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IRON (III)-CATALYZED EFFICIENT ONE-POTSYNTHESIS OF FUNCTIONALIZED DIHYDROBENZO[4,5-*D*]IMIDAZO[1,2-*A*]PYRIMIDINES

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Abstract
A concise and efficient Iron(III)-catalyzed one-pot domino synthesis of functionalized dihydrobenzo[4,5-*d*]imidazo[1,2-*a*]pyrimidines has developed by reaction of 2-aminobenzimidazole with substituted aromatic aldehyde and pyruvic acid in ethanol. The presentmethodology provides a convenient, atom-economical and eco-friendly approach for the synthesis of biologically important imidazopyrimidinesfrom easily available substrates under mild reaction conditions.

Keywords: Imidazopyrimidine; One-pot; Benzimidazole; Iron-catalyzed

Introduction

In recent decades, research interests have been focused on the search of more efficient synthetic strategies for the drug like complex molecules and natural product mimic from simple and readily accessible starting materials.[I]The development of simple synthetic routes for complex organicmolecules is an important challenge in organic synthesis. The multicomponent domino reactions offer remarkable advantages from the environmental point of view including operational simplicity, facile automation and minimized waste generation because of reduction in number of extraction and purification stages, and played a critical role in the development of modern synthetic methodologies for pharmaceutical and drug discovery research.[II]The multicomponent reactions (MCRs) have, therefore, become an essential tool for generating complex molecular libraries in the screening of potential biologically and pharmacologically active candidates.[III]

Benzimidazoles and pyrimidines are the important structuralunits found in biologicallyand therapeutically active compounds, natural products and functional materials.[IV]Numerousderivativesof these structures are found individually in drugs used totreat a wide variety of medical conditions.[V]The fused imidazo[1,2-*a*]pyrimidinesscaffold are the core structural motifs in pharmacologicallyimportant molecules, with activities

spanning a diverse range of targets.[VI]Morerecently,the derivatives of imidazo[1,2-*a*]pyrimidineshave(Figure 1) reported to show prominent biological applications as lipoprotein-associated phospholipase A2 inhibitors (A)[VII], p38 kinase inhibitor (B)[VIII], anticancer (C),[IX] DPP4 inhibitor (D),[X] and androgen receptor antagonist (E).[XI]

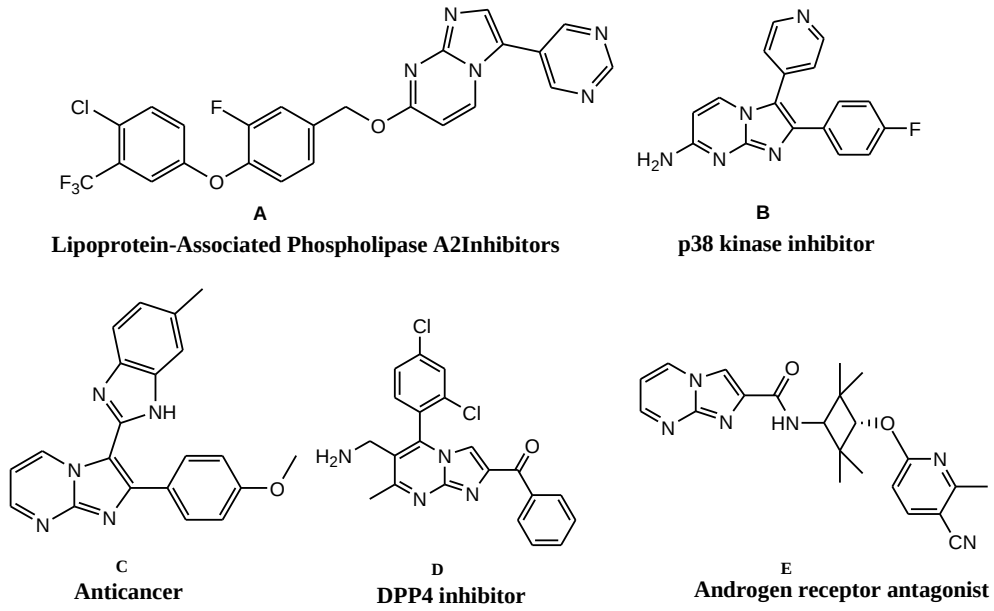
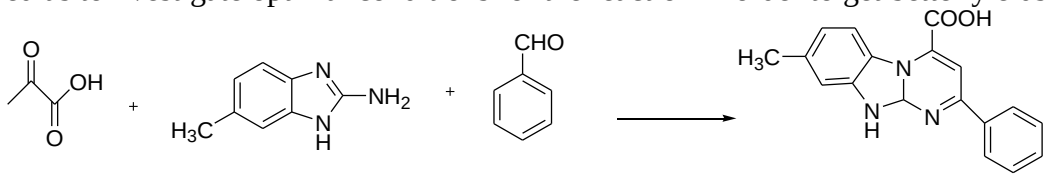


Figure 1 Biological active imidazo[1,2-*a*]pyrimidines

Therefore, due to their importance, many methods have beendeveloped for the construction of the imidazo[1,2-*a*]pyrimidinesring.[XII]However, many of these protocols require tedious workup and prolonged reaction timeconsuming starting materials with limited scope. Therefore, thedevelopment of efficient protocol for the synthesis of such privileged scaffold will be of elegant interest. Herein, we report an efficient iron(III)-catalyzed synthesis of multi-substitutedimidazo[1,2-*a*]pyrimidines via a one-pot reaction of 2-aminobezimidazolewith pyruvic acidand substituted aromatic aldehyde.

Result and discussion

Initially, we performed a three component reaction of 2-amino-6-methyl-bezimidazole **2a** with pyruvic acid **1** and benzaldehyde **3a** as a model reaction to optimise reaction conditions (Scheme 1). The reaction was carried out by refluxing a mixture of **1**, **2a** and **3a** in 2:2:2 molar ratio in methanol in the presence of $FeCl_3$ (10 mol %) at 90 °C. The desired product, dihydrobezoimidazopyrimidines**4a**, was obtained in 65% yield (Table 1, entry 1).This impelled us toinvestigate optimal conditions for the reaction in order to get better yields.



1 2a 3a 4a

Scheme 1 Model reaction

In this preliminary experiment, the reactions were carried out with different solvents, such as methanol, ethanol, toluene and DMFwe found that EtOH gave the best result. Next, we

investigated different loadings of $FeCl_3$using ethanol as solvent, in the amount of 20 mol % and 30 mol % and obtained 76% and 73% yields, respectively (Table 1, entries 3 and 5). Other catalysts, such as $AlCl_3$, $ZnCl_2$ and $SnCl_4$, showed little effectiveness on promoting the reaction (Table 1, entries 8-11). Thus, ethanol with 20 mmol % $FeCl_3$ at 90 °C was chosen as optimal conditions for all further reactions.

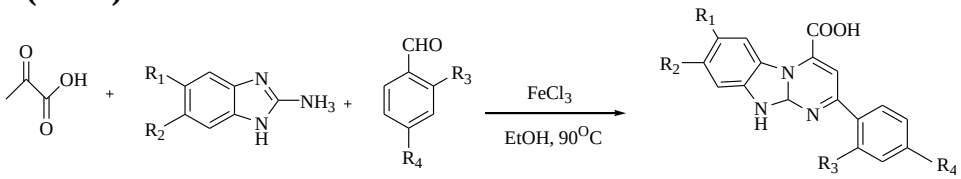
Table 1 Optimization of the reaction condition[a]

entry	Catalyst	solvent	time	yield (%)[b]
1.	$FeCl_3$ (20%)	methanol	1 hrs 15 min	65
2.	$FeCl_3$ (10%)	methanol	1 hrs30 min	60
3.	$FeCl_3$ (20%)	ethanol	55 min	76
4.	$FeCl_3$ (10%)	ethanol	60 min	68
5.	$FeCl_3$ (30%)	ethanol	1 hrs5 min	73
6.	$FeCl_3$ (20%)	DMF	2 hrs	66
7.	$FeCl_3$ (20%)	toluene	1 hrs 40 min	70
8.	$AlCl_3$	ethanol	more than 4 hrs	traces
9.	$ZnCl_2$	ethanol	2 hrs	43
10.	$ZnCl_2$	methanol	2 hrs 10 min	45
11.	$SnCl_4$	ethanol	more than 4 hrs	traces

[a]Reaction conditions: 1(2 mmol), 2a (2 mmol), 3a (2 mmol), catalyst (20% mmol), solvent (6 mL), 90 °C
[b]Isolated yield.

After optimization of the reaction conditions, to examine the scope of this protocol, particularly in regard to library construction, this methodology was evaluated by using pyruvic acid**1**, substituted 2-aminobezimidazole **2a-2c**and substituted aromatic aldehydes **3a-3e** for the library validation (Table 2). As shown in Table 2, a series of different position substituted 2-aminobezimidazole and aromatic aldehyde including either electron-withdrawing or electron-donating groups were used to synthesize the desired product in good yields.

Table 2 Synthesis of 2,10-dihydrobenzo[4,5-*d*]imidazo[1,2-*a*]pyrimidine-4-carboxylic acid derivatives **(4a-4o)**

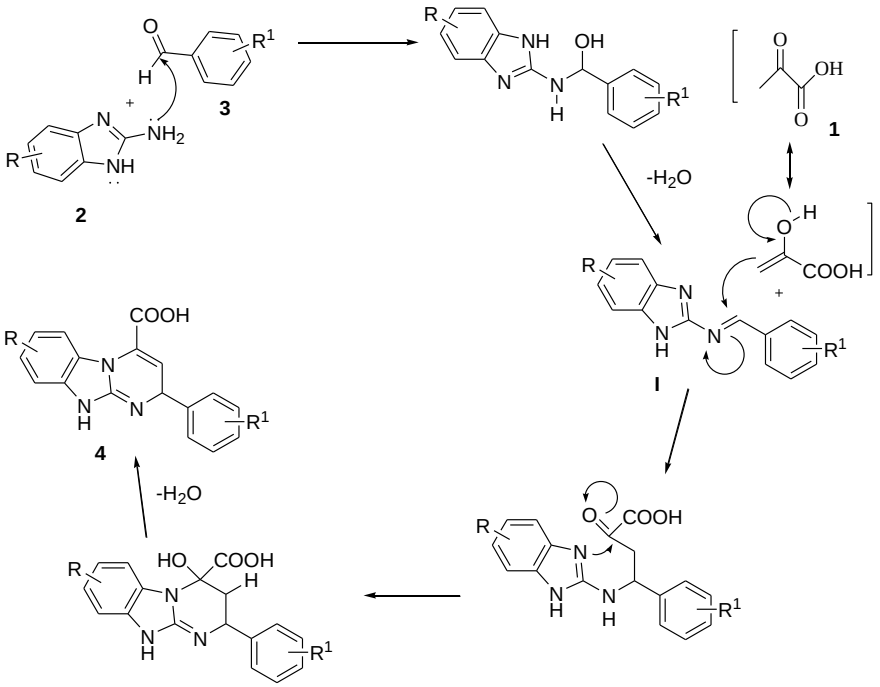


1 2 3 4(a-o)

entry	R_1/R_2	R_3/R_4	product	reaction time	yield (%)
1.	H /CH_3	H/H	4a	55 min	76
2.	H /CH_3	H /CH_3	4b	1hr	68
3.	H /CH_3	H/Cl	4c	1hr 5 min	71
4.	H /CH_3	H/OCH_3	4d	56 min	74
5.	H /CH_3	OCH_3 /H	4e	59 min	70
6.	Cl/H	H/H	4f	55 min	73
7.	Cl/H	H /CH_3	4g	56 min	70
8.	Cl/H	H/Cl	4h	1 hr 5 min	67
9.	Cl/H	H/OCH_3	4i	59 min	69
10.	Cl/H	OCH_3 /H	4j	1hr 7min	72
11.	OCH_3/H	H/H	4k	1hr	70

12.	OCH_3/H	H /CH_3	4l	56min	73
13.	OCH_3/H	H/Cl	4m	56 min	66
14.	OCH_3/H	H/OCH_3	4n	1hr 4min	69
15.	OCH_3/H	OCH_3 /H	4o	58 min	71

The reactions have taken place in one-flask domino manner, the Schiff's base adduct **I**formed from 1, 2-addition of the 2-aminobenzimidazole and aromatic aldehyde in the first step immediately undergoes *Mannich*type reaction with pyruvic acid, which on subsequent dehydrative cyclization providesdihydrobenzo[4,5-*d*]imidazo[1,2-*a*]pyrimidine-4-carboxylic acid **4**(Scheme 3)**.**



Scheme 3 Synthesis of dihydrobenzo[4,5-*d*]imidazo[1,2-*a*]pyrimidine-4-carboxylic acid

Conclusion

In conclusion, we have developed an Iron (III)-catalyzed convenient and efficient multicomponent one-pot reaction for the synthesis of multifunctional, dihydrobenzo[4,5-*d*]imidazo[1,2-*a*]pyrimidine **4(a-o)**. The mild reaction conditions and convenient procedure of purification including simple filtration and recrystallization makes the synthetic method attractive for academic research and practical applications and can be extended to prepare a library of structurally diverse drug like imidazo[1,2-*a*]pyrimidine.

Experimental

General

M.p. of all the synthesized compounds were determined on the electrothermalmelting point apparatus using open capillary tubes and are reported uncorrected. Aromaticaldehydes and pyruvic acid were purchased from commercial sources and used withoutpurification. 2-Aminobenzimidazoles wereprepared by the reported method.The purity of allthe synthesized compounds was checked by TLC. IR spectra were recorded on a *Shimadzu 8400S* FTIR spectrometer. ^{1}H and^{13}C NMR spectra were recorded on a *Bruker DRX-300*Advance Spectrometer at 300.13 and 75.47MHz, respectively. In all cases, NMR spectra wereobtained in DMSO (D_6) using TMS as internal standard. Analytical and spectral data of the synthesized compounds are in agreement with their proposedstructures.

Typical experimental procedure:
A mixture of 2-aminobezimidazole (2mmol), pyruvic acid (2 mmol), aromatic aldehydes (2 mmol), and $FeCl_3$(20% mmol) in ethanol(6ml) was stirred magnetically at 90°C for nearly 45 minute to 1 hrs 30 min. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature. Then, the precipitated product was filtered and washed with water and cooled ethanol to afford the product. The product was then dried and finally re-crystallized from ethanol to obtain pure product.

***8-Methyl-2-phenyl-2,10-dihydro-benzo[4,5-d]imidazo[1,2,-a]pyrimidine-4-carboxylic acid*(4a)** M.p.181-182°C, IR (KBr) $v(cm^{-1})$; 3280, 2970, 1735,1621, 1020, 810.^{1}H NMR (DMSO-d_6) δ(ppm):2.35 (3H, *s*, CH_3), 3.55(1H, *s*, CH), 4.08(1H, *s*, NH) 6.72(1H, *s*, H), 6.05-7.15(8H, *m*, H-Ar), 11.04(1H, *s*, OH). ^{13}C NMR (DMSO-d_6) δ(ppm):170.1, 164.7, 144.1, 138.7, 137.4, 130.8, 129.1, 128.7, 128.1, 126.5, 126.3, 119.4, 112.1, 103.1, 74.9, 20.4;Anal.Calcd(%) for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76; found C, 70.76; H, 4.93; N, 13.70.

8-Methyl-2-(4-methyl-phenyl)-2,10-dihydro-benzo[4,5-d]imidazo[1,2,-a]pyrimidine-4-carboxylic acid(4b)M.p.186-187°C, IR (KBr) $v(cm^{-1})$; 3271, 2985, 1729,1631,1370, 1022, 817. ^{1}H NMR (DMSO-d_6) δ(ppm): 2.32 (3H, *s*, CH_3), 2.38 (3H, *s*, CH_3), 3.48(1H, *s*, CH), 4.02(1H, *s*, NH), 6.73(1H, *s*, H), 6.02-7.02(7H, *m*, H-Ar), 11.2(1H, *s*, OH). ^{13}C NMR (DMSO-d_6) δ(ppm): 170.0, 164.6, 144.0, 140.0, 138.6, 134.4, 129.2, 128.9, 128.1, 126.4, 119.3, 112.4, 103.1, 74.9, 20.9, 20.5;Anal.Calcd(%) for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16; found C, 71.40; H, 5.31; N, 13.10.

***2-(4-Chloro-phenyl)-8-methyl-2,10-dihydro-benzo[4,5-d]imidazo[1,2,-a]pyrimidine-4-carboxylic acid*(4c)**M.p.196-197°C, IR (KBr) $v(cm^{-1})$; 3265, 2951, 1742,1640,1363, 1015, 810. ^{1}H NMR (DMSO-d_6) δ(ppm): 2.37 (3H, *s*, CH_3), 3.53(1H, *s*, CH), 4.1(1H, *s*, NH), 6.69(1H, *s*, H), 6.10-7.19(7H, *m*, H-Ar), 10.98(1H, *s*, OH). ^{13}C NMR (DMSO-d_6) δ(ppm): 170.2, 164.0, 144.1, 138.5, 136.1, 135.4, 130.5, 129.0, 128.2, 126.3, 119.2, 112.5, 103.3, 74.8, 20.5. Anal.Calcd(%) for $C_{18}H_{14}ClN_3O_2$: C, 63.63; H, 4.15; N, 12.37; found C, 63.54; H, 4.05; N, 12.25

***2-(4-Methoxy-phenyl)-8-methyl-2,10-dihydro-benzo[4,5-d]imidazo[1,2,-a]pyrimidine-4-carboxylic acid*(4d)**M.p.203-204°C, IR (KBr) $v(cm^{-1})$; 3283, 2977, 1733,1629,1370, 1055, 1018, 815. ^{1}H NMR (DMSO-d_6) δ(ppm): 2.31 (3H, *s*, CH_3), 3.47 (H, *s*, CH), 3.74 (3H, *s*, OCH_3), 4.10(1H, *s*, NH), 6.73(1H, *s*, H), 6.08-7.01(7H, *m*, H-Ar), 11.1(1H, *s*, OH). ^{13}C NMR (DMSO-d_6) δ(ppm): 169.9, 164.6, 163.9, 143.8, 138.6, 130.1, 129.6, 126.5, 114.2, 103.0, 74.7, 56.1, 20.5;Anal.Calcd(%) for $C_{19}H_{16}N_3O_3$: C, 68.05; H, 5.11; N, 12.53; found C, 68.0; H, 5.01; N, 12.44

***2-(2-Methoxy-phenyl)-8-methyl-2,10-dihydro-benzo[4,5-d]imidazo[1,2,-a]pyrimidine-4-carboxylic acid* (4e)**M.p.210-211°C, IR (KBr) $v(cm^{-1})$;3271, 2972, 1744,1639,1361, 1044, 1020, 811. ^{1}H NMR (DMSO-d_6) δ(ppm): 2.33 (3H, *s*, CH_3), 3.49 (H, *s*, CH), 3.71 (3H, *s*, OCH_3), 4.14(1H, *s*, NH), 6.69(1H, *s*, H), 6.11-7.06(7H, *m*, H-Ar), 11.06(1H, *s*, OH).^{13}C NMR (DMSO-d_6) δ(ppm): 170.2, 164.5, 144.1, 138.4, 130.2, 128.1, 126.1, 112.5, 103.3, 74.6, 56.2, 20.6;Anal.Calcd(%) for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53; O, 14.31; found C, 68.02; H, 5.00; N, 12.41.

***7-Chloro-2-phenyl-2,10-dihydro-benzo[4,5-d]imidazo[1,2,-a]pyrimidine-4-carboxylic acid*(4f)**M.p.207-208°C, IR (KBr) $v(cm^{-1})$; 3247,2965, 1738,1623,1375, 1012, 719. ^{1}H NMR (DMSO-d_6) δ(ppm):, 3.42(1H, *s*, CH), 4.11(1H, *s*, NH), 6.75(1H, *s*, H)6.12-7.22(8H, *m*, H-Ar), 10.9(1H, *s*, OH). ^{13}C NMR (DMSO-d_6) δ(ppm): 169.8.0, 164.2, 144.0, 141.4, 137.5, 130.7, 129.7, 128.7, 123.9, 121.4, 111.6, 103.2, 75.3, 11.4;Anal.Calcd(%) for $C_{17}H_{12}ClN_3O_2$: C, 62.68; H, 3.71; N, 12.90; found C, 62.61; H, 3.65; N, 12.73

***7-Chloro-2-(4-methyl-phenyl)-2,10-dihydro-benzo[4,5-d]imidazo[1,2,-a]pyrimidine-4-carboxylic acid*(4g).** M.p.201-202°C, IR (KBr) $v(cm^{-1})$; 3283, 2995, 1731,1623,1370, 1011,

781. ^{1}H NMR (DMSO-d_6) δ(ppm): 2.36 (3H, *s*, CH_3), 3.48(1H, *s*, CH), 4.17(1H, *s*, NH), 6.71(1H, *s*, H), 6.20-7.02(8H, *m*, H-Ar), 10.8(1H, *s*, OH). ^{13}C NMR (DMSO-d_6) δ(ppm): 170.1, 164.1, 144.1, 140.0, 134.3, 129.7, 127.8, 123.9, 121.6, 111.5, 103.1, 75.2, 20.9, 11.7;Anal.Calcd(%) for $C_{18}H_{14}ClN_3O_2$: C, 63.63; H, 4.15; N, 12.37;found C, 63.63; H, 4.15; N, 12.37

***7-Chloro-2-(4-chloro-phenyl)-2,10-dihydro-benzo[4,5-d]imidazo[1,2,-a]pyrimidine-4-carboxylic acid*(4h)** M.p.215-216°C, IR (KBr) ν(cm^{-1}); 3269, 2989, 1731,1639, 1019, 816. ^{1}H NMR (DMSO-d_6) δ(ppm): 3.51(1H, *s*, CH), 4.10(1H, *s*, NH), 6.73(1H, *s*, H), 6.10-7.19(7H, *m*, H-Ar), 11.1(1H, *s*, OH). ^{13}C NMR (DMSO-d_6) δ(ppm): 170.2, 164.4, 144.2, 141.2, 136.1, 130.3, 129.0, 123.9, 121.5, 111.7, 103.2, 75.2, 11.7;Anal.Calcd(%) for $C_{17}H_{11}Cl_2N_3O_2$: C, 56.69; H, 3.08; N, 11.67; found C, 56.61; H, 3.01; N, 11.56

***7-Chloro-2-(4-methoxy-phenyl)-2,10-dihydro-benzo[4,5-d]imidazo[1,2,-a]pyrimidine-4-carboxylic acid*(4i)**. M.p.209-210°C, IR (KBr) ν(cm^{-1}); 3287, 2975, 1742,1650,1373, 1055, 782. ^{1}H NMR (DMSO-d_6) δ(ppm): 3.55(1H, *s*, CH), 3.74(3H, *s*, OCH_3), 4.14(1H, *s*, NH), 6.68(1H, *s*, H), 6.16-6.99(7H, *m*, H-Ar), 11.2(1H, *s*, OH). ^{13}C NMR (DMSO-d_6) δ(ppm): 169.3, 164.6, 144.1, 130.0, 127.6, 123.8, 121.6, 114.2, 111.5, 103.0, 75.1, 56.1,11.4,Anal.Calcd(%) for $C_{18}H_{14}ClN_3O_3$: C, 60.77; H, 3.97; N, 11.81; found C, 60.77; H, 3.97; N, 11.81

***7-Chloro-2-(2-methoxy-phenyl)-2,10-dihydro-benzo[4,5-d]imidazo[1,2-a]pyrimidine-4-carboxylic acid*(4j)**M.p.232-233°C, IR (KBr) ν(cm^{-1}); 3266, 2989, 1740, 1642, 1373, 1051, 1022, 801. ^{1}H NMR (DMSO-d_6) δ(ppm): 3.58(1H, *s*, CH), 3.70 (3H, *s*, OCH_3), 4.20(1H, *s*, NH), 6.60(1H, *s*, H), 6.11-7.05(7H, *m*, H-Ar), 10.9(1H, *s*, OH). ^{13}C NMR (DMSO-d_6) δ(ppm): 170.1, 164.2, 144.1, 141.3, 130.0, 127.6, 123.8, 121.6, 111.5, 103.0, 75.1, 56.1, 11.4. Anal.Calcd(%) for $C_{18}H_{14}ClN_3O_3$: C, 60.77; H, 3.97; N, 11.81; found C, 60.70; H, 3.91; N, 11.71

***7-Methoxy-2-phenyl-2,10-dihydro-benzo[4,5-d]imidazo[1,2,-a]pyrimidine-4-carboxylic acid*(4k)** M.p.211-212°C, IR (KBr) ν(cm^{-1}); 2980, 1735,1630,1363, 1017, 815. ^{1}H NMR (DMSO-d_6) δ(ppm): 3.71(3H, *s*, OCH_3), 4.10(1H, *s*, NH), 6.70(1H, *s*, H), 6.12-7.11(8H, *m*, H-Ar), 10.92(1H, *s*, OH). ^{13}C NMR (DMSO-d_6) δ(ppm): 170.2, 164.3, 144.3, 139.3, 137.6, 129.1, 127.2, 125.1, 121.7, 119.2, 103.5, 20.7,12.3. Anal.Calcd(%) for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08; found C, 67.22; H, 4.61; N, 13.01

***7-Methoxy-2-(4-methyl-phenyl)-2,10-dihydro-benzo[4,5-d]imidazo[1,2-a]pyrimidine-4-carboxylic acid* (4l)** M.p.227-228°C, IR (KBr) ν(cm^{-1}); 3277, 2985, 1727,1632,1371, 1021, 809. ^{1}H NMR (DMSO-d_6) δ(ppm): 2.33 (3H, *s*, CH_3), $_3$), 3.68 (3H, *s*, OCH_3), 4.0(1H, *s*, NH), 6.75(1H, *s*, H), 5.94 -7.01(7H, *m*, H-Ar), 10.9(1H, *s*, OH). ^{13}C NMR (DMSO-d_6) δ(ppm): 169.5, 164.6, 144.0, 141.3, 136.5, 134.7, 129.4, 118.6, 110.2, 103.1, 75.2, 21.2, 13.8. Anal.Calcd(%) for $C_{18}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53; found C, 67.95; H, 5.04; N, 12.43

***2-(4-Chloro-phenyl)-7-methoxy-2,10-dihydro-benzo[4,5-d]imidazo[1,2-a]pyrimidine-4-carboxylic acid; compound with methane*(4m)** M.p.223-224°C, IR (KBr) ν(cm^{-1}); 3292, 2999, 1738,1625, 1013, 793. ^{1}H NMR (DMSO-d_6) δ (ppm): 3.61 (3H, *s*, OCH_3), 4.10(1H, *s*, NH), 6.70(1H, *s*, H), 5.90 -7.11(7H, *m*, H-Ar), 10.77(1H, *s*, OH). ^{13}C NMR (DMSO-d_6) δ(ppm): 168.9, 164.5, 144.1, 141.4, 136.6, 134.8, 130.3, 118.6, 103.1, 75.0, 21.1, 13.5. Anal.Calcd (%) $C_{18}H_{14}ClN_3O_3$: C, 60.77; H, 3.97; N, 11.81; found C, 60.72; H, 3.90; N, 11.77.

***7-Methoxy-2-(4-methoxy-phenyl)-2,10-dihydro-benzo[4,5-d]imidazo[1,2-a]pyrimidine-4-carboxylic acid*(4n)** M.p.244-245°C, IR (KBr) ν(cm^{-1}); 3243, 2968, 1718,1654, 1012, 811. ^{1}H NMR (DMSO-d_6) δ(ppm): 3.51 (3H, *s*, OCH_3), 3.61 (3H, *s*, OCH_3) 4.16(1H, *s*, NH), 6.64(1H, *s*, H), 5.94 -7.18(7H, *m*, H-Ar), 10.97(1H, *s*, OH). ^{13}C NMR (DMSO-d_6) δ (ppm):

169.6, 164.2, 143.9, 141.3, 136.5, 134.8, 130.0, 118.4, 114.2, 110.4, 103.3, 75.2, 56.1, 21.4, 13.6. Anal.Calcd(%) for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96; found C, 64.85; H, 4.82; N, 11.89

***7-Methoxy-2-(2-methoxy-phenyl)-2,10-dihydro-benzo[4,5]imidazo[1,2-a]pyrimidine-4-carboxylic acid*(4o)**M.p.255-256°C, IR (KBr) $\nu(cm^{-1})$; 3266, 2956, 1723,1629, 1023, 797. ^{1}H NMR (DMSO-d_6) δ(ppm): 3.49 (3H, *s*, OCH_3), 3.54 (3H, *s*, OCH_3) 4.11(1H, *s*, NH), 6.60(1H, *s*, H), 5.99 -7.20(7H, *m*, H-Ar),11.01(1H, *s*, OH). ^{13}C NMR (DMSO-d_6) δ(ppm): 170.1, 164.6, 144.1, 136.0, 134.5, 131.8,, 129.7, 120.6, 114.2, 103.5, 75.0, 56.0, 21.0, 13.5. Anal.Calcd(%) for $C_{20}H_{18}N_2O_3$: C, 64.95; H, 4.88; N, 11.96; found C, 64.90; H, 4.81; N, 11.88

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