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Ionic liquid supported multistep divergent synthesis of benzimidazole linked pyrrolo-/pyrido-/isoindolo-benzimidazolones

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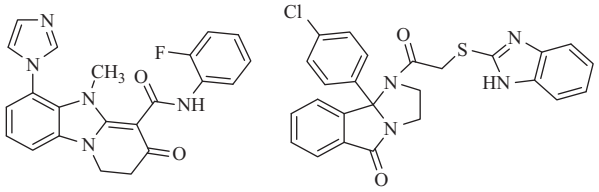
ABSTRACT

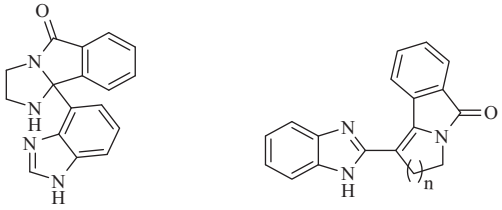
Diversity oriented parallel synthesis for bis-heterocyclic skeletal novel benzimidazole linked pyrrolo-/pyrido-benzimidazolones and benzimidazole linked isoindolo-benzimidazolones has been developed on ionic liquid support under microwave irradiation by utilizing the cascade cyclization. The key tandem transformation comprises (i) amino-alkylation of immobilized *o*-phenylenediamine with ketoacids, (ii) intramolecular cyclization through secondary amine on electrophilic imine carbon toward pentacyclic aza-ring and (iii) second amido-cyclization to deliver cycloamide ring. The synergy arises by combined use of microwave heating with ionic liquid support which is very effectively used to speed up multistep synthesis of biological interesting heterocycles.

1. Introduction

It is well known that heterocyclic compounds are the major constituents of pharmaceutical ingredients and has embraced significant space in medicinal chemistry, synthetic chemistry, and natural products. Highly functionalized various ring size bis-heterocycles with different hetero atoms and substitution patterns are of major interest in the drug discovery process.[1] Bis-heterocyclic compounds offer better binding opportunities with enzyme active site owing to its three dimensional special arrangement and consequently depict many intrinsic biological properties.[2] Particularly, bis-heterocycles comprising pyridobenzimidazoles (I) are ligands for the BZD site on GABA-A receptors and are thus useful for the treatment of disorders of the central nervous system including convulsion such as epileptic seizures, anxiety, depression, muscular spams, and attention deficit hyperactivity disorder (Fig. 1).[3] Polycyclic bis-heterocycles containing imidazopyridine, imidazopyridine, or imidazoisoindole moieties (II) constitute basic structural frameworks of potent inhibitors of respiratory syncytical virus while some imidazoisoindoles (III) show antiviral activity.[4] Benzimidazoles in combination with the pyrrolo–isoidolones (IV) exhibit anticancer activity via the inhibition of the ATPase-type catalytic activity of the Hsp90 chaperone protein.[5] The geometric assembly of bis-heterocycles characterized by the benzimidazole, as a core connected to various fused heterocycles, is apparently interesting to explore. Despite the broad range of biological activities associated with the pyrrolo[1,2-*a*]benzimidazole, pyrido[1,2-*a*]benzimidazole, and imidazo[2,1-*a*]isoindole, there are still very few reports for the construction of aforementioned three classes linked with benzimidazole motif in linear fashion as bis-heterocycles.[6] Hence, interest remains strong to develop new approaches to produce novel bis-heterocyclic molecules and further exploration of their biological applications.



BZD receptor antagonist (I) RSV replication inhibitor (II)



Antiviral agent (III) HSP90 Inhibitor (IV)

Figure 1. Biologically active bis-heterocyclic molecules.

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Integrating a variety of advanced technologies for the rapid synthesis of numerous multi-functionalized heterocyclic molecules is of high interest to provide rapid path for modern drug discovery. Owing to the disadvantages like heterogeneous reaction conditions of solid phase synthesis[7] and low loading capacity of soluble polymer supported synthesis,[8] successful implementation of ionic liquid supported synthesis in small molecule synthesis retained advantages over conventional solution phase chemistry.[9] Depending on the choice of anions and cations, the solubility of the ionic liquids can be tuned readily to control the phase trafficking in organic and aqueous phase. Ionic liquid supported synthesis has become a very effective method for the production of combinatorial libraries with high degree of chemical diversity.[10] The numerous advantages associated with the ionic liquid as a support has been strongly appealing for the green synthesis.[11] In addition to the advantages like high loading capacity and recyclability of ionic liquid support, ionic liquids absorb microwave irradiation extremely well due to the ionic conduction and thus reactions can be run in non-polar solvents.[12] Hence, application of microwave heating in ionic liquid supported synthesis is a fast growing research area.

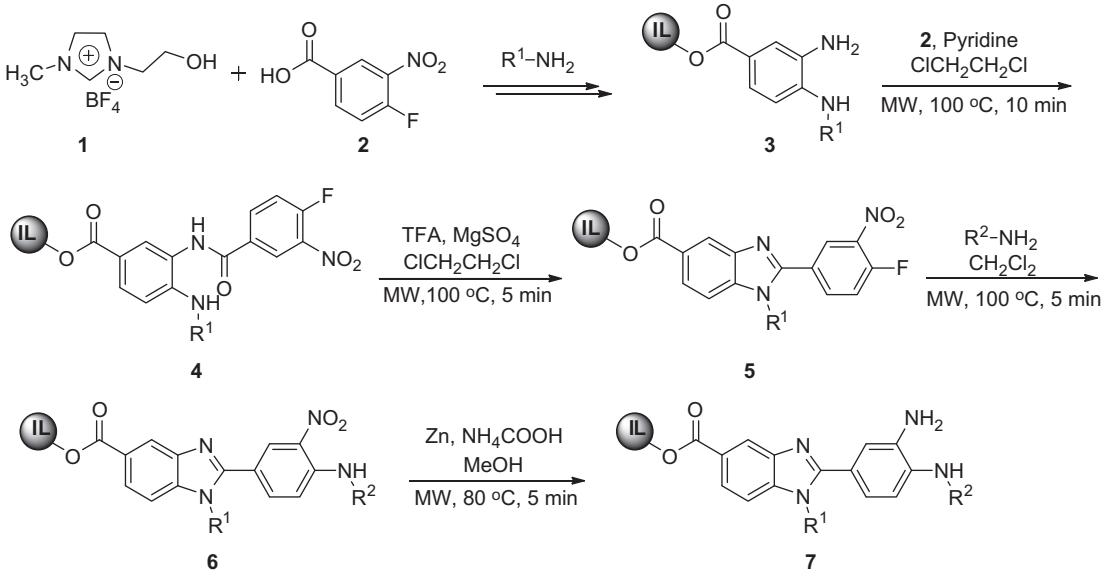
In continuation with our effort to develop multidisciplinary synergetic approaches for rapid synthesis of medicinally interesting compounds,[13] here we report the efficient synthesis of bis-heterocyclic skeletal benzimidazole linked pyrrolo-/pyrido-/isoindolone-benzimidazolones on ionic liquid support under microwave conditions.

2. Results and discussion

The readily available 3-hydroxyethyl-(1-methylimidazolium)-tetrafluoroborate **1** is selected as a suitable ionic liquid (IL) support for multistep synthesis. The present strategy commenced with the synthesis of IL immobilized *ortho*-phenylenediamine **3** from 4-fluoro-3-nitrobenzoic acid **2** with built-in structural diversity (R^1) through three step protocol. The ionic liquid **1** was attached to 4-fluoro-3-nitrobenzoic acid **2** by esterification followed by *ipso*-fluoro substitution of primary amines and subsequent reduction of nitro-group provided IL immobilized *ortho*-phenylenediamine **3** in overall good yields (Scheme 1). In an effort to attain the target molecule, compound **3** was further N-acylated at the primary amine functionality with 4-fluoro-3-nitrobenzoic acid **2**. Accordingly, anilide conjugates **4** were obtained by the condensation of acid **2** with IL conjugates **3** in presence of pyridine within 12 h in refluxing dichloroethane. However, the application of microwave irradiation at 100 °C reduced the reaction time to 10 min. By taking the distinct solubility features of the ionic liquids, purification has been carried out by precipitation of IL bound amide **4** in the low polar solvent such as ether. The IL bound amide **4** was further cyclized to benzimidazole derivative **5** in the presence of trifluoroacetic acid and magnesium sulfate under microwave irradiation in 5 min at 100 °C. However, it took 14 h to complete cyclization under refluxing conditions. The progression of this transformation was monitored directly on ionic liquid tag by the observation on the chemical shift of aromatic region in proton NMR spectrum.

IL supported fluoronitrobenzoate **5** was further treated with various primary amines in order to create second substitutional diversity in the present skeleton by *ipso*-fluoro displacement reaction. This reaction was performed in microwave conditions (100 °C) for 5 min to offer ionic liquid attached conjugate **6**, while same reaction took 5 h in refluxing condition. Here it is noteworthy to mention that primary amines did not cleave ionic liquid tag under microwave harsh condition. Further nitro-group of IL conjugate **6** was reduced by treatment with zinc and ammonium formate for 5 min under microwave irradiations at 80 °C to furnish IL conjugate diamine **7**. After completion of the reaction the IL supported conjugates **7** was precipitated with ether and obtained in pure form with good yields.

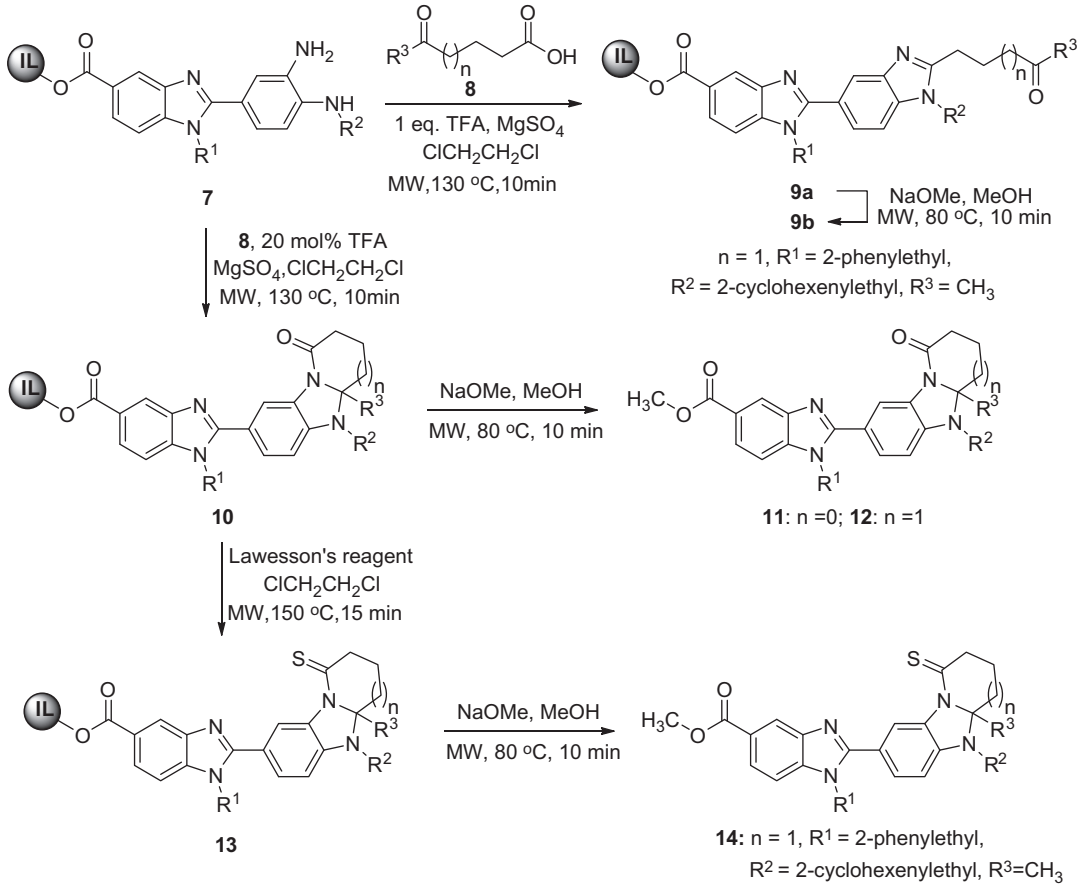
IL immobilized *ortho*-phenylenediamine **7** was used as a common scaffold to generate skeletal diversity in targeted bis-heterocyclic molecules by one pot tandem transformation using various ketoacids. The various 3-keto-acids were used to provide the pyrrolo fused benzimidazolone tricyclic skeleton while 4-keto-acids were used to achieve skeletally different tricyclic framework of pyrido fused benzimidazolones along with the substitutional diversity depending on the groups present on the ketoacids. Accordingly, IL immobilized *ortho*-phenylenediamine **7** was treated with various 3- and 4-keto-acids **8** in presence of TFA under microwave irradiations. It is noteworthy to mention that the selective product generated in the coupling of ketoacid with *o*-phenylenediamine is dependent on the quantity of TFA used in the reaction mixture. With the stoichometric amount of TFA, diamine groups of **7** cyclized with acid functionality of **8** afforded 2-alkyl



Scheme 1. Synthesis of IL supported diamine scaffold **7**.

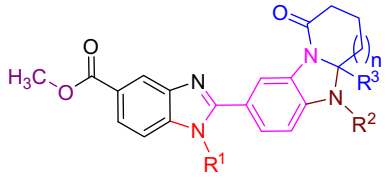
substituted bis-benzimidazoles **9a**. The formation of compound **9a** was attributed to activation of acid functionality in presence of stoichometric amount of TFA. The structure of compound **9a** was later confirmed as **9b** by removal of ionic liquid support in sodium methoxide solution. Alternatively, the intended cascade cyclization of IL diamine conjugate **7** with ketoacids **8** was successfully achieved in 20 mole % TFA in the presence of magnesium sulfate and dichloroethane under focused microwave irradiation at 110 °C for 10 min (Scheme 2). The reaction mixture was purified by precipitation, filtration, and washing to furnish IL immobilized benzimidazole linked pyrrolo/pyrido-benzimidazolone derivatives **10** with good yields (72–85%). The same reaction was carried out under conventional refluxing for 24 h to furnish the same product which clearly depicts the superiority of microwave heating over conventional heating reaction. The synthetic pathway leading to pyrrolo/pyrido-benzimidazolones through one pot cascade reactions includes (i) amino-alkylation of ionic liquid immobilized benzimidazole linked diamine with ketoacids, (ii) intramolecular cyclization through attack of secondary amine on electrophilic imine carbon toward pentacyclic aza-ring formation and (iii) intramolecular cyclization to deliver second cyclic amine ring. A variety of 4-ketoacids and 5-ketoacids were used in combination with the *N*-alkyl substitution on diamine moiety for this tandem transformation to furnish pyrrolo-/pyrido-benzimidazoles with substitutional diversity as depicted in Table 1. The formation of pyrrolo/pyrido-benzimidazolone derivatives **10** was confirmed by proton NMR spectrum and mass spectrum directly with IL support. The ionic liquid support was cleaved from **10** using sodium methoxide methanol solution under microwave irradiation at 110 °C in 10 min to obtain benzimidazole linked pyrrolo/pyrido-benzimidazolone derivatives **11** and **12**. The ionic liquid was removed from the reaction mixtures through precipitation by ether and filtration. The characterization of recovered ionic liquid shows 96% purity and 68% recovery after first cycle. The recovered ionic liquid was recycled in the synthetic process. The separated desired products were subjected to HPLC analysis for crude purity. Further column chromatography purification furnished benzimidazole linked pyrrolo[1,2-*a*]benzimidazolones **11** and benzimidazole linked pyrido[1,2-*a*]benzimidazolones **12** in good yields[14] (Table 1). The structure of final products was confirmed by spectroscopic analysis. The appearance of the peaks due to alkyl protons present on ketoacid moiety and the absence of peaks corresponding to amine and acid protons were observed in the proton NMR spectrum of compound **11** and **12**. Additionally, the stereogenic quaternary carbon has appeared around 89.5 ppm in the ^{13}C NMR spectrum along with the amide carbonyl carbon absorbance peak at 175 ppm. The formation of amide bond is further confirmed by the IR spectroscopy which depicts amide frequency band around 1720 cm^{-1}; particularly little higher due to the ketonic nature of *tert*-aminde carbonyl functionality.

In order to expand the intended diversity profile of resulting bis-heterocyclic molecules, the additional sulfur element was incorporated in the skeleton. The IL supported benzimidazole linked pyrido-benzimidazolone **10** was treated with Lawesson's reagent in toluene under focused microwave conditions at 150 °C. The thio derivative of IL supported pyrido-benzimidazolone **13** was obtained in good yield in 15 min while the same reaction took 18 h under the refluxing condition in toluene (Scheme 2). Further removal of IL support affords the benzimidazole linked thiopyrido-benzimidazolone **14**.

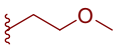
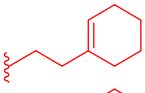
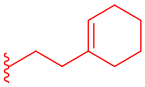
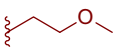
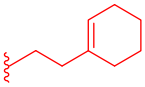
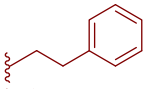
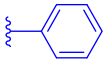
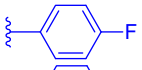
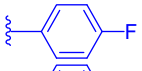
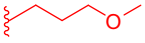
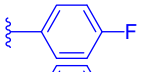
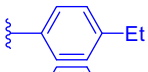
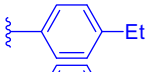
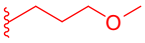
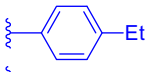
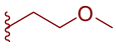
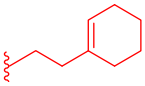
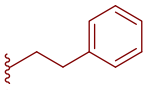
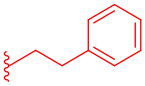


Scheme 2. Synthesis of pyrrolo-benzimidazolones and pyrido-benzimidazolones.

Table 1
Benzimidazole linked pyrrolo-/pyrido-benzimidazolones

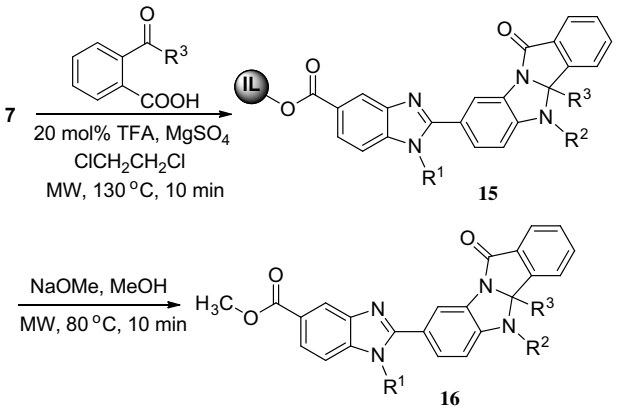


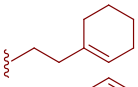
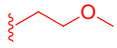
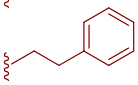
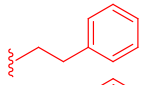
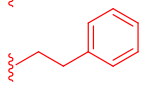
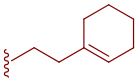
11 (n=0); **12** (n=1)

Entry	R^1	R^2	R^3	MASS[a]	Yields (%)[b]
11a				476	80
11b				526	82
11c				528	85
11d				636	75
11e				570	78
11f				570	75
11g				582	73
11h				580	72
11i				580	75
11j				592	76
12a				490	80
12b				588	81
12c				536	80
12d				566	78
12e				566	75
12f				578	77

[a] Mass (LRMS) were detected as M^+.
[b] The overall yields were determined on the weight of purified samples obtained over two steps from **7** (%).

The scope of present cascade process was further extended by exploring *ortho*-ketobenzoic acids with selective ionic liquid conjugated diamines under the same reaction conditions to offer skeletally distinct bis-heterocyclic molecules. The IL immobilized diamine **7** was treated with 2-acetylbenzoic acid with 20 mole % TFA in dichloroethane under microwave irradiation at 110 °C (Scheme 3). After 10 min, an IL supported isoindolo-benzimidazolones **15** were obtained in good yields which were purified by simple precipitation and washing in ether. The same reaction required 24 h for complete cyclization in the refluxing condition. The outcome of tandem transformation on aromatic ketobenzoic acid is confirmed by analyzing the structure of compound **15** directly on ionic liquid support. The successive removal of ionic liquid support from **15** furnishes benzimidazole linked isoindolobenzimidazolones **16** with good yield (Scheme 3). The structure of **18** was confirmed by observing the absence of peaks corre-



Entry	R^1	R^2	R^3	Mass[a]	Yields[b]
16a			—CH_3	574	79
16b			—CH_3	572	80
16c			—CH_3	570	80
16d			—CH_3	622	82

Scheme 3. Synthesis of benzimidazole linked isoindolo-benzimidazolones. [a]Mass (LRMS) were detected as M^+. [b]The overall yields were determined on the weight of purified samples obtained over two steps from **7** (%).

sponding to amine and acid protons together with the emergence of the new peaks due to aromatic protons of 2-acetyl benzoic acid moiety in the proton NMR spectrum of compound **16** along with amide frequency band around 1720 cm^{-1} in the IR spectra.

It is noteworthy to mention that the ionic liquid support is stable in microwave harsh conditions. Owing to high polar microwave absorbance medium created by the ionic liquid support, time taken to attain the desired reaction temperatures for all the reactions under microwave exposure has substantially shortened and reactions can run in low polar solvent media. The monitoring reaction progress is practicable by conventional spectroscopic methods with ionic liquid support.

3. Conclusion

We have successfully developed rapid and efficient solution phase approach to synthesize benzimidazole linked pyrrolo[1,2-*a*]benzimidazolones, pyrido[1,2-*a*]benzimidazolones, and isoindolo[1,2-*a*]benzimidazoles with three sets of diversity on ionic liquid support under microwave conditions. A cascade reaction was systematically applied to furnish skeletally diverse bis-heterocyclic molecular libraries. This tandem transformation involves aminoalkylation, intramolecular cyclization to form benzimidazole, and successive cyclization to furnish fused cycloamide ring. Use of ionic liquid as support for multistep organic synthesis possesses the advantages like high loading soluble support, homogeneous reaction phase, and recyclability. The powerful potential of multidisciplinary synthetic approach, integrating ionic liquid support, and microwave synthesis with multistep synthesis has great potential to produce biologically interesting molecules for drug discovery.

Acknowledgments

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14. *General procedure:* (All microwave experiments performed under CEM Discover Microwave system at the frequency of 2450 Hz and 0–300 W power in closed vessel system.) To the solution of **7** in ethylenedichloride (9 mL), various aliphatic 3- or 4-keto-acids **8** (1.5 equiv) were added, followed by addition of dry $MgSO_4$ and 20 mole % trifluoroacetic acid. The reaction mixture was subjected to microwave irradiation for 10 min at 110 °C. The reaction mixture was filtered and then precipitated by ether (60 mL). The precipitate was filtered and washed with ether to get the IL immobilized benzimidazole linked pyrrolo/pyrido-benzimidazoles **10**. The solution of 0.1 M NaOMe in MeOH (10 mL) was added to the solution of **10** in methanol. The reaction mixture was subjected to microwave irradiation for 10 min at 110 °C. The cleaved ionic liquid was precipitated by addition of ether solution and separated by filtration. The filtrates were concentrated and subjected to HPLC analysis (68–99%). The products were further purified by column chromatography over silica gel using ethyl acetate/*n*-hexane (1:1) as eluent to obtain pure benzimidazole linked pyrrolo/pyrido-benzimidazoles **11** and **12** in good yields (72–85%). *Compound **11a***: ^1H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, J = 2.1 Hz, 1H), 8.17 (dd, J = 8.7, 2.1 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 6.65 (d, J = 8.7 Hz, 1H), 4.33–4.28 (m, 2H), 3.97 (s, 3H), 3.62–3.52 (m, 4H), 3.39 (s, 3H), 2.84 (m, 1H), 2.63–2.52 (m, 2H), 2.43 (m, 1H), 2.26 (pent, J = 6.4 Hz, 1H), 1.55 (s, 3H), 0.91 (d, J = 6.4 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 166.6, 154.1, 147.4, 136.5, 133.6, 130.9, 128.9, 126.8, 118.7, 114.3, 111.8, 111.4, 106.8, 89.8, 70.7, 67.1, 59.4, 53.3, 52.9, 43.4, 37.0, 33.4, 29.3, 23.5, 20.4, 20.22; MS (ESI): m/z 476 $(M)^+$; HRMS (ESI): calcd for $C_{27}H_{32}N_4O_4$: m/z 476.2424; found 490.2588 $(M)^+$; IR (neat): 2360, 1712, 1658 cm^{-1}.