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Graphical Abstract

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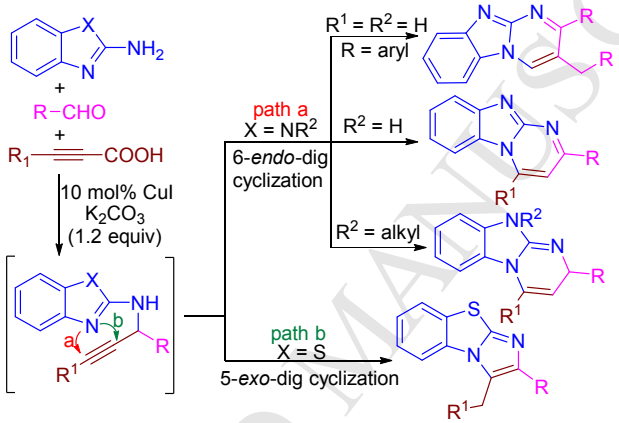

- diverse synthesis
- high atom-, step- and pot-efficiency
- assemblying pyrimidoimidazole scaffold and its C-3 position functionalization in one pot
- forming 3 or 4 new bonds in single operation

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Diverse synthesis of pyrimido[1,2-*a*]benzimidazoles and imidazo[2,1-*b*]benzothiazoles via CuI-catalyzed decarboxylic multicomponent reactions of heterocyclic azoles, aldehydes and alkynecarboxylic acids

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ABSTRACT

We have developed a straightforward approach to diverse synthesis of 2,3-, 2,4-disubstituted pyrimido[1,2-*a*]benzimidazoles, 2,4,10-trisubstituted 2,10-dihydropyrimido[1,2-*a*]benzimidazoles and 2,3-disubstituted imidazo[2,1-*b*]benzothiazoles via multicomponent reactions (MCRs) of heterocyclic azoles, aldehydes with easily storable and handling alkynecarboxylic acids. In the presence of a catalytic amount of CuI and K_2CO_3, the pyrimido[1,2-*a*]benzimidazole or imidazo[2,1-*b*]benzothiazole scaffold could be rapidly constructed through a 6-*endo*-dig or 5-*exo*-dig cyclization, respectively. The preliminary mechanistic study suggested that the formation of 2,3- disubstituted pyrimido[1,2-*a*]benzimidazoles, which completes the assembly of the scaffold and its C-3 position functionalization in one pot, undergoes a novel cascade process involving a decarboxylation, A^3 coupling, 6-*endo*-dig cyclization, nucleophilic addition and dehydration.

1. Introduction

Fused heterocyclic compounds are key structural scaffolds in a broad variety of natural products, drug molecules, and functional materials. Among them, pyrimido[1,2-*a*]benzimidazoles and imidazo[2,1-*b*]benzothiazoles have been related to an extensive range of pharmacological activities, such as anti-asthmatic,[1] antitumor,[2] antibacterial,[3] etc,[4] and thus play a significant role in drug discovery. In addition, due to their interesting photophysical properties, such kinds of compounds have also been widely employed in other technological fields, for instance, as bipolar host materials in organic light-emitting diodes[5] (Fig. 1).

As a consequence, great efforts have been devoted to the construction of pyrimido[1,2-*a*]benzimidazole and imidazo[2,1-*b*]benzothiazole frameworks, and a number of elegant methods[6-10] have been established. Among them, employing the A^3-coupling-based multicomponent reactions (MCRs) of heterocyclic azoles, aldehydes and alkynes to assemble these two kinds of structural cores has attracted considerable attention owing to the expeditious formation of heterocyclic systems and

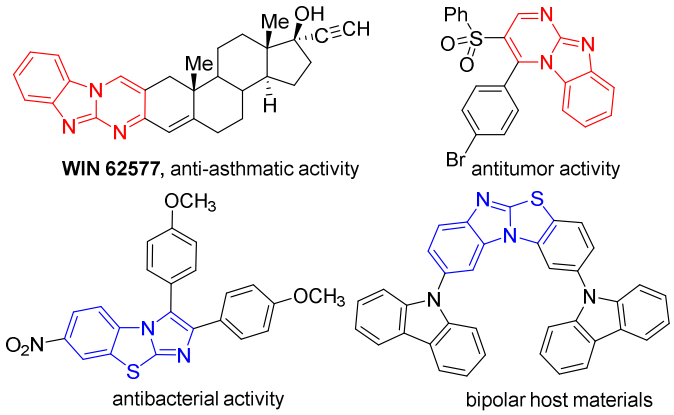

Fig. 1. Representative drug candidates and functional molecules containing pyrimido[1,2-*a*]benzimidazole or imidazo[2,1-*b*]benzothiazole moiety.

the highly pot-, step- and atom-economic manner of this MCRs.[7,10] However, the A^3-coupling-based multicomponent protocol still suffers from some limitations. For example, low-

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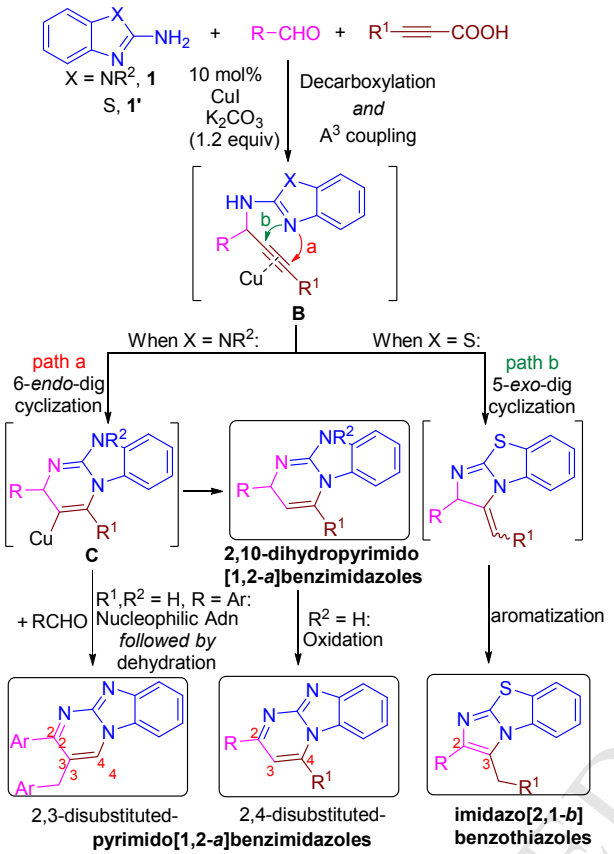
molecular-weight alkynes, such as gaseous acetylene, are not compatible in this one-pot procedure. Alkynecarboxylic acids, a kind of commercially available, easily storable and handling compounds, are appealing surrogates for alkynes, especially those in gaseous state at room temperature. With or without transition-metal catalysts, alkynecarboxylic acids can undergo decarboxylation, followed by various cascade reactions, such as coupling reactions, acylation, etc., to afford 1,3-diynes, 1,4-enynes and other useful compounds.[11]



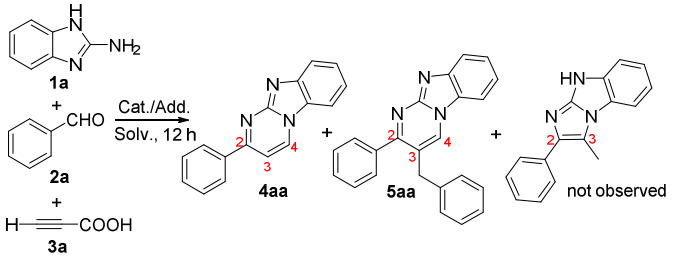
Scheme 1. Our work: diverse synthesis of pyrimido[1,2-*a*]benzimidazoles and imidazo[2,1-*b*]benzothiazoles via decarboxylic MCRs.

In view of the significance of fused heterocyclic compounds and the convenience of using alkynecarboxylic acids as alkyne sources, we were interested in developing a facile and straightforward approach to the diverse synthesis of pyrimido[1,2-*a*]benzimidazoles and imidazo[2,1-*b*]benzothiazoles via the decarboxylic MCRs of heterocyclic azoles, aldehydes and alkynecarboxylic acids. Herein, we'd like to report some interesting results of our investigation (Scheme 1). In the presence of a catalytic amount of CuI and K_2CO_3, a propargylamine intermediate **B** could be *in situ* generated through decarboxylation and A^3 coupling. Using different types of heterocyclic azoles (**1** or **1'**) as the reacting substance, **B** could undergo 6-*endo*-dig cyclization (X = NR^2, **1**) or 5-*exo*-dig cyclization (X = S, **1'**) to form the pyrimido[1,2-*a*]benzimidazole skeleton or the imidazo[2,1-*b*]benzothiazole skeleton, respectively. More interestingly, when propargylic acid, aromatic aldehyde and 2-aminobenzoimidazole (R^1 = R^2 = H, R = Ar) were employed in the MCRs as substrates, the cyclized intermediate **C** could further occur nucleophilic addition with the other molecular aldehyde, followed by dehydration, to lead to 2,3-disubstituted pyrimido[1,2-*a*]benzimidazoles, in which four new chemical bonds were formed in a single operation without isolating the intermediates or changing the reaction conditions. To the best of our knowledge, one-pot methods for completing the assembly of the pyrimido[1,2-*a*]benzimidazole scaffold and its *C*-3 position functionalization in a cascade process hasn't been reported yet.

Results and discussion

Initially, 2-aminobenzoimidazole (**1a**), benzaldehyde (**2a**) and propiolic acid (**3a**) were chosen as the model substrates to optimize the reaction conditions (Table 1). In the presence of 10 mol% CuI in DMSO at 110 °C, the MCR happened and delivered a 6-*endo*-dig product, 2-phenylimidazo[1,2-*a*]benzopyrimidine **4aa**, in 32% yield (Entry 1). When 1.2 equiv. of K_2CO_3 was introduced into the reaction system, the yield of **4aa** was decreased to 16%. Interestingly, another product, 3-benzyl-2-phenylimidazo[1,2-*a*]benzopyrimidine **5aa**, which was installed an additional benzyl group in the C3-position comparing with **4aa**, was obtained in 32% yield (Entry 2). The structure of **5aa** was firmly confirmed by NMR, MS as well as X-ray analysis (see the Supplementary Information, Fig. S1). We then adjusted the ratio of the three reactants and found that with the increase of the amount of aldehyde **1a**, **5aa** became to the major product while the yield of **4aa** was further degraded (65% *vs* 7%, **5aa** *vs* **4aa**, Entry 3). The following investigation of the catalyst, including different Pd(II), Au(III), Ag(I), Fe(III), Cu(I), Cu(II) salts, showed that the low-cost and non-toxic CuI was the most effective catalyst for the formation of **5aa** (Entries 3-13). Other commonly used inorganic bases were also examined, and the best result was achieved when K_2CO_3 was utilized as the reaction additive (Entries 3, 14 and 15). Reaction in other solvents didn't lead to any improvement in the yields (Entries 16-18). It is noted that in all cases, no 5-*exo*-dig product, 3-benzyl-2-methylimidazo[1,2-*a*]benzoimidazole, was observed at all. Thus, the optimal conditions were finalized with **1**, **2** (2.1 equiv), **3** (1.2 equiv), CuI (10 mol%) and K_2CO_3 (1.2 equiv) in DMSO at 110 °C for 12 h.

Table 1 Optimization of the reaction conditions[a,b]

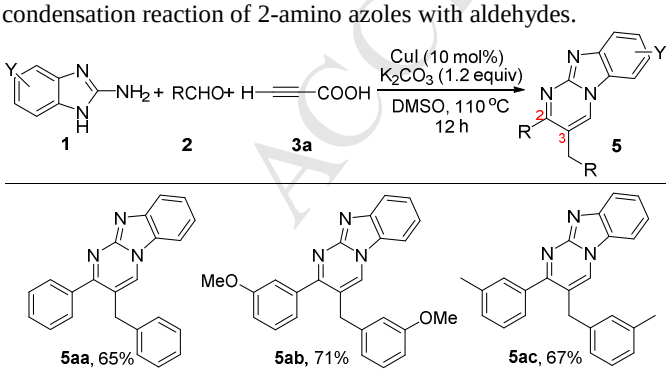


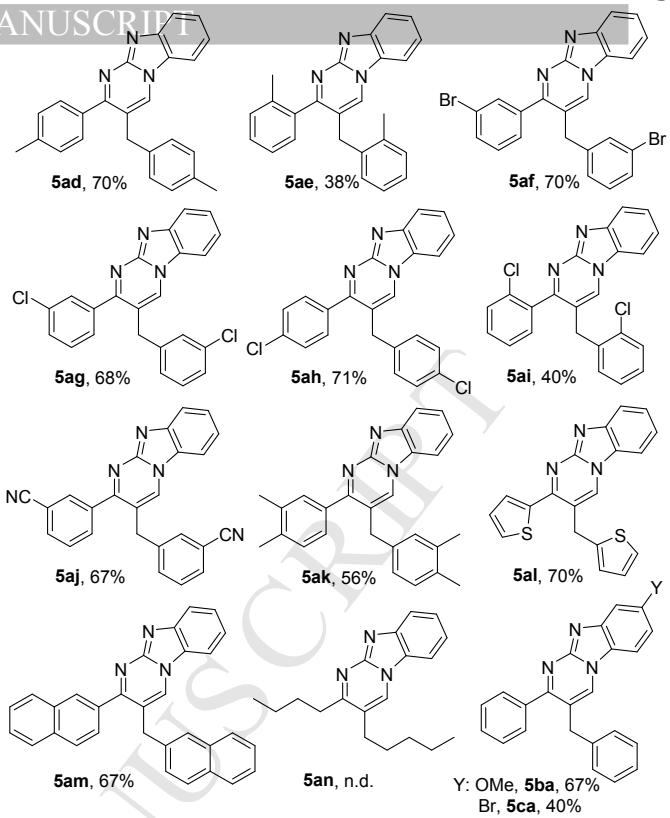
Entry	Ratio of **1a**/**2a**/**3a**	Cat. (10 mol%)	Add. (1.2 equiv)	Solv. (110 °C)	Results **4aa**	**5aa**
1	1: 1.1: 1.2	CuI	-	DMSO	32%	0
2	1: 1.1: 1.2	CuI	K_2CO_3	DMSO	16%	32%
3	1: 2.1: 1.2	CuI	K_2CO_3	DMSO	7%	65%
4	1: 2.1: 1.2	$PdCl_2$	K_2CO_3	DMSO	0	0
5	1: 2.1: 1.2	$AuCl_3$	K_2CO_3	DMSO	15%	12%
6	1: 2.1: 1.2	$Fe(OTf)_3$	K_2CO_3	DMSO	Trace	0
7	1: 2.1: 1.2	AgOTf	K_2CO_3	DMSO	Trace	0
8	1: 2.1: 1.2	CuCl	K_2CO_3	DMSO	10%	12%
9	1: 2.1: 1.2	CuBr	K_2CO_3	DMSO	8%	18%
10	1: 2.1: 1.2	$CuCl_2$	K_2CO_3	DMSO	4%	0
11	1: 2.1: 1.2	$CuBr_2$	K_2CO_3	DMSO	14%	20%

11	1: 2.1: 1.2	$Cu(OTf)_2$	K_2CO_3	DMSO	12%	18%
12	1: 2.1: 1.2	$Cu(acac)_2$	K_2CO_3	DMSO	8%	36%
13	1: 2.1: 1.2	CuI/ $Cu(OTf)_2$	K_2CO_3	DMSO	12%	32%
14	1: 2.1: 1.2	CuI	K_2HPO_4	DMSO	17%	12%
15	1: 2.1: 1.2	CuI	$CsCO_3$	DMSO	20%	38%
16	1: 2.1: 1.2	CuI	K_2CO_3	DMF	18%	30%
17	1: 2.1: 1.2	CuI	K_2CO_3	CH_3CN	13%	Trace
18	1: 2.1: 1.2	CuI	K_2CO_3	$PhCH_3$	Trace	Trace

[a] All reactions were carried out with **1a** (1 mmol), **2a**, **3a**, catalyst and additive in Solvents at 110 °C for 12 h in a sealed tube. [b] Isolated yields.

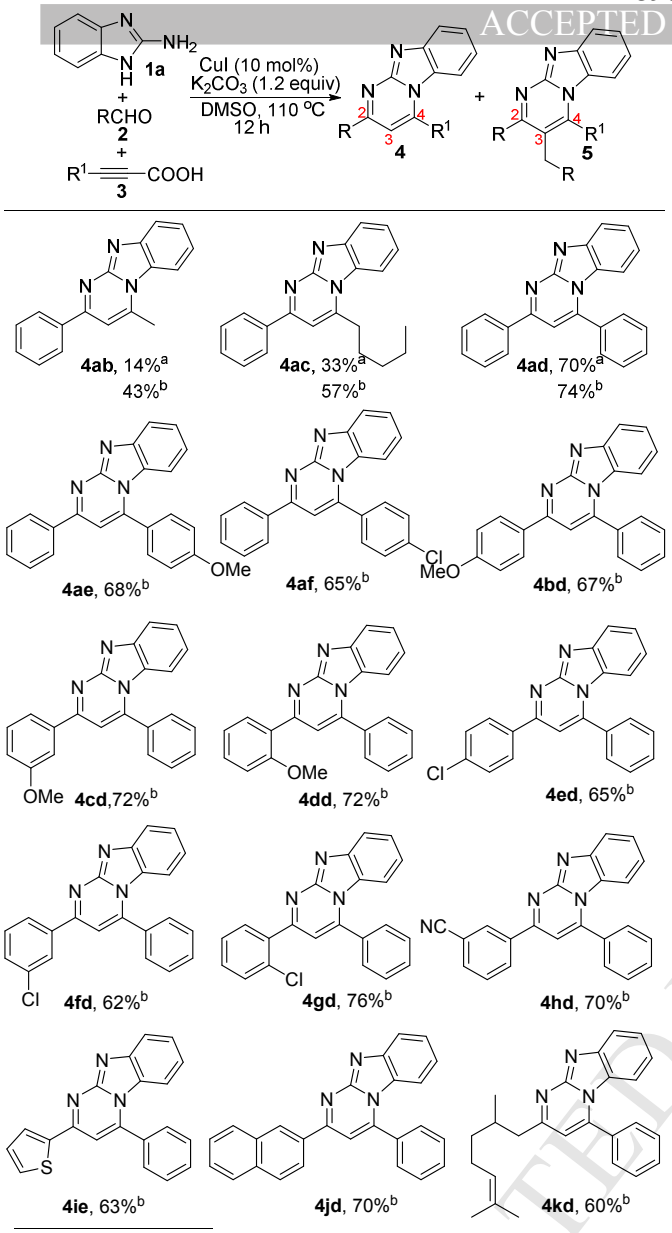
With the optimal conditions in hand, we first investigated the substrate scope of this new MCR using different aldehydes (**2**) and substituted 2-aminobenzoimidazoles (**1**), and the results are illustrated in Scheme 2. To our delight, the MCR of **1a**, **3a** with a variety of aromatic aldehydes performed smoothly, providing the corresponding 2,3-disubstituted pyrimido[1,2-*a*]benzimidazoles in moderate yields (Scheme 2, **5aa**-**5ak**). Generally, the aldehydes with substituents in ortho position of the phenyl ring resulted in relatively lower yields (**5ea** and **5ia**, 38-40%) than those with substituents in para and/or meta positions (**5ac**, **5ad**, **5ag**, **5ah** and **5ak**, 56-70%), indicating that the steric hindrance from the ortho-substituent on the phenyl ring has a big impact on this transformation. However, the electronic effect was found not to influence the cascade process too much. Most of the electron-deficient and electron-rich aromatic aldehydes were well tolerated under the optimal condition and furnished the desired products **5** in similar yields (**5aa**, **5ab**, **5ac**, **5af**, **5ag** and **5aj**, 65-71%). Polycyclic aromatic and heteroaromatic aldehydes were also compatible with this procedure and the corresponding products were attained in practical yields (**5al** and **5am**, 67-70%). Unfortunately, when using pentanal **2n** as aldehyde component, the starting material **1a** disappeared but no anticipated 2,3-dialkylpyrimido[1,2-*a*]benzimidazole was detected, which reveals that aliphatic aldehydes are not suitable substrates for the direct formation of **5** (**5an**). 2-Aminobenzoimidazoles bearing different substituents on the phenyl ring were also employed in the reaction system. It was found that imidazole substrates with electron-donating group were more efficient than those with electron-withdrawing group (**5ba**, 67% *vs* **5ca**, 40%). This is probably because the former [Y = electron-donating group, such as OMe (**1b**)] has higher reactivity towards the proposed condensation reaction of 2-amino azoles with aldehydes.





Scheme 2. Synthesis of 2,3-disubstituted pyrimido[1,2-*a*]benzimidazoles **5** from **3a**, different aldehydes **2** and **1**. Unless otherwise noted, all reactions were carried out with **1** (1 mmol), **2** (2.1 equiv), **3a** (1.2 equiv), CuI (10 mol%) and K_2CO_3 (1.2 equiv) in DMSO at 110 °C for 12 h in a sealed tube.

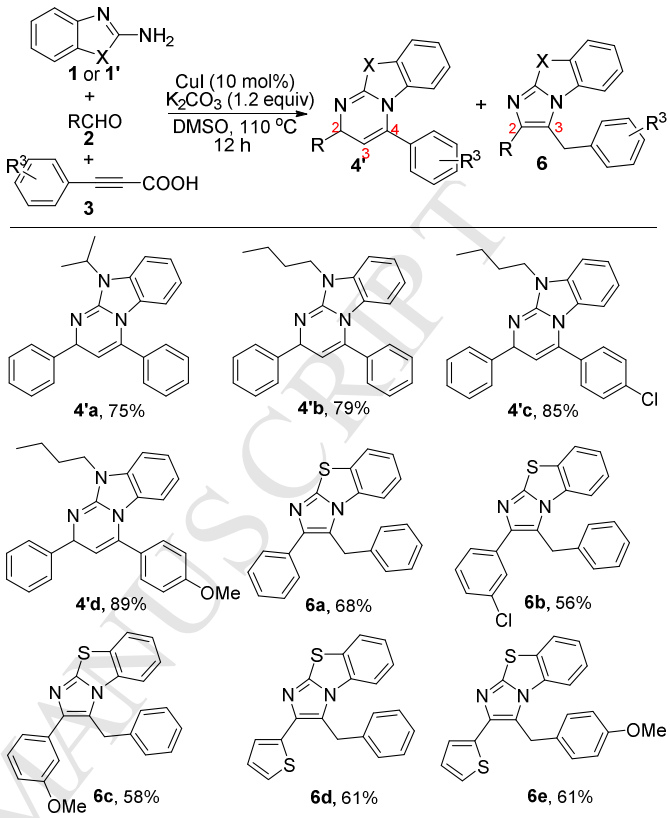
Next, we focused on the substrate scope in terms of different alkynecarboxylic acids (Scheme 3, **4ab**-**4af**). Surprisingly, no matter if alkyl substituted (**3b**, **3c**) or aryl substituted propiolic acid (**3d**) was employed in the MCR, under the above standard conditions, only 2,4-disubstituted imidazo[1,2-*a*]benzopyrimidine **4** (which doesn't bear any substituent in C-3 position) was obtained with no compound **5** formed (**4ab**[a]-**4ad**[a]). After further optimizing the reaction conditions, the yield of **4** could be enhanced slightly (**4ab**[b]-**4ad**[b], from 14-70% to 43-74%). Moreover, 3-arylpropiolic acids, regardless of the electronic nature of the substituents on the aryl ring, led to better outcomes compared to 3-alkylpropiolic acids substrates (**4ad**[b]-**4af**[b], 65-74% *vs* **4ab**[b]-**4ac**[b], 43-60%). The MCRs of **1a**, 3-substituted propiolic acid **3a** with other aldehydes could also occur to give the C3-positional unfunctionalized **4** as the only pyrimidoimidazole products in moderate yields (Scheme 3, **4bd**-**4kd**), which is consistent with our previous observation from **4ab**-**4af**. The aldehyde component was proved to have little effect on the formation of compound **4**. Various aromatic, heteroaromatic, polycyclic aromatic as well as aliphatic aldehydes were all well tolerated for this one-pot transformation. Interestingly, when 3*H*-imidazo[4,5-*b*]pyridin-2-ylamine **1d** was used as the substrate, the MCR of **1d**, benzaldehyde **2a** and phenylpropiolic acid **3d** also occurred and delivered the pyrido imidazo[1,2-*a*]pyrimidine product **7** in 42% yield with regio-specificity. The structure of **7** is determined by NMR, HRMS and X-ray analysis (See the Supporting Information, Scheme S1 and Figure S3). The changed chemoselectivity (from **5** to **4**) probably attributes to the increased steric hindrance of C-4 position in imidazo[1,2-*a*]benzopyrimidines.



[a] the ratio of **1a**/**2**/**3** = 1:2.1:1.2
[b] the ratio of **1a**/**2**/**3** = 1:1.1:1.2

Scheme 3. Synthesis of 2,4-disubstituted pyrimido[1,2-*a*]benzimidazoles **4** from **1a**, different propiolic acids **3** and aldehydes **2**. All reactions were carried out with **1a** (1 mmol), **2** (2.1 or 1.1equiv), **3a** (1.2 equiv), CuI (10 mol%) and K_2CO_3 (1.2 equiv) in DMSO at 110 °C for 12 h in a sealed tube.

The scope of this MCR was further elaborated with different types of heterocyclic azoles. As shown in Scheme 4, by treatment of CuI (10 mol%) and K_2CO_3 (1.2 equiv) in DMSO at 110 °C, 1-alkyl-2-aminobenzoimidazole (X = NR, **1**), benzaldehyde (**2a**) and 3-aryl propiolic acid (**3**) could react and delivered 2,10-dihydropyrimido[1,2-*a*]benzimidazoles **4'** in good yields via a cascade process of decarboxylation, A^3 coupling and subsequent 6-*endo*-dig cyclization (**4'a**-**4'd**). It was found that the MCR is independent of either the N1-positional alkyl group in 2-aminobenzoimidazole (**4'a**, **4'b**) or the substituent in the aryl ring of propiolic acid (**4'c**, **4'd**). However, to our surprise, when 2-aminobenzothiazole (X = S, **1'**) was used as the reactant, under the same conditions, 3-benzyl-2-phenylimidazo[2,1-*b*]benzothiazole **6a**, a product involved a 5-*exo*-dig cyclization instead of a 6-*endo*-dig mode, was isolated as the major product in 68% yield (**6a**). Moreover, changing the aldehye or 3-aryl propiolic acid component didn't affect the reaction pathway and only imidazo[2,1-*b*]benzothiazole scaffold was constructed as a result (**6b**-**6e**). That is to say, the cascade cyclization in the MCR mainly relies on the heterocyclic azole component, especially the heteroatom in 1-position.

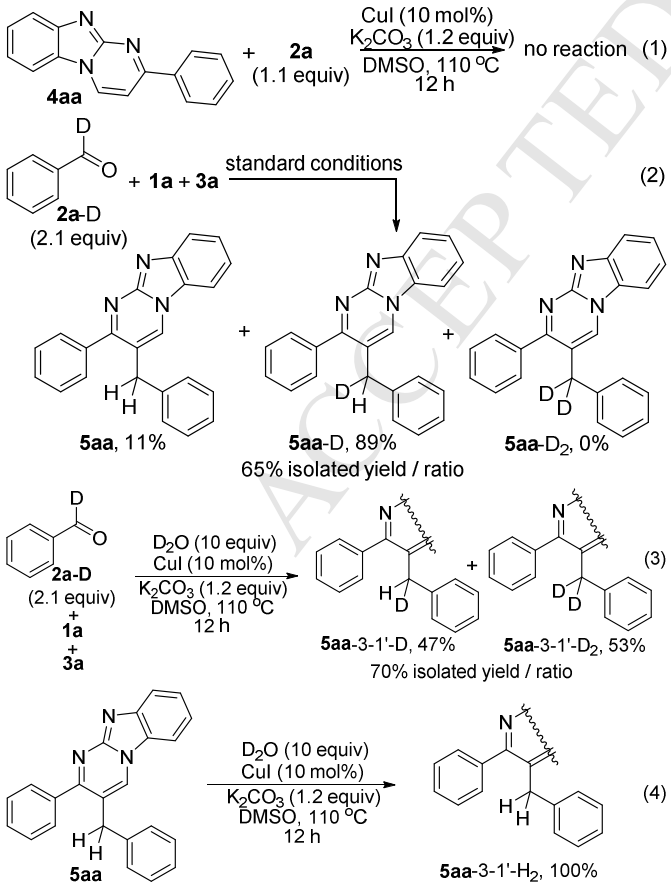


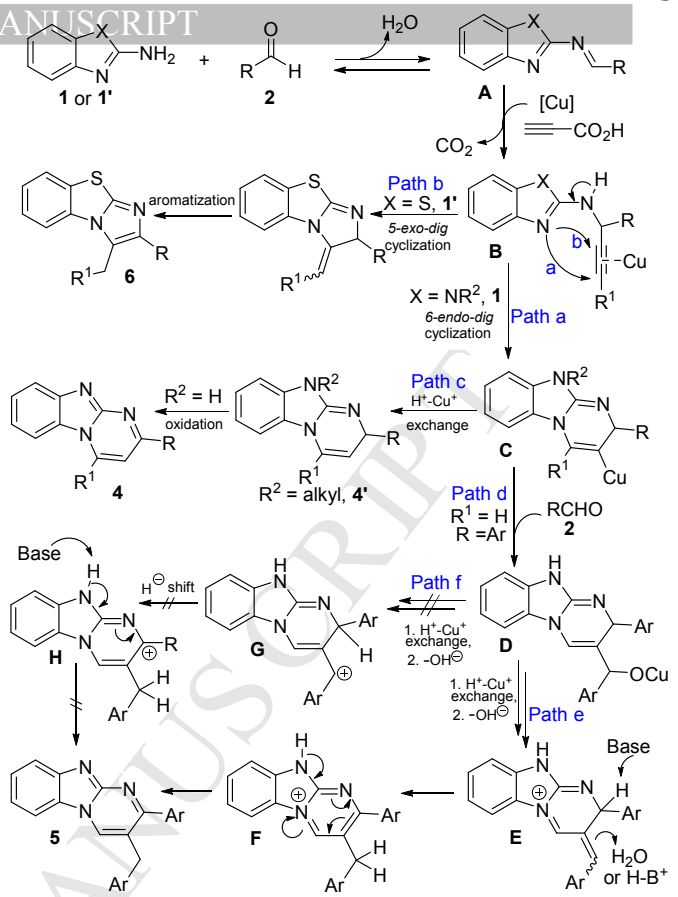
Scheme 4. Synthesis of 2,10-dihydropyrimido[1,2-*a*]benzimidazoles **4'** and imidazo[2,1-*b*]benzothiazoles **6** from different heterocyclic azinesazoles, aldehydes and alkynecarboxylic acids. Unless otherwise noted, all reactions were carried out with **1** (1 mmol), **2** (1.1 equiv), **3** (1.2 equiv), CuI (10 mol%) and K_2CO_3 (1.2 equiv) in DMSO at 110 °C for 12 h in a sealed tube.

To gain some insight into the reaction mechanism, especially the formation pathway for compound **5**, we carried out a series of experiments (see the Supporting Information for details). In the presence of CuI (10 mol%) and K_2CO_3 (1.2 equiv) in DMSO at 110 °C, 2-phenylimidazo[1,2-*a*]benzopyrimidine **4aa** couldn't react with benzylaldehyde **2a** to install the substituent in *C-3* position, implying that the novel product **5** isn't formed from compound **4** [Eq. (1)]. Deuterium reagents, C_6H_5CDO (**2a**-D) and D_2O, were then introduced into the reaction system to figure out the source of the benzylic protons in **5**. Under the standard conditions, the MCR of C_6H_5CDO, **1a** and **3a** offered the non-deuterated **5aa** in 11% proportion and the monodeuterated product **5aa**-D in 89% proportion (calculated by ^{1}H NMR), with no dideuterated product **5aa**-D_2 observed [Eq. (2)]. When 10 equiv. of D_2O was also brought into the reaction system[12], the benzylic monodeuterated **5aa**-3-1'-D was obtained in 47% proportion, along with 53% of the benzylic dideuterated **5aa**-3-1'-D_2 (calculated by ^{1}H NMR) [Eq. (3)]. Furthermore, under the same conditions, the benzylic H/D exchange of **5aa** didn't happen [Eq. (4)]. The outcomes of these three experiments suggest that one of the benzylic protons of product **5** may come from the aldehyde and the other from

the proton source generated during the reaction, such as H_2O.

Based on the above preliminary experimental results and previous literature reports[7,11e,13-14], a plausible mechanism of this one-pot MCR was proposed in Scheme 5. Initially, the condensation of azole and aldehyde furnishes the imine **A**, together with 1 equiv of water. Imine **A** then undergoes nucleophilic addition with alkynyl copper, which is generated through the decarboxylation of alkynecarboxylic acid, to yield the propargylamine **B**. When the heteroatom in 1-position is sulfur (X = S), **B** experiences a 5-*exo*-dig cyclization, followed by aromatization, to produce the imidazo[2,1-*b*]benzothiazole **6** (Path a); when the heteroatom is nitrogen (X = N), a 6-*endo*-dig cyclization takes place to form the intermediate **C** (Path b), which can be converted into the dihydropyrimido[1,2-*a*]benzimidazole **4'** via Cu/H exchange (R^2 = alkyl) or pyrimido[1,2-*a*]benzimidazole **4** via Cu/H and subsequent oxidation[7] (R^2 = H) (Path c). For propiolic acid and aromatic aldehyde substrates, **C** can further attack on the second molecular aldehyde, giving the addition intermediate **D** (Path d). **D** may predominantly go through Path e to form the final product **5**. Concretely, intermediate **E** was first generated with the participation of lone pair electrons in *N*-3; then, the base, which is indispensable for the formation of **5** (Table 1, 1 and 3), extracts the proton in *C*-2 position and simultaneously, the benzylic carbon obtains a proton from water (or H-Base$^+$), yielding the intermediate **F**; **F** undergoes aromatization to afford the final 2,3-disubstituted pyrimido[1,2-*a*]benzimidazole **5**. Another pathway, Path f, involved an intermolecular hydride transfer (**G** to **H**), was ruled out by the control experiment [Eq. (3)] in which no dideuterated product **5aa**-D_2 was observed. In addition, for propiolic acid, the generation of the propargylamine **B** may undergo an alternative pathway proposed by Lee and coworkers (see the Supporting Information for details).[11e]





Scheme 5. Control experiments and proposed mechanism

Conclusion

In summary, we have developed a facile and economic protocol for assembling pyrimido[1,2-*a*]benzimidazole and imidazo[2,1-*b*]benzothiazole scaffolds via decarboxylic multicomponent reactions of heteroclyclic azoles, aldehydes and alkynecarboxylic acids. By the treatment with a catalytic amount of CuI and K_2CO_3, biologically potent 2,3-, 2,4-disubstituted pyrimido[1,2-*a*]benzimidazoles, 2,4,10-trisubstituted 2,10-dihydropyrimido[1,2-*a*]benzimidazoles and 2,3-disubstituted imidazo[2,1-*b*]benzothiazoles were obtained diversely in moderate to good yields. The mechanistic study indicated that a novel cascade process including a decarboxylation, A^3 coupling, 6-*endo*-dig cyclization, nucleophilic addition and dehydration is involved in the direct formation of 2,3-disubstituted pyrimido[1,2-*a*]benzimidazoles. Notable features of this new approach include readily available starting materials, easily storable and handling alkyne sources, common and inexpensive catalysts, convenient operations, and no need for isolating the reaction intermediates. The reaction should therefore have widespread applications in the rapid construction of various pyrimidoimidazole and imidazothiazole derivatives which has bright prospect in medicine, materials and other important fields.

Experimental section

General

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker Avance 400 or 600 instrument. Chemical shifts (δ) are referenced to internal TMS, DMSO-d_6 or $CDCl_3$. High-resolution mass spectra were recorded on a Bruker Impact mass spectrometer. Melting points were determined by using a Stuart Scientific SMP10 instrument and are uncorrected. IR spectra were recorded in the ATR mode on a Nicolet 6700 FT-IR

Thermo Scientific spectrometer; only the more significant peaks are reported. All reagents and solvents were obtained commercially and used as received without further purification. Reactions were monitored by TLC on glass-backed plates coated with a 0.2 mm thickness of silica gel 60 F254; chromatograms were visualized by UV radiation (254 nm) or by staining with phosphomolybdic acid, 2,4-dinitrophenylhydrazine and $KMnO_4$. Flash column chromatography was performed on 300–400 mesh silica gel.

*4.2.1 General Procedure for the Synthesis of 2,3-Disubstituted Pyrimido[1, 2-a]benzimidazoles (**5aa-5ma**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), the aldehyde (2.1 mmol, 2.1 equiv.), the alkyne carboxylic acid (1.2 mmol, 1.2 equiv.), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (1.2 mmol, 1.2 equiv.), and DMSO (4 mL) were placed in a 10 mL reaction tube. The reaction mixture was tightly sealed and heated at 110 °C for 12 h. After cooling, the mixture was poured into CH_2Cl_2 (30 mL), washed with water (2×10 mL), saturated aqueous NH_4Cl (3×10 mL) and brine (2×10 mL), and then dried with Na_2SO_4 and passed through a celite pad. Evaporation of the solvent under reduced pressure provided the crude product, which was purified by column chromatography on silica gel with petroleum ether:ethyl acetate (V:V = 3:1−1:1) or methylbenzene: ethyl acetate (V:V = 6:1−2:1) as the eluent to afford the final product.

*4.2.2 3-Benzyl-2-phenylpyrimido[1,2-a]benzimidazole (**5aa**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), benzaldehyde (0.21 mL, 2.1 mmol), propiolic acid (74.2 μL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **5aa** (217.8 mg, 65%) as a yellow solid after chromatography; mp 228−230 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 5.6 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.46-7.44 (m, 3H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.32 – 7.22 (m, 3H), 7.06 (d, *J* = 7.2 Hz, 2H), 4.11 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 150.2, 145.0, 138.4, 138.3, 132.8, 129.5, 128.8, 128.8, 128.8, 128.2, 127.8, 126.8, 126.1, 121.6, 120.4, 118.8, 110.7, 36.5; IR (KBr): ν = 3059, 3021, 1630, 1603, 1513, 1484, 1446, 1419, 762, 736, 714, 698 cm^{-1}; HR-MS (ESI): m/z = 336.1504, calcd. for $[C_{23}H_{16}N_3+H]^+$: 336.1501.

*4.2.3 3-(3-Methoxybenzyl)-2-(3-methoxyphenyl)pyrimido[1,2-a]benzimidazole (**5ab**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 3-methoxybenzaldehyde (0.25 mL, 2.1 mmol), propiolic acid (74.2 μL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **5ab** (280.5 mg, 71%) as a yellow semi-solid after chromatography; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.18-7.11 (m, 2H), 7.09 (s, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.60 (d, *J* = 7.6 Hz, 1H), 6.53 (s, 1H), 4.02 (s, 2H), 3.72 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 159.8, 159.3, 149.8, 144.7, 140.1, 139.3, 132.9, 129.6, 129.1, 126.5, 126.0, 121.4, 120.9 (2C), 120.1, 118.3, 115.6, 114.4, 113.8, 111.9, 110.7, 55.1, 55.0, 36.3; HR-MS (ESI): m/z = 396.1710, calcd for $[C_{25}H_{21}N_3O_2+H]^+$: 396.1712.

*4.2.4 3-(3-Methylbenzyl)-2-(3-methylphenyl)-pyrimido[1,2-a]benzimidazole (**5ac**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 3-methylbenzaldehyde (0.26 mL, 2.1 mmol), propiolic acid (74.2 μL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **5ac** (243.3 mg, 67%) as a yellow solid after chromatography; mp 152−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.41-7.32 (m, 4H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.85 (s, 1H), 4.06 (s, 2H), 2.39 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1, 150.1, 145.0, 138.6, 138.5, 138.2, 138.1, 132.6, 130.2, 129.6 (2C), 128.7, 128.1, 127.6,126.7, 126.1, 125.9, 125.8, 121.5, 120.5, 119.0, 110.6, 36.5, 21.4, 21.3; IR (KBr): ν = 3019, 1734, 1601, 1506, 1483, 1443, 1421, 1335, 1260, 790, 728 cm^{-1}; HR-MS (ESI): m/z = 364.1820, calcd for $[C_{25}H_{21}N_3+H]^+$: 364.1814.

*4.2.5 3-(4-Methylbenzyl)-2-(4-methylphenyl)pyrimido[1,2-a]benzimidazole (**5ad**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 4-methylbenzaldehyde (0.26 mL, 2.1 mmol), propiolic acid (74.2 μL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **5ad** (254.2 mg, 70%) as a yellow solid after chromatography; mp 170−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 2H), 7.08 (d, *J* = 7.6 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 4.03 (s, 2H), 2.39 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 150.1, 144.8, 139.6, 136.4, 135.4, 135.4, 132.7, 129.5, 128.9 (2C), 128.7, 126.6, 126.0, 121.3, 120.2, 119.0, 110.6, 36.0, 21.3, 21.0; IR (KBr): ν = 3014, 1708, 1628, 1598, 1511, 1478, 1445, 1305, 1259, 1029, 756, 730 cm^{-1}; HR-MS (ESI): m/z = 364.1821, calcd for $[C_{25}H_{21}N_3+H]^+$: 364.1814.

*4.2.6 3-(2-Methylbenzyl)-2-(2-methylphenyl)pyrimido[1,2-a]benzimidazole (**5ae**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 2-methylbenzaldehyde (0.26 mL, 2.1 mmol), propiolic acid (74.2 μL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **5ae** (138.0 mg, 38%) as a yellow solid after chromatography; mp 158−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.37-7.34 (m, 2H), 7.33 (s, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.27-7.25 (m, 1H), 7.23-7.16 (m, 3H), 7.05 (d, *J* = 7.2 Hz, 1H), 3.76 (s, 2H), 2.21 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 145.0, 144.8, 137.7, 136.3, 135.6, 135.4, 131.5, 130.8, 130.6, 130.0, 129.0, 127.7, 127.4, 126.8, 126.5, 126.2, 125.8, 121.6, 120.6, 119.3, 110.5, 33.8, 19.5, 19.3; IR (KBr): ν = 3013, 1710, 1605, 1513, 1485, 1443, 1310, 1254, 1029, 759, 730 cm^{-1}; HR-MS (ESI): m/z = 364.1824, calcd for $[C_{25}H_{21}N_3+H]^+$: 364.1814.

*4.2.7 3-(3-Bromobenzyl)-2-(3-bromophenyl)pyrimido[1,2-a]benzimidazole (**5af**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 3-bromobenzaldehyde (0.25 mL, 2.1 mmol,), propiolic acid (74.2 μL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **5af** (343.6 mg, 70%) as a yellow solid after chromatography; mp 164−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.66 (s, 1H), 7.57 (t, *J* = 8.0 Hz, 2H), 7.45 – 7.35 (m, 3H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.14 (t, *J* = 7.8 Hz, 2H), 6.93 (d, *J* = 7.6 Hz, 1H), 4.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 149.6, 145.0, 140.4, 139.8, 133.0, 132.5, 131.7, 131.6, 130.3, 130.1, 129.8, 127.3, 127.2, 126.6, 126.5, 122.9, 122.4, 122.0, 120.5, 117.7, 110.9, 36.1; IR (KBr): ν = 3057, 1734, 1600, 1567, 1510, 1474, 1445, 1421, 1253, 1218, 1050, 794, 758, 731,

698 cm^{-1}; HR-MS (ESI): m/z = 491.9714, calcd for $[C_{23}H_{15}Br_2N_3+H]^+$: 491.9711.

*4.2.8 3-(3-Chlorobenzyl)-2-(3-chlorophenyl)pyrimido[1,2-a]benzimidazole (**5ag**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 3-chlorobenzaldehyde (0.25 mL, 2.1 mmol), propiolic acid (74.2 µL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **5ag** (274.0 mg, 68%) as a yellow solid after chromatography; mp 175−177 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.55-7.51 (m, 1H), 7.45 – 7.38 (m, 3H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.22-7.20 (m, 2H), 7.00 (s, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 4.05 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 149.6, 144.9, 140.1, 139.6, 134.6, 134.3, 133.0, 130.0, 129.6 (2C), 128.8, 128.8, 127.1, 126.8, 126.7, 126.5, 126.4, 122.0, 120.5, 117.7, 110.9, 36.1; IR (KBr): *v* = 3055, 1741, 1565, 1513, 1476, 1448, 1253, 1213, 933, 788, 738 cm^{-1}; HR-MS (ESI): m/z = 404.0723, calcd for $[C_{23}H_{15}Cl_2N_3+H]^+$: 404.0721.

*4.2.9 3-(4-Chlorobenzyl)-2-(4-chlorophenyl)pyrimido[1,2-a]benzimidazole (**5ah**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 4-chlorobenzaldehyde (295.2 mg, 2.1 mmol), propiolic acid (74.2 µL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **5ah** (286.1 mg, 71%) as a yellow solid after chromatography; mp 188−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.42 –7.36 (m, 3H), 7.28 – 7.25 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 4.06 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 149.8, 145.0, 136.7, 136.5, 136.0, 133.0, 132.9, 130.2, 130.0, 129.1, 128.6, 126.6, 126.5, 122.0, 120.6, 117.9, 110.7, 35.9; IR (KBr): *v* = 3060, 1731, 1683, 1512, 1485, 1442, 1421, 1254, 1090, 1012, 835, 735, 541 cm^{-1}; HR-MS (ESI): m/z = 404.0729, calcd for $[C_{23}H_{15}Cl_2N_3+H]^+$: 404.0721.

*4.2.10 3-(2-Chlorobenzyl)-2-(2-chlorophenyl)pyrimido[1,2-a]benzimidazole (**5ai**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 2-chlorobenzaldehyde (0.25 mL, 2.1 mmol), propiolic acid (74.2 µL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **5ai** (161.2 mg, 40%) as a yellow solid after chromatography; mp 187−189 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.40 –7.37 (m, 1H), 7.38 – 7.35 (m, 1H), 7.33 – 7.32 (m, 1H), 7.31 – 7.30 (m, 2H), 7.22 – 7.13 (m, 2H), 7.01 (d, *J* = 7.2 Hz, 1H), 4.02 (s,1H) , 3.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 149.7, 144.8, 137.2, 135.4, 134.2, 132.1, 131.9, 131.2, 130.4, 130.3, 130.0, 129.8, 129.5, 128.6, 127.1, 127.0, 126.2, 121.8, 120.5, 118.4, 110.7, 33.6; IR (KBr) *v* = 3055, 1752, 1628, 1602, 1515, 1475, 1439, 1306, 1262, 1031, 741 cm^{-1}; HR-MS (ESI): m/z = 404.0722, calcd for $[C_{23}H_{15}Cl_2N_3+H]^+$: 404.0721.

*4.2.11 3-(3-Cyanobenzyl)-2-(3-cyanophenyl)pyrimido[1,2-a]benzimidazole (**5aj**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 3-cyanobenzaldehyde (275.3 mg, 2.1 mmol), propiolic acid (74.2 µL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **5aj** (258.0 mg, 67%) as a yellow solid after chromatography; mp 198−200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.74 – 7.67 (m, 3H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.27 (s, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 4.12 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.7, 149.4, 145.0, 139.5, 139.2, 133.4, 133.0, 133.0, 132.8, 132.1, 132.1, 130.9, 129.8, 129.5, 126.9, 126.5, 122.5, 120.7, 118.2, 117.9, 116.8, 113.1, 112.8, 111.0, 36.1; IR (KBr): *v* = 3040, 2222, 1727, 1516, 1481, 1447, 1261, 1159, 1052, 797, 727, 689 cm^{-1}; HR-MS (ESI): m/z = 386.1416, calcd for $C_{25}H_{15}N_3+H]^+$: 386.1406.

*4.2.12 3-(3,4-Dimethylbenzyl)-2-(3,4-dimethylphenyl) pyrimido[1,2-a]benzimidazole (**5ak**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 3, 4-dimethylbenzaldehyde (0.28 mL, 2.1 mmol,), propiolic acid (74.2 µL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **5ak** (219.1 mg, 56%) as a yellow solid after chromatography; mp 166-168 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.46 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.86-6.84 (m, 2H), 4.06 (s, 2H), 2.34 (s, 3H), 2.31 (s, 3H), 2.26 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 150.1, 144.8, 138.2, 136.9, 136.4, 135.9, 135.7, 134.8, 132.6, 130.2, 130.0, 129.9, 129.2, 126.6, 126.2, 126.1, 125.8, 121.2, 120.0, 119.1, 110.6, 36.0, 19.6, 19.6, 19.5, 19.2; IR (KBr): *v* = 3047, 1726, 1509, 1478, 1446, 1303, 1261, 996, 741, 577, 538, 500, 458, 419 cm^{-1}; HR-MS (ESI): m/z = 392.2128, calcd for $[C_{27}H_{25}N_3+H]^+$: 392.2127.

*4.2.13 2-(Thiophen-2-yl)-3-(thiophen-2-ylmethyl)pyrimido[1,2-a]benzimidazole (**5al**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 2-thiophenecarboxaldehyde (0.20 mL, 2.1 mmol), propiolic acid (74.2µL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **5al** 242.9 mg, 70%) as a yellow solid after chromatography; mp 202−204 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 3.6 Hz, 1H), 7.58 (d, *J* = 4.0 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 5.2 Hz, 1H), 7.13 – 7.09 (m, 1H), 7.04 – 7.00 (m, 1H), 6.89-6.88 (m, 1H), 4.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 149.7, 145.4, 142.6, 140.5, 133.1, 131.4, 130.2, 128.2, 127.5, 126.8, 126.5, 126.4, 125.2, 121.7, 120.3, 116.5, 110.5, 31.7; IR (KBr): *v* = 3048, 1715, 1494, 1425, 1257, 1211, 963, 910 cm^{-1}; HR-MS (ESI): m/z = 348.0637, calcd for $C_{19}H_{13}N_3\ S_2+H]^+$: 348.0629.

*4.2.14 2-(Naphthalen-2-yl)-3-(naphthalne-2-ylmethyl)pyrimido [1,2-a]benzimidazole (**5am**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 2-naphthaldehyde (327.9 mg, 2.1 mmol), propiolic acid (74.2 µL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **5am** (291.5 mg, 67%) as a yellow solid after recrystallization; mp 252–254 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (s, 1H), 8.13 (s, 1H), 8.02 (d, *J* = 4.8 Hz, 1H), 7.90 (t, *J* = 9.2 Hz, 2H), 7.85 – 7.82 (m, 1H), 7.79 (d, *J* = 8.4 Hz, 3H), 7.71 – 7.67 (m, 1H), 7.57-7.46 (m, 7H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 4.33 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 136.0, 135.6, 133.7, 133.5, 133.1, 132.8, 132.4, 129.0, 128.8, 128.7, 128.1, 127.72, 127.70, 127.6, 127.5, 127.2, 126.9, 126.6, 126.5, 126.3, 126.2, 126.0, 121.7, 120.6, 118.7, 110.7, 36.9 ; IR (KBr): *v* = 3296, 3053, 1727, 1602, 1510, 1443, 1261, 952, 894, 818, 738 cm^{-1}; HR-MS (ESI): m/z = 436.1822, calcd for $[C_{31}H_{21}N_3+H]^+$: 436.1814.

*4.2.15 3-Benzyl-8-methoxy-2-phenylpyrimido[1,2-a]benzimidazole (**5ba**)*

2-Amino-8-methoxybenzimidazole (163.1 mg, 1.0 mmol), benzaldehyde (0.11 mL, 1.1 mmol), propiolic acid (74.2 μL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **5ba** (252.1 mg, 67%) as a yellow solid after chromatography; mp 198−200 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.62 (d, *J* = 3.2 Hz, 3H), 7.46 (s, 3H), 7.32 – 7.23(m, 4H), 7.06 (d, *J* = 7.2 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 1H), 4.11 (s, 2H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ164.4, 160.4, 159.1, 136.8, 132.6, 131.2, 129.4, 129.4, 128.9, 128.9, 128.9, 128.3, 127.7, 126.90, 112.9, 111.1, 103.8, 55.8, 36.5; IR (KBr): *ν* = 3053, 2994, 2831, 1607, 1545, 1526, 1513, 1477, 1442, 1422, 1251, 1203, 1157, 1105, 953, 815, 795, 695 cm^{-1}; HR-MS (ESI): m/z = 366.1606, calcd for $[C_{24}H_{19}N_3O+H]^+$: 366.1604.

*4.2.16 3-Benzyl-8-bromo-2-phenylpyrimido[1,2-a]benzimidazole (**5ca**)*

2-Amino-8-bromobenzimidazole (210.9 mg, 1.0 mmol), benzaldehyde (0.11 mL, 1.1 mmol), propiolic acid (74.2 μL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **5ca** (165.2 mg, 40%) as a yellow solid after chromatography; mp 202−204 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.84 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 6.4 Hz, 3H), 7.48-7.37 (m, 3H), 7.29 – 7.21 (m, 3H), 7.00 (d, *J* = 6.0 Hz, 2H), 4.04 (s, 2H). ^{13}C NMR (100MHz, $CDCl_3$) δ 166.4, 150.3, 143.7, 138.0, 132.5, 129.8, 129.6, 129.0, 128.9, 128.8, 128.4, 127.1, 121.8, 119.8, 114.4, 113.7, 109.4, 100.0, 36.6; IR (KBr): *ν* = 3048, 2899, 1633, 1508, 1453, 1332, 1217, 1185, 1138, 1093, 945, 797, 696 cm^{-1}; HR-MS (ESI): m/z = 414.0606, calcd for $[C_{23}H_{16}BrN_3+H]^+$: 414.0599.

*4.3.1 General Procedure for the Synthesis of 2,4-Disubstituted Pyrimido[1,2-a]benzimidazoles (**4aa-4ld**) and 2,4,10-Trisubstituted 2,10-Dihydropyrimido[1,2-a]benzimidazoles (**4'a-4'd**)*

2-Aminobenzimidazole or 1-alkyl-2-aminobenzimidazole (1.0 mmol), the aldehyde (1.1 mmol, 1.1 equiv.), the alkyne carboxylic acid (1.2 mmol, 1.2 equiv.), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (1.2 mmol, 1.2 equiv.), and DMSO (4 mL) were placed in a 10 mL reaction tube. The reaction mixture was tightly sealed and heated at 110 °C for 12 h. After cooling, the mixture was poured into CH_2Cl_2 (30 mL), washed with water (2×10 mL), saturated aqueous NH_4Cl (3×10 mL) and brine (2×10 mL), and then dried with Na_2SO_4 and passed through a celite pad. Evaporation of the solvent under reduced pressure provided the crude product, which was purified by column chromatography on silica gel with petroleum ether:ethyl acetate (V:V = 3:1−1:1, containing 1% NEt_3) as the eluent to afford the final product.

*4.3.2 2-Phenylpyrimido[1,2-a]benzimidazole (**4aa**)*[15]

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), benzaldehyde (0.11 mL, 1.1 mmol), propiolic acid (74.2 μL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4aa** (39.2 mg, 16%) as a yellow solid after chromatography; mp 205–207 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (d, *J* = 7.2 Hz, 1H), 8.30 – 8.24 (m, 2H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.56 – 7.51 (m, 3H), 7.41 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.6, 151.0, 145.0, 136.6, 133.0, 131.4, 129.0, 127.8, 127.0, 126.3, 121.9, 120.4, 110.4, 103.9; IR (KBr): *ν* = 3046, 1699, 1593, 1526, 1487, 1445, 1305, 1267, 1210, 1031, 969, 772, 741, 705 cm^{-1}; HR-MS (ESI): m/z = 246.1032, calcd for $[C_{16}H_{11}N_3+H]^+$: 246.1031.

*4.3.3 4-Methyl-2-phenylpyrimido[1,2-a]benzimidazole (**4ab**)*[16]

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), benzaldehyde (0.11 mL, 1.1 mmol), 2-butynoic acid (100.8 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4ab** (111.4 mg, 43%) as a yellow solid after chromatography; mp 168–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 – 8.21 (m, 2H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.51 – 7.47 (m, 3H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.11 (s, 1H), 3.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 152.0, 147.9, 145.5, 136.6, 131.1, 128.8, 128.0, 127.7, 125.8, 121.5, 120.2, 114.5, 104.4, 21.0; IR (KBr): *ν* = 3052, 2921, 1733, 1621, 1598, 1527, 1437, 1309, 1231, 1021, 758, 736, 691, 545 cm^{-1}; HR-MS (ESI): m/z = 260.1191, calcd for $[C_{17}H_{13}N_3+H]^+$: 260.1188.

*4.3.4 4-Amyl-2-phenylpyrimido[1,2-a]benzimidazole (**4ac**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), benzaldehyde (0.11 mL, 1.1 mmol), 2-octynoic acid (0.17 mL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4ac** (179.6 mg, 57%) as a yellow solid after chromatography; mp 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 – 8.21 (m, 2H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.50 – 7.46 (m, 3H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.08 (s, 1H), 3.27 (t, *J* = 7.6 Hz, 2H), 1.97 – 1.85 (m, 2H), 1.63 – 1.51 (m, 2H), 1.50 – 1.42 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 152.2, 152.0, 145.5, 136.7, 131.0, 128.8, 127.7, 127.4, 125.7, 121.5, 120.2, 114.7, 102.8, 33.2, 31.4, 25.8, 22.4, 13.9; IR (KBr): *ν* = 3055, 2922, 1738, 1627, 1601, 1575, 1532, 1493, 1441, 1350, 1308, 1233, 1024, 760, 738, 689, 545 cm^{-1}; HR-MS (ESI): m/z = 316.1823, calcd for $[C_{21}H_{21}N_3+H]^+$: 316.1814.

*4.3.5 2,4-Diphenylpyrimido[1,2-a]benzimidazole (**4ad**)*[7a]

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), benzaldehyde (0.11 mL, 1.1 mmol), phenylpropiolic acid (175.3 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4ad** (237.5 mg, 74%) as a yellow solid after chromatography; mp 198−200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (m, 2H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.69 (m, 5H), 7.59 – 7.51 (m, 3H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.27 (s, 1H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 152.1, 149.3, 145.5, 136.7, 132.6, 131.3, 131.0, 129.4, 128.9, 128.4, 127.8, 127.4, 125.9, 121.1, 120.2, 114.5, 105.3; IR (KBr): *ν* = 3057, 1623, 1592, 1530, 1484, 1444, 1394, 1357, 1304, 762, 734, 698 cm^{-1}; HR-MS (ESI): m/z = 322.1337, calcd for $[C_{22}H_{15}N_3+H]^+$: 322.1344.

*4.3.6 4-(4-Methoxyphenyl)-2-phenylpyrimido[1,2-a]benzimidazole (**4ae**)*[6j]

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), benzaldehyde (0.11 mL, 1.1 mmol), 4-methoxyphenylpropiolic acid (211.2 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4ae** (238.7 mg, 68%) as a yellow solid after chromatography; mp 217−219 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (m, 2H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.55 – 7.48 (m, 3H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.22 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.7, 161.0, 152.3, 149.4, 145.5, 136.7, 131.2, 129.9, 128.9, 127.8, 127.6, 125.8, 124.8, 121.0, 120.1, 114.7, 114.7, 105.4, 55.6; IR (KBr): *ν* = 3017, 1619, 1597, 1533, 1484, 1449, 1306, 1217, 1085, 1015, 839, 822, 760, 738, 686 cm^{-1}; HR-MS (ESI): m/z = 352.1452, calcd for $[C_{23}H_{17}N_3O+H]^+$] 352.1450.

*4.3.7 4-(4-Chlorophenyl)-2-phenylpyrimido[1,2-a] benzimidazole (**4af**)*[6j]

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), benzaldehyde (0.11 mL, 1.1 mmol), 4-chlorophenylpropiolic acid (216.0 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4af** (230.8 mg, 65%) as a yellow solid after chromatography; mp 231−233 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (m, 2H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.52 – 7.47 (m, 3H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.20 (s, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 148.0, 145.5, 145.5, 137.3, 136.4, 133.6, 131.3, 130.9, 129.8, 129.7, 128.8, 127.7, 125.9, 121.3, 120.3, 114.3, 105.3; IR (KBr): *ν* = 3043, 1672, 1641, 1610, 1594, 1537, 1515, 1495, 1444, 13006, 1284, 1258, 1177, 1025, 831, 763, 737, 687; HR-MS (ESI): m/z = 356.0951, calcd for $[C_{22}H_{14}ClN_3+H]^+$: 356.0955.

*4.3.8 2-(4-Methoxyphenyl)-4-phenylpyrimido[1,2-a]benzimidazole (**4bd**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 4-methoxybenzaldehyde (0.13 mL, 1.1 mmol), phenylpropiolic acid (175.3 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4bd** (235.2 mg, 67%) as a yellow solid after chromatography; mp 194−196 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.68-7.28 (m, 5H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.12 (s, 1H), 6.95 (m, 3H), 6.60 (d, *J* = 8.4 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 160.5, 152.2, 148.9, 145.3, 132.6, 130.9, 129.4, 129.2, 129.0, 128.3, 127.4, 125.6, 120.8, 119.8, 114.3, 114.2, 104.8, 55.3; IR (KBr): *ν* = 3071, 3043, 1595, 1528, 1483, 1442, 1303, 1215, 1042, 760, 738, 706 cm^{-1}; HR-MS (ESI): m/z = 352.1452, calcd for $[C_{23}H_{17}N_3O+H]^+$: 352.1450.

*4.3.9 2-(3-Methoxyphenyl)-4-phenylpyrimido[1,2-a]benzimidazole (**4cd**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 3-methoxybenzaldehyde (0.13 mL, 1.1 mmol), phenylpropiolic acid (175.3 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4cd** (252.8 mg, 72%) as a yellow solid after chromatography; mp 214−216 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (br s, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.78 – 7.72 (m, 2H), 7.71-7.69 (m, 1H), 7.67 (br s, 1H), 7.66 (br s, 2H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.25 (s, 1H), 7.08 (dd, *J* = 10.4, 2.4 Hz, 1H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H),3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 160.2, 152.1, 149.2, 145.4, 138.0, 132.6, 131.1, 129.8, 129.4, 128.4, 127.4, 125.9, 121.2, 120.2, 120.1, 118.2, 114.5, 112.1, 105.4, 55.6; IR (KBr): *ν* = 3054, 3020, 1625, 1593, 1526, 1483, 1448, 1261, 1209, 1171, 1036, 874, 797, 767, 734, 702 cm^{-1}; HR-MS (ESI): m/z = 352.1444, calcd for $[C_{23}H_{17}N_3O+H]^+$: 352.1450.

*4.3.10 2-(2-Methoxyphenyl)-4-phenylpyrimido[1,2-a]benzimidazole (**4dd**)*[7b]

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 2-methoxybenzaldehyde (0.13 mL, 1.1 mmol), phenylpropiolic acid (175.3 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4dd** (252.8 mg, 72%) as a yellow solid after chromatography; mp 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 8.4Hz, 1H), 7.70 -7.69 (m, 3H), 7.64 -7.63 (m, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.30 – 7.23 (m, 2H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 8.0 Hz, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 4.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.7, 155.7, 149.0, 145.6, 136.2, 134.9, 133.6, 132.0, 130.5, 129.5, 129.4, 129.4, 127.7, 126.2, 125.3, 122.8, 120.6, 120.1, 114.2, 111.6, 56.7; IR (KBr): *ν* = 3057, 2938, 2838, 2476, 1597, 1515, 1476, 1444, 1351, 1289, 1255, 1163, 1111, 1018, 749, 701 cm^{-1}; HR-MS (ESI): m/z = 352.1446, calcd for $[C_{23}H_{17}N_3O+H]^+$: 352.1450.

*4.3.11 2-(4-Chlorophenyl)-4-phenylpyrimido[1,2-a]benzimidazole (**4ed**)*[7a]

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 4-chlorobenzaldehyde (154.6 mg, 1.1 mmol), phenylpropiolic acid (175.3 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4ed** (230.8 mg, 65%) as a yellow solid after chromatography; mp 197−199 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.22 (m, 2H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.73 (m, 1H), 7.70 – 7.62 (m, 4H), 7.45 (m, 3H), 7.20 (s, 1H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.7, 151.8, 149.6, 145.3, 137.6, 135.0, 132.3, 131.1, 129.4, 129.2, 129.0, 128.3, 127.3, 126.1, 121.3, 120.2, 114.5, 104.9; IR (KBr): *ν* = 3075, 3049, 3029, 2919, 2849, 1625, 1592, 1532, 1483, 1446, 1397, 1304, 1218, 1092, 820, 767 cm^{-1}; HR-MS (ESI): m/z = 356.0948, calcd for $[C_{22}H_{14}ClN_3+H]^+$: 356.0955.

*4.3.12 2-(3-Chlorophenyl)-4-phenylpyrimido[1,2-a]benzimidazole (**4fd**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 3-chlorobenzaldehyde (0.12 mL, 1.1 mmol), phenylpropiolic acid (175.3 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4fd** (220.1 mg, 62%) as a yellow solid after chromatography; mp 196−198 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (m, 1H), 8.19 (m, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.70 (m , 5H), 7.54 – 7.43 (m, 3H), 7.24 (s, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 149.7, 145.6, 138.4, 135.1, 132.4, 131.2, 131.1, 130.1, 129.9, 129.4, 128.4, 128.3, 127.9, 126.1, 125.8, 121.4, 120.3, 114.6, 105.0; IR (KBr): *ν* = 3064, 1623, 1590, 1528, 1486, 1443,1391, 1303, 1216, 1085, 766, 741, 703 cm^{-1}; HR-MS (ESI): m/z = 356.0954, calcd for $[C_{22}H_{14}ClN_3+H]^+$: 356.0955.

*4.3.13 2-(2-Chlorophenyl)-4-phenylpyrimido[1, 2-a]benzimidazole (**4gd**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 2-chlorobenzaldehyde (0.12 mL, 1.1 mmol), phenylpropiolic acid (175.3 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4gd** (269.8 mg, 76%) as a yellow solid after chromatography; mp 194−196 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.0 Hz, 1H), 7.96 (dd, *J* = 6.4, 2.8 Hz, 1H), 7.71 – 7.67 (m, 1H), 7.65 (m, 4H), 7.53 – 7.46 (m, 2H), 7.43 (m, 2H), 7.25 (s, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 151.8, 151.8, 148.2, 145.3, 137.1, 132.3, 132.2, 132.0, 131.0, 131.0, 130.3, 129.3, 128.3, 127.2, 125.9, 121.3, 120.4, 114.7, 109.6; IR (KBr): *ν* = 3071, 3043, 1595, 1528, 1483, 1442, 1303, 1215, 1042, 760, 738, 706 cm^{-1}; HR-MS (ESI): m/z = 356.0951, calcd for $[C_{22}H_{14}ClN_3+H]^+$: 356.0955.

*4.3.14 3-(4-Phenybenzo[4,5]imidazo[1,2-a]pyrimidin-2yl)benzonitrile (**4hd**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 3-Cyanobenzaldehyde (144.2 mg, 1.1 mmol), Phenylpropiolic acid (175.3 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4hd** (242.3 mg, 70%) as a yellow solid after chromatography; mp = 154−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (m, 2H), 7.96 (d, *J* = 8.0 Hz, 1H),

7.78 (d, *J* = 7.6 Hz, 1H), 7.76 – 7.61 (m, 6H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.22 (s, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.3, 151.5, 150.2, 145.6, 137.8, 134.1, 132.2, 131.8, 131.3, 131.2, 129.8, 129.5, 128.3, 127.3, 126.3, 121.7, 120.4, 118.2, 114.7, 113.3, 104.6; IR (KBr): *v* = 3066, 2227, 1624, 1588, 1527, 1484, 1444, 1389, 1304, 767, 740, 703 cm^{-1}; HR-MS (ESI): m/z = 347.1291, calcd for $[C_{23}H_{14}N_4+H]^+$: 347.1297.

*4.3.15 2-Thienyl-4-phenylpyrimido[1,2-a]benzimidazole (**4id**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 2-thenaldehyde (0.10 mL, 1.1 mmol), phenylpropiolic acid (175.3 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4id** (206.1 mg, 63%) as a yellow solid after chromatography; mp 210−212 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 3.7 Hz, 1H), 7.74 – 7.61 (m, 5H), 7.59 (d, *J* = 5.0 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.17 (t, *J* = 4.4 Hz, 1H), 7.09 (s, 1H), 7.00 (t, *J* = 7.8 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 149.1, 145.5, 143.0, 132.4, 131.6, 131.1, 129.4, 128.7, 128.4 (2C), 127.7, 125.8, 121.1, 120.1, 114.3, 114.2, 104.6; IR (KBr): *v* = 3063, 1621, 1594, 1519, 1485, 1421, 1301, 1257, 1206, 762, 735, 703 cm^{-1}; HR-MS (ESI): m/z = 328.0900, calcd for $[C_{20}H_{13}N_3S+H]^+$: 328.0908.

*4.3.16 2-Naphthyl-4-phenylpyrimido[1,2-a]benzimidazole (**4jd**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), 2-naphthaldehyde (171.8 mg, 1.1 mmol), phenylpropiolic acid (175.3 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4jd** (259.7 mg, 70%) as a yellow solid after chromatography; mp 184−186 °C; ^{1}H NMR (600 MHz, DMSO-*d*6): δ = 8.71 (s, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 8.08 (d, *J* = 7.9 Hz, 1H), 8.03 (d, *J* = 8.7 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.73 (m, 1H), 7.62 (m, 2H), 7.48 (m, 1H), 7.25 – 7.23 (m, 2H), 7.20(m, 1H), 6.97 (d, *J* = 7.6 Hz, 2H), 6.90 (d, *J* = 6.6 Hz, 1H), 6.08 (s, 1H), 5.37 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-*d*6): δ = 169.2, 142.7, 140.6, 136.3, 134.6, 133.04, 133.01, 132.5, 129.5, 129.3, 129.1, 128.5, 128.4, 128.2, 127.6, 126.9, 125.7, 123.6, 123.4, 122.3, 119.6, 110.0, 64.3, 60.3; IR (KBr): *v* = 3112, 3057, 3028, 1642, 1561, 1502, 1457, 1418, 1060, 835, 735, 701, 469 cm^{-1}; HR-MS (ESI): m/z = 372.1499, calcd for $[C_{26}H_{17}N_3+H]^+$: 372.1501.

*4.3.17 2-Citronellyl-4-phenylpyrimido[1,2-a]benzimidazole (**4kd**)*

2-Aminobenzimidazole (133.5 mg, 1.0 mmol), citronellal (0.20 mL, 1.1 mmol), phenylpropiolic acid (175.3 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4kd** (221.5 mg, 60%) as a yellow solid after chromatography; mp 75-77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.4 Hz, 1H), 7.72 – 7.55 (m, 5H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.61 (s, 1H), 5.10 (t, *J* = 6.8 Hz, 1H), 2.96 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.71 (dd, *J* = 13.6, 8.4 Hz, 1H), 2.28 – 2.16 (m, 1H), 2.13-1.99 (m, 2H), 1.67 (s, 3H), 1.60 (s, 3H), 1.53 – 1.44 (m, 1H), 1.38 – 1.23 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 151.8, 148.3, 144.7, 132.2, 131.3, 130.8, 129.2, 128.2, 127.2, 125.5, 124.3, 120.7, 119.9, 114.3, 108.9, 46.2, 36.9, 32.6, 25.5, 25.4, 19.5, 17.6; IR (KBr): *v* = 3056, 2961, 2907, 2851, 1628, 1593, 1526, 1484, 1449, 1304, 1287, 760, 738, 700 cm^{-1}; HR-MS (ESI): m/z = 370.2288, calcd for $[C_{25}H_{27}N_3+H]^+$: 370.2283.

*4.3.18 10-Isopropyl-2,4-diphenyl-2,10-dihydropyrimido[1,2-a]benzimidazole (**4'a**)*

1-Isopropyl-2-aminobenzimidazole (175.1 mg, 1.0 mmol), benzaldehyde (0.11 mL, 1.1 mmol), phenylpropiolic acid (175.3 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4'a** (262.9 mg, 72%) as a red solid after chromatography; mp 70−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.6 Hz, 2H), 7.39 (m, 2H), 7.33 (q, *J* = 7.6 Hz, 4H), 7.25 (m, 2H), 7.15 (d, *J* = 7.6 Hz, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 6.84 (t, *J* = 7.8 Hz, 1H), 6.60 (d, *J* = 7.6 Hz, 1H), 6.16 (d, *J* = 3.6 Hz, 1H), 5.37 (d, *J* = 3.6 Hz, 1H), 5.17 (m, 1H), 1.64 (dd, *J* = 11.2, 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.2, 142.7, 142.1, 139.5, 130.4, 130.2, 128.9, 128.0, 127.9, 127.6, 126.6, 125.7, 121.3, 120.3, 108.9, 108.6, 97.2, 59.4, 45.2, 20.3, 20.1; IR (KBr): *v* = 3059, 2976, 2930, 1616, 1582, 1483, 1344, 738, 700 cm^{-1}; HR-MS (ESI): m/z = 388.1789, calcd for $[C_{25}H_{23}N_3+Na]^+$: 388.1790.

*4.3.19 10-Butyl-2,4-diphenyl-2,10-dihydropyrimido[1,2-a]benzimidazole (**4'b**)*

1-Butyl-2-aminobenzimidazole (189.1 mg, 1.0 mmol), benzaldehyde (0.11 mL, 1.1 mmol), phenylpropiolic acid (175.3 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4'b** (314.7 mg, 83%) as a red solid after chromatography; mp 53−55 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.6 Hz, 2H), 7.31 (m, 2H), 7.25 (q, *J* = 7.6 Hz, 4H), 7.17 (m, 2H), 6.97 – 6.88 (m, 2H), 6.77 (t, *J* = 7.2 Hz, 1H), 6.51 (d, *J* = 7.6 Hz, 1H), 6.08 (d, *J* = 3.6 Hz, 1H), 5.29 (d, *J* = 3.2 Hz, 1H), 4.03 (t, *J* = 7.2 Hz, 2H), 1.86 – 1.74 (m, 2H), 1.41 (m, 2H), 0.94 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 142.6, 142.2, 139.5, 131.8, 129.9, 128.9, 128.0, 127.9, 127.6, 126.7, 125.7, 121.5, 120.5, 108.8, 106.9, 97.3, 59.4, 41.1, 30.2, 20.2, 13.8; IR (KBr): *v* = 3046, 2954, 2923, 2856, 1633, 1602, 1527, 1487, 1452, 1375, 1260, 1096, 1014, 811, 767, 738, 703 cm^{-1}; HR-MS (ESI): m/z = 402.1939, calcd for $[C_{26}H_{25}N_3+Na]^+$) 402.1946.

*4.3.20 10-Butyl-4-(4-chlorophenyl)-2-phenyl-2,10-dihydropyrimido[1,2-a]benzimidazole (**4'c**)*

1-Butyl-2-aminobenzimidazole (189.1 mg, 1.0 mmol), benzaldehyde (0.11 mL, 1.1 mmol), 4-chlorophenylpropiolic acid (216.7 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4'c** (351.2 mg, 85%) as a red liquid after chromatography; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.2 Hz, 2H), 7.37 – 7.22 (m, 7H), 7.06 – 6.97 (m, 2H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.56 (d, *J* = 7.6 Hz, 1H), 6.14 (d, *J* = 3.6 Hz, 1H), 5.32 (d, *J* = 3.6 Hz, 1H), 4.10 (t, *J* = 7.2 Hz, 2H), 1.91 – 1.82 (m, 2H), 1.51-1.45 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.6, 142.6, 141.4, 139.3, 133.7, 131.7, 129.6, 129.0, 127.99, 127.96, 127.7, 125.6, 121.8, 120.6, 108.7, 107.1, 96.7, 58.7, 41.2, 30.2, 20.1, 13.8; IR (KBr): *v* = 3062, 2908, 2870, 1727, 1683, 1622, 1545, 1480, 1347, 1079, 913, 726, 690 cm^{-1}; HR-MS (ESI): m/z = 414.1735, calcd for $[C_{26}H_{24}ClN_3+H]^+$: 414.1737.

*4.3.21 10-Butyl-4-(4-methoxyphenyl)-2-phenyl-2,10-dihydropyrimido[1,2-a]benzimidazole (**4'd**)*

1-Butyl-2-aminobenzimidazole (189.1 mg, 1.0 mmol), benzaldehyde (0.11 mL, 1.1 mmol), 4-methoxyphenylpropiolic acid (211.2 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **4'd** (356.0 mg, 87%) as a red liquid after chromatography; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.4 Hz, 2H), 7.35-7.31 (m, 4H), 7.26 (d, *J* = 7.2 Hz, 1H), 7.02-6.95 (m, 2H), 6.86-6.82 (m, 3H), 6.62 (d, *J* = 7.6 Hz, 1H), 6.11 (d, *J* = 3.6 Hz, 1H), 5.35 (d, *J* = 3.6 Hz, 1H), 4.10 (t, *J* = 7.2 Hz, 2H), 3.74 (s, 3H), 1.91 – 1.82 (m, 2H), 1.51-1.45 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ =

159.3, 149.6, 142.1, 139.5, 135.0, 131.7, 129.9, 128.0, 127.9, 127.5, 125.6, 121.5, 120.5, 114.1, 108.9, 106.9, 97.6, 58.7, 55.2, 41.2, 30.2, 20.1, 13.8; IR (KBr): *v* = 2962, 2917, 1618, 1511, 1483, 1240, 1173, 1028, 728, 697 cm^{-1}; HR-MS (ESI): m/z = 410.2232, calcd for $[C_{27}H_{27}N_3O+H]^+$: 410.2232.

*4.4.1 General Procedure for the Synthesis of Imidazo[2,1-b]thiazoles (**6a-6e**)*

2-Benzothiazolamine (150.2 mg, 1.0 mmol), the aldehyde (1.1 mmol, 1.1 equiv.), the alkyne carboxylic acid (1.2 mmol, 1.2 equiv.), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (1.2 mmol, 1.2 equiv.), and DMSO (4 mL) were placed in a 10 mL reaction tube. The reaction mixture was tightly sealed and heated at 110 °C for 12 h. After cooling, the mixture was poured into CH_2Cl_2 (30 mL), washed with water (2×10 mL), saturated aqueous NH_4Cl (3×10 mL) and brine (2×10 mL), and then dried with Na_2SO_4 and passed through a celite pad. Evaporation of the solvent under reduced pressure provided the crude product, which was purified by column chromatography on silica gel with petroleum ether:ethyl acetate (V:V = 20:1−2:1) as the eluent to afford the final product.

*4.4.2 3-Benzyl-2-phenyimidazo[2,1-b]benzothiazole (**6a**)*

2-Benzothiazolamine (150.2 mg, 1.0 mmol), benzaldehyde (0.11 mL, 1.1 mmol), phenylpropiolic acid (175.3 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **6a** (231.2 mg, 68%) as a red solid after chromatography; mp 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 – 7.64 (m, 3H), 7.41 – 7.37 (m, 2H), 7.35 – 7.30 (m, 3H), 7.31– 7.25 (m, 4H), 7.21 – 7.16 (m, 2H), 4.64 (s, 2H); ^{13}C NMR (100 MHz): δ = 147.1, 145.4, 137.6, 134.2, 132.7, 130.2, 129.1, 128.5, 127.5, 127.3, 127.3, 126.8, 125.8, 124.2, 124.0, 121.4, 113.0, 30.7; IR (KBr): *v* = 3083, 2923, 2371, 2338, 1544, 1493, 1459, 1065, 1000, 911 cm^{-1}; HR-MS (ESI): m/z = 341.1110, calcd for $[C_{22}H_{16}N_2S+H]^+$: 341.1112.

*4.4.3 3-Benzyl-2-(3-chlorophenyl)imidazo[2,1-b]benzothiazole (**6b**)*

2-Benzothiazolamine (150.2 mg, 1.0 mmol), 3-chlorobenzaldehyde (0.12 mL, 1.1 mmol), phenylpropiolic acid (175.3 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **6b** (209.5 mg, 56%) as a red solid after chromatography; mp 137–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (s, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.49 (m, 1H), 7.35 – 7.28 (m, 3H), 7.26 – 7.19 (m, 5H), 7.1 – 7.13 (m, 2H), 4.57 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3, 144.0, 137.2, 136.0, 134.5, 132.6, 130.3, 129.7, 129.1, 127.5, 127.5, 127.2, 127.0 126.0, 125.1, 124.4, 124.1, 122.1, 113.1, 30.7. IR (KBr): *v* = 3061, 2956, 2787, 1771, 1732, 1701, 1560, 1541, 1506, 1487, 989, 941, 909, 874, 839, 817, 779, 740, 611, 570, 533, 504 cm^{-1}; HR-MS (ESI): m/z = 375.0722, calcd for $[C_{22}H_{15}ClN_2S+H]^+$: 375.0723.

*4.4.4 3-Benzyl-2-(3-methoxyphenyl)imidazo[2,1-b]benzothiazole (**6c**)*

2-Benzothiazolamine (150.2 mg, 1.0 mmol), 3-methoxybenzaldehyde (0.13 mL, 1.1 mmol), phenylpropiolic acid (175.3 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **6c** (214.6 mg, 58%) as a red liquid after chromatography; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8.4 Hz, 1H), 7.34 – 7.21 (m, 8H), 7.16-7.11 (m, 2H), 6.84 (d, *J* = 7.2 Hz, 2H), 4.59 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 147.0, 145.3, 137.5, 135.5, 132.7, 130.2, 129.4, 129.0, 127.5, 126.8, 125.8, 124.2, 124.0, 121.6, 119.6, 113.6, 113.0, 112.3, 55.0, 30.8; IR (KBr): *v* = 3065, 3025, 2835, 1605, 1578, 1499, 1459, 1424, 1367, 1246, 1224, 1050, 1028, 867, 779, 739, 721, 696 cm^{-1}; HR-MS (ESI): m/z = 371.1222, calcd for $[C_{23}H_{18}N_2OS+H]^+$: 371.1218.

*4.4.5 3-Benzyl-2-(thiophen-2-yl)imidazo[2,1-b]benzothiazole (**6d**)*

2-Benzothiazolamine (150.2 mg, 1.0 mmol), 2-thenaldehyde (0.19 mL, 2.1 mmol,), propiolic acid (74.2 μL, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **6d** (211.1 mg, 61%) as a red liquid after chromatography; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 – 7.51 (m, 1H), 7.35 – 7.31 (m, 1H), 7.29 – 7.24 (m, 2H), 7.20 (m, 5H), 7.15 – 7.10 (m, 2H), 6.97 (dd, *J* = 4.8 , 3.6Hz, 1H), 4.59 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.1, 139.9, 137.1, 136.9, 132.5, 130.1, 128.9, 127.5, 127.4, 126.8, 125.9, 124.6, 124.2, 124.0, 123.2, 121.1, 112.8, 30.7; IR (KBr): *v* = 3016, 2946, 1641, 1525, 1486, 847, 774, 952, 740, 574, 482 cm^{-1}; HR-MS (ESI): m/z = 347.0675; calcd for $[C_{20}H_{14}N_2S_2+H]^+$: 347.0677.

*4.4.6 3-(4-Methoxybenzyl)-2-phenylimidazo[2,1-b]benzothiazole (**6e**)*

2-Benzothiazolamine (150.2 mg, 1.0 mmol), benzaldehyde (0.1mL, 1.1 mmol), 4-methoxyphenylpropiolic acid (211.2 mg, 1.2 mmol), CuI (19.8 mg, 0.1 mmol, 10 mol%), K_2CO_3 (165.8 mg, 1.2 mmol), gave **6d** (199.8 mg, 54%) as a red liquid after chromatography; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 3H), 7.38 (m, 3H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.23 (t, *J* = 6.0 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.57 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 147.1, 145.4, 134.4, 133.0, 130.4, 129.5, 128.6, 128.6, 127.4, 127.3, 126.0, 124.3, 124.2, 122.0, 114.6, 113.3, 55.2, 30.1; IR (KBr): *v* = 3056, 2998, 2240, 2201, 1668, 1591, 1501, 1416, 1299, 1253, 1214, 1163, 1019, 914, 833 cm^{-1}; HR-MS (ESI): m/z = 371.1213, calcd for $[C_{23}H_{18}N_2OS+H]^+$: 371.1218.

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