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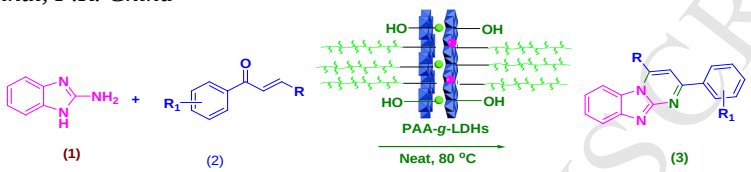

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An efficient and green synthesis of benzo[4,5]imidazo[1,2-a]pyrimidines using highly active and stable poly acrylic acid-supported layered double hydroxides

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ABSTRACT

A facile and efficient method for the synthesis of benzo[4,5]imidazo[1,2-a]pyrimidines has been achieved via highly active and reusable heterogeneous poly acrylic acid-supported layered double hydroxides (PAA-*g*-LDHs) catalyst promoted one-pot reaction of 1H-benzo[d]imidazol-2-amine, with *α,β*-unsaturated carbonyl compounds under solvent-free conditions. PAA-*g*-LDHs catalyst was successfully synthesized via reversible addition-fragmentation chain-transfer polymerization using grafting reaction and was characterized by different analytical techniques. The significant features of this reaction include expedient one-pot process, short reaction time, excellent yields, wide substrate scope and operational simplicity. Also, the catalyst could be reused for several consecutive runs without any apparent loss in its catalytic activity.

1. Introduction

Since decades, heterogeneous supported catalysts have attracted much attention due to their inherent advantages, such as ease of handling, greater selectivity, stability, inexpensive, environmental compatibility, and catalysts can be recovered without measurable changes in their catalytic activity and selectivity.[1] Therefore, catalytic system have been obtained enormous significance in pollution preventing processes in the synthetic organic chemistry. Among them, polymer supported catalytic systems have received attracted great attention in synthetic organic chemistry and chemical industries because of they have high catalytic activity with enhanced reaction rates by high surface area, non-flammability with high thermal stability, cleaner product yields with improved product selectivity by decrease waste production, and easy to separation from reaction products for further reusability with regard to the effortlessness of the process and environmental reaction condition.[2]In addition to these merits, small crystal size, hydrophobic cavity, and as good candidates for polymer supporting applications layered double hydroxides (LDHs)[3] are applied for the preparation of of various solid-supported reagents[4] and used as heterogeneous supported catalysts in organic synthesis.

Either in pharmaceutical agents or numerous organic materials,[5] which are showing a wide variety of biological activities, such as anti-cancer, antibacterial, anti-inflammatory activities, anti-alzheimer's activity, anti-hypertensive agents, V1b receptor antagonists, anti-TMV, anti-tumor, anti-metabolic and antimalarial agents[6] omnipresent backbone of either naturally or synthetically obtained either one or more nitrogen(s) containing heterocycles. Furthermore, they can be used as dyes, biosensors, for visualization of biomolecules as pH-sensitive fluorescent material, and also in laser technologies.[7] Amongst them, benzo[4,5]imidazo[1,2-*a*]pyrimidines structure bearing two main cores of nitrogen containing heterocycles (a imidazol and a pyrimidine ring) is originated broadly in biologically interesting compounds and natural products. As mentioned above, this core unit have a broad range of biological and pharmacological activities include anti-TMV, anti-vascular hypertension, anti-cancer/anti-tumor, anti-inflammatory, anti-metabolic, antimalarial agents and antimicrobial activities.[8] In addition, these derivatives are also played a role of antagonists of the paralyzing action of anti-diabetic activity and are significant core motifs in a wide range of biologically active compounds that are frequently used in pharmaceuticals, agrochemicals and medicinal

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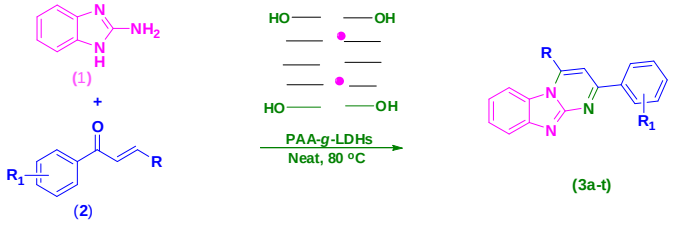
chemistry.[8,9] Consequently, these structures are significant synthetic targets for bio-organic chemists.

In an ongoing study of design and synthesis of biologically active molecules under heterogeneous catalysis[10] and with the above two significant areas of findings, herein, we prepared a novel poly acrylic acid grafted layered double hydroxides (PAA-*g*-LDHs) as a recyclable heterogeneous catalyst and it was successfully applied for the construction of benzo[4,5]imidazo[1,2-*a*]pyrimidines (**3**) in one-pot synthesis by coupling of 1*H*-benzo[d]imidazol-2-amine (**1**), with *α,β*-unsaturated carbonyl compounds (**2**) at 80 °C under solvent-free conditions (**Scheme 1**).

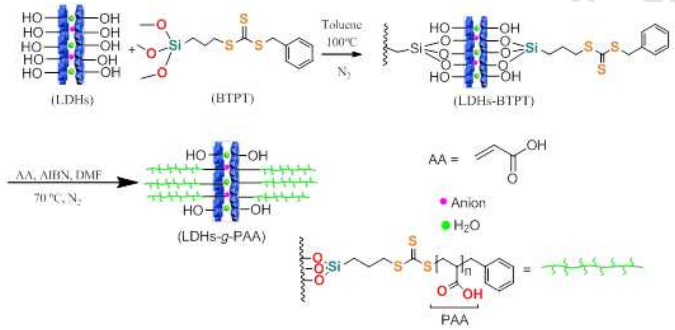


Scheme-1: Synthesis of benzo[4,5]imidazo[1,2-a]pyrimidines.

2. Results and Discussion

Synthesis of LDHs-g-POEGMA

The synthesis of PAA-*g*-LDHs has been successfully described by an efficient and convenient approach of reversible addition-fragmentation chain-transfer (RAFT) polymerization reaction through the modified reported procedure.[11] Initially surface modification of LDHs (LDHs → LDHs-BTPT) with S′-(3-trimethoxysilyl) propyltrithiocarbonate (BTPT) was performed in first step as prescribed in reported procedure and later followed by 2, 2′-azobis (2-methylpropionitrile) (AIBN) initiated RAFT process using poly acrylic acid (PAA) in the next step was obtained white powder, PAA-g-LDHs.



Scheme -2: Synthesis of PAA-*g*-LDHs.

XRD spectra of PAA-g-LDHs

The crystalline nature of the synthesized LDHs, LDHs-BTPT and PAA-*g*-LDHs were confirmed with the reference LDHs (35-0964) by XRD spectrum (**Fig. 1**). The newly synthesized LDHs (**Fig. 1b**), LDHs-BTPT (**Fig. 1c**) and PAA-*g*-LDHs (**Fig. 2d**) peaks are perfectly indexed to tetragonal phase of referenced LDHs (**Fig. 1a**) with 2θ values of 11.68, 23.47, and 35 respectively with corresponding crystal planes of (003), (006), and (012). These results are revealed that the grafting of polymer did not alter the crystallinity of the LDHs.

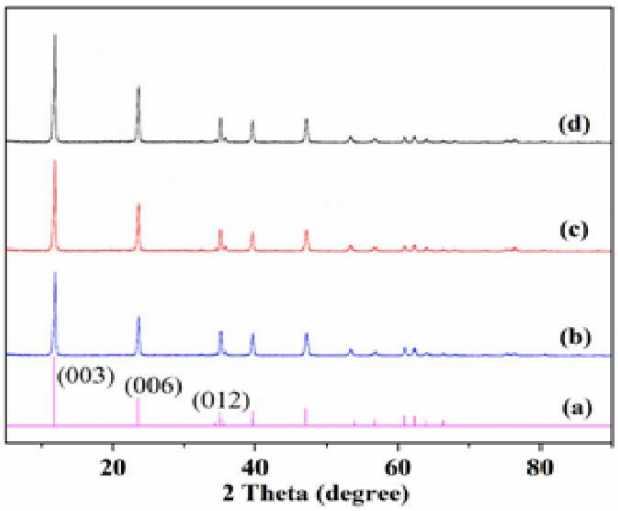


Fig. 1. X-ray diffraction patterns of (a) the referrence of LDHs (35-0964), (b) synthesized LDHs, (c) LDHs-BTPT, (d) PAA-*g*-LDHs.

TGA analysis of PAA-g-LDHs

In order to know the thermal degradation properties of LDHs, LDHs-BTPT, and PAA-*g*-LDHs performed a TGA of them and interpreted in **Fig. 2**. At first, Herein, a closer relationship was observed for LDHs and LDHs-BTPT. But on the other hand, PAA-*g*-LDHs was shown clear deviation from them and it could be explained as below. At first stage, due to release of absorbed water the LDHs (**Fig. 2a**) and LDHs-BTPT (**Fig. 2b**) ware showed a closer decomposition starting at 123.5 ºC and lost 12.7% of weight. At 211.76 & 223.3 °C they were showed a second degradation curve due to losing of 21.0% of weight corresponding to the interlayer anions. Finally, the weight loss of 41.2 and 42.8% respectively were shown between 330 - 800 °C since encapsulated organic molecules decamped at high temperature. But on the other hand, the newly prepared PAA-g-LDHs was significantly start degradation at 147 °C and shown a slower degradation up to 800 ºC with weight loss of 81.6% (**Fig. 2c**). Compare to LDHs and LDHs-BTPT the higher starting degradation temperature of PAA-g-LDHs is due to the coverage of polymer layers (38.8%) which were prevented the escape of absorbed water and interlayer anions. Therefore, the TGA results demonstrated that the brush polymers were successfully decorated onto the LDHs.

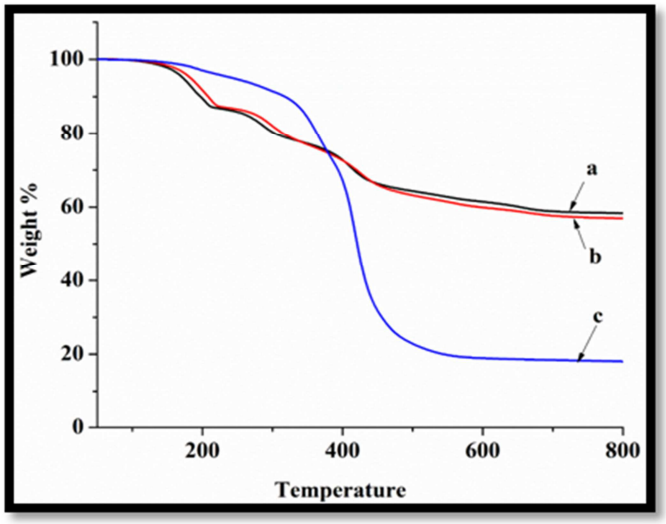


Fig. 2. TGA spectra of (a) LDHs, (b) LDHs-BTPT, and (c) PAA-g LDHs.

Surface morphologies of PAA-g-LDHs

When observed the surface morphology of pristine LDHs displays separate distinctly (**Fig. 3a**) but after grafting by RAFT polymerization with PPA resulted PAA-g-LDHs could be visualized relatively irregular shape which is due to covering of polymer layer of PAA chains (**Fig. 3b**).

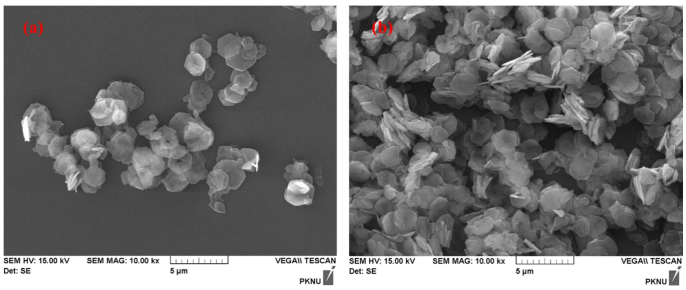


Fig. 3. SEM pictures of (a) LDHs, and (b) PAA-g-LDHs.

XPS spectra of PAA-g-LDHs

The bonding nature of LDHs after PPA grafting was measured by surface modification analysis by XPS spectra and which showed the dominated elemental peaks of O, Mg and Al corresponding of LDHs (**Fig. 4**). In addition, a strong C signal along with more intensive O signal (associated with the grafted PAA) was also observed. The characteristic peaks for C 1s included 2 peaks at 284.9 eV (C-C bonding), 288.7 eV (O-C=O bonding of carboxylic acid groups) suggesting that the polymer was successfully introduced onto the LDH surface by covalent linkages and resulting the formation of PAA-g-LDHs (See in full details at supporting information **Fig. S1-S3**).

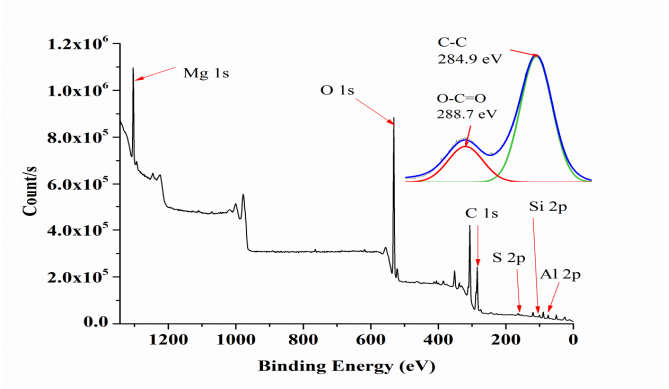


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Fig.4. XPS spectra of PAA-*g*-LDHs.

FT-IR spectra of PAA-g-LDHs

In addition to above all experimental data, FT-IR spectrum (**Fig.5c**) of the synthesized PAA-*g*-LDHs was also clearly evidenced about the successful drafting of PPA on LDHs-BTPT which is resulted two new absorption bands at 1715 cm^{-1} corresponding to stretching vibration of C=O and a broad band from 3700 to 3000 cm^{-1} due to the -OH groups of carboxylic acid of PAA moieties. At the same time, in addition to the regular absorption bands of LDHs (**Fig. 5a**) at 3450 cm^{-1} (Al–OH), 1355 cm^{-1} (interlayer Cl^-) and a broad peak from 790 to 440 cm^{-1} (M–O and O–M–O), the BTPT (**Fig. 5b**) and PAA-*g*-LDHs were showed a distinguishable absorption band at 2918 cm^{-1} owing to methylene group supporting the successful synthesis of the new catalyst.

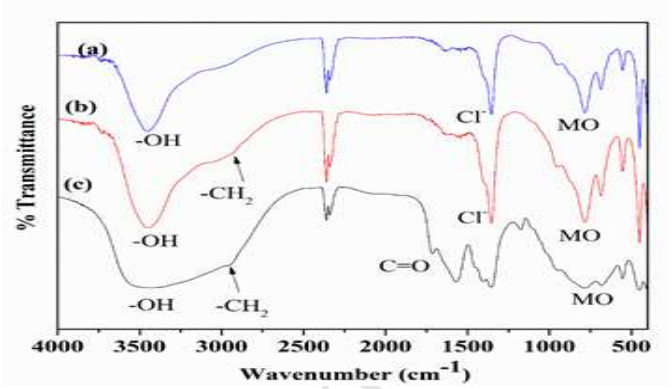


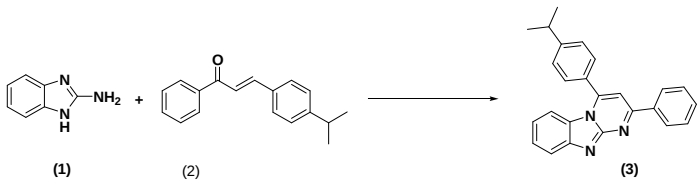
Fig. 5. FTIR results: (a) LDHs, (b) LDHs-BTPT, (c) PAA-*g*-LDHs

Application of PAA-*g*-LDHs for the synthesis of benzo[4,5]imidazo[1,2-a]pyrimidines

To adopt an efficient and environmentally benign procedure to the newly synthesized catalyst, a one-pot condensed cyclo-addition reaction of 1*H*-benzo[d]imidazol-2-amine (**1**) and (*E*)-3-(4-isopropylphenyl)-1-phenylprop-2-en-1-one (**2**) was performed and achieved the benzo[4,5]imidazo[1,2-*a*]pyrimidines (**3a-t**) good to excellent yields (**Table 2**).

At first we are performed a model reaction using an equimolar ratio of 1*H*-benzo[d]imidazol-2-amine (**1**) and (*E*)-3-(4-isopropylphenyl)-1-phenylprop-2-en-1-one (**2a**) to find the suitable conditions, and the results are presented at **Table 1**. When run the reaction at 80 °C for 8 h under solvent and catalyst-free conditions desired product **3a** was obtained in low yield (**Table 1**, entry 1). Gratifyingly, the desired **3a** was offered excellent yield (92%) even within 20 min, when carried out the reaction in presence of 10 mg of PAA-*g*-LDHs under solvent-free condition at 80 °C. (**Table 1**, entry 2).The catalyst ratio also should played a vital role in this reaction. Therefore, we examined the model reaction using 15 mg of PAA-*g*-LDHs and could not further improve the yield of the product (**Table 1**, entry 2). When the model reaction was studded using 5 mg of catalyst (**Table 1**, entry 3) under neat, we observed the product yield was decreased and reaction time also increased. However, no more increments were found for product **3a** when the reaction temperature was increasing from 80 to 100 °C (**Table1**, entry 4). Subsequently, the effects of solvents were investigated. All solvent mediums found that the rate of reactions were slower and resulted moderate yields and prolonged reaction times (**Table 1**, entries 9–12). But the model reaction already showed better result under solvent-free condition (**Table 1**, entry 2).

Table 1: Optimization of reaction conditions for the synthesis of **3a**[a]



Entry	Solvent	Catalyst	Tem (°C)	Time (min)	Yield[b] (%)
1	Neat	Neat	80	480	25

[c]2	Neat	PAA-*g*-LDHs (10 mg)	80	20	92, 91, 90, 89
3	Neat	PAA-*g*-LDHs (15 mg)	80	20	92
[c]4	Neat	PAA-*g*-LDHs (5 mg)	80	65	70
5	Neat	PAA-*g*-LDHs (10 mg)	100	20	92
6	Acetonitrile	PAA-*g*-LDHs (10 mg)	80	55	75
7	DMF	PAA-*g*-LDHs (10 mg)	120	85	79
8	THF	PAA-*g*-LDHs (10 mg)	80	85	65
9	Water	PAA-*g*-LDHs (10 mg)	100	110	45
10	Toluene	PAA-*g*-LDHs (10 mg)	100	75	65
11	Dioxane	PAA-*g*-LDHs (10mg)	80	70	80
12	Benzene	PAA-*g*-LDHs (10 mg)	80	125	74
13	Neat	PAA	80	80	70
14	Neat	LDHs	80	60	80
15	Neat	LDHs-BTPT	80	60	77
16	Neat	*PSP*TSA	80	60	80
17	Neat	*P*TSA	80	120	65
18	Neat	Proline	80	86	74
19	Neat	$InCl_3$	80	110	75
20	Neat	$FeCl_3$	80	90	70

[a]Reaction 1H-benzo[d]imidazol-2-amine (**1**, 1 mmol) and ((*E*)-3-(4-isopropylphenyl)-1-phenylprop-2-en-1-one (**2a**, 1 mmol); [b]Isolated yield; [c]Catalyst was reused four times.

To confirm the catalytic activity and merits of the PAA-*g*-LDHs a comparison study was conducted with various catalysts, including LHDs, and LDHs-BTPT and also PAA as a controlled catalyst under neat conditions at 80 °C and observed moderate to good catalytic properties (**Table 1,** entries 13–20). Herein, compared to that of PAA-*g*-LDHs, the substrate, LDHs, intermediate (LDHs-BTPT) and the used controlled PAA are showed lower yields (**Table 1**, entries 13-15). Even in them, the LDHs showed better yield rather than PAA, because of may be the hydroxyl groups should facilitating better hosting than the PAA. But, on the other hand, the intermediate, LDHs-BTPT was showed lesser yield than the LDHs. It might be decreasing the hosting effect of LDHs-BTPT surface due to grafting of BTPT. On the other hand, the simple organic acids and metallic salts and amino acid, Proline, are also showed the similar results with lower yields (**Table 1**, entries 16-20). From these overall results demonstrated that 10 mg PAA-*g*-LDHs under solvent-free **conditions** at 80 °C are optimized reaction conditions for the synthesis of **3a** (**Table 1**, entry 2).

In the context of financial viability and sustainable development of catalyst, the PAA-*g*-LDHs was isolated by the simple filtration using 10 mL of ethyl acetate (EA) and washed the precipitated catalyst with acetone and dried in an oven. Then the dried catalyst was used for further four consecutive cycles and obtained the product, **3a** in excellent yields in order of 92%, 91%, 90% and 89% (**Table 1**, entry 2). These data demonstrate that the high stability and reusability of the catalyst under those optimized reaction conditions.

Next we studied the catalytic activity of PAA-*g*-LDHs, and were successfully engaged for the synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidines (**3b-t**) *via* different *α,β*-unsaturated carbonyl compounds were reacted with 1*H*-benzo[*d*]imidazol-2-amine. The reaction occurred well in all of these cases, afforded good yields of product (**Table 2**). A variety of functional groups substituted on the aromatic ring of *α,β*-unsaturated carbonyl compounds, such as methoxy, ethoxy, isopropyl and methyl have preceded the reaction smoothly and resulted in the corresponding products in good to excellent yields. The halogen-containing aldehydes such as –Cl, –Br, and –F were also subjected to the reaction conditions, and obtained in good to excellent yields of the desired products.

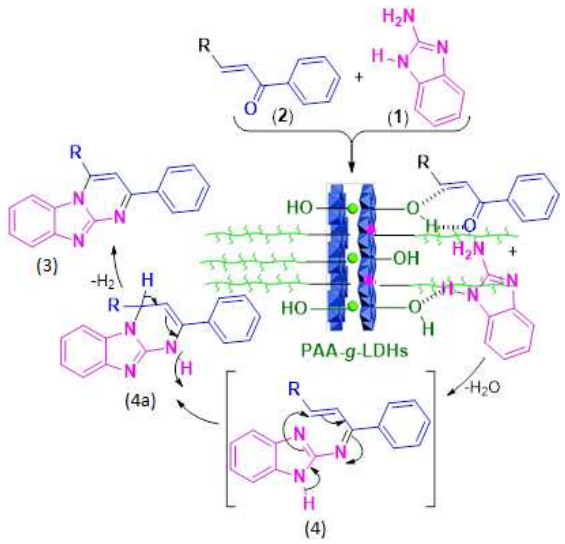
Table 2: Synthesis of benzo[4,5]imidazo[1,2-a]pyrimidines[a]

Entry	R_1	R	Product	Time (min)	Yield[b] (%)
1	H	4-CH-$(CH_3)_2$-C_6H_4	3a	20	92
2	H	3-OMe -C_6H_4	3b	22	89
3	H	4-Cl-C_6H_4	3c	22	90
4	H	4-Me-C_6H_4	3d	28	91
5	H	4-F-C_6H_4	3e	24	90
6	H	3-4-5-OMe -C_6H_2	3f	29	91
7	H	4-OEt-C_6H_4	3g	20	92
8	H	3-NO_2-C_6H_4	3h	25	85
9	H	3-Br-C_6H_4	3i	29	89
10	3-OMe	3-Me-C_6H_4	3j	28	91
11	3-Me	2-Me-C_6H_4	3k	24	91
12	4-Me	3-F-C_6H_4	3l	28	89
13	4-Me	4-Me-C_6H_4	3m	23	90
14	4-Br	2-F-C_6H_4	3n	29	91
15	4-Me	4-CH-$(CH_3)_2$-C_6H_4	3o	22	92
16	4-Me	3-4-5-OMe -C_6H_2	3p	25	89
17	4-Me	4-Br-C_6H_4	3q	29	88
18	4-F	2-Cl-C_6H_4	3r	26	87
19	4-F	4-F-C_6H_4	3s	25	89
20	4-Br	3-Me-C_6H_4	3t	27	87

[a]Reaction of 1H-benzo[d]imidazol-2-amine (**1**, 1 mmol) and *α,β*-unsaturated carbonyl compounds (**2**, 1 mmol) catalyzed by 5 mg of PAA-*g*-LDHs under neat conditions at 80 °C. [b]Isolated yield.

Based upon the results, herein, a reasonable reaction mechanism has been proposed (**Scheme 3**). At first, the reactants, *α,β*-unsaturated carbonyl compounds (**2**) and 1H-benzo[d]imidazol-2-amine (**1**) are interacted by the catalyst PAA-*g*-LDHs and they aligned on the surface of the catalyst with the formation of either hydrogen bonding or n→π/π→π interaction. After that close proximate of ketone group of chalcone would be combine with 1°-amine and forms the imine intermediate (**4**) which on rapid intramolecular cyclization gave another intermediate, **4a**. Finally by elimination of H_2 molecule obtained the desired benzo[4,5]imidazo[1,2-a]pyrimidines (**3**)

conveniently. In this mechanism, the catalyst PAA-*g*-LDHs should plays a key role, help as acid at initial step to form the imine intermediate and later it's acting as strong base in the final step for the removal of H_2 molecule to get the desired product.



Scheme: 3 plausible mechanisms.

3. Conclusion

In summary, we have developed first time an efficient and highly active PAA-*g*-LDHs catalyst for the synthesis of benzo[4,5]imidazo[1,2-a]pyrimidines under neat conditions. The notable features of this procedure are its high catalytic activity, inexpensiveness, analytical simplicity, non-volatile, lack of diffusion phenomena, reusability, high thermal stability, good structural stability short reaction time, excellent yields, and operational simplicity and mild reaction conditions.

4. Experimental

4.1 General

Chemicals were purchased from Aldrich and Alfa Aesar Chemical Companies. NMR spectra were recorded in ppm in $CDCl_3$ on a Jeol JNM ECP 400 NMR instrument using TMS as an internal standard. Mass spectra were recorded on a Jeol JMS-700 mass spectrometer. An Elmasonic S 100 H (with a frequency of 35 kHz and a nominal power 550 W) ultrasonic bath was used for ultrasonic irradiation. All melting points were determined using open capillaries on an Electrothermal-9100 (Japan) instrument. Fourier transform infrared (FTIR) spectra were measured on a Agilent Cary 600 FTIR spectrometer. Thermogravimetric analysis (TGA) was conducted with Perkin-Elmer Pyris 1 analyzer (USA). The morphology analyzes of the hybrids were carried out by using scanning electron microscopy (SEM) images equipped (Hitachi JEOL-JSM-6700F system, Japan). Surface composition of samples was investigated by an X-ray Photoelectron Spectroscopy (XPS) (Thermo VG Multilab 2000) in an ultra-high vacuum with Al Ka radiation. The 1H-NMR spectrum of BTPT was recorded using a JNM-ECP 400 (JEOL) spectrophotometer in $CDCl_3$. LDHs was prepared according to reported procedure.[11]

4.2. Anchoring of BTPT onto LDHs surface (LDHs-BTPT)

The mixture of 0.7g of LDHs and 20 ml of dry toluene was stirred at 100 °C. Then, 0.724 g (2 mmol) of BTPT in 10 ml dry toluene was injected into the flask under N_2. The reaction was conducted for 24 h. The crude product was filtered off and washed with DCM for three times to remove all unreacted BTPT. The final product was dried under vacuum overnight.

4.3. Preparation of PAA-g-LDHs by RAFT polymerization

2 g of AA, 0.080 g of LDHs-BTPT, 20 mg of AIBN, and 4 ml of dry DMF were placed in a round bottom flask. The polymerization reaction was performed at 70 °C for 10 h under N_2. The mixture was precipitated in diethyl ether and washed three times with methanol. The product was dried under vacuum at 40 °C overnight.

4.4. Synthesis of 4-(4-isopropylphenyl)-2-phenylbenzo[4,5]imidazo[1,2-a]pyrimidine (4a).

A mixture of 1H-benzo[d]imidazol-2-amine (**1**, 1 mmol) and ((*E*)-3-(4-isopropylphenyl)-1-phenylprop-2-en-1-one (**2a**, 1 mmol) and PAA-*g*-LDHs (10 mg) was stirred at 80 °C under solvent-free condition for 20 min. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the mixture was washed with ethyl acetate and filtered to recover the catalyst. The filtrate was evaporated, and the crude product was recrystallized from ethanol to afford pure **3a** in excellent yield 92%.

4.4.1 4-(4-isopropylphenyl)-2-phenylbenzo[4,5]imidazo[1,2-a]pyrimidine (**4a**). Yield 92%; yellow solid; Mp: 204-206 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J*=8.4 Hz, 2H), 7.93 (d, *J* =7.7, Hz, 1H), 7.61-7.71 (m, 5H), 7.40 (t, *J*=7.7 Hz, 1H), 7.35 (d, *J*=8.1 Hz, 2H), 7.20 (s, 1H), 6.98 (t, *J*=7.7 Hz, 1H), 6.65 (d, *J*=8.4 Hz, 1H), 2.93-3.0 (m, 1H), 1.28 (d, *J*=6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.06, 152.69, 149.18, 134.30, 132.69, 131.04, 129.42, 128.47, 127.95, 127.11, 125.80, 121.04, 120.13, 114.54, 105.23, 34.17, 23.85; HRMS (ESI, m/z): calcd for $C_{25}H_{21}N_3$ (M+H+) 363.1735, found: 363.1730.

4.4.2. 4-(3-methoxyphenyl)-2-phenylbenzo[4,5]imidazo[1,2-a]pyrimidine **(4b).** Yield 89%; yellow solid; Mp: 180-182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J*=8.1, 1H), 7.95 (d, *J* =8.4 Hz, 1H), 7.62-7.70 (m, 5H), 7.50 (s, 1H), 7.40-7.45 (m, 2H), 7.12 (t, *J*=7.7 Hz, 1H), 6.98 (d, *J*=8.4 Hz, 2H), 6.68 (d, *J*=8.4 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.26, 158.07, 152.28, 147.64, 145.37, 132.88, 132.20, 131.98, 130.85, 129.32, 128.53, 127.41, 126.62, 125.68, 121.33, 120.87, 120.12, 114.59, 111.54, 110.10, 55.71; HRMS (ESI, m/z): calcd for $C_{23}H_{17}N_3O$ ($M+H^+$) 351.1372, found: 351.1365.

4.4.3. 4-(4-chlorophenyl)-2-phenylbenzo[4,5]imidazo[1,2-a]pyrimidine **(4c).** Yield 90%; yellow solid; Mp: 228-230 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J*=8.8 Hz, 2H), 7.90 (d, *J* =8.1 Hz, 1H), 7.63-7.73 (m, 5H), 7.42 (d, *J*=8.8 Hz, 3H), 7.14 (s, 1H), 6.98 (t, *J*=8.1 Hz, 1H), 6.64 (d, *J*=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.66, 151.93, 149.62, 145.57, 137.61, 135.07, 132.49, 131.20, 129.48, 129.18, 129.06, 128.44, 127.44, 126.05, 121.35, 120.25, 114.63, 104.92; HRMS (ESI, m/z): calcd for $C_{22}H_{14}ClN_3$ ($M+H^+$) 355.0876, found: 355.0870.

4.4.4. 2-phenyl-4-(p-tolyl)benzo[4,5]imidazo[1,2-a]pyrimidine **(4d).** Yield 91%; yellow solid; Mp: 209-211 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J*=8.4 Hz, 2H), 7.93 (d, *J* =8.4 Hz, 1H), 7.61-7.66 (m, 3H), 7.38-7.41 (m, 1H), 7.33 (d, *J*=8.1 Hz, 1H), 7.27 (d, *J*=8.1 Hz, 2H), 7.19 (s, 1H), 7.16 (d, *J*=8.1 Hz, 1H), 6.98 (t, *J*=7.7 Hz, 1H), 6.64 (d, *J*=8.4 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.09, 152.29, 149.19, 145.52, 141.88, 133.92, 132.69, 131.06, 129.71, 128.42, 128.99, 128.47, 127.80, 127.53, 126.67, 125.84, 121.06, 120.14, 114.53, 105.23, 21.55;

HRMS (ESI, m/z): calcd for $C_{23}H_{17}N_3$ ($M+H^+$) 335.1422, found: 335.1427.

4.4.5. 4-(4-fluorophenyl)-2-phenylbenzo[4,5]imidazo[1,2-a]pyrimidine **(4e).** Yield 90%; yellow solid; Mp: 202-204 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21-8.24 (m, 2H), 7.89 (d, *J* =8.1 Hz, 1H), 7.64-7.71 (m, 5H), 7.39 (t, *J*=7.5 Hz, 1H), 7.11 (t, *J*=8.4 Hz, 3H), 6.97 (t, *J*=7.7 Hz, 1H), 6.62 (d, *J*=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.73, 151.96, 149.47, 145.47, 136.93, 132.47, 131.13, 129.93, 129.83, 129.41, 128.40, 127.38, 125.91, 121.20, 120.12, 116.05, 115.83, 114.56, 104.90; HRMS (ESI, m/z): calcd for $C_{22}H_{14}FN_3$ ($M+H^+$) 339.1171, found: 339.1168.

4.4.6. 2-phenyl-4-(3,4,5-trimethoxyphenyl)benzo[4,5]imidazo[1,2-a]pyrimidine **(4f).**Yield 91%; yellow solid; Mp: 241-243 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J*=8.4 Hz, 1H), 7.67-7.71 (m, 5H), 7.53 (s, 2H), 7.39 (t, *J*=7.3 Hz, 1H), 7.16 (s, 1H), 6.97 (t, *J*=7.7 Hz, 1H), 6.62 (d, *J*=8.4 Hz, 1H), 3.95 (s, 6H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 160.15, 153.40, 149.08, 145.33, 140.98, 132.45, 131.75, 129.34, 128.70, 128.40, 127.38, 125.80, 121.08, 119.89, 114.42, 104.92, 60.94, 56.33; HRMS (ESI, m/z): calcd for $C_{25}H_{21}N_3O_3$ (M+H+) 411.1582, found: 411.1576.

4.4.7. 4-(4-ethoxyphenyl)-2-phenylbenzo[4,5]imidazo[1,2-a]pyrimidine **(4g).** Yield 92%; yellow solid; Mp: 212-214 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J*=7.7, 2H), 7.90 (s, 1H), 7.61-7.65 (m, 5H), 7.37 (s, 1H), 7.10 (s, 1H), 6.89-6.96 (m, 3H), 6.61 (d, *J*=7.7 Hz, 1H), 4.0 (q, *J*=7.0 Hz, 2H), 1.39 (t, *J*=7.0 Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.71, 160.49, 148.90, 145.44, 132.63, 130.93, 129.42, 129.31, 128.78, 128.42, 125.59, 120.78, 119.87, 114.61, 114.41, 104.84, 63.61, 14.74; HRMS (ESI, m/z): calcd for $C_{24}H_{19}N_3O$ ($M+H^+$) 365.1528, found: 365.1522.

4.4.8. 4-(3-nitrophenyl)-2-phenylbenzo[4,5]imidazo[1,2-a]pyrimidine **(4h).** Yield 85%; yellow solid; Mp: 228-230 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J*=7.7, 2H), 7.19 (d, *J* =6.2 Hz, 1H), 7.61-7.68 (m, 4H), 7.55 (t, *J*=7.3 Hz, 1H), 7.45 (t, *J*=6.6 Hz, 2H), 7.05 (t, *J*=7.7 Hz, 2H), 6.79 (s, 1H), 6.75 (d, *J*=7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.59, 149.57, 148.42, 145.24, 133.62, 133.24, 131.89, 131.56, 131.37, 130.68, 129.48, 128.36, 126.32, 124.74, 121.83, 120.38, 114.93, 107.89; HRMS (ESI, m/z): calcd for $C_{22}H_{14}N_4O_2$ ($M+H^+$) 366.1116, found: 366.1110.

4.4.9. 4-(3-bromophenyl)-2-phenylbenzo[4,5]imidazo[1,2-a]pyrimidine **(4i).** Yield 89%; yellow solid; Mp: 195-197 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.83 (d, *J* =7.3 Hz, 1H), 7.61-7.65 (m, 6H), 7.43 (t, *J*=7.0 Hz, 2H), 7.28 (t, *J*=7.7 Hz, 1H), 7.17 (s, 1H), 7.01 (t, *J*=7.3 Hz, 1H), 6.75 (d, *J*=7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.75, 148.32, 139.18, 133.58, 132.35, 131.95, 131.15, 129.39, 128.33, 127.84, 125.95, 121.42, 121.37, 114.85, 109.83; HRMS (ESI, m/z): calcd for $C_{22}H_{14}BrN_3$ ($M+H^+$) 400.2707, found: 400.2700.

4.4.10. 2-(3-methoxyphenyl)-4-(m-tolyl)benzo[4,5]imidazo[1,2-a]pyrimidine **(4j).** Yield 91%; yellow solid; Mp: 186-188 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J*=8.1, 1H), 7.95 (d, *J* =8.1 Hz, 1H), 7.51 (d, *J*=8.1 Hz, 2H), 7.48 (s, 1H), 7.41-7.44 (m, 4H), 7.11 (t, *J*=7.3 Hz, 1H), 7.02 (d, *J*=7.7 Hz, 1H), 6.98 (d, *J*=8.1 Hz, 1H), 6.77 (d, *J*=8.1 Hz, 1H), 3.88 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.23, 158.06, 147.93, 145.36, 141.14, 132.14, 131.99, 129.95, 128.41, 126.68, 125.64, 121.32, 120.76, 120.05, 114.75, 111.53, 110.16, 55.70, 21.68; HRMS (ESI, m/z): calcd for $C_{24}H_{19}N_3O$ ($M+H^+$) 365.1528, found: 365.1524.

4.4.11. 2-(m-tolyl)-4-(o-tolyl)benzo[4,5]imidazo[1,2-a]pyrimidine (**4k**). Yield 91%; yellow solid; Mp: 182-184 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J*=8.1 Hz, 1H), 7.62 (d, *J*=7.7 Hz, 1H), 7.50 (d, *J*=8.1 Hz, 2H), 7.42 (d, *J*=7.7 Hz, 3H), 7.23-7.35 (m, 3H), 7.02 (t, *J*=7.7 Hz, 1H), 6.92 (s, 1H), 6.82 (d, *J*=8.1 Hz, 1H), 2.63 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.57, 149.10, 145.35, 141.42, 137.87, 137.08, 131.48, 130.00, 129.78, 129.70, 129.48, 128.21, 126.02, 125.80, 121.01, 120.19, 114.78, 109.16, 21.65, 21.05; HRMS (ESI, m/z): calcd for $C_{24}H_{19}N_3$ ($M+H^+$) 349.1579, found: 349.1573.

4.4.12. 4-(3-fluorophenyl)-2-(p-tolyl)benzo[4,5]imidazo[1,2-a]pyrimidine (**4l**). Yield 89%; yellow solid; Mp: 238-240 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21-8.24 (m, 2H), 7.90 (d, *J*=7.3 Hz, 1H), 7.51 (d, *J*=7.7 Hz, 2H), 7.44 (d, *J*=7.7 Hz, 2H), 7.39 (t, *J*=7.7 Hz, 1H), 7.11 (t, *J*=7.3 Hz, 3H), 6.98 (t, *J*=7.3 Hz, 1H), 6.73 (d, *J*=8.4 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.05 (d, J = 245.2Hz), 159.72, 149.77, 141.49, 132.84, 130.03, 129.90, 129.82, 129.57, 128.27, 125.87, 121.08, 120.06, 116.03, 115.82, 114.72, 104.96, 21.70; HRMS (ESI, m/z): calcd for $C_{23}H_{16}FN_3$ ($M+H^+$) 353.1328, found: 353.1335.

4.4.13. 2,4-di-p-tolylbenzo[4,5]imidazo[1,2-a]pyrimidine **(4m).** Yield 90%; yellow solid; Mp: 218-220 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J*=8.1 Hz, 2H), 7.92 (d, *J*=8.1 Hz, 1H), 7.49 (d, *J*=8.1 Hz, 2H), 7.43 (d, *J*=8.1 Hz, 2H), 7.38 (d, *J*=7.7 Hz, 1H), 7.24 (d, *J*=8.1 Hz, 2H), 7.14 (s, 1H), 6.98 (t, *J*=8.1 Hz, 1H), 6.73 (d, *J*=8.1 Hz, 1H), 2.53 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.95, 149.39, 141.73, 141.33, 133.90, 129.99, 129.74, 129.63, 128.30, 127.72, 125.71, 120.86, 120.03, 114.65, 105.20, 21.69, 21.52; HRMS (ESI, m/z): calcd for $C_{24}H_{19}N_3$ ($M+H^+$) 349.1579, found: 349.1581.

4.4.14. 4-(4-isopropylphenyl)-2-(p-tolyl)benzo[4,5]imidazo[1,2-a]pyrimidine (**4n**). Yield 91%; yellow solid; Mp: 186-188 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J*=8.4 Hz, 2H), 7.94 (s, 1H), 7.50 (d, *J*=8.1 Hz, 2H), 7.44 (d, *J*=7.7 Hz, 2H), 7.40 (d, *J*=7.3 Hz, 1H), 7.35 (d, *J*=8.1 Hz, 2H), 7.18 (s, 1H), 6.99 (t, *J*=7.3 Hz, 1H), 6.75 (d, *J*=8.1 Hz, 1H), 2.93-3.00 (m, 1H), 2.54 (s, 3H), 1.28 (d, *J*=7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.06, 152.63, 141.37, 134.38, 130.04, 128.34, 127.94, 127.10, 125.76, 120.93, 120.08, 114.69, 105.30, 34.18, 23.86, 21.72; HRMS (ESI, m/z): calcd for $C_{26}H_{23}N_3$ ($M+H^+$) 377.1892, found: 377.1888.

4.4.15. 2-(p-tolyl)-4-(3,4,5-trimethoxyphenyl)benzo[4,5]imidazo[1,2-a]pyrimidine **(4o).** Yield 92%; yellow solid; Mp: 262-264 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J*=8.1, 1H), 7.54-7.56 (m, 4H), 7.47 (d, *J*=8.1 Hz, 2H), 7.42 (t, *J*=7.7 Hz, 1H), 7.16 (s, 1H), 7.01 (t, *J*=7.6 Hz, 1H), 6.73 (d, *J*=8.1 Hz, 1H), 3.97 (s, 6H), 3.93 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.30, 153.53, 149.45, 145.50, 141.49, 131.97, 130.07, 128.35, 125.89, 121.08, 120.03, 114.63, 105.04, 61.04, 56.45, 21.72; HRMS (ESI, m/z): calcd for $C_{26}H_{23}N_3O_3$ ($M+H^+$) 425.1739, found: 425.1735.

4.4.16. 2-(p-tolyl)-4-(4-bromophenyl)benzo[4,5]imidazo[1,2-a]pyrimidine (**4p**). Yield 89%; yellow solid; Mp: 240-242 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J*=8.1 Hz, 1H), 7.85 (d,

J=7.7 Hz, 1H), 7.67 (d, *J*=8.1 Hz, 1H), 7.53 (d, *J*=8.1 Hz, 2H), 7.43-7.48 (m, 4H), 7.31 (t, *J*=7.5 Hz, 1H), 7.17 (s, 1H), 7.06 (t, *J*=6.9 Hz, 1H), 6.87 (d, *J*=8.4 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.85, 148.58, 145.43, 141.55, 139.32, 133.63, 132.04, 131.15, 130.08, 129.47, 128.31, 127.88, 127.43, 126.02, 121.47, 121.32, 120.46, 114.95, 109.89, 21.74; HRMS (ESI, m/z): calcd for $C_{23}H_{16}BrN_3$ ($M+H^+$) 414.2972, found: 414.2968.

4.4.17. 4-(2-chlorophenyl)-2-(4-fluorophenyl)benzo[4,5]imidazo[1,2-a]pyrimidine **(4q).** Yield 88%; yellow solid; Mp: 250-252 ^oC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J*=7.3, 1H), 7.64-7.71 (m, 5H), 7.47 (t, *J*=7.3, 1H), 7.34-7.40 (m, 1H), 7.31 (d, *J* =8.1 Hz, 1H), 7.13 (t, *J* =8.1 Hz, 1H), 7.06 (t, *J*=8.4 Hz, 1H), 6.88 (s, 1H), 6.78 (d, *J*=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.77, 159.26, 157.27, 151.50, 149.23, 145.43, 133.96, 132.08, 131.26, 131.17, 129.45, 128.40, 126.23, 125.90, 121.61, 120.67, 114.91, 114.83, 114.61, 110.11; HRMS (ESI, m/z): calcd for $C_{22}H_{13}ClFN_3$ ($M+H^+$) 373.0782, found: 373.0785.

4.4.18. 2,4-bis(4-fluorophenyl)benzo[4,5]imidazo[1,2-a]pyrimidine **(4r).** Yield 87%; yellow solid; Mp: 256-258 ^oC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49-8.55 (m, 1H), 8.96 (d, *J*=8.1 Hz, 1H), 7.62-7.73 (m, 5H), 7.45 (t, *J*=8.1 Hz, 1H), 7.34 (s, 1H), 7.08 (t, *J*=8.4 Hz, 1H), 7.03 (t, *J*=8.5 Hz, 1H), 6.90-6.95 (m, 1H), 6.71 (d, *J*=8.4, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.46 (d, *J*= 250.2Hz), 156.92, 151.67, 149.24, 145.41, 133.23, 133.13, 132.42, 131.16, 129.44, 128.43, 126.12, 121.35, 120.27, 114.73, 112.48, 108.52, 108.39, 104.66 ; HRMS (ESI, m/z): calcd for $C_{22}H_{13}F_2N_3$ ($M+H^+$) 357.1077, found: 357.1072.

4.4.19. 4-(3-bromophenyl)-2-(p-tolyl)benzo[4,5]imidazo[1,2-a]pyrimidine (**4s**). Yield 89%; yellow solid; Mp: 244-246 ^oC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J*=8.4 Hz, 2H), 7.92 (s, 1H), 7.57 (d, *J*=8.1 Hz, 2H), 7.52 (d, *J*=8.1 Hz, 2H), 7.45 (d, *J*=7.7 Hz, 2H), 7.40 (t, *J*=6.4 Hz, 1H), 7.12 (s, 1H), 7.00 (t, *J*=7.3 Hz, 1H), 6.75 (d, *J*=8.4 Hz, 1H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.66, 149.94, 141.57, 135.55, 132.11, 130.09, 129.23, 128.30, 126.00, 121.25, 120.15, 114.80, 104.92, 21.75; HRMS (ESI, m/z): calcd for $C_{23}H_{16}BrN_3$ ($M+H^+$) 414.2972, found: 414.2978.

4.4.20. 2-(4-bromophenyl)-4-(2-fluorophenyl)benzo[4,5]imidazo[1,2-a]pyrimidine **(4t).** Yield 87%; yellow solid; Mp: 205-207 ^oC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, *J*=6.6, 1H), 7.97 (d, *J*=6.6, 1H), 7.64-7.72 (m, 5H), 7.54-7.57 (m, 1H), 7.46 (t, *J*=7.3, 1H), 7.36 (s, 1H), 7.02-7.09 (m, 2H), 6.73 (d, *J*=7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.71 (d, *J* = 240.5Hz), 156.25, 149.49, 145.56, 135.42, 134.25, 131.27, 129.52, 128.46, 126.30, 121.59, 118.52, 118.26, 114.86, 108.59, 108.45; HRMS (ESI, m/z): calcd for $C_{22}H_{13}BrFN_3$ ($M+H^+$) 418.2611, found: 418.2615.

Supporting Information

All Compounds NMR spectra were provided as Supplementary material.

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