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Novel approach towards 2-substituted aminobenzimidazoles on imidazolium ion tag under focused microwave irradiation

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ABSTRACT

We have developed an efficient, parallel synthesis of 2-substituted aminobenzimidazoles via intramolecular ring closing reactions of imidazolium ion tag immobilized *o*-phenylenediamine with various isothiocyanates. The methodology is based on the attachment of 4-fluoro-3-nitro benzoic acid into the imidazolium ion tag, which enables the S_NAr reactions with different amines followed by neutral reduction to furnish *o*-phenylenediamines under microwave irradiation. The substituted isothiocyanates are reacted with *o*-phenylenediamines to form monothiourea, which is further activated by methyl iodide to undergo desulfurization in one pot manner. The ionic liquid bound 2-substituted aminobenzimidazoles were finally cleaved from the support with sodium methoxide to generate target compounds in good yields and high purities with two points of structural diversity. This synthetic protocol has promising features of extremely short reaction time, operational simplicity, good yields, as well as widespread applications, leading to a facile and straightforward admittance to structurally diverse 2-substituted aminobenzimidazole analogues with potential bioactivities.

1. Introduction

The interest in the design and the synthesis of novel chemical entities based on 'privileged structures' containing heterocyclic moieties has grown considerably in recent years.[1] The rapid synthesis of bioactive heterocycles is used for lead identification and optimization in drug discovery since their efficiency serves as both biomimetics and reactive pharmacophores[2] Because of the several disadvantages, such as slower product conversion rate, heterogeneous nature, non linear kinetics associated with the solid supported synthesis,[2–5] chemists have used the ionic liquid phase organic synthesis as a viable alternative.[6] In recent years, ionic liquids (ILs) have received constant attention as eco-friendly green reaction media[7] as well as catalyst[8] in organic synthesis. Due to their several interesting properties, such as excellent thermal and chemical stability, zero vapour pressure, non-flammability and effortless recyclability, ionic liquid serves as an appealing tool for an organic chemist.[9] With the variation of cations and anions, the solubility of the ionic liquids is adjusted for phase separation from organic as well as aqueous media, which would make them for further reuse.[10,11] The advantages associated with the ionic-liquid supported synthesis are that IL-supported products can be purified by simply washing the product mixture with solvents to remove un-reacted reagents and side products in which IL-bound product remains insoluble. In recent years microwave irradiation as a non conventional energy source has become a unique and invaluable technique in the rapid synthesis of small molecules. Moreover, it has been observed that with the use of microwave irradiation, shorter reaction times, higher yields and enhanced product purities have been achieved.[12] In continuation to our ongoing research program aimed at the heterocyclic synthesis, we explore the expeditious synthesis of biologically significant compounds through synergies arised from the combination of MW and ILs.[13]

Highly substituted benzimidazole and its amino derivatives are considered as important therapeutic scaffolds, which have long been known as a promising class of biologically active compounds.[14,15] This functionality is commonly contained in mebendazole (Fig. 1, A) as a potent anthelmintic drug. Similarly, astemizole containing 2-aminobenzimidazole moiety is a second generation anti-histamine agent with a long duration of action (Fig. 1, B). Furthermore, the 2-aminobenzimidazole moiety has been used selectively for inhibition of the NF-κB antigen receptor pathway (Fig. 1, C).[16] More recently, this privileged scaffold is used as selective Raf-kinase inhibitor (Fig. 1, D).[17]

Different synthetic protocols are available to synthesize the 2-aminobenzimidazole ring. This involves the S_NAr reaction of chlorobenzimidazole or methylsulfonyl benzimidazole with an amine nucleophiles under solvent-less conditions.[18] The most common method for the synthesis of 2-aminobenzimidazole is the cyclodesulfurization of monothioureas with desulfurizing agents,

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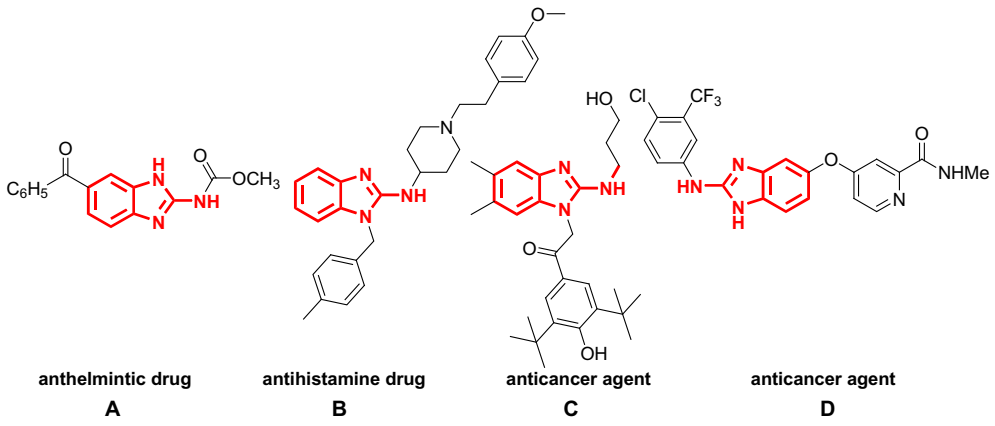


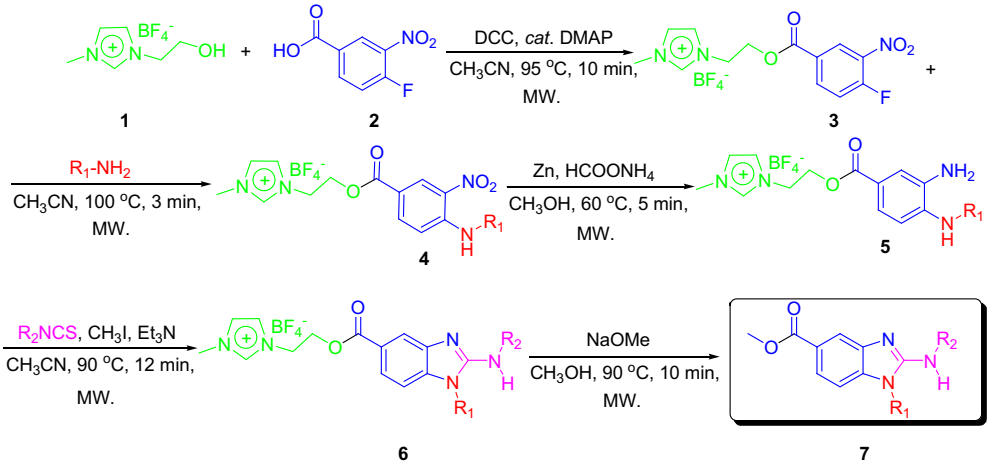
Fig. 1. Biologically active benzofused *N*,*N* heterocycles.

such as carbodiimides, tosylchloride, mercury(II) oxide, mercury(II) chloride, and EDPBT.[19,20] Inspired by the recent development of ionic liquid as support, we became interested in the development of a novel and efficient method to construct benzofused *N*,*N* heterocycles utilizing the ionic liquid as support and one pot heterocyclisation with isothiocyantes.

2. Results and discussion

The synthesis of ionic liquid support **1** equipped with hydroxyl group linker, 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate ([hydemim][BF_4]) was prepared in two steps.[11e] The ionic liquid **1** was reacted with 4-fluoro-3-nitro benzoic acid **2** in the presence of catalytic amount of 4-dimethylaminopyridine and *N*,*N*′-dicyclohexylcarbodiimide (DCC) in anhydrous CH_3CN at room temperature for 72 h to attach the carboxylic acid to ionic liquid tag (Scheme 1). However, this coupling reaction was finished in 12 h under refluxing conditions. Significantly, upon application of microwave irradiation in a closed vessel system under pressure (95 °C) further reduced the reaction time to 10 min. After completion of the reaction, the suspended dicyclohexyl urea (DCU) was filtered off and ionic liquid conjugates **3** were precipitated with ether, which remove the excess un-reacted reagents.

To this end, the ionic liquid bound *o*-fluoronitrobenzene **3** was reacted with readily available primary amines as the first building block via an *ipso*-fluoro nucleophilic aromatic substitution (S_NAr) reaction to obtain IL-bound *o*-nitro anilines **4**. The reactions were completed within 10 h at ambient temperature. The application of microwave irradiation (100 °C) further reduced the reaction time to 3 min compared to that of refluxing condition (3 h). The reaction proceeded smoothly with various amines without cleavage of the ester bond at the ionic liquid attached site even under MW harsh condition. Subsequently, the resulting mixture was purified again by precipitation to obtain immobilized conjugates **4**. The *o*-nitro group in ionic liquid conjugates **4** was reduced with neutral condition, such as Zn/$HCOONH_4$ in methanol under microwave irradiation at 60 °C for 5 min. Formation of the amine conjugates **5** was confirmed by the directly observation of aromatic region change in the conventional proton NMR. Upon completion of the reaction, reaction mixture was filtered to remove the zinc dust. The reaction mixture was evaporated and acetonitrile was added to salt out the ammonium formate to obtain the compound **5**. In an effort to attain the target molecule, ionic liquid bound *o*-phenylenediamine **5** underwent key synthetic sequence of the efficient ring closure reaction. It has been realized that the elaboration of intermediate **5** to the desired core structure required one carbon electrophile, which could be attached through reaction with isothiocyantes. In an attempt to understand the scope of the cyclisation reaction, we reported here the cyclodesulfurization of the resulted monothioura by the condensation of amine functionality with isothiocyanates moiety activated by methyl iodine in triethyl amine. This one pot reaction provides a more practical route to the targeted compounds. The reaction was successfully finished in conventional refluxing condition for 5 h, whereas the application of microwave



Scheme 1. General strategy of microwave-assisted synthesis of 2-substituted aminobenzimidazoles on imidazolium ion tag.

irradiation condition (90 °C) reduced the reaction time to 12 min. After completion of the reaction, the reaction mixtures were purified by precipitation with ether to obtain 2-substituted aminobenzimidazoles on ionic tag **6** in good yields. The proposed multistep mechanism of the one pot formation of benzimidazole with methyl iodide is shown in Fig. 2. The initial step of the reaction involved the nucleophilic attack on isothiocyante moiety by the primary amine functionality of conjugates **5** followed by the activation of the C=S bond by methyl iodide to facilitate the formation of intermediate A. Furthermore, the intermediate A after cyclisation and electron reorganization by triethyl amine generated the target compound **6b** as shown in Fig. 2.

Further insight into the mechanism for the formation of the intermediate A has been confirmed from the study of the ^{1}H, ^{13}C NMR, and mass spectrum after cleavage. Here, we have observed that the starting material **5** upon cleavage from the ionic liquid support obtained **D**, which shows a peak at 3.81 and 52.0 ppm corresponds to the CH group of cyclopentyl moiety in proton and carbon NMR spectrum, respectively. It is interesting to observe that after reaction with allyl isothiocyanates and subsequent cleavage, the chemical shifts of CH proton of cyclopentyl moiety remain unchanged for intermediate **B** as shown in Fig. 3. Here if the secondary amine moiety of ionic liquid conjugates **5** attacked the C=S moiety of allyl isothiocyanates to generate the intermediate **C**, the chemical shifts CH group of cyclopentyl moiety are expected more downfield. The observed selectivity may be because of the presence of ester functionality on the aromatic ring, which deactivated the secondary amine and facilitated the coupling of isothiocyanate exclusively with primary amine. The formation of intermediates **A** and **B** has been confirmed by the isolation and subsequent cleavage of ionic liquid support (see Supplementary data).

The 2-substituted aminobenzimidazoles **6** were finally cleaved from ion support using 0.1 M NaOMe solution in MeOH at room temperature within 12 h. However, in a bid to shorten the reaction time, we applied the microwave irradiation in a closed vessel condition (90 °C), which eventually finished in 12 min as compared to 3 h in refluxing conditions. Upon completion of the reaction as judged by TLC, the reaction mixture was concentrated and ionic liquid support was precipitated by ether, which was removed by filtration. The filtrates were evaporated and subjected to HPLC analysis, which indicated the 71–97% crude purity of title compounds. Finally column chromatography purification afforded the 2-substituted aminobenzimidazoles in good overall yields (Table 1).

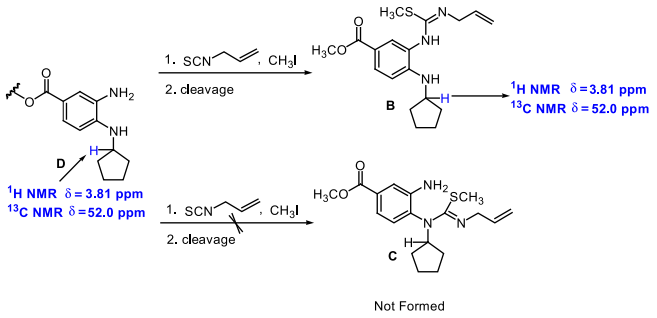


Fig. 3. The two possible routes for the formation of 2-substituted aminobenzimidazoles on ionic liquid support.

By utilizing the desired reaction sequence, we have synthesized various 2-substituted aminobenzimidazoles derivatives **7** with two points of structural diversity as shown in Table 1. The data exhibit that after five-step syntheses sequence 2-substituted aminobenzimidazoles derivatives were rapidly synthesized on the ionic liquid support under microwave irradiation in excellent overall yields and purities.

The main advantage of using the ionic liquid as the support was its direct monitoring reaction progress by standard analytical techniques, such as proton and carbon NMR and mass spectroscopy. Otherwise, ionic liquid bound product must be clipped off, and purified by column to confirm their structures. Herein, we first demonstrated the quantitative product conversion by regular proton NMR and mass spectroscopy in each intermediate step with an attached IL-tag. It has been found that the three protons Ha, Hb and Hc of free IL-tag appeared at 8.64, 7.45 and 7.34 ppm, respectively in spectra A (Fig. 4). The chemical shift of these three protons were shifted to more downfield along with the appearance of three more peaks at 8.67, 8.57 and 7.65 ppm due to the attachment of 4-fluoro-3-nitro benzoic acid. Formation of *o*-nitroaniline conjugates **4** were confirmed from the appearance of NH peak at 8.44 ppm in spectra C, which was further established by upfield shift of Hf proton. Subsequent reduction of *o*-nitro anilines **4** to the *o*-phenylenediamines **5** was observed by the shifting of Hd protons to 7.35 ppm from 8.57 ppm. Establishment of benzimidazole ring was evident from the appearance of Hd, He and Hf protons to the downfield region due to electron withdrawing nature of benzimidazole derivatives.

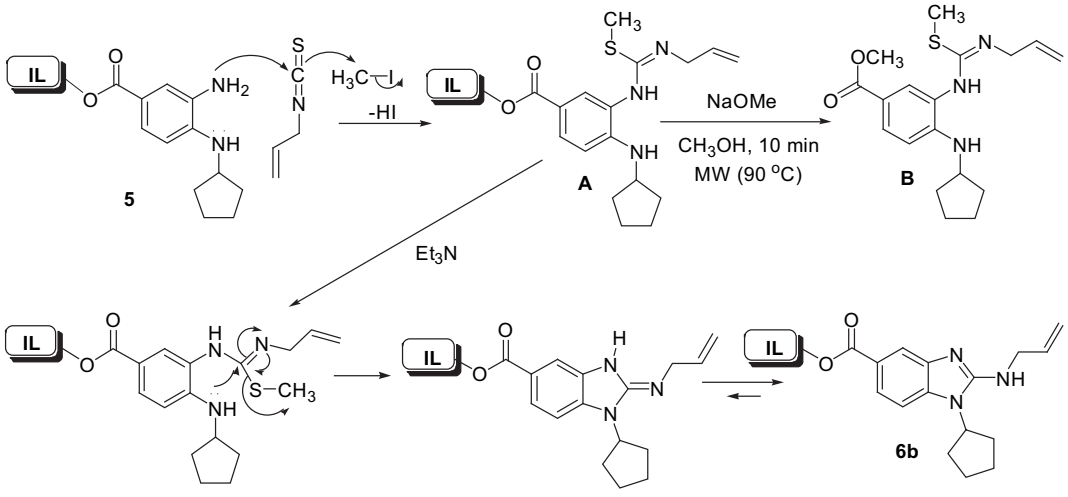
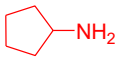
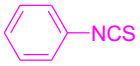
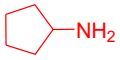
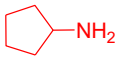
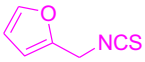
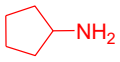
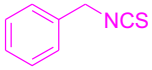
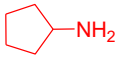
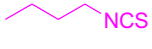
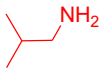
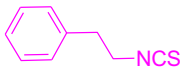
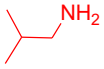
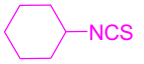
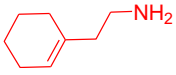
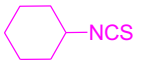
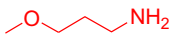
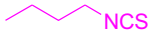
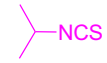
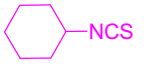
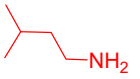
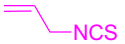
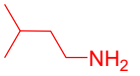
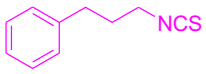
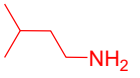
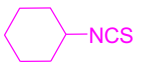


Fig. 2. Proposed mechanism for the formation of 2-substituted aminobenzimidazoles **6b** on ionic tag.

Table 1
Synthesis of 2-substituted aminobenzimidazol derivatives **7a**–**n** using microwave irradiation on ionic liquid tag

Entry	R_1NH_2	R_2NCS	Purity[a] (%)	Yield[b] (%)	LRMS[c]
7a			92	94	335[d]
7b			97	91	300
7c			71	84	340
7d			78	88	350[d]
7e			86	91	316
7f			75	79	351
7g			96	89	329
7h			88	78	381
7i			91	93	319
7j			93	85	289
7k			82	91	329
7l			86	90	301
7m			81	87	379
7n			77	91	343

[a] Determined by HPLC analysis (UV detection at 254 nm) of the crude product (%).
[b] Determined based on the weight of purified samples after performing the column chromatography (%).
[c] LRMS were detected with ESI ionization source.
[d] Compounds **7a** and **7d** were characterized by comparison of ^1H and ^{13}C NMR spectra with literature data.[21]

Finally, the cleavage of product **7** from ionic liquid support was confirmed by observing the absence of set of three signals at 9.50, 8.00 and 7.95 ppm due to ionic liquid moiety in spectra F. Moreover, all the intermediates of IL-supported products could be confirmed with mass spectra (MS), which has been shown in Table 2.

3. Conclusions

In summary, we have accomplished a concise synthesis of structurally diverse 2-substituted aminobenzimidazole frameworks through one pot cyclisation reaction of isothiocyanates and ionic-liquid supported *o*-phenylenediamine derivatives. The present synthetic approach is the first of its kind towards the synthesis of 2-substituted aminobenzimidazole derivatives with high efficiency, good yields, operational simplicity, as well as broad scope of substrate tolerance at a considerably reduced time and cost with microwave-assisted organic reactions on ionic liquid support. This method could be successfully extended to other heterocyclic compounds. High power microwave irradiation allowed us to reduce the total reaction time to 40 min compared to that of several hours under refluxing conditions. The key advantages of ionic liquid support afford product isolation and byproduct separation easily by ether precipitation with higher loading capacity than other homogeneous or heterogeneous supports. The diverse library construction and subsequent results of biological evaluation of these compounds will be reported in due course.

4. Experimental section

4.1. General procedure for the synthesis of ionic liquid (IL) bound 4-fluoro-3-nitro benzoic acid 3

4-Fluoro-3-nitro benzoic acid **2** (0.573 g, 3.14 mmol, 1.34 equiv), 1-methyl-3-ethyl imidazolium tetrafluoroborate **1** (0.50 g, 2.34 mmol, 1.0 equiv) and *N*,*N*′-dimethylamino pyridine (DMAP) (0.005 g) are placed in a dry, nitrogen-purged 100 mL round-bottom flask containing dry CH_3CN (15 mL). To the mixtures was added dropwise *N*,*N*′-dicyclohexylcarbodiimide (DCC) (0.675 g, 3.28 mmol, 1.4 equiv) dissolved in dry CH_2Cl_2 (5 mL) for a period of 5 min. The reaction mixtures were stirred for another 15 min at room temperature. Then this O-acylation reaction was carried out in a tube under microwave radiation to 95 °C for 10 min at 72 W (Biotage initiator, model no: Initiator US, 355286, 10429-22T, using IR sensor as internal probe for the control of temperature and compressed air system for cooling). After the completion of the reaction, the insoluble DCU byproduct was allowed to settle, and the reaction mixtures were filtered and washed with CH_3CN (50 mL×3). The solvent was evaporated, and the residue was again precipitated with cold ether, which was filtered through fritted funnel to remove any un-reacted acid and DCC, finally collected and dried under vacuum as a white solid. ^1H NMR (300 MHz, acetone-d_6) δ 9.16 (s, 1H), 8.64 (dd, J=7.2, 2.1 Hz, 1H), 8.49–8.44 (m, 1H), 7.92 (d, J=1.7 Hz, 1H), 7.74 (d, J=1.7 Hz, 1H), 7.65 (dd, J=7.2, 2.1 Hz, 1H), 4.90 (t, J=5.8 Hz, 2H), 4.84 (t, J=5.8 Hz, 2H) 4.06 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 163.6, 160.1, 156.5, 137.7, 137.5, 127.9, 124.5, 123.5, 119.8, 119.5, 64.5, 48.4, 36.2; MS (ESI) m/z 294 ($M-BF_4^-$).

4.2. General procedure for the synthesis of ionic liquid (IL) bound 4-cyclopentylamino-3-nitro benzoic acid 4b

Cyclopentyl amine (0.535 g, 6.28 mmol, 2.0 equiv) was added to the ionic liquid bound 4-fluoro-3-nitro benzoic acid **3** (1.20 g, 3.14 mmol, 1.0 equiv) solution in dry CH_3CN (10 mL) at room temperature for 5 min. The reaction mixtures were subsequently heated with stirring in a 10 mL microwave process vial for 3 min at 73 W in the appropriate mode of pressure and temperature. After completion of the reaction time, the reaction mixtures were precipitated with slow addition of cold ether (100 mL), which was filtered through a fritted funnel to obtain the ionic liquid bound 4-cyclopentylamino-3-nitro benzoic acid **4b** as a yellow solid in high purity. ^1H NMR (300 MHz, acetone-d_6) δ 9.21 (s, 1H), 8.69 (s, 1H), 8.39 (s, NH), 8.06 (d, J=8.7 Hz, 1H), 7.96 (s, 1H), 7.74 (s, 1H), 74.18 (d, J=8.7 Hz, 1H), 4.86 (t, J=4.5 Hz, 2H), 4.75 (t, J=4.5 Hz, 2H), 4.20 (quint, J=5.9 Hz, 1H), 4.08 (s, 3H), 2.23–2.09 (m, 3H), 1.81–1.61 (m, 5H); ^{13}C NMR (75 MHz, acetone-d_6) δ 164.6, 147.5, 137.7, 136.4, 131.3, 129.3, 124.4, 123.5, 116.2, 115.6, 63.4, 54.6, 49.0, 36.2, 33.4, 24.6; MS (ESI) m/z 359 ($M-BF_4^-$).

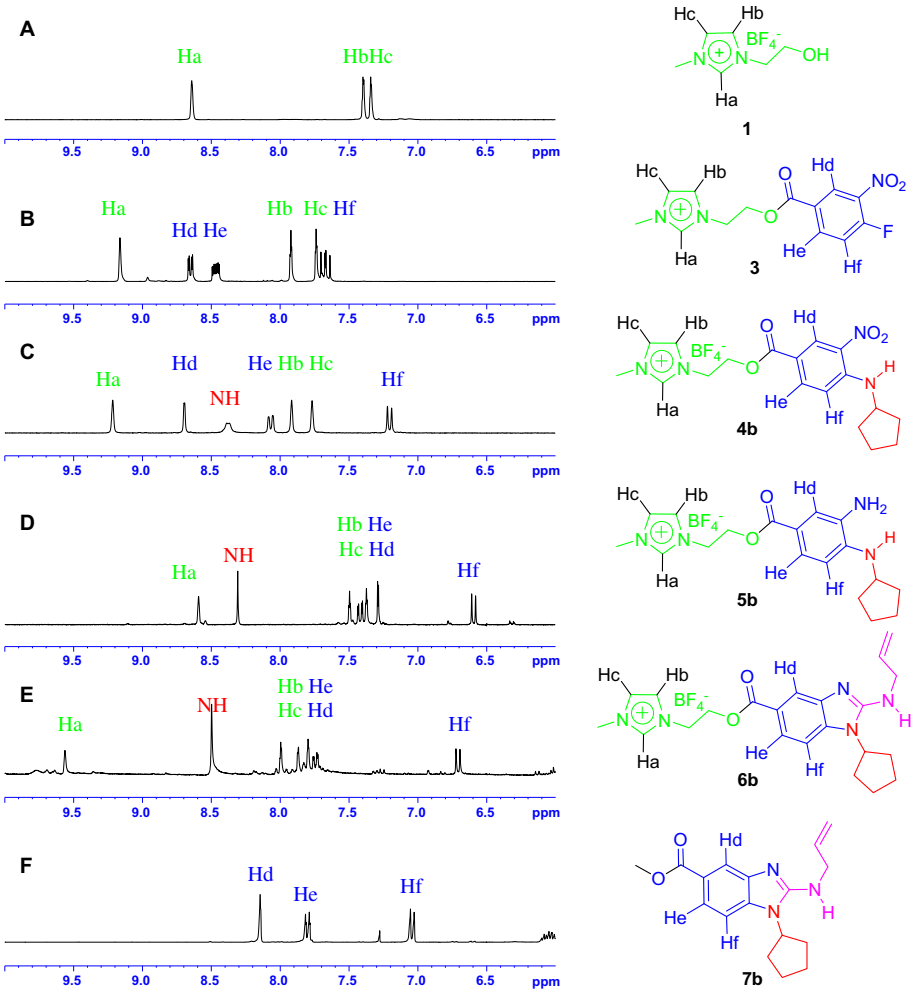


Fig. 4. Stepwise monitoring of 2-substituted aminobenzimidazol derivatives by ^{1}H NMR spectroscopy.

Table 2
Mass spectral study of ionic-liquid supported intermediates

Entry	Products	ESI (Mass)	Yields (%)
1	**3**	M^{+}=294	96
2	**4b**	M^{+}=359	93
3	**5b**	M^{+}=329	94
4	**6b**	M^{+}=398	91

4.3. General procedure for the preparation of the ionic liquid (IL) bound 3-amino-4-cyclopentylamino benzoic acid 5b

To a solution of **4b** (1.28 g, 2.85 mmol, 1.0 equiv) in dry methanol (10 mL), Zn (1.30 m, 20.0 mmol, 7.0 equiv) and ammonium formate (2.7 m, 42.8 mmol, 15.0 equiv) were added. The reaction mixtures were subsequently heated with stirring in a 10 mL microwave process vial at 60 W for 5 min to complete reduction of nitro group. After completion, the reaction mixtures were then subjected to centrifugation to remove Zn and the supernatant liquid was concentrated by rotary evaporation to remove methanol. Acetonitrile (10 mL) was then added to salt out ammonium formate. The reaction mixtures were filtered through fritted funnel to remove ammonium formate to obtain the ionic liquid bound 3-amino-4-cyclopentylamino benzoic acid **5b** as a pale brownish solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 9.17 (s, 1H), 8.30 (s, NH), 7.85 (d, J=1.6 Hz, 1H), 7.72 (d, J=1.6 Hz, 1H), 7.65 (dd, J=8.5, 1.9 Hz, 1H), 7.12 (d, J=1.9 Hz, 1H), 6.68 (d, J=8.5 Hz, 1H), 4.78 (t, J=4.4 Hz, 2H), 4.64 (t, J=4.5 Hz, 2H), 4.04 (s, 3H), 3.90 (quint, J=6.0 Hz, 1H), 2.09–2.05 (m, 3H), 1.70–1.60 (m, 5H); ^{13}C NMR (75 MHz, acetone-d_6) δ 166.1, 144.9, 137.7, 136.1, 127.9, 124.3, 123.5, 120.4, 115.9, 109.6, 62.5, 54.5, 49.3, 36.2, 33.3, 24.3; MS (ESI) m/z 329 ($M-BF_4^-$).

4.4. General procedure for the preparation of ionic liquid bound 2-allylamino-1-Cyclopentyl-1*H*-benzo[*d*]imidazole carboxylates 6b

To a stirred solution of ionic liquid bound 3-amino-4-cyclopentylamino benzoic acid **5b** (1.10 g, 2.63 mmol, 1.0 equiv) in dry CH_3CN (5 mL), allyl isothiocyanate (0.781 g, 7.89 mmol, 3.0 equiv), CH_3I (1.11 g, 7.89 mmol, 3.0 equiv) and triethyl amine (Et_3N) (0.80 g, 7.89 mmol, 3.0 equiv) were added in a sequential order. The reaction mixtures were exposed under pressured microwave irradiation to (90° C, 1 bar) for 12 min at 70 W. Upon cyclisation, the crude product mixtures were purified by precipitation with cold ether (100 mL×3) and dried to obtain the conjugate **6b** as a pale brownish solid in high purity. ^{1}H NMR (300 MHz, acetone-d_6) δ 9.42 (s, 1H), 8.36 (s, NH), 7.89 (d, J=1.6 Hz, 1H), 7.83–7.70 (m, 2H), 7.62–7.59 (m, 1H), 6.80 (d, J=8.5 Hz, 1H), 5.89 (m, 1H), 5.40 (dd, J=15.1, 1.3 Hz, 1H), 5.25 (dd, J=10.1, 1.3 Hz, 1H), 4.66 (t, J=4.4 Hz, 2H), 4.54 (t, J=4.5 Hz, 2H), 3.89 (s, 3H), 3.17 (m, 1H), 1.98–1.95 (m, 3H), 1.66–1.55 (m, 5H); ^{13}C NMR (75 MHz, acetone-d_6) δ 165.4, 152.0, 148.9, 137.3, 135.1, 131.8, 131.6, 124.1, 123.4, 117.6, 117.1, 63.1, 62.8, 50.0, 56.3, 47.4, 47.3, 37.2, 33.4, 33.0, 24.3, 9.0; MS (ESI) m/z 398 ($M-BF_4^-$).

4.5. General procedure for the cleavage of ionic liquid bound 2-allylamino-1-cyclopentyl-1*H*-benzo[*d*]imidazole-5-carboxylic acid derivatives 6b

To a solution of conjugates **6b** (0.95 g, 2.67 mmol, 1.0 equiv) in methanol (20 mL), NaOMe (0.10 g, 1.88 mmol, 0.7 equiv) was added and irradiated under pressured microwave irradiation at (90° C, 4 bar) for 10 min at 75 W. After completion of the reaction, the crude product was precipitated with excess of cold ether (100 mL), the ionic liquid was filtered off and subjected to evaporation. The residue was dried under vacuum, and subjected to crude HPLC analysis with UV detection at λ=254 nm (column: Sphereclone 5 μ Si (250×4.6 mm); gradient: 35% ethyl acetate in hexane; flow rate: 1 mL/min). The slurry obtained was loaded on silica gel column and eluted with a mixture of ethyl acetate and hexane (2:3) to get the title compounds **7b** as a brown solid in good yields.

*4.5.1. 1-Cyclopentyl-2-(phenylamino)-1H-benzo[d]imidazole-5-carboxylic acid methyl ester (**7a**).* Pale yellow solid. ^{1}H NMR (300 MHz) δ 8.23 (d, *J*=1.3 Hz, 1H), 7.87 (dd, *J*=8.4, 1.3 Hz, 1H), 7.40 (d, *J*=8.0 Hz, 2H), 7.26 (d, *J*=8.4 Hz, 1H), 7.20 (t, *J*=8.0 Hz, 2H), 6.94 (t, *J*=7.4 Hz, 1H), 4.81 (quint, *J*=8.7 Hz, 1H), 3.93 (s, 3H), 2.19–2.13 (m, 4H), 2.00 (quint, *J*=7.0 Hz, 2H), 1.78 (quint, *J*=7.0 Hz, 2H); ^{13}C NMR (300 MHz) δ 168.2, 151.6, 141.2, 140.8, 135.9, 129.6, 123.9, 123.2, 123.0, 119.4, 119.3, 109.9, 56.3, 52.4, 30.2, 25.7; IR (cm^{-1}, KBr): 3270, 1707; MS (ESI) *m*/*z* 336 (MH$^+$).

*4.5.2. 2-Allylamino-1-cyclopentyl-1H-benzo[d]imidazole-5-carboxylic acid methyl ester (**7b**).* Brown solid. ^{1}H NMR (300 MHz) δ 8.17 (d, *J*=1.3 Hz, 1H), 7.79 (dd, *J*=8.4, 1.3 Hz, 1H), 7.18 (d, *J*=8.4 Hz, 1H), 6.03 (m, 1H), 5.32 (dd, *J*=17.1, 1.3 Hz, 1H), 5.21 (dd, *J*=10.3, 1.3 Hz, 1H), 4.78 (br s, NH), 4.60 (quint, *J*=8.3 Hz, 1H), 4.21 (d, *J*=5.2 Hz, 2H), 3.96 (s, 3H), 2.16–2.11 (m, 4H), 1.98 (quint, *J*=7.0 Hz, 2H), 1.80 (quint, *J*=7.0 Hz, 2H); ^{13}C NMR (300 MHz) δ 168.3, 154.8, 141.8, 136.8, 134.8, 123.6, 122.2, 118.4, 117.3, 109.0, 55.6, 52.3, 43.4, 29.9, 25.6; IR (cm^{-1}, KBr): 3251, 1712; MS (ESI) *m*/*z* 300 (MH$^+$); HRMS (ESI, *m*/*z*) calcd for $C_{17}H_{22}N_3O_2$: *m*/*z* 300.1712; found 300.1711.

*4.5.3. 1-Cyclopentyl-2-(furan-3-yl-methylamino)-1H-benzo[d]imidazole-5-carboxylic acid methyl ester (**7c**).* White solid. ^{1}H NMR (300 MHz) δ 8.18 (d, *J*=1.2 Hz, 1H), 7.78 (dd, *J*=8.3, 1.2 Hz, 1H), 7.37 (d, *J*=1.0 Hz, 1H), 7.18 (d, *J*=8.3 Hz, 1H), 6.33 (m, 2H), 5.01 (br s, NH), 4.73 (d, *J*=7.1 Hz, 2H), 4.56 (quint, *J*=8.2 Hz, 1H), 3.95 (s, 3H), 2.18–2.05 (m, 4H), 1.98 (quint, *J*=7.3 Hz, 2H), 1.79 (quint, *J*=7.3 Hz, 2H); ^{13}C NMR (300 MHz) δ 168.4, 154.8, 151.8, 142.7, 142.3, 136.9, 123.5, 122.2, 118.7, 110.9, 109.1, 108.4, 55.6, 52.3, 41.1, 30.0, 25.5; IR (cm^{-1}, KBr): 3295, 1710; MS (ESI) *m*/*z* 340 (MH$^+$); HRMS (ESI, *m*/*z*) calcd for $C_{19}H_{22}N_3O_2$: *m*/*z* 340.1661; found 340.1659.

*4.5.4. 2-(Benzylamino)-1-cyclopentyl-1H-benzo[d]imidazole-5-carboxylic acid methyl ester (**7d**).* Pale white solid. ^{1}H NMR (300 MHz) δ 8.19 (d, *J*=1.3 Hz, 1H), 7.80 (dd, *J*=8.4, 1.3 Hz, 1H), 7.44 (d, *J*=7.9 Hz, 2H), 7.39–7.29 (m, 3H), 7.18 (d, *J*=8.4 Hz, 1H), 4.86 (br s, NH), 4.75 (s, 2H), 4.54 (quint, *J*=8.7 Hz, 1H), 3.93 (s, 3H), 2.19–2.13 (m, 4H), 2.00 (quint, *J*=7.8 Hz, 2H), 1.79 (quint, *J*=7.8 Hz, 2H); ^{13}C NMR (300 MHz) δ 168.3, 154.9, 141.9, 138.6, 136.8, 129.2, 128.5, 128.2, 123.6, 122.3, 118.6, 109.1, 55.7, 52.3, 48.3, 30.0, 25.5; IR (cm^{-1}, KBr): 3249, 1714; MS (ESI) *m*/*z* 350 (MH$^+$); HRMS (ESI, *m*/*z*) calcd for $C_{21}H_{24}N_3O_2$: *m*/*z* 350.1868; found 350.1866.

*4.5.5. 2-(Butylamino)-1-cyclopentyl-1H-benzo[d]imidazole-5-carboxylic acid methyl ester (**7e**).* Pale white solid. ^{1}H NMR (300 MHz) δ 8.17 (d, *J*=1.4 Hz, 1H), 7.77 (dd, *J*=8.4, 1.4 Hz, 1H), 7.17 (d, *J*=8.4 Hz, 1H), 4.68 (br s, NH), 4.64 (quint, *J*=8.2 Hz, 1H), 3.96 (s, 3H), 3.57 (q, *J*=7.5 Hz, 2H), 2.15–2.01 (m, 4H), 2.00 (quint, *J*=7.1 Hz, 2H), 1.81 (quint, *J*=7.1 Hz, 2H), 1.70 (quint, *J*=7.5 Hz, 2H), 1.43 (sext, *J*=7.5 Hz, 2H), 0.94 (t, *J*=7.5 Hz, 2H); ^{13}C NMR (300 MHz) δ 168.2, 154.8, 141.1, 136.5, 123.6, 122.3, 117.9, 109.0, 55.6, 52.3, 44.0, 32.2, 29.2, 25.6, 20.5, 14.2; IR (cm^{-1}, KBr): 3322, 1709; MS (ESI) *m*/*z* 316 (MH$^+$); HRMS (ESI, *m*/*z*) calcd for $C_{18}H_{26}N_3O_2$: *m*/*z* 316.2025; found 316.2027.

*4.5.6. 1-Isobutyl-2-(phenylethylamino)-1H-benzo[d]imidazole-5-carboxylic acid methyl ester (**7f**).* Pale yellow solid. ^{1}H NMR (300 MHz) δ 8.18 (d, *J*=1.3 Hz, 1H), 7.78 (dd, *J*=8.3, 1.3 Hz, 1H), 7.33–7.31 (m, 2H), 7.25–7.16 (m, 3H), 7.01 (d, *J*=8.3 Hz, 1H), 4.35 (t, *J*=6.0 Hz, 1H), 3.92 (s, 3H), 3.82 (q, *J*=6.6 Hz, 2H), 3.51 (d, *J*=7.5 Hz, 2H), 3.03 (t, *J*=6.6 Hz, 2H), 1.95 (sext, *J*=6.0 Hz, 1H), 0.85 (d, *J*=6.0 Hz, 6H); ^{13}C NMR (300 MHz) δ 168.5, 155.5, 142.4, 139.2, 139.1, 129.3, 129.1, 127.1, 123.5, 122.2, 118.4, 107.4, 52.3, 50.3, 44.5, 35.8, 28.9, 20.5; IR (cm^{-1}, KBr): 3326, 1691; MS (EI) *m*/*z* 351 (M$^+$); HRMS (EI, *m*/*z*) calcd for $C_{21}H_{25}N_3O_2$: *m*/*z* 351.1947; found 351.1942.

*4.5.7. 2-(Cyclohexylamino)-1-isobutyl-1H-benzo[d]imidazole-5-carboxylic acid methyl ester (**7g**).* White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J*=1.4 Hz, 1H), 7.77 (dd, *J*=8.3, 1.4 Hz, 1H), 7.02 (d, *J*=8.3 Hz, 1H), 4.08 (d, *J*=7.5 Hz, 1H), 3.98 (m, 1H), 3.89 (s, 3H), 3.65 (d, *J*=7.4 Hz, 2H), 2.17–2.13 (m, 2H), 1.93 (sext, *J*=6.6 Hz, 1H), 1.77–1.49 (m, 4H), 1.31–1.22 (m, 4H), 0.97 (d, *J*=6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 154.9, 142.5, 138.9, 123.4, 122.0, 118.2, 107.3, 52.2, 52.2, 50.3, 34.2, 29.1, 26.0, 25.1, 20.7; IR (cm^{-1}, KBr): 3326, 1706; MS (EI) *m*/*z* 329 (M$^+$); HRMS (EI, *m*/*z*) calcd for $C_{19}H_{27}N_3O_2$: *m*/*z* 329.2103; found 329.2110.

*4.5.8. 1-(2-Cyclohexenylethyl)-2-cvyclohexylamino-1H-benzo[d]imidazole-5-carboxylic acid methyl ester (**7h**).* White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J*=1.4 Hz, 1H), 7.79 (dd, *J*=8.3, 1.4 Hz, 1H), 7.03 (d, *J*=8.3 Hz, 1H), 5.41 (m, 1H), 4.12 (d, *J*=7.5 Hz, 1H), 3.94 (t, *J*=6.8 Hz, 2H), 3.90 (s, 3H), 3.84 (m, 1H), 2.34 (t, *J*=6.8 Hz, 2H), 2.20–2.17 (m, 2H), 1.93–1.90 (m, 4H), 1.75–1.61 (m, 2H), 1.59–1.46 (m, 8H), 1.28–1.23 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 154.6, 142.3, 138.4, 134.2, 125.4, 123.5, 122.1, 118.3, 106.9, 52.2, 52.2, 42.2, 37.0, 34.3, 29.2, 26.1, 25.6, 25.3, 23.1, 22.3. IR (cm^{-1}, KBr): 3361, 1708; MS (EI) *m*/*z* 381 (M$^+$); HRMS (EI, *m*/*z*) calcd for $C_{23}H_{31}N_3O_2$: *m*/*z* 381.2416; found 381.2410.

*4.5.9. 2-(Butylamino)-1-(3-methoxypropyl)-1H-benzo[d]imidazole-5-carboxylic acid methyl ester (**7i**).* Pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J*=1.4 Hz, 1H), 7.78 (dd, *J*=8.3, 1.4 Hz, 1H), 7.02 (d, *J*=8.3 Hz, 1H), 5.41 (m, NH), 4.00 (t, *J*=6.0 Hz, 2H), 3.89 (s, 3H), 3.54–3.48 (m, 2H), 3.38 (s, 3H), 3.33 (t, *J*=6.0 Hz, 2H), 2.01 (t, *J*=6.0 Hz, 2H), 1.66 (quint, *J*=7.5 Hz, 2H), 1.41 (sext, *J*=7.5 Hz, 2H), 0.94 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 154.4, 142.2, 138.4, 123.6, 122.3, 117.9, 106.8, 68.0, 58.9, 52.3, 43.6, 38.7, 32.3, 28.7, 20.5, 14.2; IR (cm^{-1}, KBr): 3320, 1708; MS (EI) *m*/*z* 319 (M$^+$); HRMS (EI, *m*/*z*) calcd for $C_{17}H_{25}N_3O_2$: *m*/*z* 319.1896; found 319.1890.

*4.5.10. 1-Butyl-2-isopropylamino-1H-benzo[d]imidazole-5-carboxylic acid methyl ester (**7j**).* White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.78 (d, *J*=8.3 Hz, 1H), 7.04 (d, *J*=8.3 Hz, 1H), 4.31 (m, 1H), 4.09 (d, *J*=7.2 Hz, 1H), 3.95 (s, 3H), 3.86 (t, *J*=7.2 Hz, 2H), 1.72 (quint, *J*=7.2 Hz, 2H), 1.41–1.36 (m, 2H), 1.33 (d, *J*=6.5 Hz, 6H), 0.94 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 154.7, 142.6, 138.5, 123.5, 122.1, 118.4, 106.9, 52.2, 45.6, 42.5, 31.4, 23.9, 20.6, 14.1; IR (cm^{-1}, KBr): 3241, 1714; MS (EI) *m*/*z* 289 (M$^+$);

HRMS (EI, *m*/*z*) calcd for $C_{16}H_{23}N_3O_2$: *m*/*z* 289.1790; found 289.1783.

*4.5.11. 1-Butyl-2-cyclohexylamino-1H-benzo[d]imidazole-5-carboxylic acid methyl ester (**7k**).* White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J*=1.4 Hz, 1H), 7.77 (dd, *J*=8.3, 1.4 Hz, 1H), 7.01 (d, *J*=8.3 Hz, 1H), 4.21 (d, *J*=7.5 Hz, 1H), 3.98 (m, 1H), 3.88 (s, 3H), 3.83 (t, *J*=7.1 Hz, 2H), 2.15–2.13 (m, 2H), 1.77–1.61 (m, 5H), 1.52–1.21 (m, 7H), 0.92 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 154.8, 142.6, 138.6, 123.3, 121.9, 118.2, 106.9, 52.2, 52.2, 42.5, 34.2, 31.3, 26.0, 25.3, 20.6, 14.1; IR (cm^{-1}, KBr): 3215, 1708; MS (EI) *m*/*z* 329 (M^+); HRMS (EI, *m*/*z*) calcd for $C_{19}H_{27}N_3O_2$: *m*/*z* 329.2103; found 329.2113.

*4.5.12. 2-Allylamino-1-1sopentyl-1H-benzo[d]imidazole-5-carboxylic acid methyl ester (**7l**).* Pale brownish solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J*=1.5 Hz, 1H), 7.77 (dd, *J*=8.3, 1.5 Hz, 1H), 7.04 (d, *J*=8.3 Hz, 1H), 6.04 (m, 1H), 5.28 (dd, *J*=17.1, 1.4 Hz, 1H), 5.17 (dd, *J*=10.2, 1.4 Hz, 1H), 4.63 (m, NH), 4.19 (d, *J*=6.7 Hz, 2H), 3.93–3.87 (m, 5H), 1.62–1.60 (m, 3H), 0.96 (d, *J*=6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 155.1, 142.3, 138.5, 135.0, 123.5, 122.3, 118.5, 116.9, 107.0, 52.3, 46.2, 41.2, 37.9, 26.3, 22.8; IR (cm^{-1}, KBr): 3220, 1714; MS (EI) *m*/*z* 301 (M^+); HRMS (EI, *m*/*z*) calcd for $C_{17}H_{23}N_3O_2$: *m*/*z* 301.1790; found 301.1788.

*4.5.13. 1-Isopentyl-2-phenylpropylamino-1H-benzo[d]imidazole-5-carboxylic acid methyl ester (**7m**).* Pale white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J*=1.4 Hz, 1H), 7.81 (dd, *J*=8.3, 1.4 Hz, 1H), 7.33–7.19 (m, 5H), 7.02 (d, *J*=8.3 Hz, 1H), 4.15 (m, 1H), 3.91 (s, 3H), 3.74 (t, *J*=7.5 Hz, 2H), 3.67–3.66 (dt, *J*=5.8, 6.7 Hz, 2H), 2.78 (t, *J*=7.5 Hz, 2H), 2.11 (q, *J*=7.5 Hz, 2H), 1.63 (sext, *J*=6.7 Hz, 1H), 1.56 (quint, *J*=7.5 Hz, 2H), 0.97 (d, *J*=6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 155.2, 142.3, 141.9, 138.4, 128.9, 128.9, 126.5, 123.6, 122.3, 118.4, 106.9, 52.3, 43.7, 41.1, 38.9, 33.9, 31.6, 26.2, 22.8; IR (cm^{-1}, KBr): 3221, 1711; MS (EI) *m*/*z* 379 (M^+); HRMS (EI, *m*/*z*) calcd for $C_{23}H_{29}N_3O_2$: *m*/*z* 379.2260; found 379.2264.

*4.5.14. 2-Cyclohexylamino-1-1sopentyl-1H-benzo[d]imidazole-5-carboxylic acid methyl ester (**7n**).* White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J*=1.3 Hz, 1H), 7.80 (dd, *J*=8.2, 1.3 Hz, 1H), 7.03 (d, *J*=8.2 Hz, 1H), 4.06 (d, *J*=7.5 Hz, 1H), 3.91 (m, 1H), 3.89 (s, 3H), 3.85 (t, *J*=7.5 Hz, 2H), 2.18–2.15 (m, 2H), 1.79–1.59 (m, 6H), 1.58–1.48 (m, 2H), 1.28–1.25 (m, 3H), 1.00 (d, *J*=6.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 154.7, 142.6, 138.5, 123.5, 122.1, 118.4, 106.9, 52.3, 52.1, 41.0, 37.9, 34.3, 26.1, 26.0, 25.2, 22.9; IR (cm^{-1}, KBr): 3324, 1714; MS (EI) *m*/*z* 343 (M^+); HRMS (EI, *m*/*z*) calcd for $C_{20}H_{29}N_3O_2$: *m*/*z* 343.2260; found 343.2262.

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Supplementary data

General experimental procedures and representative ^{1}H NMR, ^{13}C NMR, Crude HPLC, LRMS, HRMS and FT-IR spectral data of compounds **7a**–**n** as well as the intermediates are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.06.068.

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