

## Synthesis and Characterization of imidazo[1,2-a]pyrimidine

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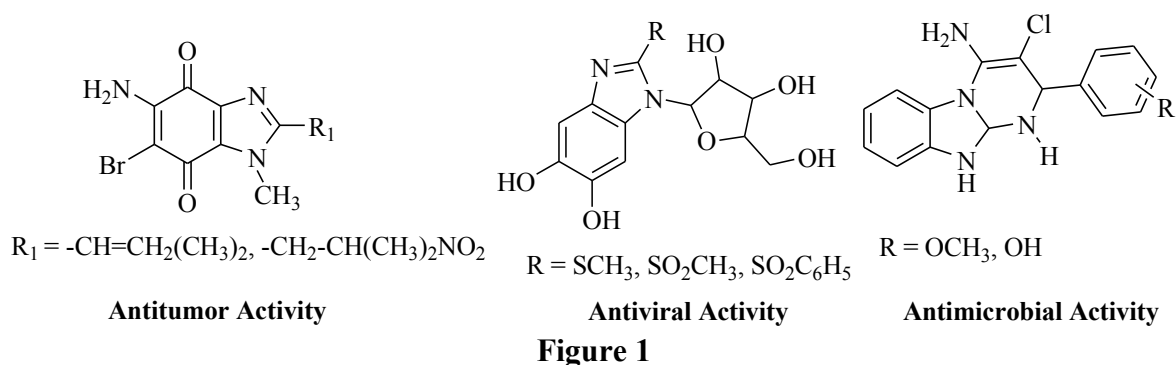
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**ABSTRACT.** An efficient protocol for the synthesis of imidazo[1,2-a]pyrimidine was developed by using three component one-pot Biginelli synthesis. The synthesized compounds were characterized by spectroscopic techniques like FT-IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and mass spectroscopy.

### 1. INTRODUCTION

The development of the Biginelli reaction has advanced considerably since its discovery 115 years ago. Mechanistic insights have provided rational modifications to the experiment protocols, allowing pyrimidines to be synthesized in high yield. The interesting and diverse biological activity of pyrimidines has been explored through the generation of libraries of compounds via microwave, solid-phase, and fluorous-phase technologies. Imidazo[1,2-a]pyrimidine is an extension of the well-elaborated pyrimidine system, has been used due to their therapeutic and pharmacological properties such as Antimicrobial [1-4] antimalarial [5], antiproliferative [6], protein kinase inhibitor [7], hypotensive, spasmolytic, anesthetic activity [8], diuretic [9], anti-inflammatory [10], antiamebic [11], antineoplastic activity [12]. Some examples of reported biologically active compounds of Imidazo[1,2-a]pyrimidine are depicted in figure 1.



Thus in view of above facts our plan was to synthesised novel analogues of imidazo[1,2-a]pyrimidine with potential biological activities, we set upon a synthetic strategies involving 2-amino-benzimidazol as building block. Although different strategies have been employed for the synthesis of these compounds, [13–17] these methods suffer from drawbacks such as long reaction times, cumbersome isolation of the products and harsh reaction conditions. Herein, we report an efficient one-pot multi-component synthesis of imidazo[1,2-a]pyrimidine afforded excellent yields from 2-amino-benzimidazole, aldehydes and ethyl 3-oxo hexanoate respectively by simple fusion followed by adding catalytic amount of dimethylformamide (*Scheme 1*). Synthesis of fifteen novel analogues of imidazo[1,2-a]pyrimidine containing an appropriate 1,3-bifunctional synthon has been undertaken. The structures of all the newly synthesized compounds were elucidated by FT-IR, mass spectra, <sup>1</sup>H NMR, <sup>13</sup>C NMR and elemental analysis.

## 2. EXPERIMENTAL

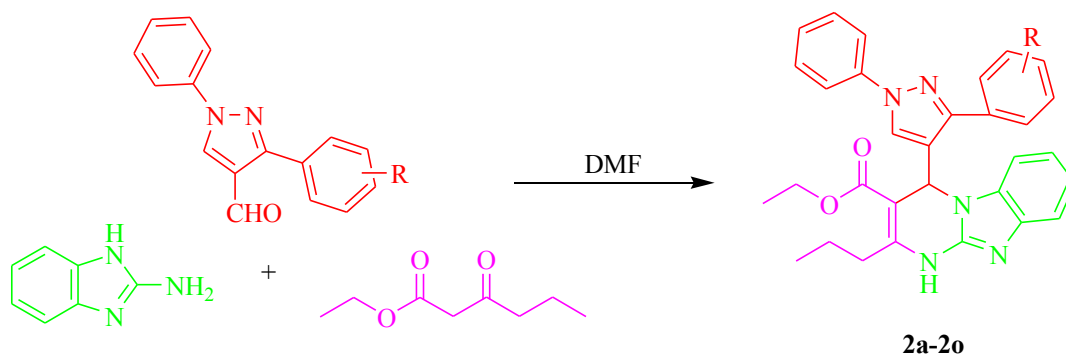
Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. IR spectra were recorded Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR was determined in DMSO- $d_6$  solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

### 2.1 General procedure for the synthesis of 7-(aryl)-4,7-dihydro-5-propyl- benzimidazo[1,2-*a*]pyrimidine-6-carboxamides

A mixture of the 2-aminobenzimidazole (0.01 mol), ethyl 3-oxohaxenoate (0.01 mol) and an appropriate aromatic aldehyde (0.01 mol) was fused in 0.4 mL of DMF for 10-12 min. After cooling, methanol (~10 mL) was added. The reaction mixture was allowed to stand overnight and then filtered to give the solid imidazo[1,2-*a*]pyrimidine products, which were crystallized from ethanol and subsequently dried in air.

#### 2.1.1 7-(2-methoxy phenyl)-4,7-dihydro-5-propyl- benzimidazo[1,2-*a*]pyrimidine-6-carboxamides (2l)

Yield: 85%; mp 176-178 °C; IR ( $\text{cm}^{-1}$ ): 2956 (C-H asymmetrical stretching of  $\text{CH}_3$  group), 2870 (C-H asymmetrical stretching of  $\text{CH}_3$  group), 1703 (C=N stretching), 1693 (N-H deformation of pyrimidine ring), 1502, 1462 and 1423 (C=C stretching of aromatic ring), 1462 (C-H asymmetrical deformation of  $\text{CH}_3$  group), 1357 (C-H symmetrical deformation of  $\text{CH}_3$  group), 1332 (C-N stretching), 806 (C-H out of plane bending of 1,4-disubstitution);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  ppm: 0.84-0.87 (t, 3H), 1.04-1.12 (t, 3H), 1.36-1.39 (d, 2H), 2.01 (s, 4H), 3.26 (s, 3H), 4.04-4.08 (m, 2H), 6.5 (s, 1H), 6.70-6.71 (d, 2H), 6.86- 6.92 (d, 2H), 6.96-7.00 (t, 1H), 7.05-7.08 (t, 1H), 7.26-7.35 (m, 1H), 7.36-7.40 (m, 1H), 7.47-7.51 (m, 2H), 7.81-7.83 (d, 2H), 8.92 (s, 1H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  ppm : 13.11, 21.52, 30.64, 33.06, 42.50, 46.30, 54. 53, 94.57, 109.61, 116.40, 119.41, 120.26, 121.21, 122.27, 125.96, 126.52, 127.89, 129.53, 130.72, 131.29, 139.02, 142.30, 145.35, 148.16, 150.37, 156.50, 157.25, 206.44; MS:  $m/z$  533; Anal. Calcd. for  $\text{C}_{26}\text{H}_{25}\text{BrN}_6\text{O}_2$ : C, 72.03; H, 5.86; N, 13.12. Found: C, 72.01; H, 5.22; N, 13.14%.



Scheme -1

No	Comp.	R	Molecular Formula	Molecular Weight	Yield (%)
1	2a	H	C <sub>31</sub> H <sub>29</sub> N <sub>5</sub> O <sub>2</sub>	503.59	75%
2	2b	2-Cl	C <sub>31</sub> H <sub>28</sub> ClN <sub>5</sub> O <sub>2</sub>	538.04	63%
3	2c	2-F	C <sub>31</sub> H <sub>28</sub> FN <sub>5</sub> O <sub>2</sub>	521.58	60%
4	2d	2-Br	C <sub>31</sub> H <sub>28</sub> BrN <sub>5</sub> O <sub>2</sub>	582.49	65%
5	2e	4-Cl	C <sub>31</sub> H <sub>28</sub> ClN <sub>5</sub> O <sub>2</sub>	538.04	68%
6	2f	4-F	C <sub>31</sub> H <sub>28</sub> FN <sub>5</sub> O <sub>2</sub>	521.58	63%
7	2g	4-Br	C <sub>31</sub> H <sub>28</sub> BrN <sub>5</sub> O <sub>2</sub>	582.49	70%
8	2h	2-NO <sub>2</sub>	C <sub>31</sub> H <sub>28</sub> N <sub>6</sub> O <sub>4</sub>	548.59	62%
9	2i	3-NO <sub>2</sub>	C <sub>31</sub> H <sub>28</sub> N <sub>6</sub> O <sub>4</sub>	548.59	65%
10	2j	4-NO <sub>2</sub>	C <sub>31</sub> H <sub>28</sub> N <sub>6</sub> O <sub>4</sub>	548.59	67%
11	2k	2-OH	C <sub>31</sub> H <sub>29</sub> N <sub>5</sub> O <sub>3</sub>	519.59	73%
12	2l	2-OCH <sub>3</sub>	C <sub>32</sub> H <sub>31</sub> N <sub>5</sub> O <sub>3</sub>	533.62	85%
13	2m	4-OCH <sub>3</sub>	C <sub>32</sub> H <sub>31</sub> N <sub>5</sub> O <sub>3</sub>	533.62	87%
14	2n	2-CH <sub>3</sub>	C <sub>32</sub> H <sub>31</sub> N <sub>5</sub> O <sub>2</sub>	517.62	81%
15	2o	4-CH <sub>3</sub>	C <sub>32</sub> H <sub>31</sub> N <sub>5</sub> O <sub>2</sub>	517.62	90%

### 3. RESULTS AND DISCUSSION

The Biginelli reaction is an efficient and simple protocol for the synthesis of benzimidazo[1,2-a]pyrimidine [18]. The first step is a nucleophilic addition of N<sub>2</sub> of the aminoazole to a carbonyl carbon of aldehyde, followed by subsequent cyclization with respective 1,3-carbonyl compound to form the dihydropyrimidine ring. An alternate sequence is also possible and cannot be excluded [19], which is the initial formation of an enamine by reaction of aminoazole with respective 1,3-carbonyl followed by cyclocondensation. The third alternative involving the formation of arylidene derivatives as intermediates requires the presence of a strong base [20] and is most likely not possible for the case described herein.

### 4. CONCLUSION

Herein, The synthesis of Fifteen novel analogues of benzimidazo[1,2-a]pyrimidine containing an appropriate 1,3-bifunctional synthon has been undertaken. The structures of all the newly synthesized compounds were elucidated by FT-IR, mass spectra, <sup>1</sup>H NMR, <sup>13</sup>C NMR and elemental analysis. In nutshell, we have reported a simple, efficient approach towards synthesis of benzimidazo[1,2-a]pyrimidine in excellent yield.

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