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A concise synthesis of 2-(2-aminothiophene)-benzimidazoles by one-pot multicomponent reaction†

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A one-pot synthesis of 2-aminothiophene linked benzimidazoles was achieved by utilizing 2-cyanomethyl benzimidazoles in a modified Gewald multicomponent reaction. The synthetic strategy of the reaction involved treatment of 2-(cyanomethyl)-benzimdazole with aldehydes containing an active methylene group and sulfur powder under refluxing conditions. The multicomponent reaction proceeded *via* Knoevenagel condensation of 2-(cyanomethyl)-benzimdazole with aldehyde to generate an α,β-unsaturated nitrile followed by cyclization with molecular sulfur under basic conditions to give biologically relevant 2-(2-aminothiophene)-benzimidazoles in good yields.

Introduction

Despite innumerable discoveries in the field of medicinal chemistry, various diseases originating from either microorganisms or malfunction of body organs post many challenges. This has caused organic chemists to search for new biologically active molecules which are more challenging and interesting. Aminothiophenes are one of the few widely study molecular architectures for their diverse biological properties. A few examples of medicinally important 2-aminothiophenes are shown in Fig. 1.

Olanzapine (**I**) is a widely used antipsychotic drug for the treatment of schizophrenia or bipolar disorder.[1] Tinoridine (**II**) is an anti-inflammatory drug,[2] while fully substituted 2-aminothiophene (**III**) is an agonist of allosteric enhancers at the adenosine A1 receptor.[3] 2-Aryl or 2-heteroaryl substituted benzimidazoles are known for antitumor and anti helminthiasis activity. Thiophene linked benzimidazole (**IV**) is active against helminthiasis infection in humans and other mammals.[4]

The Gewald multicomponent reaction is an elegant and promising synthetic route for the synthesis of 2-aminothiophenes.[5] The parent reaction involves Knoevenagel condensation of cyanoacetate with an aldehyde or ketone having an α-CH_2 group followed by cyclisation with molecular sulfur under basic conditions.[6] Many modified versions of this reaction have been reported. These include use of various activated nitriles such as malononitrile, cyanoacetic esters, and cyanoacetamide. Modern methods such as microwave irradiation,[7] electrochemical activation,[8] use of a solid support,[9] ionic liquid,[10] polymer supported reactions,[11] use of nano-sized catalysts[12] are applied advantageously for synthesis of widely functionalized 2-aminothiophenes using Gewald reaction in recent years.

The synthesis of 2-aryl or 2-heteroaryl benzimidazoles is mostly limited to use of *o*-phenylenediamine. The reaction involves condensation of *o*-phenylenediamine with a carbonyl compound or its precursor at elevated temperature or in acidic catalyst. The reaction is generally associated with harsh reaction conditions, long reaction time and moderate yields of product. Recently a few examples of high product yields under mild reaction conditions have been reported.[13] Ellman and co-workers have employed Rh(I)-catalyzed C–H activation of benzimidazoles for the synthesis of 2-aryl/heteroaryl substituted benzimidazoles.[14] However most of these reports are limited to the synthesis of 2-(3-furyl)-benzimidazole. 2-Thiophene linked benzimidazoles with molecular diversity on both benzimidazole and thiophene rings can serve as potential candidates for SAR-based drug discovery studies as they contain two pharmacophores, *i.e.* benzimidazole and 2-aminothiophene moieties. A straightforward method that enables synthesis of 2-aminothiophene linked benzimidazoles with various substituents on both benzimidazole and thiophene rings will be of great advantage in the development of new small chemical entities to explore novel biological profiles.

We were involved in the diversity-oriented synthesis of functionalized benzimidazoles and their use in medicinally important scaffolds.[15] In the current study, we disclose a well planned and executed synthesis of 3-(2-aminothiphene)-benzimidazoles utilizing a multicomponent reaction on 2-cyanomethyl benzimidazoles.

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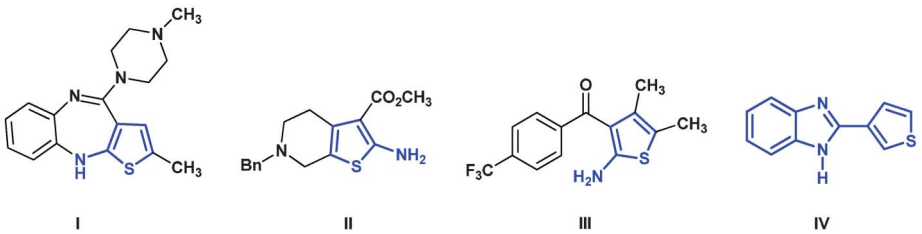


Fig. 1 Biologically important aminothiophenes.

Result and discussion

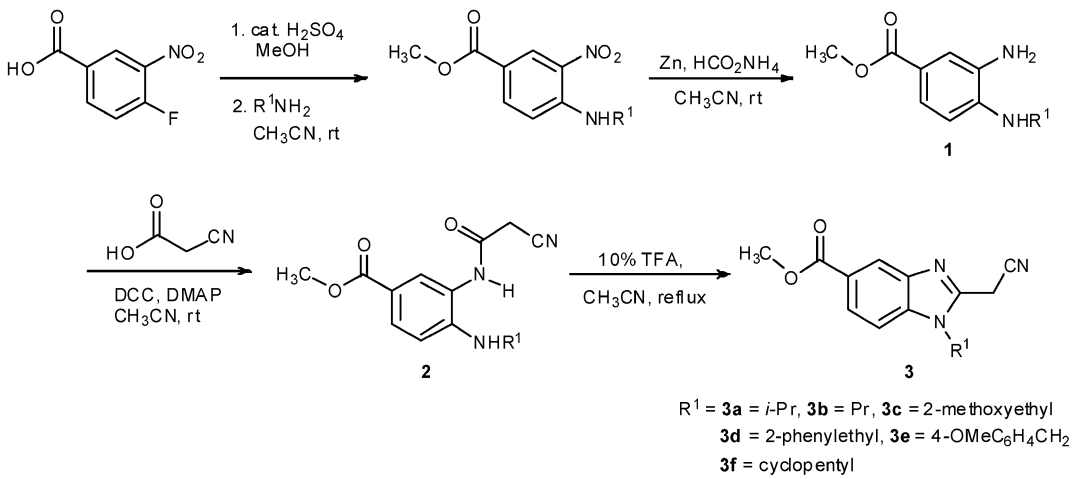
The study began with the synthesis of various *N*-alkylated 2-(cyanomethyl)-benzimidazoles (Scheme 1). The sulfuric acid catalyzed methyl esterification of 3-amino-4-flurobenzoic acid was followed by aromatic nucleophilic substitution of fluorine with various amines and reduction of the nitro group yielded corresponding methyl-3,4-diaminobenzoates **1**. The condensation of primary amine of **1** with cyanoacetic acid gave α-cyanoacetamide **2** that was cyclized under acidic conditions using TFA to obtain the desired 2-cyanomethyl benzimidazoles **3** in very good yields.[15,18]

The initial one-pot reaction was performed on benzimdazole **3a** (R^1 = isopropyl) and 3-phenylpropanal using piperidine, sulfur powder in refluxing dichloroethane that yielded benzimidazole linked 2-aminothiophene **4a** in 70% yield (Scheme 2). We quickly screened a few organic solvents such as toluene, acetonitrile and ethanol to optimize the conversion. This revealed ethanol as a better solvent to give high yield of product (entries 1–4) probably due to the better solubility of sulfur in ethanol (Table 1).

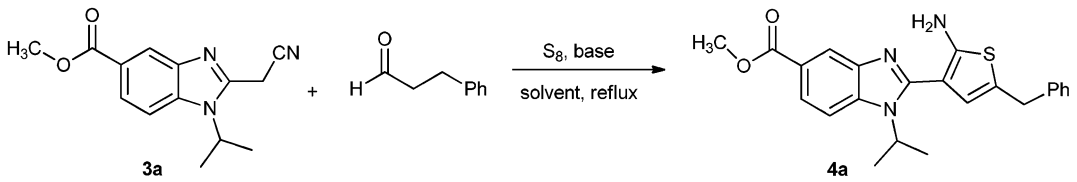
All reactions were then performed in refluxing conditions for 1.5 h with various bases (1.5 eq). When the reaction was performed using morpholine, DMAP or K_2CO_3 as a base, a moderate yield of the desired 2-aminothiophene **4a** was obtained (entries 8–10). However the yield of product **4a** were poor when the reaction was performed using Et_3N, DBU, imidazole, or *t*-BuOK as a base (entries 5–7 and 11). Comparable yields of product were obtained when the reaction was conducted using either piperidine or cesium fluoride as a base (entries 4 and 12). We preferred piperidine over CsF for the current studies due to the toxic and corrosive nature of cesium fluoride.

Under the optimized conditions, various *N*-alkyl benzimidazoles (**3a–f**) were treated with a number of α-methylene aldehydes to demonstrate the scope and generality of this protocol (Table 2). Various *N*-alkyl substituent groups on the benzimidazole nitrogen did not have any significant effect on reaction output and good yield of products was obtained in all cases. Benzimidazoles with nitrogen substituents such as cyclopentyl ring or 4-methoxy benzyl group with an active methylene group also reacted smoothly. Various aldehydes reacted smoothly and no change in reactivity was observed. Our method enables easy manipulation of the C-5 substituent (R^2) in the product thiophene molecule which can be used as a handle for SAR studies of these molecular frameworks in medicinal chemistry.

The structure of product **4e** (R^1 = propyl, R^2 = ethyl) was further confirmed by single crystal X-ray diffraction (Fig. 2).[16] The molecule takes a confirmation in which the *N*-alkyl substituent on the benzimidazole ring and free C-2 amino group on the thiophene ring are placed far from each other to



Scheme 1 Synthesis of 2-(cyanomethyl)-1-alkyl benzimidazoles.



Scheme 2 Multicomponent reaction on 2-(cyanomethyl)-*N*-isopropyl benzimidazole.

avoid possible steric crowding when they are close to each other.

The mechanism of product formation is proposed in Scheme 3. Initially, Knoevenagel condensation between 2-cyanomethylbenzimdazole and an aldehyde yields Knoevenagel condensation adduct, α,β-unsaturated nitrile **5**. Under basic conditions, α-sulfur generates a sulfide anion which simultaneously attacks on **5** to generate anion **6** that reacts with polysulfide to deliver ylidene sulfur adduct **7**. Intramolecular nucleophilic attack of S^- on the nitrile carbon delivers a cyclic adduct **8** that further tautomerizes to yield 2-aminothiophene benzimidazole **4**. We attempted a reaction between separately prepared Knoevenagel condensation adduct **5**, sulfur and propanal in absence of base and no product formation was observed. This confirmed the important role of a base in formation of adduct **7** and subsequent cyclization (Scheme 3).

Next, we demonstrated that the free amine group in the product 2-aminothiophenes can be a handle to increase molecular diversity. 2-Aminothiphene **4t** was mixed with maleic anhydride in dichloroethane and subjected to microwave irradiation at 100 °C for 5 min. The reaction yielded pyrrole-2,5-dione substituted thiophene **9** in 74% yield. The reaction involves nucleophilic attack of the amine nitrogen on the anhydride carbonyl group to generate intermediate amido acid which yields the observed pyrrole dione **9** after second nucleophilic attack and dehydration. Similarly 2-aminothiophene **4j** on treatment with uracil-derived bromomethyl pyrimidinonedione in the presence of triethylamine in refluxing acetonitrile gave highly substituted thiophene linked pyrrole **10** in 76% yield. The reaction proceeded *via* nucleophilic displacement of bromide by nitrogen and subsequent condensation with the benzoyl carbonyl group and dehydration to generate the pyrrole moiety in the observed product (Scheme 4).

In recent years ionic liquids (ILs) have emerged as an eco-friendly green reaction media.[17] Numerous advantages associated with IL-supported synthesis encouraged us to apply it for our current reaction system. In order to test the feasibility of an IL-supported reaction, we subjected IL-supported 2-cyanomethylbenzimidazole **IL-3** to the Gewald multicomponent reaction conditions.[18] Treatment of **IL-3** with 3-phenylpropanal and sulfur powder using piperidine as a base in acetonitrile resulted in smooth reaction to yield desired product **IL-4** in 76% yield as confirmed by mass analysis directly with ionic liquid support intact. Removal of the ionic liquid support using sodium methoxide gave 2-aminothiophene **4a** in overall 72% yield after precipitation (Scheme 5). Use of the ionic liquid as a soluble support facilitates purification by simple precipitation along with advantages like high loading capacity, homogeneous reaction conditions, and monitoring of the reaction progress by conventional NMR spectroscopy.

Table 1 Reaction optimization studies of the modified Gewald reaction[a]

Entry	Base	Solvent	Yield of **4a** (%)
1	Piperidine	DCE	70
2	Piperidine	Toluene	65
3	Piperidine	CH_3CN	67
4	Piperidine	EtOH	80
5	Et_3N	EtOH	43
6	DBU	EtOH	45
7	Imidazole	EtOH	35
8	Morpholine	EtOH	61
9	DMAP	EtOH	65
10	K_2CO_3	EtOH	59
11	*t*-BuOK	EtOH	23
12	CsF	EtOH	80

[a] All reactions were performed using 1.0 mmol benzimidazole, 1.2 mmol aldehyde, 1.5 mmol S, and 1.5 mmol of base in 5 mL solvent.

Conclusions

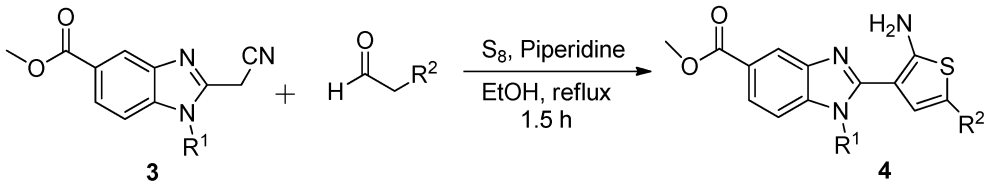
We report here the first one-pot multicomponent reaction on 2-(cyanomethyl)-benzimdazoles using various aldehydes containing an active methylene group and molecular sulfur under basic reaction conditions. Our method presents a simple and efficient route toward the generation of a combined novel fused, heterocyclic skeleton which is of substantial intellectual appeal resembling a drug-like molecule. We have also achieved a multicomponent condensation reaction on an ionic liquid support to afford the benzimidazole linked thiophene. The rapid synthesis and screening of a focused combinatorial library including the combination of these two heterocycles will certainly provide ample opportunity to discover interesting biological activity.

Experimental section

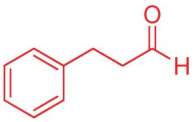
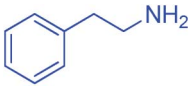
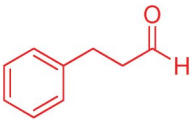
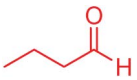
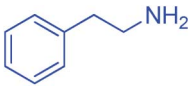
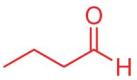
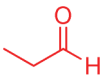
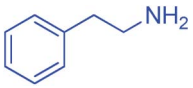
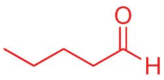
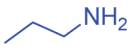
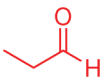
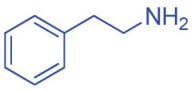
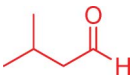
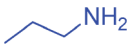
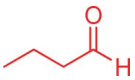
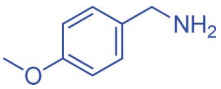
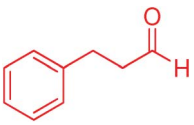
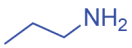
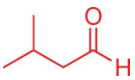
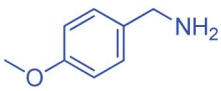
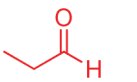
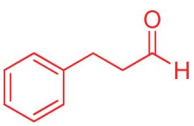
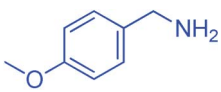
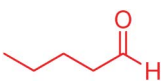
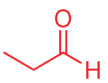
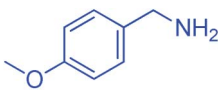
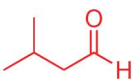
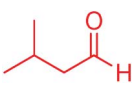
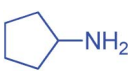
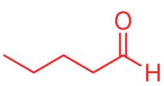
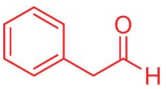
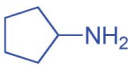
General procedure for multicomponent reaction

A reaction flask was charged with 2-(cyanomethyl)-benzimidazole (1.0 mmol), an aldehyde (1.2 mmol), sulfur powder (48

Table 2 One-pot multicomponent reaction of various benzimidazoles, aldehydes and molecular sulfur



3 4

Entry	R^1	R^2-CH_2CHO	Yield (%)	Entry	R^1	R^2-CH_2CHO	Yield (%)
4a			80	**4k**			72
4b			82	**4l**			71
4c			80	**4m**			86
4d			72	**4n**			81
4e			69	**4o**			79
4f			78	**4p**			85
4g			76	**4q**			86
4h			82	**4r**			85
4i			78	**4s**			74
4j			85	**4t**			80

mg, 1.5 mmol) and piperidine (148 μL, 1.5 mmol) in ethanol (5 mL). The reaction mixture was heated to reflux for 1.5 h. The progress of reaction was monitored by TLC. After completion, the reaction mixture was diluted with water, concentrated on a rotovap and extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated to obtain crude product that was purified by column chromatography in reported yields.

Procedure for ionic liquid supported Gewald reaction

A reaction vessel was charged with ionic liquid conjugated 2-(cyanomethyl)-benzimidazole **IL-3** (220 mg, 0.5 mmol), an aldehyde (80 mg, 0.6 mmol), sulfur powder (24 mg, 0.75 mmol)

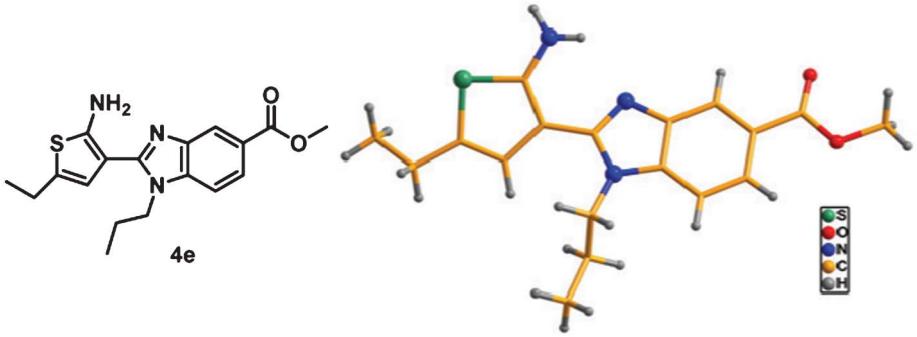
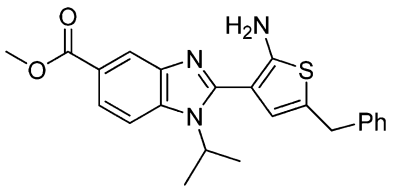


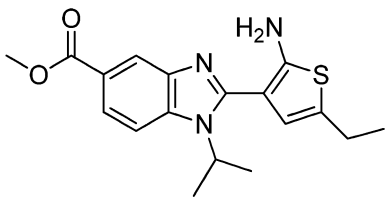
Fig. 2 X-ray crystal structure of **4e**.

and piperidine (74 μL, 0.75 mmol). Ethanol (5 mL) was added to the reaction mixture and the mixture was heated to reflux. The progress of reaction was monitored by NMR directly. After completion, the reaction mixture was concentrated on a rotovap. The residue was washed with ether to remove impurities and then treated with 0.1 M NaOMe in methanol (5 mL) for 8 h at room temperature. The mixture was filtered to remove the ionic liquid support and the filtrate was concentrated, and partitioned between water and diethyl ether. All the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated to get the product **4a** (0.212 g, 72%).



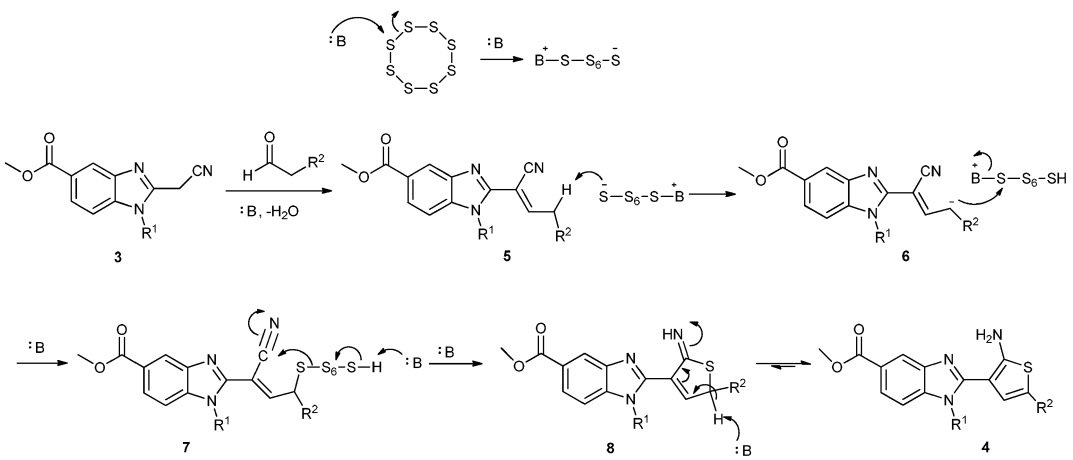
4a

Methyl 2-(2-amino-5-benzylthiophen-3-yl)-1-isopropyl-1*H*-benzo[*d*]imidazole-5-carboxylate, **4a**. ^{1}H NMR (300 MHz): δ 8.42 (s, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.36–7.22 (m, 5H), 6.56 (s, 1H), 5.66 (bs, 2H), 4.99 (sept, J = 7.0 Hz, 1H), 4.03 (s, 2H), 3.95 (s, 3H), 1.65 (d, J = 7.0 Hz, 6H). ^{13}C NMR (75 MHz): δ 167.8, 155.6, 151.7, 143.5, 139.9, 136.2, 128.6, 128.5, 127.4, 126.7, 123.7, 123.1, 122.2, 121.1, 111.6, 105.3, 52.0, 48.8, 36.1, 21.4. FTIR (KBr): cm^{-1} 3444, 3421, 1714. MS (ESI) m/z: 406 $(M + 1)^+$; Calcd m/z for $C_{23}H_{24}N_3O_2S$ $[M + H]^+$: 406.1589; Found: 406.1592.

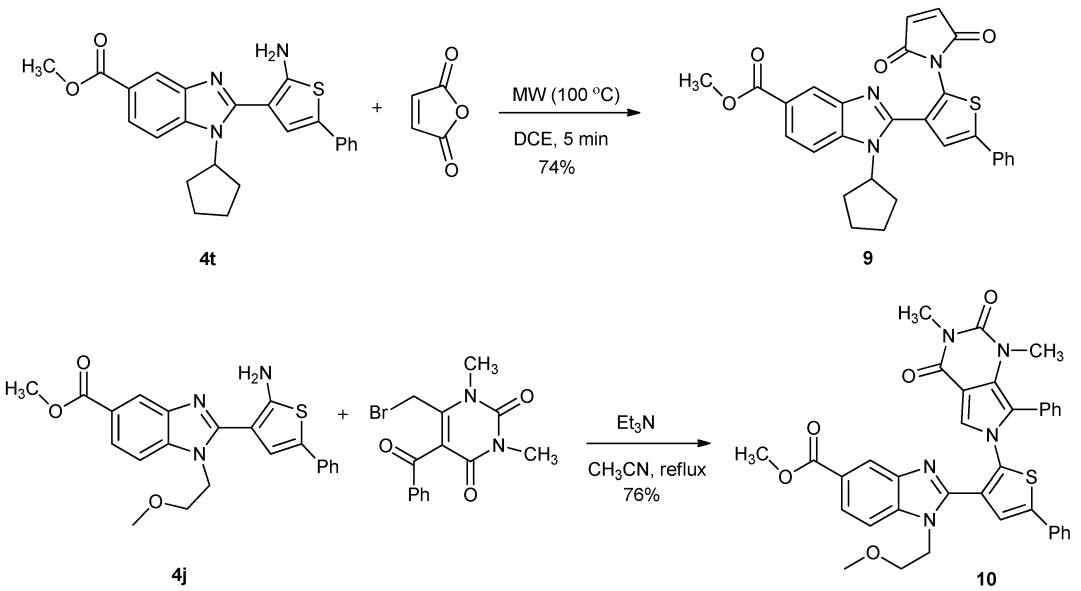


4b

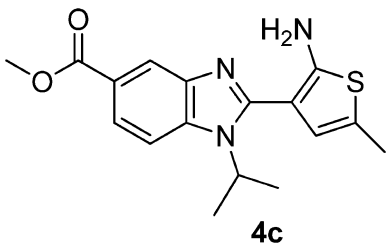
Methyl 2-(2-amino-5-ethylthiophen-3-yl)-1-isopropyl-1*H*-benzo[*d*]imidazole-5-carboxylate, **4b**. ^{1}H NMR (300 MHz): δ 8.41 (d, J = 1.5 Hz, 1H), 7.92 (dd, J = 8.6, 1.5 Hz, 1H), 7.57 (d, J = 8.6 Hz, 1H), 6.51 (s, 1H), 5.32 (bs, 2H), 5.01 (sept, J = 7.0 Hz, 1H), 3.94 (s, 3H), 2.65 (t, J = 7.3 Hz, 2H), 1.67 (d, J = 7.0 Hz, 6H), 0.98 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz): δ 168.1, 155.0, 152.1, 143.6, 136.5, 129.5, 124.2, 124.0, 123.5, 121.4, 121.2, 112.0, 105.6, 52.4, 49.2, 32.4, 25.1, 21.8, 14.0. FTIR (KBr): cm^{-1} 3442, 3421, 1714. MS (ESI) m/z: 358 $(M + 1)^+$; Calcd m/z for $C_{18}H_{22}N_3O_2S$ $[M + H]^+$: 358.1589; Found: 358.1587.



Scheme 3 A plausible mechanism for the multicomponent coupling reaction.

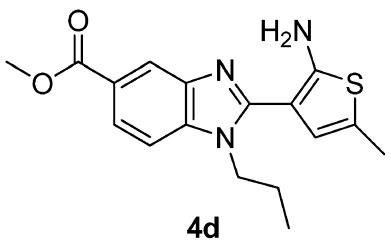


Scheme 4 Functionalization of the amino group of 2-aminothophenes.



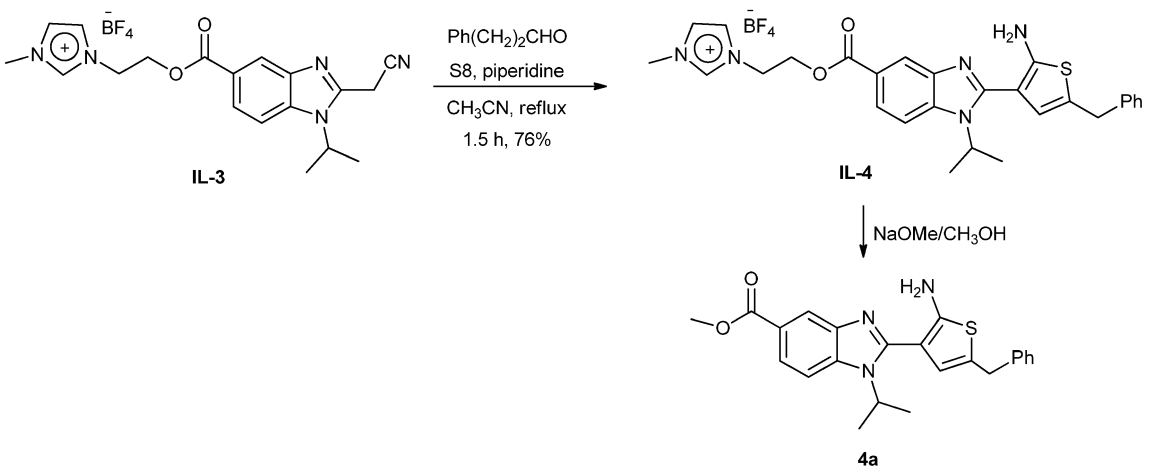
4c

Methyl 2-(2-amino-5-methylthiophen-3-yl)-1-isopropyl-1*H*-benzo[*d*]imidazole-5-carboxylate, **4c**. ^{1}H NMR (300 MHz): δ 8.40 (d, J = 1.0 Hz, 1H), 7.92 (dd, J = 8.6, 1.0 Hz, 1H), 7.55 (d, J = 8.6 Hz, 1H), 6.49 (s, 1H), 5.61 (bs, 2H), 5.00 (sept, J = 6.9 Hz, 1H), 3.93 (s, 3H), 2.36 (s, 3H), 1.66 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz): δ 167.8, 154.6, 151.7, 143.5, 136.2, 123.7, 123.1, 123.0, 121.7, 121.1, 52.2, 48.7, 21.4, 15.1. FTIR (KBr): cm^{-1} 3421, 1714. MS (ESI) m/z: 330 (M + 1)$^+$; Calcd m/z for $C_{17}H_{20}N_3O_2S$ [M + H]$^+$: 330.1276; Found: 330.1276.



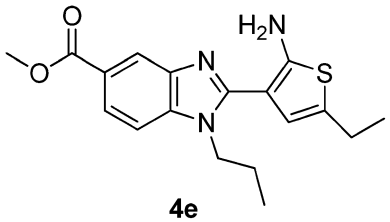
4d

Methyl 2-(2-amino-5-methylthiophen-3-yl)-1-propyl-1*H*-benzo[*d*]imidazole-5-carboxylate, **4d**. ^{1}H NMR (300 MHz): δ 8.38 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H),



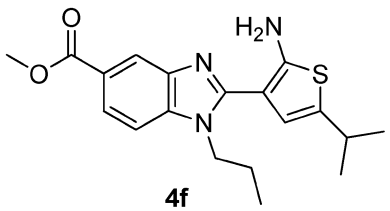
Scheme 5 One-pot, multicomponent reaction on ionic liquid support.

6.64 (s, 1H), 4.23 (t, J = 7.5 Hz, 2H), 3.95 (s, 3H), 2.38 (s, 3H), 1.92 (sext, J = 7.5 Hz, 2H), 1.02 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz): δ 168.2, 156.5, 152.3, 142.3, 138.6, 124.5, 124.0, 123.0, 121.1, 120.8, 52.4, 46.9, 23.7, 15.7, 11.7. FTIR (KBr): cm^{-1} 3417, 1712. MS (ESI) m/z: 330 $(M + 1)^+$; Calcd m/z for $C_{17}H_{20}N_3O_2S$ $[M + H]^+$: 330.1276; Found: 330.1276.



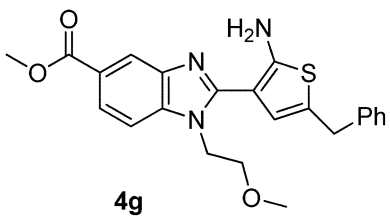
4e

Methyl 2-(2-amino-5-ethylthiophen-3-yl)-1-propyl-1*H*-benzo[*d*]imidazole-5-carboxylate, **4e**. ^{1}H NMR (300 MHz): δ 8.39 (s, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 6.68 (s, 1H), 4.25 (t, J = 7.7 Hz, 2H), 3.95 (s, 3H), 2.74 (q, J = 7.5 Hz, 2H), 1.94 (sext, J = 7.7 Hz, 2H), 1.30 (t, J = 7.7 Hz, 3H), 1.00 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz): δ 168.2, 156.5, 152.3, 142.3, 138.6, 124.5, 124.0, 123.0, 121.1, 120.8, 52.4, 46.9, 23.8, 23.7, 15.7, 11.7. FTIR (KBr): cm^{-1} 3417, 1712. MS (ESI) m/z: 344 $(M + 1)^+$; Calcd m/z for $C_{18}H_{22}N_3O_2S$ $[M + H]^+$: 344.1433; Found: 344.1431.



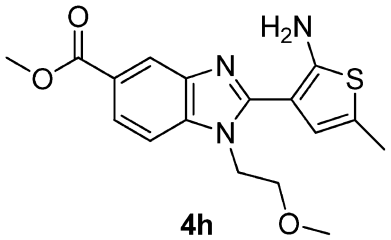
4f

Methyl 2-(2-amino-5-isopropylthiophen-3-yl)-1-propyl-1*H*-benzo[*d*]imidazole-5-carboxylate, **4f**. ^{1}H NMR (300 MHz): δ 8.37 (s, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 8.5 Hz, 1H), 6.65 (s, 1H), 6.21 (bs, 2H), 4.17 (t, J = 7.8 Hz, 2H), 3.95 (s, 3H), 3.00 (sept, J = 6.8 Hz, 1H), 1.87 (sext, J = 7.3 Hz, 2H), 1.29 (d, J = 6.8 Hz, 6H), 0.99 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz): δ 168.2, 156.2, 152.6, 142.6, 138.7, 136.0, 124.2, 123.8, 120.8, 117.8, 109.0, 104.2, 52.4, 46.8, 30.0, 24.7, 23.7, 11.6. FTIR (KBr): cm^{-1} 3419, 1712. MS (ESI) m/z: 358 $(M + 1)^+$; Calcd m/z for $C_{19}H_{24}N_3O_2S$ $[M + H]^+$: 358.1589; Found: 358.1586.



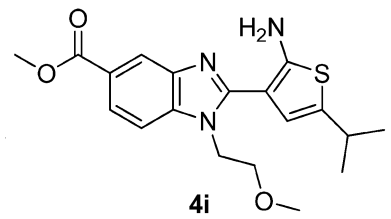
4g

Methyl 2-(2-amino-5-benzylthiophen-3-yl) -1-(2-methoxyethyl)-1*H*-benzo[*d*]imidazole-5-carboxylate, **4g**. ^{1}H NMR (300 MHz): δ 8.39 (s, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.36–7.27 (m, 5H), 6.83 (s, 1H), 4.43 (t, J = 5.7 Hz, 2H), 4.03 (s, 2H), 3.95 (s, 3H), 3.76 (t, J = 5.7 Hz, 2H), 3.29 (s, 3H). ^{13}C NMR (75 MHz): δ 168.1, 157.3, 152.5, 142.3, 140.3, 138.8, 129.0, 127.2, 127.0, 124.7, 124.2, 122.3, 120.8, 109.7, 104.5, 71.3, 59.6, 52.4, 45.4, 36.5. FTIR (KBr): cm^{-1} 3407, 1712. MS (ESI) m/z: 422 $(M + 1)^+$; Calcd m/z for $C_{23}H_{24}N_3O_3S$ $[M + H]^+$: 422.1538; Found: 422.1536.



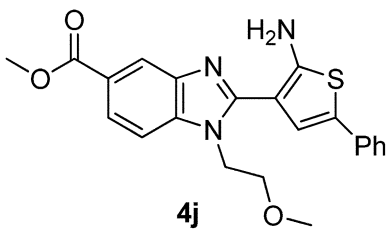
4h

Methyl 2-(2-amino-5-methylthiophen-3-yl)-1-(2-methoxyethyl)-1*H*-benzo[*d*]imidazole-5-carboxylate, **4h**. ^{1}H NMR (300 MHz): δ 8.37 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 6.77 (s, 1H), 4.46 (t, J = 5.7 Hz, 2H), 3.95 (s, 3H), 3.82 (t, J = 5.7 Hz, 2H), 3.34 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (75 MHz): δ 168.2, 156.5, 152.6, 142.5, 138.9, 124.6, 124.1, 122.9, 121.8, 120.8, 109.7, 104.8, 71.4, 59.7, 52.4, 45.3, 15.7. FTIR (KBr): cm^{-1} 3444, 3417, 1714. MS (ESI) m/z: 346 $(M + 1)^+$; Calcd m/z for $C_{23}H_{20}N_3O_3S$ $[M + H]^+$: 346.1225; Found: 346.1223.



4i

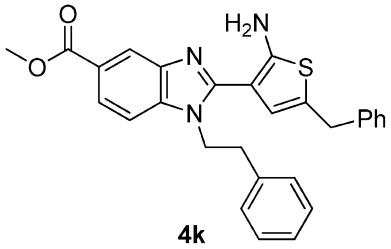
Methyl 2-(2-amino-5-isopropylthiophen-3-yl)-1-(2-methoxyethyl)-1*H*-benzo[*d*]imidazole-5-carboxylate, **4i**. ^{1}H NMR (300 MHz): δ 8.38 (d, J = 1.5 Hz, 1H), 7.96 (dd, J = 8.6, 1.5 Hz, 1H), 7.39 (d, J = 8.6 Hz, 1H), 6.85 (s, 1H), 6.13 (bs, 2H), 4.46 (t, J = 5.8 Hz, 2H), 3.94 (s, 3H), 3.84 (t. J = 5.8 Hz, 2H), 3.35 (s, 3H), 3.05 (sept, J = 6.8 Hz, 1H), 1.31 (d, J = 6.8 Hz, 6H). ^{13}C NMR (75 MHz): δ 167.8, 155.5, 152.5, 142.4, 138.6, 135.8, 124.1, 123.6, 120.5, 118.4, 109.1, 104.1, 71.0, 59.3, 52.0, 45.0, 30.0, 29.7, 24.3. FTIR (KBr): cm^{-1} 3421, 3330, 171. MS (ESI) m/z: 374 $(M + 1)^+$; Calcd m/z for $C_{19}H_{24}N_3O_3S$ $[M + H]^+$: 374.1538; Found: 374.1536.



4j

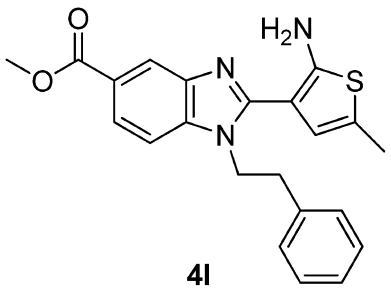
Methyl 2-(2-amino-5-phenylthiophen-3-yl)-1-(2-methoxyethyl)-1*H*-benzo[*d*]imidazole-5-carboxylate, **4j**. ^{1}H NMR (300 MHz): δ 8.40 (s, 1H), 8.00 (d, J = 7.0 Hz, 1H), 7.54 (s, 1H), 7.48–7.33 (m, 5H), 7.23 (t, J = 7.3 Hz, 1H), 4.53 (t, J = 5.6 Hz, 2H), 3.96 (s, 3H), 3.90 (t, J = 5.6 Hz, 2H), 3.38 (s, 3H). ^{13}C NMR (75 MHz): δ 168.1, 158.0, 152.3, 142.2, 138.6, 134.6, 129.3, 126.9, 126.7, 125.0, 124.9, 124.3, 120.8, 109.7, 106.1, 71.3, 59.7, 52.4,

45.7. FTIR (KBr): cm^{-1} 3228, 1687. MS (ESI) *m/z*: 408 $(M + 1)^+$; Calcd *m/z* for $C_{22}H_{22}N_3O_3S$ $[M + H]^+$: 408.1382; Found: 408.1383.



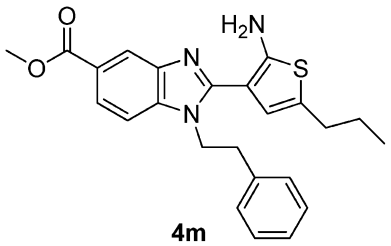
4k

Methyl 2-(2-amino-5-benzylthiophen-3-yl)-1-phenethyl-1*H*-benzo[*d*]imidazole-5-carboxylate, **4k**. ^{1}H NMR (300 MHz): δ 8.39 (s, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.39–7.21 (m, 9H), 7.02 (dd, J = 7.5, 1.6 Hz, 2H), 6.64 (s, 1H), 4.45 (t, J = 7.7 Hz, 2H), 4.01 (s, 2H), 3.96 (s, 3H), 3.08 (t, J = 7.7 Hz, 2H). ^{13}C NMR (75 MHz): δ 168.1, 157.2, 152.2, 142.3, 140.2, 138.3, 137.6, 129.3, 129.1, 129.0, 127.4, 127.1, 124.6, 124.1, 121.4, 120.8, 109.2, 104.5, 52.5, 46.9, 36.5, 36.4. FTIR (KBr): cm^{-1} 3421, 3330, 1712. MS (ESI) *m/z*: 468 $(M + 1)^+$; Calcd *m/z* for $C_{28}H_{26}N_3O_2S$ $[M + H]^+$: 468.1746; Found: 468.1744.



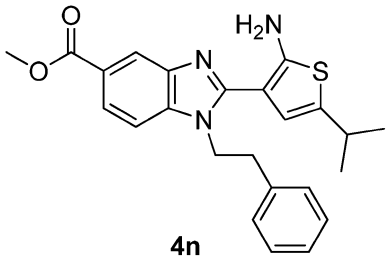
4l

Methyl 2-(2-amino-5-methylthiophen-3-yl)-1-phenethyl-1*H*-benzo[*d*]imidazole-5-carboxylate, **4l**. ^{1}H NMR (300 MHz): δ 8.39 (d, J = 1.3 Hz, 1H), 7.93 (dd, J = 8.5, 1.3 Hz, 1H), 7.33–7.25 (m, 3H), 7.21 (d, J = 8.5 Hz, 1H), 7.14 (dd, J = 7.0, 1.7 Hz, 2H), 6.63 (d, J = 1.2 Hz, 1H), 6.07 (bs, 2H), 4.52 (t, J = 7.5 Hz, 2H), 3.96 (s, 3H), 3.16 (t, J = 7.5 Hz, 2H), 2.39 (d, J = 1.2 Hz, 3H). ^{13}C NMR (75 MHz): δ 168.0, 155.9, 152.0, 142.3, 138.1, 137.4, 128.9, 128.7, 127.1, 124.1, 123.6, 122.6, 120.8, 52.0, 46.3, 36.1, 15.2. FTIR (KBr): cm^{-1} 3388, 1691. MS (ESI) *m/z*: 392 $(M + 1)^+$; Calcd *m/z* for $C_{21}H_{22}N_3O_2S$ $[M + H]^+$: 392.1433; Found: 392.1431.



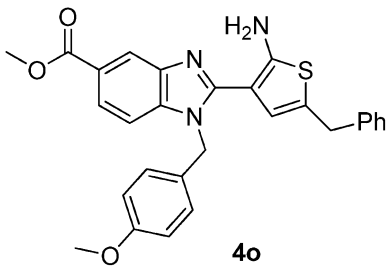
4m

Methyl 2-(2-amino-5-propylthiophen-3-yl)-1-phenethyl-1*H*-benzo[*d*]imidazole-5-carboxylate, **4m**. ^{1}H NMR (300 MHz): δ 8.38 (d, J = 1.3 Hz, 1H), 7.93 (dd, J = 8.5, 1.3 Hz, 1H), 7.32–7.20 (m, 4H), 7.13 (dd, J = 7.8, 1.3 Hz, 2H), 6.64 (s, 1H), 4.50 (t, J = 7.6 Hz, 2H), 3.95 (s, 3H), 3.15 (t, J = 7.8 Hz, 2H), 2.33 (t, J = 7.3 Hz, 2H), 1.66 (sept, J = 7.3 Hz, 2H), 1.01 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz): δ 168.2, 156.2, 152.4, 142.7, 138.5, 137.7, 129.3, 129.0, 128.9, 127.5, 124.5, 124.0, 121.0, 120.2, 109.1, 104.7, 52.4, 46.8, 36.5, 34.2, 24.9, 14.0. FTIR (KBr): cm^{-1} 3421, 1712. MS (ESI) *m/z*: 420 $(M + 1)^+$; Calcd *m/z* for $C_{24}H_{26}N_3O_2S$ $[M + H]^+$: 420.1746; Found: 420.1749.



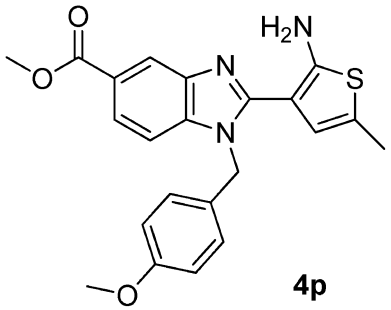
4n

Methyl 2-(2-amino-5-isopropylthiophen-3-yl)-1-phenethyl-1*H*-benzo[*d*]imidazole-5-carboxylate, **4n**. ^{1}H NMR (300 MHz): δ 8.40 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.33–7.23 (m, 4H), 7.15 (d, J = 6.6 Hz, 2H), 6.67 (s, 1H), 4.52 (d, J = 7.8 Hz, 2H), 3.96 (s, 3H), 3.17 (d, J = 8.0 Hz, 2H), 3.03 (quint, J = 6.8 Hz, 1H), 1.33 (d, J = 6.8 Hz, 6H). ^{13}C NMR (75 MHz): δ 168.2, 155.8, 152.5, 142.8, 138.5, 137.7, 129.3, 129.0, 127.5, 124.5, 124.0, 121.0, 109.0, 104.5, 52.4, 46.8, 36.5, 30.1, 24.8. FTIR (KBr): cm^{-1} 3411, 3275, 1709. MS (ESI) *m/z*: 420 $(M + 1)^+$; Calcd *m/z* for $C_{24}H_{26}N_3O_2S$ $[M + H]^+$: 420.1746; Found: 420.1742.



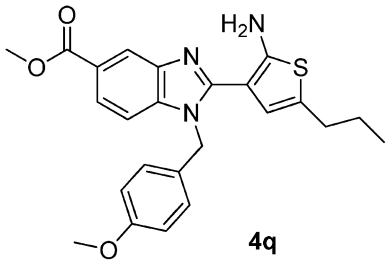
4o

Methyl 2-(2-amino-5-benzylthiophen-3-yl)-1-(4-methoxybenzyl)-1*H*-benzo[*d*]imidazole-5-carboxylate, **4o**. ^{1}H NMR (300 MHz): δ 8.44 (d, J = 1.0 Hz, 1H), 7.93 (dd, J = 8.4, 1.0 Hz, 1H), 7.32–7.15 (m, 6H), 6.96 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.48 (s, 1H), 6.26 (bs, 2H), 5.39 (s, 2H), 3.95 (s, 3H), 3.88 (s, 2H), 3.81 (s, 3H). ^{13}C NMR (75 MHz): δ 168.2, 159.5, 137.4, 153.0, 142.9, 140.2, 139.0, 136.0, 128.9, 128.3, 127.1, 127.0, 124.8, 124.3, 121.8, 120.9, 115.0, 109.4, 104.4, 55.7, 52.5, 48.3, 36.4. FTIR (KBr): cm^{-1} 3419, 1712. MS (ESI) *m/z*: 484 $(M + 1)^+$; Calcd *m/z* for $C_{28}H_{26}N_3O_3S$ $[M + H]^+$: 484.1695; Found: 484.1692.



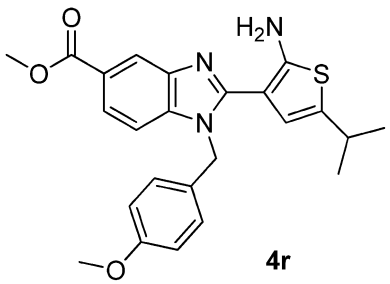
4p

Methyl 2-(2-amino-5-methylthiophen-3-yl)-1-(4-methoxybenzyl)-1*H*-benzo[*d*]imidazole-5-carboxylate, **4p**. ^{1}H NMR (300 MHz): δ 8.41 (d, J = 1.4 Hz, 1H), 7.89 (dd, J = 8.5, 1.4 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H), 7.05 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 6.44 (d, J = 1.2 Hz, 1H), 5.43 (s, 2H), 3.94 (s, 3H), 3.78 (s, 3H), 2.24 (d, J = 1.2 Hz, 3H). ^{13}C NMR (75 MHz): δ 168.2, 159.6, 156.6, 153.0, 142.9, 138.9, 128.4, 127.5, 124.7, 124.2, 122.9, 121.4, 114.9, 109.5, 104.6, 55.7, 52.4, 48.3, 15.5. FTIR (KBr): cm^{-1} 3419, 1711. MS (ESI) m/z: 408 (M + 1)$^+$; Calcd m/z for $C_{22}H_{22}N_3O_3S$ [M + H]$^+$: 408.1382; Found: 408.1379.



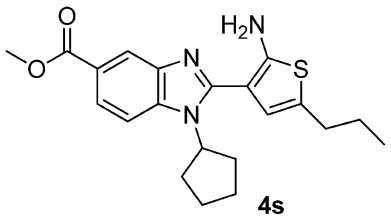
4q

Methyl 2-(2-amino-5-propylthiophen-3-yl) -1-(4-methoxybenzyl)-1*H*-benzo[*d*]imidazole-5-carboxylate, **4q**. ^{1}H NMR (300 MHz): δ 8.42 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.0 Hz, 2H), 6.46 (s, 1H), 6.22 (s, 2H), 5.42 (s, 2H), 3.94 (s, 3H), 3.78 (s, 3H), 2.52 (t, J = 7.4 Hz, 2H), 1.54 (sext, J = 6.8 Hz, 2H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz): δ 168.2, 156.3, 153.1, 142.9, 139.0, 128.7, 128.4, 124.7, 124.2, 120.9, 114.9, 109.4, 104.5, 55.7, 46.8, 32.2, 24.7, 23.7, 13.9. FTIR (KBr): cm^{-1} 3375, 3222, 1693. MS (ESI) m/z: 436 (M + 1)$^+$; Calcd m/z for $C_{24}H_{26}N_3O_3S$ [M + H]$^+$: 436.1695; Found: 436.1697.



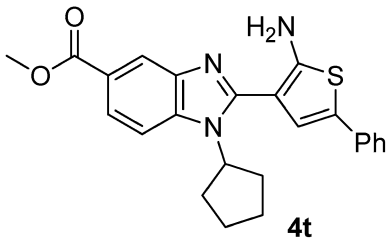
4r

Methyl 2-(2-amino-5-isopropylthiophen-3-yl)-1-(4-methoxybenzyl)-1*H*-benzo[*d*]imidazole-5-carboxylate, **4r**. ^{1}H NMR (300 MHz): δ 8.43 (s, 1H), 7.90 (dd, J = 8.4, 1.5 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 8.5 Hz, 2H), 6.85 (dd, J = 8.4, 1.5 Hz, 2H), 6.45 (s, 1H), 6.02 (bs, 2H), 5.38 (s, 2H), 3.94 (s, 3H), 3.75 (s, 3H), 2.86 (sept, J = 6.8 Hz, 1H), 1.16 (d, J = 6.8 Hz, 6H). ^{13}C NMR (75 MHz): δ 168.2, 159.5, 156.3, 153.2, 142.9, 139.1, 136.0, 128.6, 127.4, 124.6, 124.2, 120.8, 118.4, 114.9, 109.3, 104.0, 55.7, 52.4, 48.3, 29.9, 24.5. FTIR (KBr): cm^{-1} 3419, 1712. MS (ESI) m/z: 436 (M + 1)$^+$; Calcd m/z for $C_{24}H_{26}N_3O_3S$ [M + H]$^+$: 436.1695; Found: 436.1693.



4s

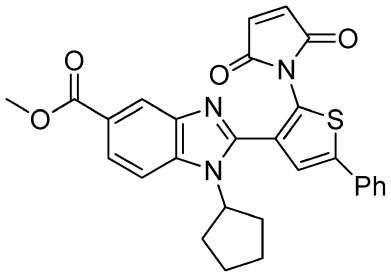
Methyl 2-(2-amino-5-propylthiophen-3-yl)-1-cyclopentyl-1*H*-benzo[*d*]imidazole-5-carboxylate, **4s**. ^{1}H NMR (300 MHz): δ 8.39 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 6.50 (s, 1H), 5.58 (bs, 2H), 5.08 (quint, J = 7.5 Hz, 2H), 3.90 (s, 3H), 2.60 (t, J = 7.5 Hz, 2H), 2.28–1.99 (m, 7H), 1.74 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz): δ 167.7, 154.7, 152.5, 143.4, 135.8, 128.8, 123.7, 123.0, 121.1, 120.8, 111.1, 57.5, 52.0, 32.0, 30.3, 25.3, 24.6, 13.5. FTIR (KBr): cm^{-1} 3421, 3326, 1714. Calcd m/z for MS (ESI) m/z: 384 (M + 1)$^+$; $C_{21}H_{26}N_3O_2S$ [M + H]$^+$: 384.1746; Found: 384.1748.



4t

Methyl 2-(2-amino-5-phenylthiophen-3-yl)-1-cyclopentyl-1*H*-benzo[*d*]imidazole-5-carboxylate, **4t**. ^{1}H NMR (300 MHz): δ 8.46 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.49–7.43 (m, 3H), 7.32 (t, J = 7.4 Hz, 2H), 7.20 (t, J = 7.4 Hz, 1H), 7.13 (s, 1H), 5.90 (bs, 2H), 5.17 (quint, J = 8.7 Hz, 1H), 3.96 (s, 3H), 2.35–2.31 (m, 2H), 2.29–2.07 (m, 4H), 1.81 (t, J = 6.1 Hz, 2H). ^{13}C NMR (75 MHz): δ 168.2, 156.9, 152.5, 143.7, 136.3, 134.5, 129.4, 127.1, 127.0, 125.0, 125.0, 124.4, 123.7, 121.7, 120.6, 111.6, 107.2, 58.1, 52.5, 30.9, 25.8. FTIR (KBr): cm^{-1} 3421, 1712. MS (ESI) m/z: 418 (M + 1)$^+$; Calcd m/z for $C_{24}H_{24}N_3O_2S$ [M + H]$^+$: 418.1589; Found: 418.1592.

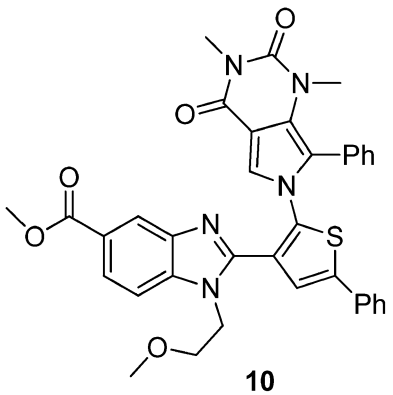
Preparation of **9**: To a dichloroethane solution of **4t** (0.15 g, 0.36 mmol) in a microwave absorbance vessel was added maleic anhydride (24 μL, 0.36 mmol) and the reaction mixture was irradiated using microwave radiation (150 W) at 100 °C for 5 min. The reaction mixture was concentrated and purified by column chromatography to get **9** (1.32 g, 74% yield).



9

Methyl 1-cyclopentyl-2-(5-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-2-phenylthiophen-3-yl)-1*H*-benzo[d]imidazole-5-carboxylate, **9**. ^{1}H NMR (300 MHz): δ 8.43 (d, J = 1.2 Hz, 1H), 7.98 (dd, J = 8.7, 1.2 Hz, 1H), 7.63 (dd, J = 8.5, 1.5 Hz, 2H), 7.53 (s, 1H), 7.48–7.36 (m, 3H), 6.79 (s, 2H), 5.00 (quint, J = 8.9 Hz, 2H), 3.94 (s, 3H), 2.35–2.25 (m, 4H), 2.18–2.02 (m, 2H), 1.86–1.79 (m, 2H). ^{13}C NMR (75 MHz): δ 168.1, 167.6, 149.5, 143.6, 136.1, 134.8, 133.0, 130.7, 129.2, 128.7, 128.1, 126.1, 124.1, 123.8, 122.8, 121.8, 111.5, 58.0, 52.1, 30.5, 25.3. FTIR (KBr): cm^{-1} 1728. MS (ESI) m/z: 498 $(M + 1)^+$; Calcd m/z for $C_{21}H_{26}N_3O_2S$ $[M + H]^+$: 498.1488; Found: 498.1478.

Preparation of **10**: To an acetonitrile solution of **4j** (50 mg, 0.12 mmol) was added 5-benzoyl-6-(bromomethyl)-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (40 mg, 0.12 mmol) and triethylamine (18 μL, 0.13 mmol). The reaction mixture was heated in an oil bath at 82 °C for 4 h. The reaction mixture was cooled to 0 °C and dil. HCl (1.0 N, 1 mL) was added to it, stirred well and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 4 mL). All the organic extracts were combined and washed with water followed by brine, dried over anhydrous Na_2SO_4 and evaporated to get a crude product that was purified by column chromatography to get **10** (60 mg, 76% yield).



10

Methyl 2-(5-(1,3-dimethyl-2,4-dioxo-5-phenyl-3,4-dihydro-1*H*-pyrrolo[3,4-*d*]pyrimidin-6(2*H*)-yl)-2-phenylthiophen-3-yl)-1-(2-methoxyethyl)-1*H*-benzo[*d*]imidazole-5-carboxylate, **10**. ^{1}H NMR (300 MHz): δ 8.35 (s, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.71 (s, 1H), 7.61 (d, J = 7.7 Hz, 2H), 7.47–7.36 (m, 3H), 7.28–7.15 (m, 2H), 6.96 (t, J = 7.8 Hz, 2H), 6.86 (s, 1H), 6.71 (dd, J = 7.7, 1.0 Hz, 2H), 3.95 (s, 3H), 3.63 (t, J = 5.0 Hz, 2H), 3.47 (s, 3H), 3.44 (t, J = 5.0 Hz, 2H), 3.31 (s, 3H), 3.27 (s, 3H). ^{13}C NMR (75 MHz): δ 167.5, 159.6, 151.6, 148.0, 142.7, 141.4, 139.5, 137.7, 135.1, 132.7, 130.2, 130.0, 129.3, 128.8, 128.4, 128.2, 127.3, 126.2, 125.6, 124.7, 124.5, 124.1, 122.5, 109.6, 105.4, 70.2, 59.2, 52.1, 44.1, 31.8, 27.8. FTIR (KBr): cm^{-1} 1701, 1659. MS (ESI) m/z: 646 $(M + 1)^+$; Calcd m/z for $C_{36}H_{32}N_5O_5S$ $[M + H]^+$: 646.2122; Found: 646.2112.

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