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Synthesis and biological evaluation of some novel derivatives of imidazole

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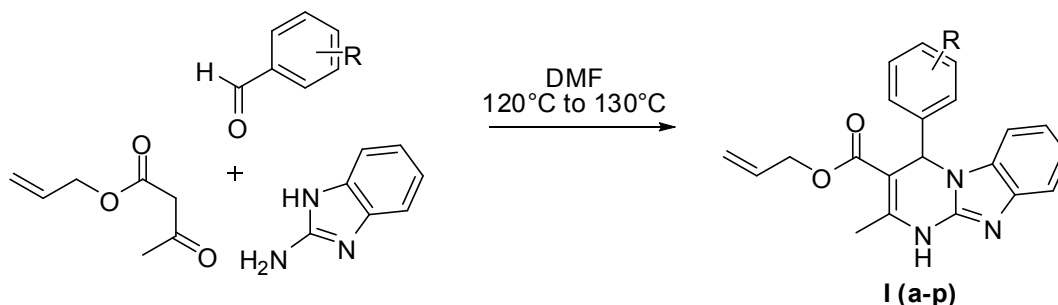
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Abstract: Imidazole is an important heterocyclic moiety in the field of medicinal chemistry and drug discovery. Imidazole is a five member ring having three carbon atoms and two nitrogen atoms out of which both the nitrogens are at first and third positions. Imidazole has wide range of therapeutic importance. Looking to the pharmacological importance of the Imidazole moiety here we have synthesized some novel derivatives of Imidazole. The newly synthesized compounds were analyzed by infrared spectroscopy, nuclear magnetic resonance and mass spectrometry techniques. The entire series of synthesized compounds was evaluated for biological activities by broth dilution method.



Keywords: Imidazole, Biological Activity, Medicinal Chemistry, Drug Discovery, Therapeutic importance

Introduction:

Imidazole is an important heterocyclic compound with the molecular formula $C_3H_4N_2$. This ring system is found to be present in many biologically active moieties, such as histidine, hormone, histamine etc. It is also found that many

drugs molecules contain an imidazole ring as a part of its structure [1-5]. Imidazole is found to present in many important bioactive molecules. The well known amino acid histidine contains imidazole as part of its structure. Imidazole is also an integral part of many pharmaceutical preparations [6].

The IUPAC name of imidazole is 1*H*-imidazole having molecular formula C₃H₄N₂. It is soluble in water and other polar solvents. Imidazole is highly polar compound having dipole moment 3.61D. It is an aromatic compound. The aromaticity of imidazole is due to presence of 6 π - electrons. One pair of electrons is from protonated nitrogen and the remaining four electrons are from the four atoms of the ring contributing one each forming aromatic sextet. It is weak base in nature. It is also found that imidazole is less basic than ammonia but more basic than pyridine. It also exhibits tautomerism property. The two tautomeric forms of imidazole are possible because the hydrogen atoms presents can be located on either of the nitrogen at position one or there [7].

Imidazole derivatives exhibit various biological activities such as anti fungal, antibacterial [8, 9], anti-inflammatory, analgesic [10, 11], anti tubercular [12, 13], anti depressant [14], anti cancer [15,16] etc. When 2-aminobenzimidazole is treated with β -keto ester along with aldehyde in one pot synthesis it will form imidazole derivative having pyrimidine ring[17-21]. This reaction is well known as Biginelli reaction. Here formed new imidazole derivatives as imidazo[1,2-*a*]pyrimidine having good to moderate antimicrobial activity [18-22].

Materials and methods:

General:All the chemicals required are obtained from Spectrochem, Finar and Sigma Aldrich. Merck Kieselgel 60F254 plates were used for TLC. The ¹H NMR spectra were recorded in DMSO d₆ on a BRUKER 400 MHz FT-NMR, with TMS as internal standard. IR Spectra were recorded on SHIMADZU FT-IR 8400 using potassium bromide pellets. Mass spectra were recorded on SHIMADZU QP-2010. The study of antimicrobial activity of newly synthesized compounds was carried out using broth dilution method for their minimum

inhibitory concentration (MIC) values.

General Procedure for the preparation of I (a-p):

Allyl-3-oxobutanoate (0.0142 mol), 2-amino benzimidazole(0.0142 mol) and different aldehydes (0.0142mol) were taken in a round bottom flask followed by the addition of dimethylformamide (DMF) (10 ml) and one drop of H₂SO₄. The reaction mass was heated at 120°C to 130° C for about one hour with constant stirring. The progress and completion of the reaction was confirmed by TLC (Mobile Phase 9:1 Methylene dichloride (MDC): Methanol and 1-2 drop of acetic acid). The reaction mixture was then poured in to ice cold water. The solid product formed was filtered and washed with water. Finally the product was re-crystallized from acetone or methanol.

Allyl 4-(4-chlorophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (Ia)

IR(cm⁻¹): 740 (Ar C-H bending), 1682 (Ar C=C bending), 1760 (COOR), 3050 (Ar C-H Stretching), NMR(DMSO, 400MHz) (δ ppm): 2.52 (3H, s), 4.47 (2H, m), 5.11 (1H, d, d, J=1.9, 8.2), 5.22 (1H, d, d, J=1.9, 8.2), 5.76 (1H, m), 6.34 (1H, s), 7.20 (4H, m), 7.40 (2H, d, J=8.4), 7.59 (2H, d, J=9.2), 10.90 (1H, s), Mass (m/z): 379.

Allyl 4-(4-bromophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (Ib)

IR (cm⁻¹): 741 (Ar C-H bending), 1685 (Ar C=C bending), 1761 (COOR), 3051 (Ar C-H Stretching), NMR(DMSO, 400MHz) (δ ppm): 2.52 (3H, s), 4.46 (2H, d, J=8.4), 5.12 (1H, d, d, J=1.9, 8.2), 5.22 (1H, d, d, J=1.9, 8.2), 5.66 (1H, m), 6.36 (1H, s), 7.12 (2H, d, J=7.9), 7.22 (2H, t, J=9.2), 7.60 (2H, d, J=7.9), 7.85 (2H, d, J=10.2), 10.90 (1H, s), Mass (m/z): 325.

Allyl 4-(4-fluorophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (Ic)

IR (cm⁻¹): 741 (Ar C-H bending), 1686 (Ar C=C bending), 1761 (COOR), 3051 (Ar C-H Stretching), NMR(DMSO, 400MHz) (δ ppm): 2.50 (3H, s), 4.47 (2H, m), 5.12 (1H, d, d, J=1.9, 8.2), 5.22 (1H, d, d, J=1.9, 8.2), 5.66 (1H, s), 6.32 (1H, s), 7.11 (2H, d, J=7.9), 7.22 (4H, m), 7.60 (2H, d, J=10.3), 11.00 (1H, s), Mass (m/z): 364.

Allyl 4-(4-nitrophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (Id)

IR (cm⁻¹): 741 (Ar C-H bending), 1686 (Ar C=C bending), 1761 (COOR), 3051 (Ar C-H Stretching), NMR(DMSO, 400MHz) (δ ppm): 2.51 (3H, s), 4.46 (2H, m), 5.11 (1H, d, d, J=1.64, 8.4), 5.22 (1H, d, d, J=1.64, 8.4), 5.66 (1H, m), 6.36 (1H, s), 7.22 (2H, t, J=9.2), 7.49 (2H, d, J=7.9), 7.60 (2H, d, J=10.2), 8.14 (2H, d, J=8.4), 10.88 (1H, s), Mass (m/z): 390.

Allyl 4-(3,4-dimethoxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (Ie)

IR (cm⁻¹): 739 (Ar C-H bending), 1684 (Ar C=C bending), 1760 (COOR), 3050 (Ar C-H Stretching), NMR(DMSO, 400MHz) (δ ppm): 2.52 (3H, s), 3.83 (6H, s), 4.50 (2H, d), 5.12 (1H, d, d, J=1.64, 8.4), 5.22 (1H, d, d, J=1.64, 8.4), 5.66 (1H, m), 6.32 (1H, s), 6.70 (1H, d, J=7.9), 6.80 (1H, d, J=10.2), 6.90 (1H, s), 7.22 (2H, t, J=9.2), 7.59 (2H, d, J=8.4), 10.92 (1H, s), Mass (m/z): 404.

Allyl 4-(2,6-dichlorophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (If)

IR(cm⁻¹): 739 (Ar C-H bending), 1684 (Ar C=C bending), 1760 (COOR), 3050 (Ar C-H Stretching), NMR(DMSO, 400MHz) (δ ppm): 2.50 (3H, s), 4.47 (2H, m), 5.12 (1H, d, d, J=1.64, 8.4), 5.22 (1H, d, d, J=1.64, 8.4), 5.66

(1H, m), 6.32 (1H, s), 7.45 (1H, t, J=9.2), 7.53 (2H, d, J=10.3), 7.22 (2H, t, J=8.4), 7.59 (2H, d, J=4.5), 10.99 (1H, s), Mass (m/z): 415.

Allyl 4-(3-bromophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (Ig)

IR (cm⁻¹): 741 (Ar C-H bending), 1686 (Ar C=C bending), 1761 (COOR), 3051 (Ar C-H Stretching), NMR(DMSO, 400MHz) (δ ppm): 2.29 (3H, s), 4.57 (2H, d), 5.28 (1H, d), 5.42 (1H, d), 5.66 (1H, s), 6.06 (1H, d), 7.22 (4H, m), 7.40 (2H, d), 7.59 (2H, d), 12.49 (1H, s), Mass (m/z): 325.

Allyl 4-(2-nitrophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (Ih)

IR (cm⁻¹): 741 (Ar C-H bending), 1686 (Ar C=C bending), 1761 (COOR), 3051 (Ar C-H Stretching), NMR(DMSO, 400MHz) (δ ppm): 2.51 (3H, s), 4.47 (2H, m), 5.12 (1H, d, d, J=1.9, 8.4), 5.22 (1H, d, d, J=1.9, 8.4), 5.60 (1H, m), 6.30 (1H, s), 7.22 (2H, t, J=10.3), 7.48 (1H, d, J=7.9), 7.52 (1H, t, J=8.4), 7.60 (2H, d, J=8.4), 7.72 (1H, t, J=9.2), 8.00 (1H, d, J=4.9), 10.92 (1H, s), Mass: (m+1) 391.

Allyl 4-(3-nitrophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (Ii)

IR (cm⁻¹): 741 (Ar C-H bending), 1686 (Ar C=C bending), 1761 (COOR), 3051 (Ar C-H Stretching), NMR(DMSO, 400MHz) (δ ppm): 2.49 (3H, s), 4.55 (2H, m), 5.18 (1H, d, d, J=1.9, 8.2), 5.24 (1H, d, d, J=1.9, 8.2), 5.88 (1H, m), 6.30 (1H, s), 7.22 (2H, t, J=9.2), 7.59 (4H, m), 8.00 (1H, d, J=5.2), 8.12 (1H, s), 11.07 (1H, s), Mass: (m+1) 391.4

Allyl 4-(2-chlorophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (Ij)

IR (cm⁻¹): 740 (Ar C-H bending), 1682 (Ar C=C bending), 1760 (COOR), 3050 (Ar C-H

Stretching), NMR(DMSO, 400MHz) (δ ppm): 2.51 (3H, s), 4.47 (2H, m), 5.12 (1H, d, d, J=1.9, 8.2), 5.22 (1H, d, d, J=1.9, 8.2), 5.56 (1H, m), 6.31 (1H, s), 7.20 (5H, m), 7.59 (2H, d, J=8.8), 7.65 (1H, d, J=5.4), 10.88 (1H, s), Mass: (m-1) 379

Allyl 4-(3-hydroxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (Ik)

IR (cm⁻¹):741 (Ar C-H bending), 1686 (Ar C=C bending), 1761 (COOR), 3051 (Ar C-H Stretching), NMR(DMSO, 400MHz) (δ ppm): 2.50 (3H, s), 4.45 (2H, m), 5.09 (1H, d, d, J=1.9, 8.4), 5.20 (1H, d, d, J=1.9, 8.4), 5.50 (1H, m), 6.30 (1H, s), 6.80 (2H, d, J=9.2), 7.00 (1H, s), 7.20 (3H, t, J=10.4), 7.60 (2H, d, J=5.4), 11.00 (1H, s), Mass: (m+1) 362.3

Allyl 4-(4-hydroxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (Il)

IR (cm⁻¹):741 (Ar C-H bending), 1686 (Ar C=C bending), 1761 (COOR), 3051 (Ar C-H Stretching), NMR(DMSO, 400MHz) (δ ppm): 2.49 (3H, s), 4.40 (2H, m), 5.10 (1H, d, d, J=1.64, 8.4), 5.21 (1H, d, d, J=1.64, 8.4), 5.40 (1H, m), 6.30 (1H, s), 6.70 (2H, d, J=10.2), 7.00 (2H, d, J=8.4), 7.22 (2H, d, J=8.2), 7.59 (2H, d, J=10.4), 10.91 (1H, s), Mass: (m+1) 362.3

Allyl 4-(4-cyanophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (Im)

IR (cm⁻¹):742 (Ar C-H bending), 1680 (Ar C=C bending), 1760 (COOR), 3050 (Ar C-H Stretching), NMR(DMSO, 400MHz) (δ ppm): 2.52 (3H, s), 4.40 (2H, m), 5.12 (1H, d, d, J=1.64, 8.2), 5.24 (1H, d, d, J=1.64, 8.2), 5.42 (1H, m), 6.29 (1H, s), 7.22 (2H, t, J=9.2), 7.41 (2H, d, J=10.3), 7.55 (4H, d, J=8.8), 11.04 (1H, s), Mass: (m+1) 371.4

Allyl 4-(4-methoxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-

3-carboxylate (In)

IR(cm⁻¹):738 (Ar C-H bending), 1685 (Ar C=C bending), 1763 (COOR), 3047 (Ar C-H Stretching), NMR(DMSO, 400MHz) (δ ppm): 2.49 (3H, s), 3.85 (3H, s), 4.42 (2H, m), 5.14 (2H, d, d, J=1.64, 8.2), 5.42 (1H, m), 6.29 (1H, s), 6.90 (2H, d, J=10.4), 7.12 (4H, m), 7.60 (2H, d, J=8.2), 10.92 (1H, s), Mass: (m+1) 376.4

Allyl 4-(3-methoxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (Io)

IR (cm⁻¹):738 (Ar C-H bending), 1685 (Ar C=C bending), 1763 (COOR), 3047 (Ar C-H Stretching), NMR(DMSO, 400MHz) (δ ppm): 2.52 (3H, s), 3.85 (3H, s), 4.40 (2H, d), 5.12 (2H, d, d, J=1.64, 8.2), 5.44 (1H, m), 6.32 (1H, s), 6.90 (2H, d, J=7.9), 7.12 (4H, m), 7.60 (2H, d, J=9.2), 10.87 (1H, s), Mass: (m+1) 376.3

Allyl 4-(4-methylphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (Ip)

IR (cm⁻¹):740 (Ar C-H bending), 1680 (Ar C=C bending), 1760 (COOR), 3052 (Ar C-H Stretching), NMR(DMSO, 400MHz) (δ ppm): 2.50 (3H, s), 2.35 (3H, s), 4.40 (2H, d, J=8.2), 5.10 (1H, d, d, J=1.64, 8.4), 5.22 (1H, d, d, J=1.64, 8.4), 5.40 (1H, m), 6.32 (1H, s), 7.11 (4H, s), 7.22 (2H, m), 7.59 (2H, m), 18.89 (1H, s), Mass: (m+1) 360.4

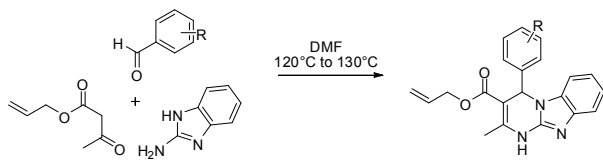
Results and Discussion:

In the present work we have prepared a new series of imidazole derivatives by Biginelli reaction. The structures of newly synthesized compounds were confirmed by IR, ¹H NMR and Mass spectral analysis. Compound **In** showed strong absorption at 739 cm⁻¹ due to aromatic C-H bending, 1616 cm⁻¹ due to aromatic C=C bending, 1685 cm⁻¹ due to alkenyl C=C stretching. Similarly for compound **In** a strong absorption observed at 1763 cm⁻¹ is due to carbonyl group of ester, 3042 cm⁻¹ due to aromatic C-H stretching.

The compound **Ia** showed singlet at 2.52 δ ppm corresponds to three protons of methyl group and singlet at 6.34 ppm for proton bonded to ipso carbon of pyrimidine ring. The mass spectrum of compound **Ic** showed the molecular ion peak at $m/z = 363$ corresponding to the molecular formula $C_{21}H_{18}FN_3O_2$.

All the synthesized compounds have been screened for antibacterial and antifungal activities by broth dilution method. From the study of the biological activity data in reference to standard drug Gentamycin for antibacterial activity and Nystatin for antifungal activity (Table-2), we found that compound **Ia** showed moderate activity against *S. aureus* and *P. aeruginosa* while compound **Ic** showed very good activity against *S. aureus* and moderate activity against *S. pyogenes*. Compound **Ig** exhibited good activity *S. aureus* while compound **Ih** showed moderate activity against *S. aureus* and good activity against *S. pyogenes*. Compound **II** found to possess moderate activity against *S. pyogenes*.

In the present study it was observed that most of the newly synthesized compounds do not possess remarkable anti-fungal activity against *C. albicans*



Scheme 1: Reaction scheme for the synthesis of the compounds I (a-p).

Table 1. Physical properties of the synthesized compounds.

Sr. No.	Compound id.	-R	Molecular Formula	Molecular Weight
1	Ia	4-Cl	$C_{21}H_{18}ClN_3O_2$	379.84
2	Ib	4-Br	$C_{21}H_{18}BrN_3O_2$	424.29
3	Ic	4-F	$C_{21}H_{18}FN_3O_2$	363.38
4	Id	4-NO ₂	$C_{21}H_{18}N_4O_4$	390.39
5	Ie	3,4-di-OCH ₃	$C_{23}H_{23}N_3O_4$	405.45
6	If	2,6-di-Cl	$C_{21}H_{17}Cl_2N_3O_2$	414.28
7	Ig	3-Br	$C_{21}H_{18}BrN_3O_2$	424.29
8	Ih	2-NO ₂	$C_{21}H_{18}N_4O_4$	390.39
9	Ii	3-NO ₂	$C_{21}H_{18}N_4O_4$	390.39
10	Ij	2-Cl	$C_{21}H_{18}ClN_3O_2$	379.84
11	Ik	3-OH	$C_{21}H_{19}N_3O_3$	361.39
12	Il	4-OH	$C_{21}H_{19}N_3O_3$	361.39
13	Im	4-CN	$C_{22}H_{18}N_4O_2$	370.40
14	In	4-OCH ₃	$C_{22}H_{21}N_3O_3$	375.42
15	Io	3-OCH ₃	$C_{22}H_{21}N_3O_3$	375.42
16	Ip	4-CH ₃	$C_{22}H_{21}N_3O_2$	359.42

Table 2. Biological activities in the terms of MIC of the synthesized compounds.

Sr. No.	Compound id	Minimum inhibitory concentration (MIC) (μ /ml)				
		Gram positive bacteria		Gram negative bacteria		Fungus
		<i>S. aureus</i> MTCC-96	<i>S. pyogenes</i> MTCC-442	<i>E. coli</i> MTCC-443	<i>P. aeruginosa</i> MTCC-1688	<i>C. albicans</i> MTCC-227
1	Ia	125	250	500	125	250
2	Ib	250	250	250	500	250
3	Ic	31.25	125	250	250	1000
4	Id	250	1000	125	500	250
5	Ie	250	500	500	1000	500
6	If	500	500	250	250	250
7	Ig	62.5	1000	500	500	500
8	Ih	125	62.5	500	500	500
9	Ii	1000	1000	1000	1000	1000
10	Ij	500	250	250	500	1000
11	Ik	1000	250	500	250	250
12	Il	1000	125	250	500	500
13	Im	500	500	500	1000	250
14	In	500	500	500	1000	500
15	Io	250	250	1000	500	500
16	Ip	500	250	250	250	1000
17	Gentamycin	0.25	0.50	0.05	1.0	-
18	Nystatin	-	-	-	-	100

S. aureus=*Staphylococcus aureus*, *S. pyogenes*=*Streptococcus pyogenes*, *E. coli*=*Escherichiacoli*, *P. aeruginosa*=*Pseudomonas aeruginosa*, *C. albicans* = *Candida albicans*. MIC= Minimum inhibitory concentration.

Conclusions:

From the present study it was found that varying the substitution in the final structure affect the biological activities. Final compounds with

fluoro, bromo and nitro groups were found to possess good antibacterial activity. It was also observed that the synthesized compounds failed to exhibit significant antifungal activity.

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