}C NMR spectra*: These were recorded at 75 MHz on a Bruker DRX-300 instrument. Chemical shifts (δ_C) are quoted in parts per million, referenced to the appropriate residual solvent peak. Degenerate peaks are suffixed by the number of carbons. *Mass spectra*: Low resolution mass spectra (*m*/*z*) were recorded on either a VG platform II or VG AutoSpec spectrometers, with only molecular ions (M^+, MH^+, MNa^+) and major peaks being reported with intensities quoted as percentages of the base peak. High resolution mass spectrometry (HRMS) measurements are valid to ±5 ppm.

4.2. General procedure for purification of PEG-tagged intermediates

Reaction mixture was diluted with cold Et_2O to effect precipitation of PEG-tagged materials from the suspended solution followed by filtration. The white filter cake was collected, washed with minimal amount of ice-cold Et_2O, and dried in vacuo. The procedures were minor modified in a manner as described by Janda.[11]

4.3. General method for preparation of PEG–L-amino acid 1

*4.3.1. PEG–L-amino acids **1**.* To a solution of PEG_{6000} (loading level 0.33 mmol g^{-1}) in CH_2Cl_2 (20 mL) were added *N*-Fmoc–L-amino acids (2.4 equiv), DCC (2.4 equiv), and DMAP (0.05 equiv). The reaction mixture was irradiated in a domestic microwave oven at 270 W for 30 min before it was filtered through a plug of Celite® 501 column. The mixture was purified by *general purification procedure* to give *PEG–Fmoc–L-amino acids*.

To a stirred solution of *PEG–Fmoc–L-amino acids* in CH_2Cl_2 (10 mL) was added piperidine (1 mL). The reaction mixture was stirred at room temperature for 1 h before it was purified in accordance with the *general procedure* to afford desired *PEG–L-amino acids **1***.

4.4. Representative example for synthesis of PEG–L-valine 1a

Using *general method*, PEG_{6000} (25 g, 4.167 mmol), *N*-Fmoc–L-valine (3.39 g, 10 mmol), DCC (2.06 g, 10 mmol), and DMAP (61.1 mg, 0.5 mmol) were employed. The resulting reaction was subjected to general purification procedure to give PEG–L-valine **1a** (27.54 g, 96%).

4.5. General method for preparation of PEG-tagged master scaffold 2

To a solution of PEG–L-amino acids **1** in CH_2Cl_2 (20 mL) were added 1,5-difluoro-2,4-dinitrobenzene (2.5 equiv) and Et_3N (5.0 equiv). The reaction vessel was equipped with a condenser and was irradiated in a domestic microwave oven at 270 W for 30 min. The resulting mixture was purified by *general procedure* to afford *PEG-tagged master scaffold* **2**.

4.6. Representative example for synthesis of PEG-tag 2a

Using *general method*, PEG–L-valine **1a** (5 g, 0.753 mmol), 1,5-difluoro-2,4-dinitrobenzene (384 mg, 1.88 mmol), Et_3N (0.525 mL, 3.765 mmol) were employed. The resulting reaction was subjected to general purification procedure to afford PEG-tag **2a** (5.13 g, 85%).

4.7. General method for preparation of PEG-tags 3 and 4

A solution of PEG-tagged master scaffold **2** in CH_2Cl_2 (20 mL) was added with amino acid methyl ester HCl salts (2.5 equiv) or primary amines (5.0 equiv) along with Et_3N (5.0 equiv) when with amino acid methyl ester HCl salts was used. The resulting mixture was irradiated in a domestic microwave oven at 270 W for 30 min. The reaction mixture was purified by *general procedure* to afford *PEG-tags* ***3*** *and* ***4***.

4.8. General method for 'one-pot' traceless reductive cyclization toward pyrazino[2,3-g]quinoxalindiones 5 (Table 1)

To a stirred solution of *PEG-tags* **3** in MeOH were added Pd/C (10 wt %) and ammonium formate (20 equiv) at room temperature. The resulting mixture was refluxed for 4 h before it was filtered through a plug of Celite® 501 column and the combined organic layer was poured into ice-cold Et_2O to effect precipitation of PEG_{6000} support. The suspended solution was filtered and the combined filtration liquid was concentrated in vacuo. The resulting pale yellow oil was purified by flash column chromatography to afford *pyrazino[2,3-g]quinoxalindiones* ***5***.

*4.8.1. 3,7-Diisopropyl-1,2,8,9-tetrahydropyrazino[2,3-g]quinoxaline-2,8-dione (**5a**).* ^{1}H NMR (300 MHz, THF-d_8): δ 11.38 (s, 1H), 8.10 (s, 1H), 6.86 (s, 1H), 3.53 (septet, J=6.8 Hz, 2H), 1.31 (d, J=6.8 Hz, 12H); ^{13}C NMR (75 MHz, THF-d_8): δ 163.1, 152.8, 131.9, 127.2, 126.8, 95.9, 28.9, 18.0; IR (cm^{-1}, neat): 2967, 2869, 1681, 1457; MS (ESI-MS) m/z: 299 (MH^+); HRMS calcd for $C_{16}H_{19}N_4O_2$: m/z 299.1508; found 299.1510.

*4.8.2. 3-Isobutyl-7-isopropyl-1,2,8,9-tetrahydropyrazino[2,3-g]quinoxaline-2,8-dione (**5b**).* ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.41 (br s, 1H), 7.94 (s, 1H), 7.10 (s, 1H), 3.43 (septet, 1H), 2.65 (d, J=6.9 Hz, 2H), 2.20 (m, 1H), 1.22 (d, J=6.6 Hz, 6H), 0.93 (d, J=6.5 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.2, 165.1, 160.8, 155.7, 155.1, 133.7, 129.1, 129.0, 127.8, 99.6, 42.2, 30.8, 27.1, 23.4, 20.9; IR (cm^{-1}, neat): 2964, 2869, 1660, 1457; MS (ESI-MS) m/z: 313 (MH^+); HRMS calcd for $C_{17}H_{21}N_4O_2$: m/z 313.1664; found 313.1666.

*4.8.3. 3-Isopropyl-7-methyl-1,2,8,9-tetrahydropyrazino[2,3-g]quinoxaline-2,8-dione (**5c**).* ^{1}H NMR (300 MHz, MeOH-d_4): δ 7.94 (s, 1H), 7.11 (s, 1H), 3.43 (septet, J=6.8 Hz, 1H), 2.40 (s, 3H), 1.22 (d, J=6.8 Hz, 6H); ^{13}C NMR (75 MHz, MeOH-d_4): δ 165.2, 158.9, 155.8, 155.1, 134.0, 133.6, 129.1, 128.9, 127.6, 99.7, 30.8, 21.3, 20.9; IR (cm^{-1}, neat): 3417, 2967, 1687, 1459; MS (ESI-MS) m/z: 271 (MH^+); HRMS calcd for $C_{14}H_{15}N_4O_2$: m/z 271.1195; found 271.1197.

4.9. General method for synthesis of diamines 7

Using the *general method* for synthesis of *pyrazino[2,3-g]quinoxalindiones* ***5*** as described above, PEG-tag **4**, Pd/C (10 wt %), and ammonium formate (20 equiv) were employed. The resulting mixture was purified by flash column chromatography to give diamines **7**.

*4.9.1. 7-Amino-6-[(3-methoxypropyl)amino]-3-(2-methylpropyl)quinoxalin-2(1H)-one (**7a**).* ^{1}H NMR (300 MHz, MeOH-d): δ 7.52 (s, 1H), 6.78 (s, 1H), 4.29–4.21 (m, 1H), 3.40 (t, J=6 Hz, 2H), 3.26 (s, 3H), 2.84–2.62 (m, 5H), 1.68 (m, 1H), 1.62 (d, J=6 Hz, 6H); ^{13}C NMR (150 MHz, MeOH-d): δ 168.9, 153.7, 149.8, 139.5, 125.6, 124.5, 119.6, 110.7, 70.3, 63.3, 57.5, 38.4, 25.3, 9.2; IR (cm^{-1}, neat): 3066, 2927, 1649; MS (ESI-MS) m/z: 305 (MH^+); HRMS calcd for $C_{16}H_{24}N_4O_2$: m/z 305.1977; found 305.1980.

*4.9.2. 7-Amino-6-[(2-methoxyethyl)amino]-3-(2-methylpropyl)quinoxalin-2(1H)-one (**7b**).* ^{1}H NMR (300 MHz, MeOH-d): δ 7.60 (s, 1H), 6.85 (s, 1H), 4.88–4.28 (m, 1H), 3.45–3.32 (m, 5H), 2.91–2.71 (m, 4H), 1.70 (d, J=9 Hz, 6H); ^{13}C NMR (75 MHz, MeOH-d): δ 168.9, 153.7, 149.9, 139.4, 125.6, 124.5, 119.6, 110.7, 72.0, 63.3, 40.1, 25.3, 9.2; IR (cm^{-1}, neat): 2949, 1658; MS (ESI-MS) m/z: 291 (MH^+); HRMS calcd for $C_{15}H_{22}N_4O_2$: m/z 291.1821; found 291.1822.

*4.9.3. 7-Amino-3-(2-methylpropyl)-6-[(2-methylpropyl)amino]quinoxalin-2(1H)-one(**7c**).* ^{1}H NMR (300 MHz, MeOH-d): δ 7.60 (s, 1H), 6.85 (s, 1H), 4.37–4.30 (m, 2H), 2.91–2.73 (m, 4H), 1.71–1.60 (m, 12H); ^{13}C NMR (75 MHz, MeOH-d): δ 169.3, 154.1, 150.3, 139.8, 126.0, 124.9, 120.0, 111.1, 63.7, 29.0, 25.7, 19.2, 9.6; IR (cm^{-1}, neat): 2924, 2856, 1657; MS (ESI-MS) m/z: (MH^+); HRMS calcd for $C_{16}H_{24}N_4O$: m/z 288.1950; found 288.1953.

*4.9.4. 7-Amino-3-(2-methylpropyl)-6-(propan-2-ylamino)quinoxalin-2(1H)-one (**7d**).* ^{1}H NMR (300 MHz, MeOH-d): δ 7.60 (s, 1H), 6.85 (s, 1H), 4.35–4.30 (m, 1H), 3.08–3.03 (m, 1H), 2.91–2.70 (m, 2H), 1.70 (d, J=9 Hz, 6H), 1.09 (d, J=6 Hz, 6H); ^{13}C NMR (75 MHz, MeOH-d): δ 169.3, 154.1, 150.3, 139.8, 126.0, 124.9, 120.0, 111.1, 63.7, 43.4, 25.7, 21.8, 9.6; IR (cm^{-1}, neat): 2931, 2856, 1655; MS (ESI-MS) m/z: 275 (MH^+); HRMS calcd for $C_{15}H_{22}N_4O$: m/z 275.1872; found 275.1873.

*4.9.5. 7-Amino-6-(cyclopentylamino)-3-(2-methylpropyl)quinoxalin-2(1H)-one (**7e**).* ^{1}H NMR (600 MHz, MeOH-d): δ 7.57 (s, 1H), 6.82 (s, 1H), 4.31–4.27 (m, 1H), 3.44 (t, J=6 Hz, 2H), 3.30–3.29 (m, 1H), 2.86 (t, J=6 Hz, 2H), 2.71–2.68 (m, 2H), 1.67 (d, J=6 Hz, 6H); ^{13}C NMR (75 MHz, MeOH-d): δ 169.3, 154.1, 150.3, 139.8, 126.0, 124.9, 120.0, 111.1, 63.7, 33.6, 25.7, 25.3, 23.8, 9.6; IR (cm^{-1}, neat): 2924, 2854, 1645; MS (ESI-MS) m/z: 301 (MH^+); HRMS calcd for $C_{17}H_{24}N_4O$: m/z 301.2028; found 301.2029.

*4.9.6. 7-Amino-3-(propan-2-yl)-6-(propan-2-ylamino)quinoxalin-2(1H)-one (**7f**).* ^{1}H NMR (300 MHz, DMSO-d): δ 10.64 (s, 1H), 7.11 (s, 1H), 6.79 (s, 1H), 6.20 (s, 1H), 2.08–1.86 (m, 1H), 1.23–1.21 (m, 1H), 1.16 (d, J=6 Hz, 6H), 0.93 (d, J=6 Hz, 3H), 0.85 (d, J=6 Hz, 3H); ^{13}C NMR (75 MHz, MeOH-d): δ 169.4, 154.1, 150.3, 139.8, 126.0, 124.9, 120.0, 111.1, 63.7, 24.3, 20.3; IR (cm^{-1}, neat): 2924, 2854, 1649; MS (ESI-MS) m/z: 261 (MH^+); HRMS calcd for $C_{14}H_{20}N_4O$: m/z 261.1715; found 261.1713.

*4.9.7. 7-Amino-6-[(2-methoxyethyl)amino]-3-methylquinoxalin-2(1H)-one (**7g**).* ^{1}H NMR (300 MHz, DMSO-d): δ 7.60 (s, 1H), 6.86 (s, 1H), 3.36 (s, 3H), 2.89–2.71 (m, 4H), 2.17 (s, 3H); ^{13}C NMR (150 MHz, MeOH-d): δ 168.9, 153.7, 149.9, 139.4, 125.6, 124.5, 119.6, 110.7, 70.3, 57.5, 38.4, 30.8; IR (cm^{-1}, neat): 2922, 2852, 1676; MS (ESI-MS) m/z: (MH^+); HRMS calcd for $C_{12}H_{16}N_4O_2$: m/z 248.1273; found 248.1270.

4.10. Synthesis of thioxoimidazo[4,5-g]quinoxalinones 8 (Table 2)

To a stirred solution of diamine **7** in DMF (5 mL) was added 1,1′-thiocarbonyldiimidazole (1.5 equiv) at room temperature. The reaction mixture was warmed to 100 °C for 2 h before it was diluted with Et_2O (20 mL) and washed with brine (2×5 mL). The combined organic layer was dried over $MgSO_4$ and contracted in vacuo. The

resulting pale yellow oil was purified by flash column chromatography to furnish *thioxoimidazo[4,5-g]quinoxalinones* ***8***.

*4.10.1. 7-Isobutyl-1-(3-methoxypropyl)-2-thioxo-2,3-dihydro-1H-imidazo[4,5-g]quinoxalin-6(5H)-one (**8a**).* ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.44 (s, 1H), 6.96 (s, 1H), 4.18–4.12 (m, 2H), 3.26 (t, 2H), 3.13 (s, 3H), 2.51 (d, J=5.8 Hz, 2H), 2.06 (m, 1H), 1.94–1.81 (m, 2H), 0.81 (d, J=6.4 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.7, 159.6, 155.5, 132.8, 130.7, 129.3, 128.8, 107.8, 95.2, 69.5, 58.5, 42.1, 41.5, 28.0, 27.1, 23.2; IR (cm^{-1}, neat): 3089, 2956, 2869, 1660, 1467; MS (ESI-MS) m/z: 347 (MH$^+$); HRMS calcd for $C_{17}H_{23}N_4O_2S$: m/z 347.1542; found 347.1540.

*4.10.2. 7-Isobutyl-1-(2-methoxyethyl)-2-thioxo-2,3-dihydro-1H-imidazo[4,5-g]quinoxalin-6(5H)-one (**8b**).* ^{1}H NMR (300 MHz, DMF-d_7): δ 12.97 (s, 1H), 12.30 (s, 1H), 7.94 (s, 1H), 7.44 (s, 1H), 4.74 (t, J=5.4 Hz, 2H), 4.00 (t, J=5.37 Hz, 2H), 3.49 (s, 3H), 2.90 (d, J=7.1 Hz, 2H), 2.49 (m, 1H), 1.16 (d, J=6.6 Hz, 6H); ^{13}C NMR (75 MHz, DMF-d_7): δ 171.9, 159.9, 155.5, 133.1, 131.5, 130.1, 129.2, 109.0, 94.9, 70.3, 58.8, 44.5, 42.3, 27.2, 22.9; IR (cm^{-1}, neat): 3417, 2956, 1664, 1417; MS (EI) m/z: 332 (M$^+$); HRMS calcd for $C_{16}H_{20}N_4O_2S$: m/z 332.1307; found 332.1306.

*4.10.3. 1,7-Diisobutyl-2-thioxo-2,3-dihydro-1H-imidazo[4,5-g]quinoxalin-6(5H)-one (**8c**).* ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.88 (s, 1H), 12.31(s, 1H), 7.71 (s, 1H), 7.04 (s, 1H), 4.06 (d, J=7.5 Hz, 2H), 2.62 (d, J=7.0 Hz, 2H), 2.18 (m, 1H), 2.32 (m, 1H), 0.88 (t, J=6.5 Hz, 12H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.4, 159.8, 155.5, 132.8, 131.1, 129.6, 128.9, 108.6, 95.0, 51.1, 42.3, 27.9, 27.1, 23.4, 20.6; IR (cm^{-1}, neat): 3411, 2958, 2869, 2658, 1467; MS (EI) m/z: 330 (M$^+$); HRMS calcd for $C_{17}H_{22}N_4OS$: m/z 330.1514; found 330.1524.

*4.10.4. 7-Isobutyl-1-isopropyl-2-thioxo-2,3-dihydro-1H-imidazo[4,5-g]quinoxalin-6(5H)-one (**8d**).* ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.89 (s, 1H), 12.29 (s, 1H), 7.79 (s, 1H), 7.03 (s, 1H), 5.41 (septet, J=5.5 Hz, 1H), 2.70 (d, J=5.8 Hz, 2H), 2.23 (m, 1H), 1.53 (d, J=5.5 Hz, 6H), 0.93 (d, J=5.8 Hz, 6H); ^{13}C (NMR 75 MHz, DMSO-d_6): δ 170.3, 159.9, 155.5, 133.3, 129.5, 128.6, 128.4, 109.3, 95.2, 48.5, 42.3, 27.3, 23.4, 20.1; IR (cm^{-1}, neat): 2952, 2850, 1633, 1461; MS (ESI-MS) m/z: 317 (MH$^+$); HRMS calcd for $C_{16}H_{21}N_4OS$: m/z 317.1436; found 317.1434.

*4.10.5. 1-Cyclopentyl-7-isobutyl-2-thioxo-2,3-dihydro-1H-imidazo[4,5-g]quinoxalin-6(5H)-one (**8e**).* ^{1}H NMR (300 MHz, DMF-d_7): δ 12.98 (s, 1H), 12.28 (s, 1H), 7.77 (s, 1H), 7.45 (s, 1H), 2.87 (d, J=6.2 Hz, 2H), 2.53–1.90 (m, 10H), 1.14 (d, J=5.8 Hz, 6H); ^{13}C NMR (75 MHz, DMF-d_7): δ 171.9, 160.0, 155.5, 133.6, 129.9, 128.9, 128.4, 109.0, 95.4, 57.0, 42.5, 28.5, 27.2, 25.5, 23.0; IR (cm^{-1}, neat): 3417, 2952, 2852, 1654, 1461; MS (ESI-MS) m/z: 343 (MH$^+$); HRMS calcd for $C_{18}H_{22}N_4OS$: m/z 342.1514; found 342.1511.

*4.10.6. 1,7-Diisopropyl-2-thioxo-2,3-dihydro-1H-imidazo[4,5-g]quinoxalin-6(5H)-one (**8f**).* ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.85 (s, 1H), 12.24 (s, 1H), 7.76 (s, 1H), 7.04 (s, 1H), 5.40 (septet, J=7.0 Hz, 1H), 3.42 (septet, J=6.8 Hz, 1H), 1.52 (d, J=6.9 Hz, 6H), 1.20 (d, J=6.8 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.4, 164.1, 154.8, 133.3, 129.4, 128.5, 128.4, 109.4, 95.1, 48.5, 30.7, 20.9, 20.2; IR (cm^{-1}, neat): 2962, 2815, 1633, 1463; MS (ESI-MS) m/z: 303 (MH$^+$); HRMS calcd for $C_{15}H_{19}N_4OS$: m/z 303.1280; found 303.1282.

*4.10.7. 1-(2-Methoxyethyl)-7-methyl-2-thioxo-2,3-dihydro-1H-imidazo[4,5-g]quinoxalin-6(5H)-one (**8g**).* ^{1}H NMR (300 MHz, DMF-d_7): δ 12.98 (s, 1H), 12.30 (s, 1H), 7.91 (s, 1H), 7.43 (s, 1H), 4.74 (t, J=5.4 Hz, 2H), 4.00 (t, J=5.4 Hz, 2H), 3.49 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (75 MHz, DMF-d_7): δ 171.8, 157.7, 155.6, 133.0, 131.5, 130.3, 129.2, 108.9, 95.0, 70.3, 58.8, 44.5, 20.7; IR (cm^{-1}, neat): 3413, 2923, 2852, 1662, 1467; MS (FABMS) m/z: 291 (MH$^+$); HRMS calcd for $C_{13}H_{14}N_4O_2S$: m/z 290.0837; found 290.0833.

4.11. Synthesis of imidazoquinoxalinones 9 (Table 3)

To a solution of diamine **7** in DMF (5 mL) were added organic halides (2.0 equiv) and Et_3N (5.0 equiv) at room temperature. The reaction mixture was stirred at such temperature for 2 h before it was diluted with Et_2O (20 mL) and washed with brine (2×5 mL). The combined organic layer was dried over $MgSO_4$ and contracted in vacuo. The resulting pale yellow oil was purified by flash column chromatography to furnish *thioxoimidazo imidazoquinoxalinones* ***9***.

*4.11.1. 2-(Allylthio)-1-butyl-7-isobutyl-1H-imidazo[4,5-g]quinoxalin-6(5H)-one (**9a**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.39 (s, 1H), 7.71 (s, 1H), 7.62 (s, 1H), 6.08 (m, 1H), 5.43 (dd, J=16.9, 1.3 Hz, 1H), 5.25 (dd, J=9.9, 0.9 Hz, 1H), 4.15 (t, J=6.8 Hz, 2H), 2.95 (d, J=6.0 Hz, 2H), 2.42 (m, 1H), 1.93–1.81 (m, 2H), 1.50–1.37 (m, 2H), 1.08 (d, J=6.6 Hz, 6H), 0.98 (t, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 157.1, 156.5, 145.1, 134.6, 132.8, 129.7, 127.9, 119.5, 107.6, 103.0, 44.8, 42.6, 35.6, 31.6, 27.6, 23.2, 20.6, 14.1; IR (cm^{-1}, neat): 2954, 2869, 1660, 1440; MS (EI) m/z: 370 (M$^+$); HRMS calcd for $C_{20}H_{26}N_4OS$: m/z 370.1827; found 370.1830.

*4.11.2. 7-Isobutyl-1-(3-methoxypropyl)-2-(methylthio)-1H-imidazo[4,5-g]quinoxalin-6(5H)-one (**9b**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.19 (s, 1H), 7.75 (s, 1H), 7.62 (s, 1H), 4.26 (d, J=6.9 Hz, 2H), 3.39 (t, J=5.7 Hz, 2H), 3.36 (s, 3H), 2.89 (t, J=7.3 Hz, 2H), 2.87 (s, 3H), 2.45–2.36 (m, 1H), 2.18–2.06 (m, 2H), 1.07 (d, J=6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 157.9, 157.0, 144.7, 134.8, 129.7, 128.0, 107.7, 102.7, 69.1, 59.1, 42.5, 41.7, 29.5, 41.7, 29.5, 27.5, 23.2, 15.0; IR (cm^{-1}, neat): 2950, 2825, 1668, 1448; MS (ESI-MS) m/z: 361 (MH$^+$); HRMS calcd for $C_{18}H_{25}N_4O_2S$: m/z 361.1698; found 361.1695.

*4.11.3. 2-(Allylthio)-7-isobutyl-1-(2-methoxyethyl)-1H-imidazo[4,5-g]quinoxalin-6(5H)-one (**9c**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.82 (s, 1H), 7.77 (s, 1H), 7.59 (s, 1H), 6.06 (m, 1H), 5.41 (dd, J=16.9, 1.2 Hz, 1H), 5.21 (d, J=9.9 Hz, 1H), 4.34 (t, J=5.6 Hz, 2H), 4.12 (d, J=7.0 Hz, 2H), 3.76 (t, J=5.5 Hz, 2H), 3.34 (s, 3H), 2.89 (d, J=7.1 Hz, 2H), 2.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 156.8, 156.7, 144.7, 134.7, 132.8, 129.8, 128.1, 119.6, 108.2, 102.8, 70.6, 59.6, 45.0, 42.6, 35.8, 27.6, 23.2; IR (cm^{-1}, neat): 2954, 2877, 1652, 1444; MS (ESI-MS) m/z: 373 (MH$^+$); HRMS calcd for $C_{19}H_{25}N_4O_2S$: m/z 373.1698; found 373.1697.

*4.11.4. 7-Isobutyl-1-isopropyl-2-(3-methylbut-2-enylthio)-1H-imidazo[4,5-g]quinoxalin-6(5H)-one (**9d**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.40 (s, 1H), 7.87 (s, 1H), 7.60 (s, 1H), 5.44 (m, 1H), 4.73 (m, 1H), 4.10 (d, J=7.9 Hz, 2H), 2.39 (d, J=7.2 Hz, 2H), 2.40 (m, 1H), 1.90–1.75 (m, 6H), 1.69 (d, J=6.9 Hz, 6H), 1.15 (d, J=6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 157.1, 156.9, 145.8, 139.3, 132.6, 129.3, 127.7, 117.9, 109.6, 102.9, 49.5, 42.6, 31.6, 27.5, 26.2, 23.1, 21.7, 18.5; IR (cm^{-1}, neat): 2954, 2856, 1656, 1461; MS (EI) m/z: 384 (M$^+$); HRMS calcd for $C_{21}H_{28}N_4OS$: m/z 384.1984; found 384.1964.

*4.11.5. 1-Cyclopentyl-2-(4-fluorobenzylthio)-7-isobutyl-1H-imidazo[4,5-g]quinoxalin-6(5H)-one (**9e**).* ^{1}H NMR (300 MHz, DMF-d_7): δ 12.31 (s, 1H), 8.07 (s, 1H), 7.82 (m, 2H), 7.75 (s, 1H), 7.35 (m, 2H), 5.12 (quintet, J=8.6 Hz, 1H), 4.93 (s, 2H), 2.93 (d, J=6.6 Hz, 2H), 2.55–2.18 (m, 9H), 1.16 (d, J=6.6 Hz, 6H); ^{13}C NMR (75 MHz, DMF-d_7): δ 132.9, 159.9, 156.2, 155.6, 145.6, 134.4, 132.6, 131.9, 131.8, 129.1, 129.0, 116.1, 115.8, 109.6, 102.6, 57.9, 42.5, 35.9, 29.5, 27.2, 25.3, 23.0; IR (cm^{-1}, neat): 3318, 2952, 2869, 1652, 1442; MS (ESI-MS) m/z: 451

(MH^+); HRMS calcd for $C_{25}H_{27}FN_4OS$: *m*/*z* 451.1968; found 451.1966.

*4.11.6. (E)-2-(3,7-Dimethylocta-2,6-dienylthio)-1,7-diisopropyl-1H-imidazo[4,5-g]quinoxalin-6(5H)-one (**9f**).* ^1H NMR (300 MHz, $CDCl_3$): δ 12.27 (s, 1H), 7.87 (s, 1H), 7.63 (s, 1H), 5.46 (t, *J*=7.9 Hz, 1H), 5.09 (m, 1H), 4.74 (septet, *J*=6.9 Hz, 1H), 4.14 (d, *J*=7.9 Hz, 2H), 3.69 (septet, *J*=6.9 Hz, 1H), 2.12–2.08 (m, 4H), 1.79 (s, 3H), 1.69 (d, *J*=6.9 Hz, 6H), 1.68 (s, 3H), 1.61 (s, 3H), 1.39 (d, *J*=6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8, 156.7, 156.4, 145.4, 142.9, 142.3, 132.5, 132.2, 129.4, 127.6, 124.1, 117.6, 109.8, 102.8, 49.6, 40.0, 31.6, 31.0, 26.8, 26.1, 21.3, 20.5, 18.1, 16.8; IR (cm^{-1}, neat): 2971, 2869, 1660, 1440; MS (ESI-MS) *m*/*z*: 439 (MH^+); HRMS calcd for $C_{25}H_{35}N_4OS$: *m*/*z* 439.2531; found 439.2528.

*4.11.7. 2-(Allylthio)-1-(2-methoxyethyl)-7-methyl-1H-imidazo[4,5-g]quinoxalin-6(5H)-one (**9g**).* ^1H NMR (300 MHz, $CDCl_3$): δ 12.31 (s, 1H), 7.71 (s, 1H), 7.59 (s, 1H), 6.06 (m, 1H), 5.40 (d, *J*=16.9 Hz, 1H), 5.21 (d, *J*=10.0 Hz, 1H), 4.30 (t, *J*=5.3 Hz, 2H), 4.10 (d, *J*=6.9 Hz, 2H), 3.74 (t, *J*=5.4 Hz, 2H), 3.32 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.0, 156.9, 156.8, 144.9, 134.9, 132.8, 129.7, 128.1, 119.6, 107.9, 103.0, 70.7, 59.6, 44.9, 35.7, 21.2; IR (cm^{-1}, neat): 2884, 1659, 1444; MS (ESI-MS) *m*/*z*: 331 (MH^+); HRMS calcd for $C_{16}H_{19}N_4O_2S$: *m*/*z* 331.1229; found 331.1226.

4.12. Preparation of imidazo[4,5-*g*]quinoxalinediones 10 (Table 4)

To a solution of diamine **7** in a mixed solvent of DMF/CH_2Cl_2 (1:10, v/v; 5 mL) was added triphosgene (1.5 equiv) at room temperature. The reaction mixture was stirred at such temperature for 2 h before it was diluted with Et_2O (20 mL) and washed with brine (2×5 mL). The combined organic layer was dried over $MgSO_4$ and contracted in vacuo. The resulting pale yellow oil was purified by flash column chromatography to furnish *thioxoimidazo imidazo[4,5-g]quinoxalinediones **10***.

*4.12.1. 7-Benzyl-1-(2-methoxyethyl)-1H-imidazo[4,5-g]quinoxaline-2,6(3H,5H)-dione (**10a**).* ^1H NMR (300 MHz, DMF-d_7): δ 12.34 (s, 1H), 11.37 (s, 1H), 7.67 (s, 1H), 7.63–7.36 (m, 5H), 7.28 (s, 1H), 4.34 (s, 2H), 4.28 (t, *J*=5.3 Hz, 2H), 3.89 (t, *J*=5.2 Hz, 2H), 3.47 (s, 3H); ^{13}C NMR (75 MHz, DMF-d_7): δ 157.4, 155.7, 155.3, 139.0, 132.0, 129.8, 129.2, 129.1, 128.9, 128.2, 126.9, 107.2, 94.8, 70.5, 58.6, 41.1, 39.9; IR (cm^{-1}, neat): 2919, 1710, 1637, 1488; MS (ESI-MS) *m*/*z*: 351 (MH^+); HRMS calcd for $C_{19}H_{19}N_4O_3$: *m*/*z* 351.1457; found 351.1460.

*4.12.2. 7-Benzyl-1-isobutyl-1H-imidazo[4,5-g]quinoxaline-2,6(3H,5H)-dione (**10b**).* ^1H NMR (300 MHz, DMSO-d_6): δ 7.35 (s, 1H), 7.28–7.12 (m, 5H), 3.57 (d, *J*=7.2 Hz), 2.04 (m, 1H), 0.81 (d, *J*=6.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.2, 156.0, 155.4, 138.3, 131.4, 129.7, 129.2, 129.0, 128.4, 127.9, 127.2, 106.7, 95.2, 48.2, 27.9, 20.4; IR (cm^{-1}, neat): 3440, 2960, 1702, 1660, 1484; MS (ESI-MS) *m*/*z*: 349 (MH^+); HRMS calcd for $C_{20}H_{21}N_4O_2$: *m*/*z* 349.1664; found 349.1662.

*4.12.3. 7-Benzyl-1-(3,3-diphenylpropyl)-1H-imidazo[4,5-g]quinoxaline-2,6(3H,5H)-dione (**10c**).* ^1H NMR (300 MHz, DMSO-d_6): δ 12.31 (s, 1H), 11.16 (s, 1H), 7.29–7.09 (m, 16H), 6.85 (s, 1H), 4.04 (s, 2H), 3.99 (t, *J*=7.5 Hz, 2H), 3.71 (t, *J*=6.8 Hz, 1H), 2.38 (dt, *J*=7.5, 6.8 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.9, 157.1, 155.4, 145.1, 138.6, 131.6, 129.9, 129.3, 129.2, 128.5, 128.4, 128.3, 127.9, 127.1. 127.0, 106.5, 95.0, 48.9, 39.9, 39.5, 33.6; IR (cm^{-1}, neat): 2958, 1716, 1644, 1488; MS (ESI-MS) *m*/*z*: 487 (MH^+); HRMS calcd for $C_{31}H_{26}N_4O_2$: *m*/*z* 487.2134; found 487.2137.

*4.12.4. 1-((Tetrahydrofuran-2-yl)methyl)-1H-imidazo[4,5-g]quinoxaline-2,6(3H,5H)-dione (**10d**).* ^1H NMR (300 MHz, DMSO-d_6): δ 12.32 (s, 1H), 11.23 (s, 1H), 8.00 (s, 1H), 7.51 (s, 1H), 6.88 (s, 1H), 4.19–4.15 (m, 1H), 1.87 (d, *J*=5.5 Hz, 2H), 3.73–3.59 (m, 2H), 1.98–1.60 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.0, 155.7, 148.3, 132.5, 129.2, 128.8, 128.4, 108.0, 94.9, 77.4, 68.1, 45.2, 29.2, 26.0; IR (cm^{-1}, neat): 2925, 2857, 1729, 1691, 1494; MS (ESI-MS) *m*/*z*: 287 (MH^+); HRMS calcd for $C_{14}H_{15}N_4O_3$: *m*/*z* 287.1144; found 287.1145.

4.13. 1,7-Diisopropyl-1*H*-imidazo[4,5-*g*]quinoxalin-6(5*H*)-one (11)

To a stirred solution of diamine **7a** (53 mg, 0.204 mmol) in DMF (5 mL) was added triphosgene (90.6 mg, 0.305 mmol) at room temperature. The reaction mixture was stirred at such temperature for 2 h before it was diluted with Et_2O (20 mL) and washed with brine (2×5 mL). The combined organic layer was dried over $MgSO_4$ and contracted in vacuo. The resulting pale yellow oil was purified by flash column chromatography to furnish *1,7-diisopropyl-1H-imidazo[4,5-g]quinoxalin-6(5H)-one **11*** (46.5 mg, 85%) as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ 12.70 (s, 1H), 8.18 (s, 1H), 7.88 (s, 1H), 7.81 (s, 1H), 4.68 (septet, *J*=6.6 Hz, 1H), 3.68 (septet, *J*=6.8 Hz, 1H), 1.65 (d, *J*=6.7 Hz, 6H), 1.36 (d, *J*=6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.7, 156.3, 145.2, 144.2, 131.3, 130.5, 128.2, 109.7, 104.9, 48.7, 31.0, 22.9, 20.7; IR (cm^{-1}, neat): 3041, 2973, 1668, 1492; MS (ESI-MS) *m*/*z*: 271 (MH^+); HRMS calcd for $C_{15}H_{19}N_4O$: *m*/*z* 271.1559; found 271.1557.

Acknowledgements

The authors thank the National Science Council of Taiwan for the financial assistance and the authorities of the National Chiao Tung University for providing the laboratory facilities. This paper is particularly supported by 'Aim for the Top University Plan' of the National Chiao Tung University and Ministry of Education, Taiwan, R.O.C.

Supplementary data

Supplementary data related to this article can be found in the online version, at doi:10.1016/j.tet.2012.03.015.

References and notes

1. (a) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449–472; (b) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529–2591.
2. (a) Carta, A.; Piras, S.; Loriga, G.; Paglietti, G. *Mini-Rev. Med. Chem.* **2006**, *6*, 1179–1200; (b) Li, X.; Yang, K. H.; Li, W. I.; Xu, W. F. *Drugs Future* **2006**, *31*, 979–989.
3. Li, Y.; Zhang, J.; Xu, W.; Zhu, H.; Li, X. *Bioorg. Med. Chem.* **2010**, *18*, 1516–1525.
4. Hirai, H.; Takahashi-Suziki, I.; Shimomura, T.; Fukasawa, K.; Machida, T.; Takaki, T.; Kobayashi, M.; Eguchi, T.; Oki, H.; Arai, T.; Ichikawa, K.; Hasako, S.; Kodera, T.; Kawanishi, N.; Nakatsuru, Y.; Kotani, H.; Iwasawa, Y. *Invest. New Drugs* **2011**, *29*, 534–543.
5. (a) Udilova, N.; Kozlov, A. V.; Bieberschulte, W.; Frei, K.; Ehrenberger, K.; Nohl, H. *Biochem. Pharmacol.* **2003**, *65*, 59–65; (b) Nohl, H.; Bieberschulte, W.; Dietrich, B.; Udilova, N.; Kozlov, A. V. *Biofactors* **2003**, *19*, 79–85.
6. Tang, P. C.; Sun, M. L. U.S. Patent 6,329,375B, 2001.
7. (a) Nicolaou, K. C.; Hanko, R.; Hartwig, W. *Handbook of Combinatorial Chemistry*; Wiley-VCH: Weinheim, 2002; (b) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74–84; (c) Patil, S. A.; Patil, R.; Miller, D. D. *Curr. Med. Chem.* **2009**, *16*, 2531–2565.
8. (a) Catarzi, D.; Colotta, V.; Varano, F.; Calabri, F. R.; Filacchioni, G.; Galli, A.; Costagli, C.; Carlà, V. *J. Med. Chem.* **2003**, *47*, 262–272; (b) Guo, W.; Hsieh, C. Y.; Huang, W.; Liu, R.; Lam, K. S.; Kung, H. J.; Song, A. Imidazoquinoxalinones for anti-tumor treatment. WO2011017219A1, 2011.
9. (a) Kou, B. B.; Zhang, F.; Yang, T. M.; Liu, G. *J. Comb. Chem.* **2006**, *8*, 841–847; (b) Lv, M.; Xu, H. *Comb. Chem. High Throughput Screen.* **2010**, *13*, 293–301.
10. (a) Zhang, W. *Tetrahedron* **2003**, *59*, 4475–4489; (b) Zhang, W. *Chem. Rev.* **2004**, *104*, 2531–2556; (c) Lin, M. J.; Zhang, W.; Sun, C. M. *J. Comb. Chem.* **2007**, *9*, 951–958.
11. Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539–2544.

12. Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489–510.
13. Harris, J. M. *Poly(ethylene glycol) Chemistry: Biotechnical and Biomedical Applications*; Plenum: New York, NY, 1992.
14. (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284; (b) Oliver Kappe, C. *Chem. Soc. Rev.* **2008**, *37*, 1127–1139.
15. Kappa, C. O.; Dallinger, D. *Nat. Rev. Drug Discov.* **2006**, *5*, 51–63.
16. (a) Chou, C. T.; Yellol, G. S.; Chang, W. J.; Sun, M. L.; Sun, C. M. *Tetrahedron* **2011**, *67*, 2110–2117; (b) Thummanagoti, S.; Chen, C. H.; Xu, Z. H.; Sun, C. M. *Mol. Divers.* **2011**, *15*, 101–107.
17. Su, W. K.; Zhong, W. H.; Bian, G. F.; Shi, X. J.; Zhang, J. P. *Org. Prep. Proced. Int.* **2004**, *36*, 499–547.
18. Still, W. C.; Kahn, M.; Mitra, M. *J. Org. Chem.* **1978**, *43*, 2923–2925.