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Multicomponent Solvent-Free Synthesis Of Benzimidazolyl Imidazo[1,2-*a*]-pyridine Under Microwave Irradiation

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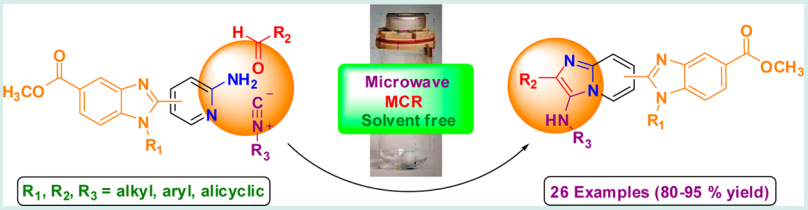
Supporting Information



ABSTRACT: A novel one-pot, three-component reaction employing variously substituted benzimidazole-linked amino pyridines, aldehydes, and isonitriles catalyzed by scandium(III) triflate under solvent-free conditions were accomplished. This new synthetic methodology facilitates the rapid generation of intricate molecular frameworks in three-dimensional fashion leading to benzimidazole-imidazo[1,2-*a*] pyridines. This approach is envisioned as an environmentally benign process and a simple operation to the biological interesting compounds. The present synthetic sequence permits the introduction of three points of structural diversity to expand chemical space with high purity and excellent yields.

KEYWORDS: *microwave irradiation, benzimidazole-imidazo[1,2-a]pyridines, solvent-free, bis-heterocyclic skeletons, three-component reaction*

INTRODUCTION

In the annals of heterocyclic chemistry, discovery of new and robust method for the synthesis of novel bis-heterocycles for therapeutic application is an important area of research. Because of the advances of high-throughput screening in the pharmaceutical industry, there is an increasing demand for the rapid breeding of novel molecular scaffolds.[1] Multicomponent reactions (MCR) have emerged as a powerful tool to construct complex molecular architecture which involves multiple bond formation in a single reaction step with high atom efficiency.[2] Multicomponent reactions coupled with microwave irradiation leading to accelarated synthesis of molecular libraries with high degree of structural diversity are of both academic and industrial significant.[3] More recently, isocyanide based multicomponent reactions have been widely utilized to afford a large number of nitrogen containing heterocyclic libraries.[4] Over the years, researchers have shown much interest in frameworks featuring the imidazo[1,2-*a*]pyridine ring system and best documented by the frequency with which the occurrence of this previleged structure as a common skeleton in many biologically active compounds.[5] Imidazo[1,2-*a*]pyridine derivatives have been found in many clinically accepted drugs, namely, zolpidem (A) and olprinone (B), as shown in (Figure 1).[6]

In addition to the aforementioned drugs, the imidazo[1,2-*a*]-pyridine pharmacophore also exhibits a wide range of therapeutic activities such as antibacterial, antiulcer, antifungal, calcium-channel blocking and cyclin-dependent kinases (CDK) inhibition.[7] More recently, compounds featuring the benzimidazole motif have shown eloquent contributions in anticancer, antimicrobial, antihelmintic (C and D) activities and against several viruses, such as HIV, influenza, and cytomegalovirus.[8] In recent years, it has been acknowledged that the combination of two privileged scaffolds in a single molecule potentially creates more active, new entities with unusual bioproperties.[9] In our journey to explore new potential drug candidates, we envision that the integration of two essential pharmacophores may provide a lead for intangible derivation of a novel chemical skeleton for drug discovery. Preparation methods for the two invidual skeletons E and F are well documented,[10] and in particular, the conventional approaches toward the synthesis of the imidazo-[1,2-*a*]pyridine motif, the skeleton E, can be summarized as (1) reaction of 2-aminopyridine with aldehydes and isonitriles,[11a,b] (2) reaction of alpha-haloketones with 2-aminopyridines in presence of base,[11c−e] and (3) Copper-catalyzed synthesis of imidazo[1,2-*a*]pyridine from 2-aminopyridines and nitroolefins through a conjugate addition/oxidation/cyclization fashion.[11f] However, most of these methods encounter limitations such as use of solid-supported materials (e.g., expensive polymer supported catalysts), longer reaction times, and elaborate precursors required prior to the key transformation leading to imidazo[1,2-*a*]pyridine cores. In a continuation with our on-going research interest[12] to introduce maximized diversity in

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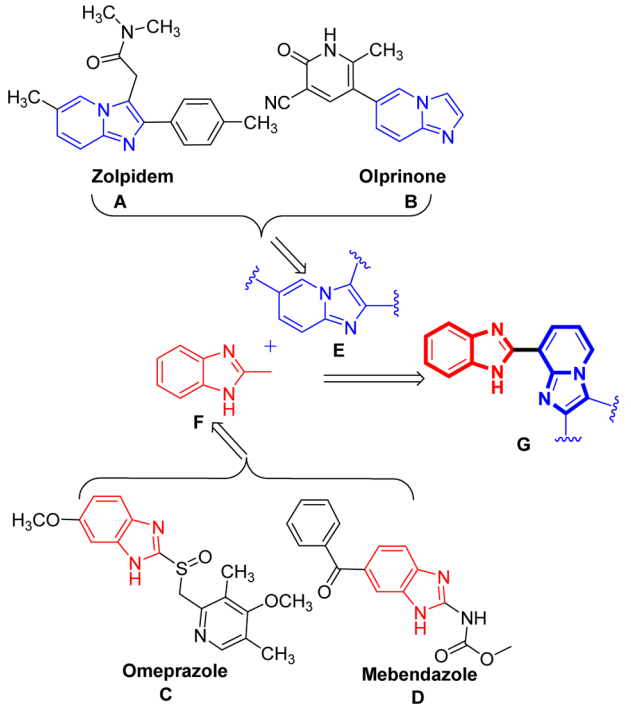

Figure 1. Design concept of the present molecular library.

the bis-heterocycles and to develop a new strategy for the efficient synthesis of the novel drug-like small molecules for biological evaluation, herein, we report our recent study for facile synthesis of benzimidazolyl-imidazo[1,2-*a*]pyridines.

We became interested in the possibility of using benzimidazole-linked 2-amino pyridine as an amine fragment to react with various aldehydes and isonitriles to afford three dimesional architechtures with multiple bond formation in a single step. The use of microwave irradiation significantly increased the reaction yield and shortened the reaction times.[13] In this context, the use of microwave irradiation under solvent-free conditions stands out as an environmentally benign and powerful tool for the rapid construction of the target molecules.

RESULTS AND DISCUSSION

To achieve our goal, we embarked our studies with the esterification of 4-fluoro-3-nitro benzoic acid **1** under microwave irradiation at 80 °C for 15 min to afford 4-fluoro-3-nitrobenzoate **2** in 98% yield (Scheme 1). To introduce the first point of diversity onto the skeleton, a variety of primary amines were reacted with 4-fluoro-3-nitrobenzoate **2** in dichloromethane under reflux for 5 h to obtain intermediate **3**. We were delighted to note that the same reaction under microwave irradiation at 80 °C was complete in 10 min. Subsequent reduction of the nitro group was achieved at 90 °C for 5 min by zinc dust and ammonium formate in methanol to furnish *o*-phenylenediamines **4** in 90% yields.

The next task is to build-up the pyridinyl complexity through an amide linkage between *o*-phenylenediamine derivatives **4** and 2-aminonicotinic acid **5**.

Accordingly, we tested general coupling protocols such as DCC/DMAP in CH_2Cl_2, EDC/HOBt/Et_3N in DMF and HBTU/HOBt/DIPEA in DMF at room temperature, under reflux and micowave conditions. However, all such attempts yielded no desired outcomes. When the coupling combination was changed to DCC/HOBt and DIPEA in DMF, amide conjugates **6** were obtained in 25% yield. Gratifyingly, using PyBOP/Et_3N in DMF gave the satisfactory result with 90% yield at room temperature for 24 h. The same transformation under microwave irradiation (160 °C) was accomplished in 10 min (Scheme 1). The selective amide linkage formation with

Scheme 1. Microwave-Assisted Synthesis of Benzimidazole-imidazo[1,2-*a*]pyridine 10

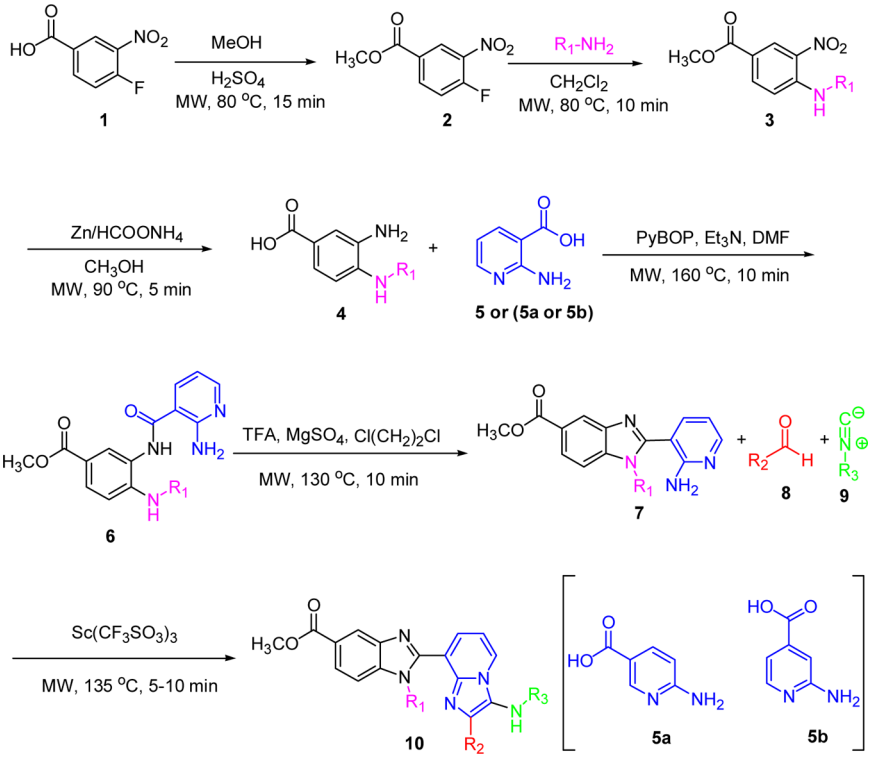

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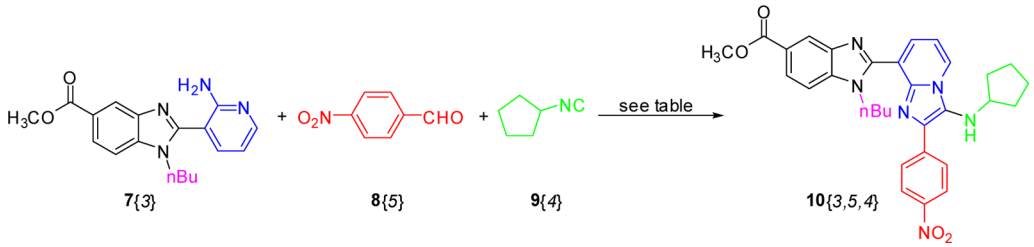
Table 1. Three-Component Reaction Optimization Leading to Benzimidazole-imidazo[1,2-*a*]pyridine 10{3,5,4}



7{3} 8{5} 9{4} 10{3,5,4}

			reaction condition[c]		
entry	catalyst	solvent	temp (°C)	time (min)	isolated yield (%)
1	TFA[a]	MeOH	135	10	no reaction
2	PTSA[a]	MeOH	135	10	10
3	$ZnCl_2$[a]	MeOH	135	10	10
4	$ZnCl_2$[a]	neat	135	10	20
5	$Sc(OTf)_3$[a]	MeOH	135	10	60
6	$Sc(OTf)_3$[b]	PEG-200	135	10	70
7	$Sc(OTf)_3$[b]	neat	135	10	95

[a]10 mol %. [b]20 mol % . [c]Microwave-assisted reaction conditions.

the primary amine in the presence of secondary amine could be the deactivating effect associated with the presence of ester functionality on the benzene ring at the para position. Further, to increase the diversity and substrate scope, the diamine **4** is attached with the aminopyridine moitey in two different positions by employing two different acids 6-aminonicotinic acid **5a** and 2-aminoisonicotinic acid **5b**. Construction of benzimidazole fragment was achieved through an intramolecular ring closure in the presence of TFA (10 mol %) and anhydrous $MgSO_4$ under microwave irradiation at 130 °C for 10 min to afford the benzimidazole-linked aminopyridine **7** in 95% yield. The key and final step in the present investigation is to accomplish the three component Groebke−Blackburn−Bienaymé reaction[14] involving benzimidazole linked aminopyridine, aldehyde and isonitrile to afford the target molecules. 4-Nitrobenzaldehyde and cyclopentyl isonitrile were chosen as the reactive components to optimize the reaction conditions (results summarized in Table 1). Initially protic acids (TFA and *p*-TSA) and Lewis acid $ZnCl_2$ were tried as a catalyst to perform the task. However all these catalysts failed to deliver the desired product with significant yield. To our delight, 60% yield was achieved in the presence of a catalytic amount of $Sc(OTf)_3$ in methanol, whereas no reaction was observed without $Sc(OTf)_3$. Further improvement was achieved under solvent-free condition with an isolated yield of 83% for 10 min and no improvement was observed with increasing reaction time.

Having obtained satisfactory results, a variety of aldehydes were employed under this optimized condition. A significant electronic effect of the sustituents on the reactivity was observed. The results showed that aldehydes containing electron-withdrawing substituents tend to react much faster than electron-rich and neutral aldehydes but all reactants were consumed within 10 min. Moreover, aliphatic aldehydes are inert under these conditions and no reaction occurred even under forcing conditions. We infer the observed reactivity was from the facile imine-formation of the electron-deficient aldehydes with intermediate **7** under $Sc(OTf)_3$ catalysis and the sequential addition of isocyanides onto the in situ formed iminium ion was also considered more rapid than that of electron-rich substrates.

Encouraged by these observations, we next turned our attention to delineate the substrate scope of this three-component reaction for the rapid access of substituted benzimdazole-imidazo[1,2-*a*]pyridines **10** (Table 2). The three component coupling of substituted benzimidazole-2-aminopyridines **7**, aldehydes **8**, and isonitriles **9** afforded a library of benzimidazole-imidazo[1,2-*a*]pyridines **10** in excellent yields by a simple one pot operation. On this basis, a plausible reaction mechanism of the three component coupling transformation is proposed (Scheme 2).

Benzimidazole-linked amino pyridine **7** condensed effectively with Lewis acid activated aldehyde **8** to give imine intermediate **a**, which subsequently underwent nucleophilic addition followed by *5-exodig* cylization with isonitrile to give the imidazo-[1,2-*a*]pyridine intermediate **b**. Upon rearomatization, the intermediate **b** furished the final compound benzimidazole-imidazo[1,2-*a*]pyridine **10** (Scheme 2). The structure of the obtained benzimidazole-imidazo[1,2-*a*]-pyridine was assigned unambiguously by a single X-ray crystallographic study[15] (Figure 2).

Thus the present methedology generates three different benzimidazole-imidazo[1,2-*a*]pyridine scaffolds where benzimidazole and imidazolopyridine linked each other with three different combinations to broaden the scope of this molecular library.

CONCLUSION

In summary, we have successfully developed a multicomponent coupling method using Groebke−Blackburn−Bienaymé reaction as a key transformation to synthesize biologically interesting benzimidazole-imidazo[1,2-*a*]pyridines under solvent-free conditions. The use of microwave irradiation in the entire synthetic sequence facilitated the transformation with high efficiency at each step. In addition, this one-pot novel reaction which integrated two different pharmacophores into one framework may lead to new hybrid molecules with interesting biological profiles. To the best of our knowledge, the present new approach is the first successful systemic synthesis of the titled bis-heterocyclic compounds.

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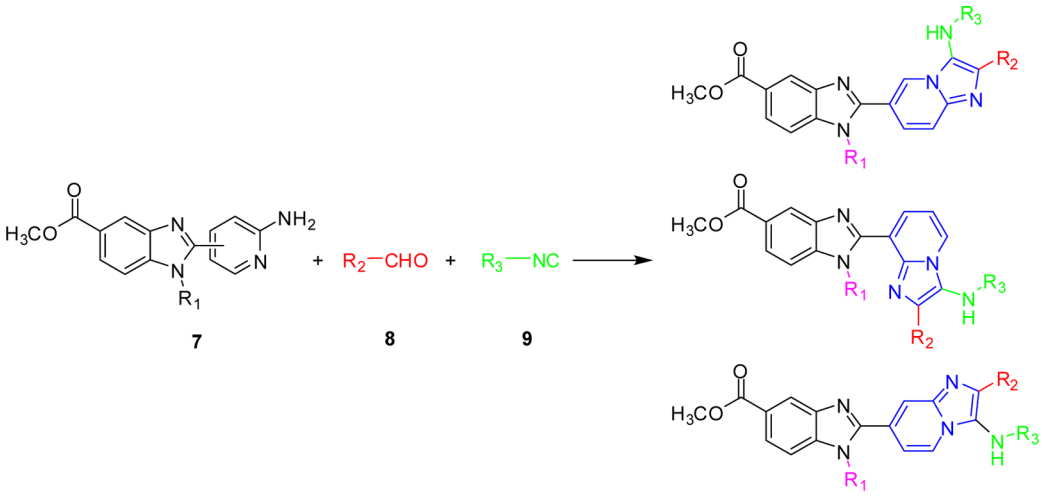
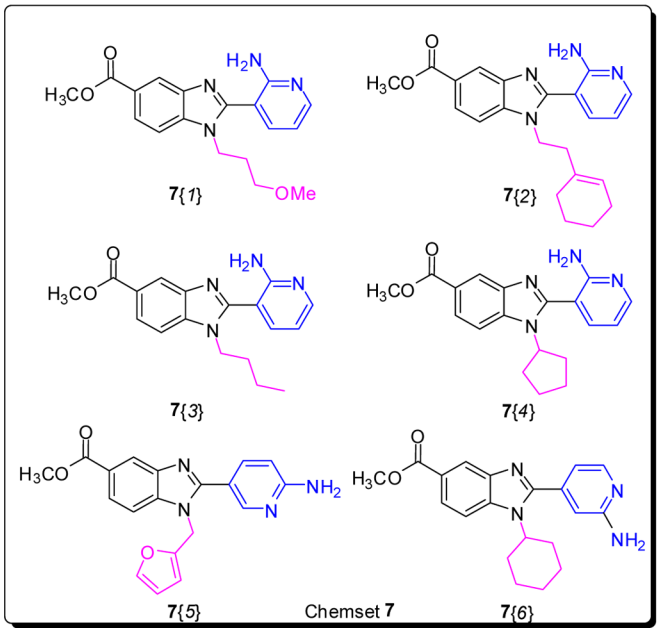
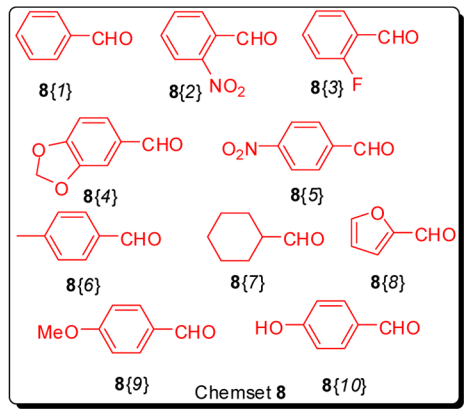
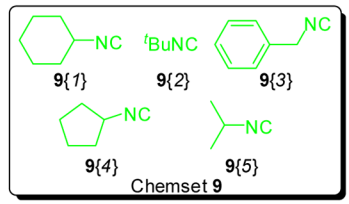
Table 2. Substrate Scope of the Reaction and Physical Properties of Compound 10









entry	product	yield (%)[a]	LRMS[b]	H-bond donor	H-bond acceptor	clogP[c]
1	10{1,1,1}	72	538	1	8	7.83
2	10{1,2,1}	83	583	1	10	7.59
3	10{1,3,1}	89	556	1	8	7.98
4	10{1,1,2}	80	512	1	8	7.04
5	10{1,4,2}	84	556	1	8	7.08
6	10{1,5,1}	86	583	1	8	7.59
7	10{2,5,2}	82	593	1	9	9.27
8	10{2,1,2}	90	548	1	7	9.52
9	10{2,4,2}	87	592	1	9	9.55
10	10{3,3,1}	81	540	1	7	9.34
11	10{3,4,3}	83	574	1	9	8.65
12	10{3,5,4}	83	553	1	9	8.39
13	10{3,5,3}	80	575	1	9	8.37
14	10{3,3,3}	77	548	1	7	8.77
15	10{3,1,5}	82	481	1	7	8.01
16	10{4,4,5}	86	537	1	9	8.04
17	10{5,6,3}	85	567	1	5	8.47
18	10{5,7,3}	78	559	1	5	8.26
19	10{5,6,1}	87	559	1	5	9.05
20	10{5,9,1}	88	575	1	6	8.57

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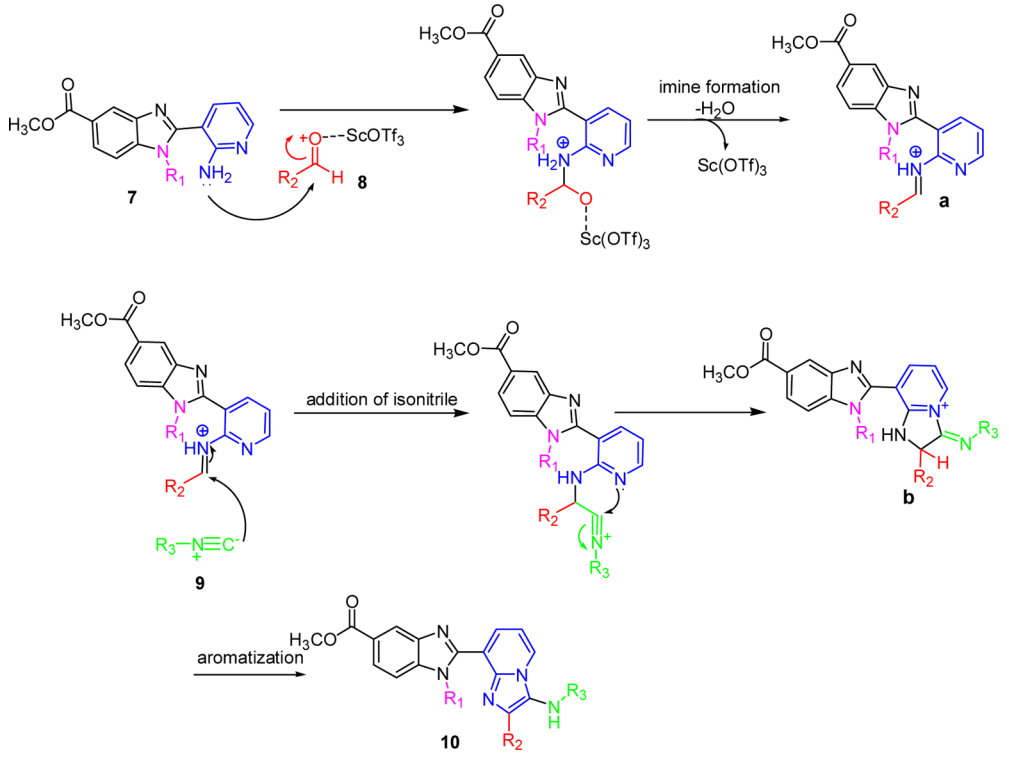
Table 2. continued

entry	product	yield (%)[a]	LRMS[b]	H-bond donor	H-bond acceptor	clogP[c]
21	**10**{*5,4,3*}	90	597	1	7	8.01
22	**10**{*6,1,3*}	85	555	1	5	9.06
23	**10**{*6,9,3*}	90	585	1	6	9.07
24	**10**{*6,8,3*}	77	545	1	5	8.44
25	**10**{*6,6,1*}	81	561	1	5	10.14
26	**10**{*6,10,1*}	83	563	2	6	9.17

[a]Isolated yields. [b]LRMS was recorded by ESI ionization method. [c]Estimated clogP by ChemBioOffice 2010.

Scheme 2. Proposed Reaction Mechanism for the Formation of 10



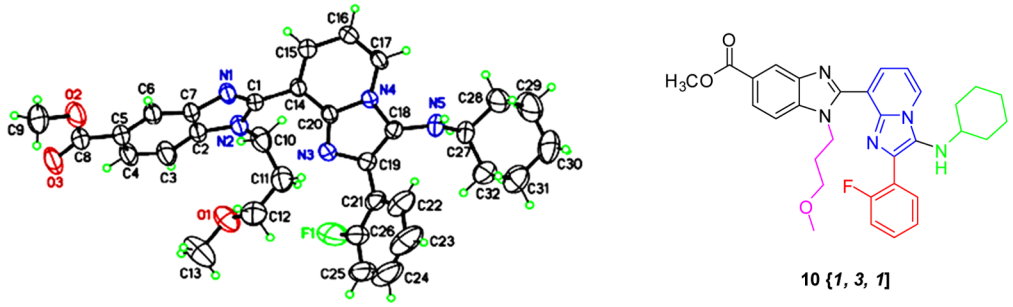


Figure 2. ORTEP diagram of compound **10**{*1,3,1*} (Table 2, entry 3).

EXPERIMENTAL PROCEDURES

Synthesis of Key Intermediate (7). Compound **4**{*3*} was prepared using our earlier reported procedure. To a solution of 2-aminonicotinic acid **5** (869 mg, 6.30 mmol, 2.0 equiv) in *N,N′*-dimethylformamide (DMF/Et_3N) (3:7) was added PyBOP (3.28 g, 6.30 mmol, 2.0 equiv) in a sequential order. The resulting slurry was stirred for 5 min at room temperature and then added 3-amino-4-(butylamino)benzoate **4**{*3*} (700 mg, 3.15 mmol, 1.0 equiv) in *N,N′*-dimethylformamide (5 mL). The reaction mixture was subsequently heated with stirring in a 10 mL microwave process vial for 10 min at 160 °C to obtain **6**{*3*}. After completion of the reaction, the by-products were filtered through filter paper. The reaction mixture was partitioned by sodium bicarbonate solution and ethyl acetate to remove the undesired impurities and dried to give methyl 3-(2-aminonicotinamido)-4-(butylamino)benzoate **6**{*3*}. To a solution of methyl 3-(2-aminonicotinamido)-4-(butylamino)benzoate **6**{*3*} (1.10 g, 3.22 mmol, 1.0 equiv) in 1,2-dichloroethane (3.0 mL), trifluoroacetic acid (2.5 mL), and $MgSO_4$ (400 mg) was added, and the mixture was subsequently heated with stirring in a 10 mL microwave process sealed vial at 130 °C for 10 min. After completion of the reaction, $MgSO_4$

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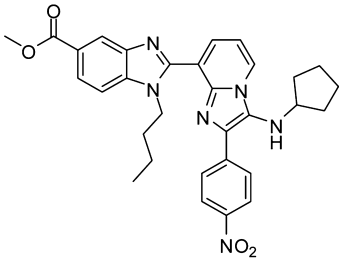
was removed by filtration and the reaction mixture was partitioned by water and ethyl acetate (100 mL) to obtain methyl 2-(2-aminopyridin-3-yl)-1-butyl-1*H*-benzo[*d*]imidazole-5-carboxylate **7**{*3*} with high purity.

Representative Example for Synthesis of Methyl 1-Butyl-2-(3-(cyclopentylamino)-2(4-nitrophenyl)imidazo[1,2-a]-pyridin-8-yl)-1H-benzo[d]imidazole-5-carboxylate ***10****{3,5,4}*.



10{*3, 5, 4*}

To a 10 mL microwave process vial methyl 2-(2-aminopyridin-3-yl)-1-butyl-1*H*-benzo[*d*]imidazole-5-carboxylate **7**{*3*} (100 mg, 0.30 mmol, 1.0 equiv), 4-nitrobenzaldehyde **8**{*5*}(68 mg, 0.45 mmol, 1.5 equiv), cyclopentyl isocyanide **9**{*4*} (43 mg, 0.45 mmol, 1.5 equiv), and scandium triflate (3 mg, 0.006 mmol) was added. The microwave vial was sealed and irradiated at 135 °C for 5 to 10 min in neat condition. After completion of the reaction, reaction mixture was diluted with dichloromethane (15 mL) and washed by 1% HCl solution. The dichloromethane was evaporated. The slurry was loaded on silica gel column and eluted with a mixture of ethyl acetate and hexane (1:1) to get the title compounds **10**{*3,5,4*} in 83% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.36 (d, J = 8.7 Hz, 2H), 8.27 (d, J = 8.7 Hz, 2H), 8.20 (d, J = 6.9 Hz, 1H), 8.12 (dd, J = 7.3, 1.2 Hz, 1H), 7.58 (dd, J = 6.9, 1.5 Hz, 2H), 6.80 (t, J = 6.9 Hz, 1H), 4.48 (t, J = 7.4 Hz, 2H), 4.00 (s, 3H), 3.73 (m, 2H), 1.83−1.76 (m, 6H), 1.73−1.62 (m, 4H), 1.13 (sext, J = 7.4 Hz, 2H), 0.69 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 152.0, 147.1, 143.5, 141.2, 139.6, 135.5, 128.7, 128.5, 127.9, 127.0, 124.9, 124.8, 124.7, 127.2, 122.8, 120.8, 112.1, 110.6, 59.8, 52.6, 45.7, 34.1, 32.0, 24.1, 20.3, 13.8. MS (ESI) m/z: 553 (MH^+). HRMS (ESI, m/z) calcd for $C_{31}H_{33}N_6O_4$: m/z 553.2563; found 553.2566 (M + H). IR (cm^{-1}, KBr): 3421, 3245, 2967, 1712, 1440, 1214.

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic data (^{1}H and ^{13}C NMR, LRMS, HRMS, FT-IR) of essential intermediates, compound **10**, and X-ray data of compound **10**{*1,3,1*}. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) Final product **10c** was crystallized by slow evaporation of a solution of ethyl acetate/hexane (1:1, v/v) at room temperature. Crystal data: Empirical formula of **10c**: $C_{32}H_{34}F_1N_5O_3$. Formula weight: 555.64. Crystal system: Monoclinic. The crystal data has been deposited at Cambridge Crystallographic Data Centre [CCDC No. 859133]. Copies of the data can be obtained free of charge via www.ccdc.ac.uk/conts/retrieving.html or CCDC, 12 union Road, 50 Cambridge CB2 1EZ, U.K.