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Microwave Controlled Reductive Cyclization: A Selective Synthesis of Novel Benzimidazole-alkyloxypyrrolo[1,2-*a*]quinoxalinones

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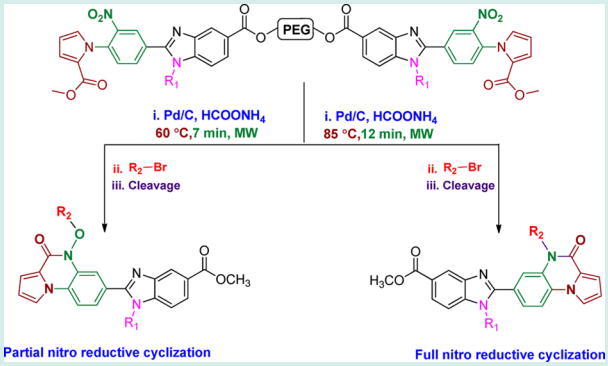
Supporting Information

ABSTRACT: An efficient cascade synthesis of novel benzimidazole linked alkyloxypyrrolo[1,2-*a*]quinoxalinones was explored on soluble polymer support under microwave irradiation. Two exclusive protocols have been developed for the partial and full reductive cyclization by controlling the microwave energy. Commencing from the same substrate, ortho nitro pyrrol carboxylates, *N*-hydroxy pyrroloquinoxalinones were obtained by partial reductive cyclization (60 °C, 7 min), and the synthesis of pyrroloquinoxalinones was accomplished by full reductive cyclization (85 °C, 12 min). This method represents the first synthesis of *N*-hydroxy pyrroloquinoxalinones using Pd/C and ammonium formate as reducing agents. Further employing a variety of alkyl bromides, the obtained pyrroloquinoxalinones were transformed to their corresponding O- and N-alkylated analogues to deliver the diversified, novel molecular entities.



KEYWORDS: *polymer supported, microwave-assisted, pyrroloquinoxalinones, reductive cyclization*

INTRODUCTION

Diversified and highly functionalized heterocyclic small molecules have tremendous importance in drug discovery owing to their unique and selective binding abilities for the biological targets with respect to their chemical functionalizations.[1] Among many nitrogen-containing privileged class of heterocyclic molecules, highly substituted benzimidazoles, such as omeprazole, a proton pump inhibitor **A** and Veliparib (ABT-888), a PARP inhibitor **B** are considered to be the important therapeutic scaffolds.[2,3] As shown in Figure 1, substituted *N*-hydroxy/lactam ring fused pyrrolo[1,2-*a*]quinoxalinones are key components for the congregation of numerous valuable heterocycles including KAT II inhibitor **C**, anti-HIV agent **D**, and adenosine A3 receptor modulator **E**.[4,5]

In view of their therapeutic significance, it is highly challenging and interesting to design a chimeric, novel biheterocylic scaffolds containing these diversified privileged structures.[6] Combination of these heterocyclic cores may increase the structural complexity of designed molecules, which may display different biological properties from the parent molecule. In this respect, the amalgamation of two or more heterocyclic cores has drawn substantial attention in medicinal chemistry.[7] Earlier, we successfully accomplished the assembly of benzimidazole linked privileged heterocycles including benzodiazapines, benzothiazole, benzoxazole, imidazo pyridines.[8] In continuation of our earlier studies, the present article describes the conglomeration of three important heterocyclic moieties, such as benzimidazole, cyclic hydroxamic acid, and pyrrolo[1,2-*a*]quinoxalinone as illustrated in Figure 1.

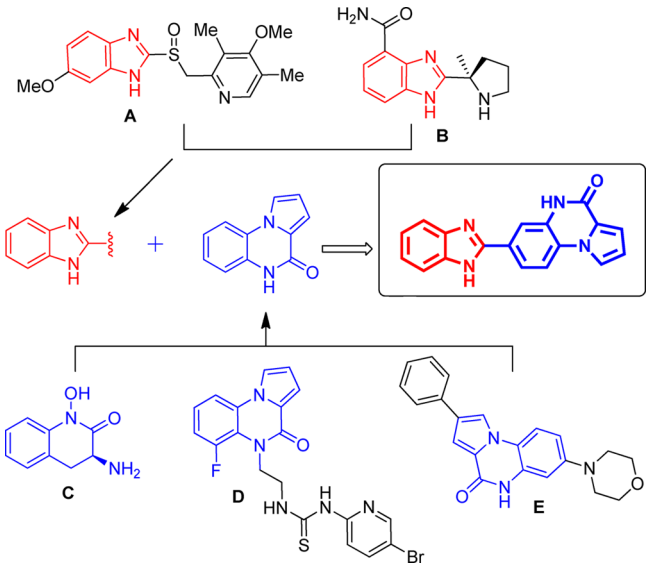


Figure 1. Design concept of the present molecular library.

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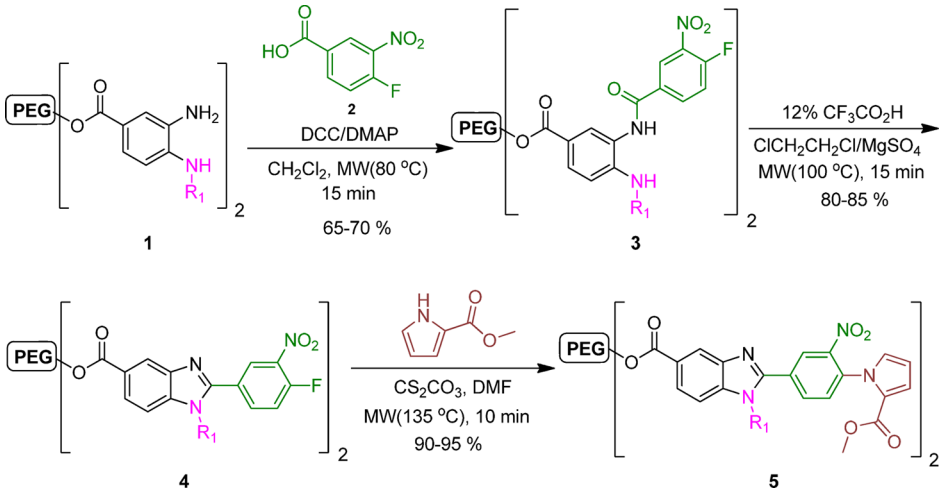
Scheme 1. Synthesis of Common Building Block 5



In general, the hydroxamic acid core is synthesized in three different ways namely oxidative cyclization, palladium catalyzed coupling and reductive cyclization.[9−11] In these methods, the substrate requires specific electronic and structural properties to furnish the desired products. Reductive cyclization is an efficient method to access lactams. Many reducing agents such as Pd/C-hydrazine, enzymes, H_2−Pt/C and zinc/ammonium chloride have been reported for the reduction of nitro groups to hydroxyl amines.[12−14] One challenge associated with these protocols is the over reduction to lactam ring. In particular, electron rich ortho substituted groups tend to furnish the lactam by eliminating the hydroxy group of the hydroxyl amine. Hence, the development of mild and controlled methods to obtain hydroxamic acids selectively is highly desirable. Recently, McAllister and co-workers demonstrated an efficient synthesis of *N*-arylhydroxamic acid by partial nitro reduction using $SnCl_2$/NaOAc. Similarly, the existing methods to obtain pyrrolo[1,2-*a*]quinoxalinone is limited.[15,16] In this report, polyethylene glycol (PEG 4000) was used as a soluble polymer support for the synthesis of the target molecules under microwave irradiation.[17] The PEG support is not only to provide homogeneous reaction conditions, but is also stable to furnish polar medium for efficient microwave enhancement.[18] Notably, this combined synthetic protocol remarkably reduces the reaction time, enhances the yields, and in turn may greatly accelerate the drug discovery process. Hence, as part of our continuous effort on the synthesis of novel biheterocycles; herein, we report a selective and reductive synthesis of pyrrolo[1,2-*a*]quinoxalinones by tuning microwave energy.

RESULTS AND DISCUSSION

As shown in Scheme 1, our synthetic strategy is commenced with the preparation of polymer immobilized key building block **5**, which is a building block to obtain benzimidazole linked pyrrolo[1,2-*a*]quinoxalinones. Sequential polymer immobilization of 4-fluoro-3-nitro benzoic acid, nucelophilic substitution with various amines and nitro reduction furnished orthophenylenediamines **1**.[19] The obtained diamines were coupled with 4-fluoro-3-nitro benzoic acid **2** through an amide linkage, which further underwent intramolecular nucleophilic addition followed by elimination of water to afford privileged benzimidazole core **4** when it was treated with catalytic TFA in dichloroethane. All these reactions were performed under microwave irradiation conditions.

The next task is the introduction of pyrrole ring via S_NAr reaction which has limited examples owing to the less-reactive pyrroles. After optimization studies, the desired benzimidazole linked methyl 1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxylate **5** was obtained in 10 min under microwave irradiation (135 °C) in 95% yield using Cs_2CO_3 as a base in DMF.[20] For comparison, the same S_NAr reaction took 18 h for completion under traditional reflux conditions. It is noteworthy to mention that the S_NAr reaction with pyrrole-2-carboxylate did not cleave the polymer support under these harsh, microwave conditions and the C−N bond formation is achieved without the use of any metal catalysts or ligands. With this key intermediate in hand, a reductive cyclization strategy was employed as a key transformation to furnish the designed chimeric heterocyclics. We report herein two distinct approaches toward the selective reductive cyclization of substituted nitro anilines using Pd/C and ammonium formate in methanol (Scheme 2). At first, we aimed to produce pyrroloquinoxalinones **6′** via reductive cylization which was obtained in 82% yield at room temperature for 10 h using Pd/C and ammonium formate as hydrogen source. To enrich the synthetic efficiency, the same reaction was performed under microwave irradiation at 70 °C for 10 min which resulted in the formation of mixture of products, one of them was identified as *N*-hydroxy pyrroloquinoxalinones **6** along with the desired pyrroloquinoxalinones **6′**. It is understood that the formation of *N*-hydroxy pyrroloquinoxalinones resulted from the partial reduction of a nitro group to an *N*-hydroxy group followed by intramolecular cyclization. The obtained *N*-hydroxy pyrroloquinoxalinones are known for their various biological applications and are present in many natural products. In addition, the synthesis of these types of lactams was never carried out by the current reduction method. Hence, these serendipitous results encouraged us to develop a method to selectively obtain the *N*-hydroxy core.

After careful screening of various reaction parameters, compound **6** was obtained successfully as a sole product at 60 °C in 7 min with 83% yield and compound **6′** was afforded at 85 °C for 12 min exclusively in 87% yield. A possible rationale for this temperature-driven product distribution could be the dual reactivity of **5** as shown in Scheme 3. At the lower temperature the in situ formation of *N*-hydroxy amine **F** during the reduction process followed by intramolecular cyclization

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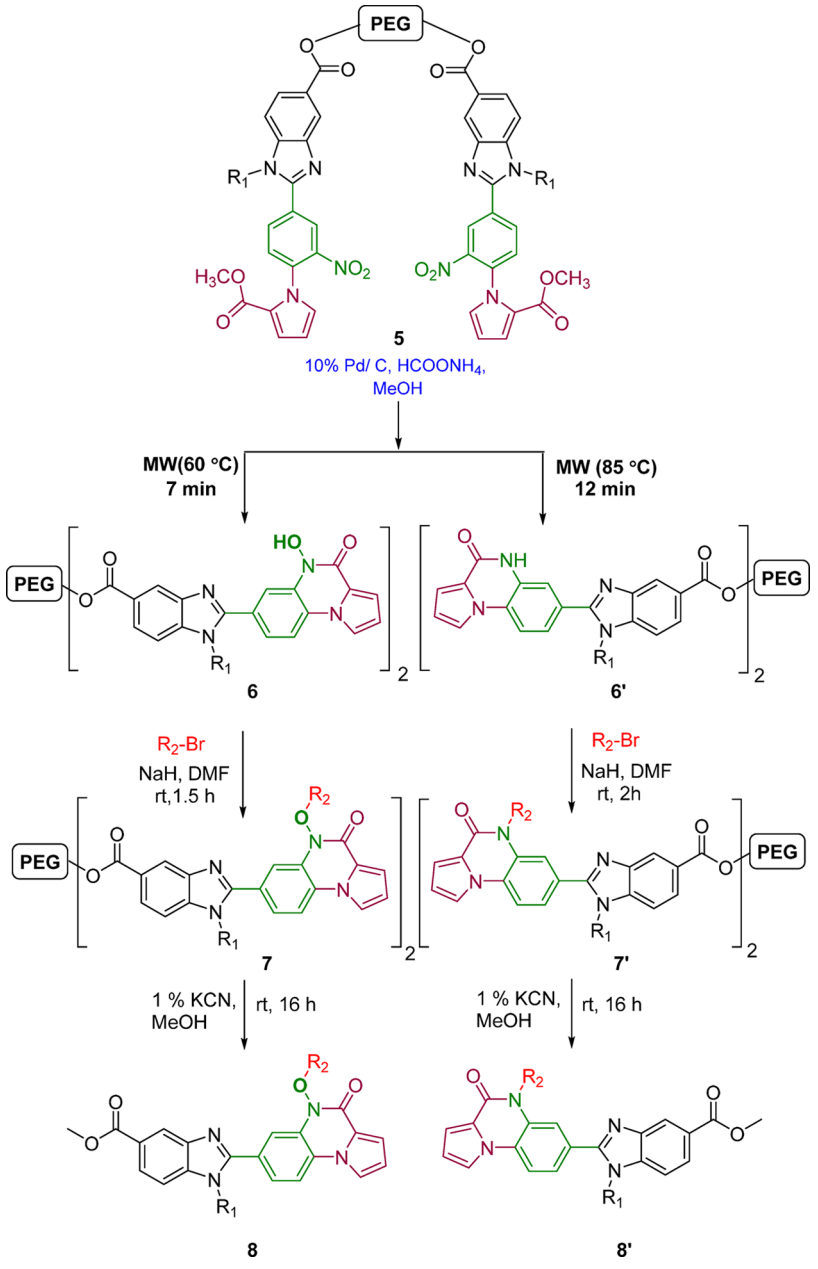
Scheme 2. Selective Nitro Reductive Cyclization to 8 and 8′



(path b) delivers the *N*-hydroxy pyrrolo[1,2-*a*]quinoxalinones **6**. Whereas, microwave irradiation at an elevated temperature triggered the rapid and complete reduction to the aniline **G** which undergoes rapid cyclization to yield pyrrolo[1,2-*a*]quinoxalinones **6′** (path c).

Moreover, it is presumed that electron rich ortho groups may accelerate the complete reduction rather than partial reduction because of the delocalization of nitrogen lone pair into the aromatic ring resulting in the elimination of *N*-hydroxy group, which would further reduce to the lactam product (path a, Scheme 3).[11] On the contrary, in our substrate the pyrrole nitrogen lone pair prefers to undergo delocalization into pyrrole ring for its aromaticity becuase of the steric effect of the carbomethoxy substituent preventing the pyrrole ring from becoming planar with the aromatic ring; thus, stabilizing the *N*-hydroxy intermediate F. Because of this steric effect, intermediate F is available for an intramolecular cyclization to afford lactam 6. However, efforts to isolate the intermediates F and G were not fruitful suggesting the subsequent intramolecular cyclization is very rapid. Changing the hydrogen sources to hydrazine or ammonium chloride resulted in a mixture of complicated products under these optimized conditions. Molecular diversity was further expanded by the reaction of various alkyl halides with polymer conjugated pyrroloquinoxalinones to produce their *N*- and *O*-alkylated derivatives at room temperature with sodium hydride (Scheme 2). The formation of the *O*- and *N*-alkylated polymer conjugates **7** and **7′** were confirmed directly from the proton NMR analysis without cleavage. Upon completion of each step, the polymer bound compound mixtures were purified by a simple washing/precipitation work up protocol which greatly enhances the synthetic efficiency. Finally, removal of polymer support was achieved by 1% potassium cyanide in methanol at room temperature. The completion of cleavage was verified by

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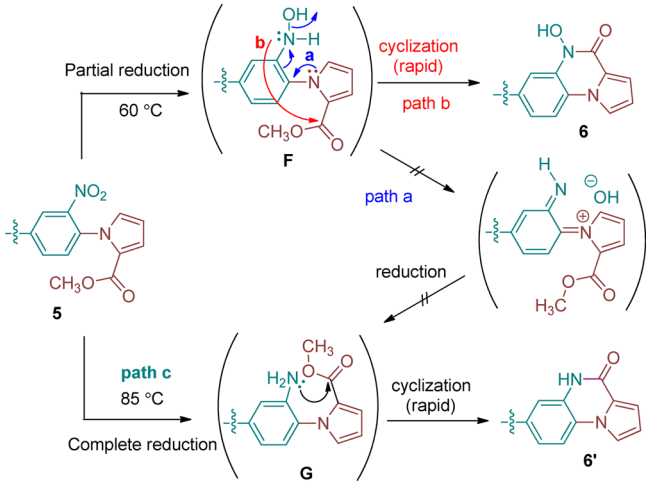
Scheme 3. Possible Reaction Pathways for the Formation of 6 and 6′



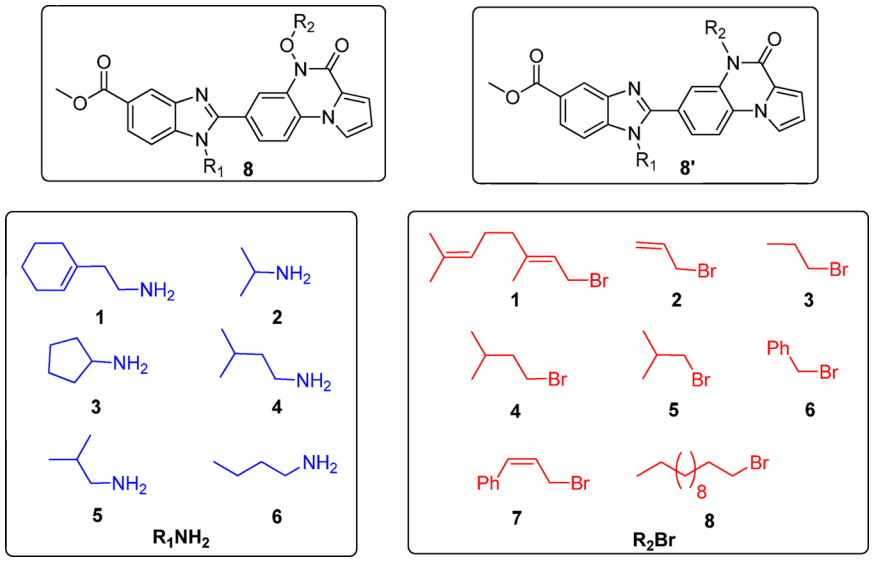
NMR before work up. The reaction mixtures were precipitated with ice cold ether and the polymer was removed by filtration to obtain the target compounds in high purity and excellent yields. The filtrates were concentrated to furnish benzimidazole-pyrrolo [1,2-*a*] quinoxalinones **8** and **8′** with good yields.

Subsequently, we explored this multistep synthetic transformation with the incorporation of different amines and saturated and unsaturated alkyl halides, and the results are summarized in Table 1. From the obtained results, it was found that *O*-alkylation is faster than the *N*-alkylation reaction. The diminished reactivity of compound **6′** is due to the presence of amide functionality which weakens the nucleophilicity whereas **6** do not possess any such a deactivating effect. Finally, the structure of the final compound **8**{*6,5*} was also unequivocally confirmed by X-ray crystallographic study. The benzimidazole ring was situated in plane with the alkyloxy-pyrrolo[1,2-*a*]quinoxalinone core as shown in Figure 2.[21]

CONCLUSION

In summary, we have developed a novel and selective synthetic approach for benzimidazole linked *N*-hydroxy pyrroloquinoxalinones and pyrroloquinoxalinones. The key steps in this multistep protocol are the aromatic nucleophilic substitution with less reactive pyrrole-2-carboxylate and their cascade reaction of reduction followed by an intramolecular lactam cyclization. The selective partial and full reductive cyclizations

Table 1. Synthesis of Benzimidazole-pyrrolo[1,2-*a*]quinoxalinones 8 and 8′



entry	product	isolated yield (%)[a]	crude purity (%)[b]
1	**8**{*1,1*}	82	88
2	**8**{*2,2*}	88	92
3	**8**{*3,3*}	76	77
4	**8**{*4,1*}	85	94
5	**8**{*4,7*}	80	82
6	**8**{*5,7*}	75	79
7	**8**{*5,4*}	78	83
8	**8**{*5,5*}	84	80
9	**8**{*6,6*}	81	83
10	**8**{*6,1*}	77	81
11	**8**{*6,4*}	60	63
12	**8**{*6,5*}	78	94
13	**8′**{*1,2*}	60	64
14	**8′**{*2,8*}	70	76
15	**8′**{*3,6*}	83	83

[a]Determined based on the weight of purified samples. [b]Purity of the crude samples after cleavage by HPLC analysis.

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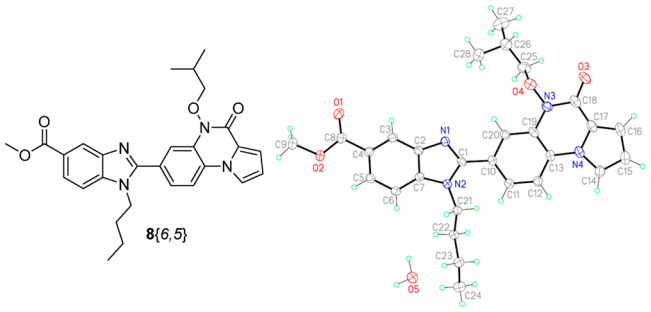

Figure 2. X-ray crystallographic structure of benzimidazole-alkyloxypyrrolo[1,2-*a*]quinoxalinone **8**{*6,5*}.

were achieved by simply tuning the microwave energy. To the best of our knowledge, this is the first systematic approach for the selective synthesis of pyrrolo[1,2-*a*]quinoxalinone by employing Pd/C and ammonium formate. Further, the isolated products were conveniently transformed to their *O* and *N*-alkylated analogues and the construction of molecular library is more efficient with the co-operative aid of microwave irradiation and soluble polymer support. Finally, combination of two privileged structures in a single molecule may lead to interesting biological profiles.

EXPERIMENTAL PROCEDURE

General Procedure for the Synthesis of Methyl 1-[2-(1-Cyclohexenyl)ethyl]-2-(5-[(2*Z*)-3,7-dimethyl-2,6-octadienyl]oxy-4-oxo-4,5-dihydropyrrolo[1,2-*a*]-quinoxalin-7-yl)-1*H*-benzo[*d*]imidazole-5-carboxylate 8{*1,1*}. To a solution of **3**{*1*} (6 g, 1.34 mmol, 1.0 equiv) in 1,2-dichloroethane (20 mL), trifluoroacetic acid (0.5 mL), and $MgSO_4$ (0.5 g) were added and irradiated in a sealed microwave vial at 100 °C for 15 min. After completion of the reaction, $MgSO_4$ was removed by filtration. The reaction mixtures were cooled and precipitated by slow addition of excess of cold ether (100 mL) and filtered to obtain compound **4**{1} in high purity as light green solid (5.16 g), 80% yield. To a solution of **4**{*1*} (5.0 g, 1.03 mmol, 1 equiv) in dimethylformamide (10 mL) was added pyrrole 2-carboxylate (0.644 g, 5.15 mmol, 5 equiv) and Cs_2CO_3 (1.67 g, 5.15 mmol, 5 equiv) in a sequential order. Then, the reaction mixtures were irradiated in a 20 mL microwave process vial for 10 min at 135 °C to obtain the polymer conjugate **5**{*1*}. After completion of the reaction, the reaction mixtures were precipitated by slow addition of cold ether and the precipitated pyrrole carboxylate bound polymer conjugates **5**{1} were filtered. The crude product was washed in succession with ether (100 mL × 3) to remove the undesired impurity and dried for next steps, (4.79 g), 85% yield. To a solution of **5**{1} (4.7 g, 0.78 mmol) in methanol, 10% Pd/C (0.91 g, 7.8 mmol, 10.0 equiv), and ammonium formate (0.49 g, 7.8 mmol, and 10.0 equiv) were added. The reaction mixtures were irradiated in a sealed microwave vial for 7 min at 60 °C. After completion, the reaction mixtures were filtered through a Celite bed to remove Pd/C and the filtrate was concentrated by rotary evaporation. The reaction mixture was dissolved in dichloromethane, filtered through a fritted funnel to remove undissolved ammonium formate and isolate PEG bound **6**{*1*}, 4.16 g, 90% yield. The polymer bound compound **6**{*1*} (4.1 g, 0.83 mmol) was dissolved in DMF. The reaction mixtures were allowed to cool using an ice bath for 20 min, NaH (0.095 g, 4.15 mmol, 5.0 equiv) was added followed by geranyl bromide (0.89 g, 4.15 mmol, 5.0 equiv) and stirried for 1 h in cold condition. Then the reaction mixture was stirred at room temperature for 24 h. After reaction completion, the reaction mixtures were precipitated by adding cold ether. The residue was washed, collected and dried under high vacuum to obtain polymer bound **7**{*1,1*}, (4.79 g), 85% yield. To a solution of polymer bound compound **7**{*1,1*} (3.5 g, 0.69 mmol) in methanol (20 mL), KCN (100 mg) was added and stirred for 24 h at room temperature. The cleavage reaction was monitored by TLC and proton NMR. After completion of the reaction, excess of cold ether (100 mL) was added, the unbound polymer was filtered off and filtrate was subjected to evaporation. The resulting slurry was loaded on silica gel column and eluted with a mixture of ethyl acetate and hexane (1:4) to get the title compounds **8**{*1,1*} in 82% yield.

*Methyl 1-[2-(1-Cyclohexenyl)ethyl]-2-(5-[(2Z)-3,7-dimethyl-2,6-octadienyl]oxy-4-oxo-4,5-dihydropyrrolo[1,2-a]-quinoxalin-7-yl)-1H-benzo[d]imidazole-5-carboxylate **8**{1,1}:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J = 1.3 Hz, 1H), 8.07 (dd, J = 8.6, 1.3 Hz, 1H), 7.95 (d, J = 1.5 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.73 (dd, J = 8.5, 1.4 Hz, 1H), 7.67 (dd, J = 8.4, 1.6 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 7.34 (dd, J = 8.4, 1.3 Hz, 1H), 6.73 (dd, J = 8.2, 1.4 Hz, 1H), 5.58 (t, J = 7.5 Hz, 1H), 5.27 (m, 1H), 5.03 (m, 1H), 4.86 (d, J = 7.5 Hz, 2H), 4.38 (t, J = 6.9 Hz, 2H), 3.97 (s, 3H), 2.43 (t, J = 7.3 Hz, 2H), 2.04−2.03 (m, 3H), 1.80−1.77 (m, 7H), 1.63 (m, 3H), 1.54 (m, 3H), 1.51−1.45 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 154.5, 152.5, 147.7, 143.0, 139.4, 133.2, 132.3, 129.6, 128.0, 125.3, 125.2, 125.0, 124.9, 124.1, 124.0, 123.9, 122.7, 117.4, 116.4, 115.4, 115.0, 114.4, 114.3, 110.4, 72.6, 52.5, 44.5, 40.1, 38.4, 28.7, 26.7, 26.0, 25.5, 23.0, 22.3, 18.0, 17.2; MS (ESI) m/z 619 (MH^+); HRMS (ESI, m/z) calcd for $C_{38}H_{43}N_4O_4$ m/z 619.3284; Found 619.3280 (M + H); IR(cm^{-1}, KBr) 2925, 1712, 1673, 1295.

General Procedure for the Preparation of Methyl 2-(5-Allyl-4-oxo-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1-(2-(cyclohex-1-en-1-yl)ethyl)-1*H*-benzo[d]imidazole-5-carboxylate 8′{*1,2*}. To a solution of **5**{*1*} (4.7 g, 0.78 mmol) in methanol, 10% Pd/C (0.91 g, 7.8 mmol, 10.0 equiv) and ammonium formate (0.49 g, 7.8 mmol, and 10.0 equiv) were added. The reaction mixtures irradiated in a sealed microwave vial for 12 min at 85 °C. After reaction completion, the reaction mixtures were filtered through a Celite bed to remove Pd/C and the filtrate was concentrated by rotary evaporation. The reaction mixture was dissolved in dichloromethane, filtered through a fritted funnel to remove undissolved ammonium formate and isolate PEG bound **6**′{*1*}, 3.03 g, 80% yield. The polymer bound compound **6**′{*1*}(3.0 g, 0.616 mmol) was dissolved in DMF. The reaction mixtures were allowed to cool using an ice bath for 20 min, NaH (0.073 g, 3.08 mmol, 5.0 equiv) was added followed by allyl bromide (0.39 g, 3.08 mmol, 5.0 equiv) and stirried for 1 h in cold condition. Then the reaction mixture was stirred at room temperature for 24 h. After the completion, the reaction mixtures were precipitated by adding cold ether. The residue was washed and collected and dried under high vacuum to obtain polymer bound 7′{*1,1*}, (2.16 g), 71% yield. To a solution of polymer bound compound 7′{*1,1*}(2.1 g, 0.42 mmol) in methanol (20 mL), KCN (100 mg) was added and stirred for 24 h at room temperature. The cleavage reaction was monitored by TLC and proton NMR. After reaction completion, excess of cold ether (100 mL) was added, the unbound polymer was filtered off and filtrate was subjected to evaporation. The resulted slurry was loaded on

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silica gel column and eluted with a mixture of ethyl acetate and hexane (1:4) to get the title compound **8′**{*1,2*} in 60% yield.

Methyl 2-[5-(Allyloxy)-4-oxo-4,5-dihydropyrrolo[1,2-a]-quinoxalin-7-yl]-1-[2-(1-cyclohexenyl)ethyl]-1H-benzo[d]-imidazole-5-carboxylate ***8′****{1,2}:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, J = 1.5 Hz, 1H), 8.09 (dd, J = 8.6, 1.5 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.76 (dd, J = 8.2, 1.4 Hz, 1H), 7.68 (d, J = 1.4 Hz, 1H), 7.64 (dd, J = 8.4, 1.5 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.33 (dd, J = 8.2, 1.3 Hz, 1H), 6.77 (dd, J = 8.3, 1.2 Hz, 1H), 6.00 (m, 1H), 5.34 (d, J = 8.2 Hz, 2H), 5.20 (d, J = 6.2 Hz 1H), 5.01 (m, 1H), 4.41 (t, J = 7.2 Hz, 2H), 3.99 (s, 3H), 2.37 (t, J = 7.2 Hz, 2H), 1.84−1.77 (m, 6H), 1.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 155.5, 154.5, 139.2, 133.2, 132.1, 130.2, 125.6, 125.3, 125.1, 125.0, 124.2, 123.5, 122.6, 117.9, 117.7, 117.0, 115.4, 114.5, 114.2, 110.5, 52.6, 44.3, 44.0, 38.1, 28.7, 25.5, 22.9, 22.3; MS (ESI) m/z 507 (MH^+); HRMS (ESI, m/z) calcd for $C_{31}H_{31}N_4O_4$ m/z 507.2396; Found 507.2394 (M + H); IR (cm^{-1}, KBr) 2923, 1714, 1643, 1378.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental procedures and representative ^{1}H NMR, ^{13}C NMR, crude HPLC, LRMS, HRMS, and FT-IR spectral data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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