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Efficient Syntheses of Novel Substituted Imidazole Derivatives with their Antibacterial Activity

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Abstract: ***Imidazole, a five - membered heterocyclic compound containing two nitrogen atoms at non - adjacent positions, is an essential building block in both organic chemistry and biochemistry. It serves as a versatile moiety in drug design, catalysis, and materials science. Imidazole derivatives exhibit a wide range of biological activities, such as antimicrobial, anti - inflammatory, and anticancer properties. Due to their structural resemblance to histidine, imidazole compounds also play key roles in enzyme catalysis and metal ion coordination. This paper explores the synthesis, functionalization, and applications of imidazole and its derivatives, with a focus on their biochemical significance and the design of novel imidazole - based therapeutic agents. Additionally, the potential for imidazole in industrial processes, such as coordination chemistry and polymer synthesis, is discussed, highlighting its adaptability and importance in multiple fields of research. Imidazole and its derivatives have gained prominence in catalytic applications due to their ability to stabilize reactive intermediates and enhance reaction rates. The unique electronic properties of the imidazole ring make it an excellent candidate for use as a ligand in organocatalysis, as well as in metal - catalyzed reactions. Looking at the importance of this nuclei, in this study we synthesized phenyl substituted imidazole derivatives and to evaluate these derivatives for antimicrobial and antimalarial activity against plasmodium falciparum strain.***

Keywords: Imidazole, Heterocyclic Compound, Phenyl substituted imidazoles, Antimicrobial Activity

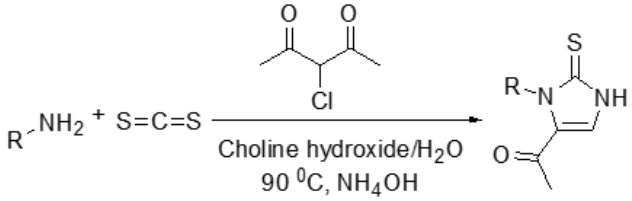
1. Introduction

The heterocyclic imidazoles are a significant class of organic compounds which occur in nature from post - translational modification of threonine and serine residues in peptides [1, 2]. They are key building blocks of natural products, pharmaceuticals, and synthetic intermediates [3 - 5]. Imidazoles have not only attracted great interest due to their appearance as subunits of various biologically active natural products but also because of their utilities as valuable precursors in many useful synthetic transformations [6]. Imidazoles play a vital role in the manufacture of various biologically active drugs as brain derived neurotrophic factor inducers [7], analgesic [8], trypanocidal activity [9], antimitotic agents with pro - apoptotic activity [10]. Over the years, a number of methods have been devised for the synthesis of imidazoles [11]. Classically, the cyclic thiourea synthesis was the most common route to imidazole, which involves cyclisation of 2, 3 - dihydro - 4 - methyl - 2 - thioxo - 1H - imidazolyl) ethenone [12].

In recent decades, microbial diseases are more prevalent than they were during the first half of the last century and are still difficult to be diagnosed clinically. To combat them, various synthetic and semi - synthetic antimicrobial drugs have been used in clinical practice [13, 14]. Aromatic and heterocyclic compounds have been reported to exhibit antimicrobial behavior [15 - 18]. But, in the treatment of microbial infections only limited numbers of efficacious antimicrobial drugs are used even after availability of a number of antimicrobial agents. Many of the currently available drugs are toxic, enable recurrence because they are bacteriostatic/fungistatic and not bactericidal/fungicidal or lead to the development of resistance due in part to the prolonged periods of administration. The impact is more acute in developing countries due to non - availability of desired medicines [19, 20]. There is a real perceived need for the discovery of new compounds that are endowed with antibacterial and antifungal activities, possibly acting through mechanism of actions, which are distinct from those of well - known classes of antimicrobial agents to which many clinically relevant pathogens are now resistant [21 - 23].

The derivatives of Imidazole have become increasingly important in the past few years because of their use in intermediates for the preparation of new biological materials. The imidazole ring is present in numerous pharmacologically important compounds, including those used as antibiotics [24] and antiproliferative [25]. The wide range of biological activities of imidazoles includes anti - inflammatory [26], analgesic [27], antibacterial, antifungal [28], hypoglycaemic [29], antiproliferative [30], anti - tuberculosis [31], muscle relaxant [32] and HIV inhibitor activity. [33] In addition, imidazole derivatives are useful synthetic intermediates and can be used as diversity scaffolds in combinatorial chemistry [34] and also as peptidomimetics. [35] Standard drugs used in some of the medicinally important derivatives containing imidazole are Trimethadione etc. which possess antiepileptic [36] properties. The imidazole derivatives have raised considerable attention to medicinal research, and a large number of investigations on their synthesis and biological activities have been reported during the last ten years [37 - 39].

Looking at the importance of these heterocyclic nuclei, it is thought of interest to devote some attention for the synthesis of phenyl substituted imidazole derivatives and to evaluate these derivatives for antimicrobial and antimalarial activity against *plasmodium falciparum* strain.



Scheme: Synthesis of Imidazole derivatives
Various compounds will be synthesized in accordance with the above scheme.

Table 1: Synthesis of 2 - thioxo - 1H - imidazoles of general formula

Compound No.	M. Formula	R	M. Point (ºC)	Time (h)	Yield (%)
1	$C_{16}H_{20}N_2OS$	4 - Tert - butyl phenyl	135 - 140	16	65.1
2	$C_{12}H_{10}F_2N_2OS$	2, 4 - Difluoro phenyl	132 - 135	16	63.3
3	$C_{14}H_{16}N_2OS$	2, 3 - Dimethyl phenyl	133 - 134	16	67.1
4	$C_{15}H_{18}N_2OS$	4 - Isopropyl phenyl	131 - 133	16	64.2
5	$C_{14}H_{10}F_6N_2OS$	3, 5 - Trifluoromethyl phenyl	115 - 117	16	50.2
6	$C_{12}H_{10}F_2N_2OS$	3, 4 - Difluoro phenyl	120 - 122	16	50.1
7	$C_{13}H_{13}ClN_2OS$	3 - Chloro - 4 - methyl phenyl	134 - 136	16	54.8
8	$C_{12}H_{11}FN_2OS$	2 - Fluoro phenyl	135 - 137	16	53.7
9	$C_{14}H_{16}N_2OS$	2, 4 - Dimethyl phenyl	130 - 132	16	65.3
10	$C_{13}H_{14}N_2OS_2$	4 - (Methyl thio) phenyl	129 - 131	16	67.3
11	$C_{13}H_{11}F_3N_2OS$	3 - Trifluoromethyl phenyl	116 - 118	16	55.2

2. Experimental

All the Chemicals bought from GLR, AVRA, Alfa - Aesar and Lobachem, Finar, Labchem high purity LR grade solvents. Reactions were done under inert atmosphere of argon gas. ABB Bomem MB - 104 - FTIR spectrophotometer was used for recording infrared spectra (4000 - 200 cm^{-1}). The AC - 400F - NMR spectrometer, with Me_4Si as internal standard was used for recording ^{1}HNMR spectra at 400 MHz. The investigation of elements were conveyed with the help of an 1110 - CNNO - S (Carlo - Erba EA) analyzer. There is good covenant between observed and considered values.

General procedure: A solution of amine **1** (1.0 mmol), **2** CS_2 (1.5 mmol) in **3** ammonium hydroxide solution 28% in NH_3 (2.0 mmol), was stir at normal temperature for 15 minute. Formerly Triton - B (1.5 mmol) was additional and again stir for additional 30 minutes, then 3 - chloro - 2, 4 - pentanedione **4** (1.0 mmol) was dropwise added at room temperature. The reaction mass was reflux at 80ºC for 2 hours. The TLC technique was used for observing the progress of reaction. When the reaction was achieved, added a small volume of water and extracted the product thrice by adding 30 mL of $CH_3CO_2C_2H_5$. The crude product was recovered from organic layer after separating and washing it with saturated brine followed by drying and purification $CH_3CO_2C_2H_5$: n - C_6H_{14} (1: 5) as eluent to givefinal general formula **5**.

Spectral data analysis of the synthesized compounds

1 - (1 - (4 - tert - butylphenyl) - 4 - methyl - 2, 3 - dihydro - 2 - thioxo - 1H - imidazol - 5 - yl) ethanone (1):
Pale yellow solid, Melting point: 135 - 140ºC, Molecular formula: $C_{16}H_{20}N_2OS$, Calculated elemental analysis (%): H = 6.99, C = 66.63, O = 5.55, N = 9.71, S = 11.12. Observed (%): H = 7.03, C = 66.93, N = 9.81, O = 5.75, S = 11.22.1HNMR 400MHz ($CDCl_3$): δ 7.881 (broad singlet, 1H), 7.422 (doublet, 2H, *J* = 6.8 Hz), 7.240 (singlet, 2H), 2.588 (singlet, 3H), 2.445 (singlet, 3H), 1.326 (singlet, 9H). MS (Electrospray ionisation): *m/e* $[M]^+$ calculated = 288.41, Found $[M - 1]^{-:}$ 287.40.

1 - (1 - (2, 4 - difluorophenyl) - 4 - methyl - 2, 3 - dihydro - 2 - thioxo - 1H - imidazol - 5 - yl) ethanone (2):
Pale yellow solid, Melting point: 132 - 135ºC, Molecular formula: $C_{12}H_{10}F_2N_2OS$, Calculated elemental analysis (%): C = 53.72, H = 3.76, F = 14.16, N = 10.44, O = 5.96, S = 11.95. Observed (%): C = 53.92, H = 3.86, F = 14.24, N = 10.52, O = 7.82, S = 14.95.1HNMR 400MHz ($CDCl_3$): δ 7.881 (broad singlet, 1H), 7.896 - 7.816 (multiplet, 2H), 6.848 (singlet, 1H), 2.589 (singlet, 3H), 2.455 (singlet, 3H). MS (Electrospray ionisation): *m/e* $[M]^+$ calculated = 268.28, Found $[M - 1]^{-:}$ 267.21.

1 - (2, 3 - dihydro - 4 - methyl - 1 - (2, 3 - dimethylphenyl) - 2 - thioxo - 1H - imidazol - 5 - yl) ethanone (3):
Pale yellow solid, Melting point: 133 - 134ºC, Molecular formula: $C_{14}H_{16}N_2OS$, Calculated elemental analysis (%): H = 6.19, C = 64.58, N = 10.76, O = 6.15, S = 12.32. Observed (%): H = 6.05, C = 64.62, N = 13.76, O = 7.53, S = 14.32.1HNMR 400MHz ($CDCl_3$): δ 8.282 (broad singlet, 1H), 7.291 (doublet, 1H, *J* = 7.2 Hz), 7.179 (triplet, 1H, *J* = 7.6 Hz), 7.133 (doublet, 1H, *J* = 7.2 Hz), 2.503 (singlet, 3H), 2.373 (singlet, 3H), 2.337 (singlet, 3H), 2.23 (singlet, 3H). MS (Electrospray ionisation): *m/e* $[M]^+$ calculated = 260.35, Found $[M - 1]^{-:}$ 259.05.

1 - (2, 3 - dihydro - 1 - (4 - isopropylphenyl) - 4 - methyl - 2 - thioxo - 1H - imidazol - 5 - yl) ethanone (4):
Off white solid, Melting point: 131 - 133ºC, Molecular formula: $C_{15}H_{18}N_2OS$, Calculated elemental analysis (%): H = 6.61, C = 65.66, N = 10.21, O = 5.83, S = 11.69. Observed (%): H = 6.51, C = 65.72, N = 10.02, O = 6.52, S = 14.62.1HNMR 400MHz ($CDCl_3$): δ 8.282 (broad singlet, 1H), 7.272 (doublet, 1H, *J* = 8.0 Hz), 6.885 (doublet, 1H, *J* = 4.4 Hz), 6.846 (doublet, 1H, *J* = 6.4 Hz), 6.689 (doublet, 1H, *J* = 6.4 Hz), 4.598 - 4.507 (multiplet, 1H), 2.580 (singlet, 3H), 2.452 (singlet, 3H), 1.354 (doublet, 6H, *J* = 7.6 Hz). MS (Electrospray ionisation): *m/e* $[M]^+$ calculated = 274.38, Found $[M - 1]^{-:}$ 273.35.

1 - (1 - (3, 5 - bis (trifluoromethyl) phenyl) - 4 - methyl - 2, 3 - dihydro - 2 - thioxo - 1H - imidazol - 5 - yl) ethanone (5):
Pale yellow solid, Melting point: 115 - 117ºC, Molecular formula: $C_{14}H_{10}F_6N_2OS$, Calculated elemental analysis (%): C = 45.66, H = 2.74, F = 30.95, N = 7.61, O = 4.34, S = 8.71. Observed (%): C = 45.21, H = 2.52, F = 32.91, N = 9.64, O = 5.59, S = 10.71.1HNMR 400MHz ($CDCl_3$): δ

8.282 (broad singlet, 1H), 7.988 (singlet, 1H), 7.818 (singlet, 1H), 7.587 (singlet, 1H), 2.567 (singlet, 3H), 2.511 (singlet, 3H). MS (Electrospray ionisation): *m/e* $[M]^+$ calculated = 368.3, Found $[M - 1]^{-:}$ 367.05.

1 - (1 - (3, 4 - difluorophenyl) - 4 - methyl - 2, 3 - dihydro - 2 - thioxo - 1H - imidazol - 5 - yl) ethanone (6):
Pale yellow solid, Melting point: 120 - 122ºC, Molecular formula: $C_{12}H_{10}F_2N_2OS$, Calculated elemental analysis (%): C = 53.72, H = 3.76, F = 14.16, N = 10.44, O = 5.96, S = 11.95. Observed (%): H = 3.36, C = 53.72, F = 12.26, O = 6.97, N = 13.52, S = 13.97.1HNMR 400MHz ($CDCl_3$): δ 7.976 (broad singlet, 1H), 7.407 - 7.354 (multiplet, 1H), 7.216 - 7.148 (multiplet, 1H), 7.074 - 7.032 (multiplet, 1H), 2.590 (singlet, 3H), 2.463 (singlet, 3H). MS (Electrospray ionisation): *m/e* $[M]^+$ calculated = 268.28, Found $[M - 1]^{-:}$ 267.21.

1 - (1 - (3 - chloro - 4 - methylphenyl) - 4 - methyl - 2, 3 - dihydro - 2 - thioxo - 1H - imidazol - 5 - yl) ethanone (7):
Off white solid, Melting point: 134 - 136ºC, Molecular formula: $C_{13}H_{13}ClN_2OS$, Calculated elemental analysis (%): H = 4.67, C = 55.61, Cl =12.63, O = 5.70, N = 9.98, S = 11.42. Observed (%): H = 4.71, C = 55.61, Cl =16.53, O = 5.63, N = 10.65, S = 13.47.1HNMR 400MHz ($CDCl_3$): δ 8.690 (broad singlet, 1H), 7.374 (singlet, 1H), 7.253 (doublet, 1H, *J* = 8.4 Hz), 7.151 (doublet, 1H, *J* = 6.0 Hz), 2.559 (singlet, 3H), 2.450 (singlet, 3H), 2.364 (singlet, 1H). MS (Electrospray ionisation): *m/e [*$M]^+$ calculated = 280.88, Found $[M - 1]^{-:}$ 279.85.

1 - (1 - (2 - fluorophenyl) - 4 - methyl - 2, 3 - dihydro - 2 - thioxo - 1H - imidazol - 5 - yl) ethanone (8):
Off white solid, Melting point: 135 - 137ºC, Molecular formula: $C_{12}H_{11}FN_2OS$, Calculated elemental analysis (%): H = 4.43, C = 57.58, N = 11.19, F = 7.59, O = 6.39, S = 12.81. Observed (%): H = 4.72, C = 57.78, F = 7.95, O = 6.79, N = 13.52, S = 15.92.1HNMR 400MHz ($CDCl_3$): δ 7.886 (triplet, 1H, *J* = 8.4 Hz), 7.675 (broad singlet, 1H), 7.225 - 7.133 (multiplet, 2H), 7.144 - 7.063 (multiplet, 1H), 2.631 (singlet, 3H), 2.480 (singlet, 3H). MS (Electrospray ionisation): *m/e* $[M]^+$ calculated = 250.29, Found $[M - 1]^{-:}$ 249.05.

1 - (2, 3 - dihydro - 4 - methyl - 1 - (2, 4 - dimethylphenyl) - 2 - thioxo - 1H - imidazol - 5 - yl) ethanone (9):
Off white solid, Melting point: 130 - 132ºC, Molecular formula: $C_{14}H_{16}N_2OS$, Calculated elemental analysis (%): H = 6.19, C = 64.58, N = 10.76, O = 6.15, S = 12.32. Observed (%): H = 6.92, C = 64.75, N = 10.83, O = 6.45, S = 12.45.1HNMR 400MHz ($CDCl_3$): δ 8.454 (broad singlet, 1H), 7.317 (doublet, 1H, *J* = 8.0 Hz), 7.113 (singlet, 1H), 7.083 (doublet, 1H, *J* = 8.0 Hz), 2.477 (singlet, 3H), 2.366 (singlet, 3H), 2.346 (singlet, 3H), 2.277 (singlet, 3H). MS (Electrospray ionisation): *m/e* $[M]^+$ calculated = 260.35, Found $[M - 1]^{-:}$ 259.05.

1 - (2, 3 - dihydro - 4 - methyl - 1 - (4 - (methylthio) phenyl) - 2 - thioxo - 1H - imidazol - 5 - yl) ethanone (10):
Off white solid, Melting point: 129 - 132ºC, Molecular formula: $C_{13}H_{14}N_2OS_2$, Calculated elemental analysis (%): H = 5.07, C = 56.09, O = 5.75, N = 10.06, S = 23.04. Observed (%): H = 5.25, C = 56.23, N = 10.37, S = 23.33, O = 5.94.1HNMR 400MHz ($CDCl_3$): δ 8.454 (broad singlet, 1H), 7.355 (doublet, 2H, *J* = 6.8 Hz), 7.147 (doublet, 2H, *J* = 6.8 Hz), 2.543 (singlet, 3H), 2.141 (singlet, 3H), 1.993 (singlet, 3H). MS (Electrospray ionisation): *m/e* $[M]^+$ calculated = 279.39, Found $[M - 1]^{-:}$ 278.05.

1 - (1 - (3 - (trifluoromethyl) phenyl) - 4 - methyl - 2, 3 - dihydro - 2 - thioxo - 1H - imidazol - 5 - yl) ethanone (11):
Pale yellow solid, Melting point: 116 - 118ºC, Molecular formula: $C_{13}H_{11}F_3N_2OS$, Calculated elemental analysis (%): C = 51.99, H = 3.69, F = 18.98, N = 9.33, S = 10.68, O = 5.33. Observed (%): H = 3.85, C = 52.35, F = 19.32, N = 9.51, O = 5.74, S = 12.13.1HNMR 400MHz ($CDCl_3$): δ 7.933 (broad singlet, 1H), 7.649 (singlet, 1H), 7.604 (doublet, 1H, *J* = 8.0 Hz), 7.519 (triplet, 1H, *J* = 8.0 Hz), 7.384 (doublet, 1H, *J* = 7.6 Hz), 2.620 (singlet, 3H), 2.484 (singlet, 3H). MS (Electrospray ionisation): *m/e* $[M]^+$ calculated = 300.3, Found $[M - 1]^{-:}$ 299.05.

Antimicrobial activity
Due to the resistance of the bacteria and fungiagainst marketed drugs there is always need for the better chemotherapeutic drugs againstthem. The synthesized compounds were screened against 04 bacterial and 03 fungal stains which include*Streptococcus pyogenes (*MTCC 442), *Staphylococcus aureus (*MTCC96), *Pseudomonas aeruginosa (*MTCC1688), *Escherichia coli (*MTCC 443), *Candida albicans (*MTCC 227), *Aspergillus clavatus* (MTCC 1323) and *Aspergillus niger* (MTCC 282) for antimicrobial activities employing existing drugs*Chloramphenicol and Nystatin*as positive control**.**

Antimicrobial activity of synthesized compounds: The MIC of the synthesized compounds was determined using Andrew's micro dilution tube andcompared with standard drugs, as positive control, and pure Dimethyl sulfoxide as negative control. The MIC values were obtained from observed turbidity in inoculated tubes.

Antimicrobial results: The antimicrobial activity against the bacterial fungal stainsare illustrated in **Table - 2**.

Table 2: Antimicrobial potency in terms of MIC (µg/mL) using micro dilutions

Compounds	E. coli	S. pyogenus	S. aureus	A. niger	P. aeruginosa	C. albicans	A. clavatus
1	700	90	90	800	387	890	890
2	210	490	240	390	396	190	>1100
3	190	480	140	>1100	246	980	900
4	55	115	90	486	128	>1100	>1100
5	490	185	190	>900	510	486	>1100
6	290	480	185	790	90	487	980
7	89	230	55	498	245	280	400
8	498	468	480	>1100	198	470	>900
9	95	90	480	>1100	246	980	1100
10	98	240	460	990	494	990	>1200
11	580	230	480	970	465	970	>800
Chloram - phenicol	48	48	48	48	---	---	---
Nystatin	---	---	---	---	95	95	95

It was found that Compound **7** exhibited MIC of 55µg/mL which was lowest among all synthesized compounds, so it is most effective against *S. aureus (*Gram - positive bacteria) whereas compound **4** exhibitedbetter activity against Gram - negative bacteria, *E. coli* with MIC of 55.0 µg/mL. Compound **2** effective against yeast (*C. albicans, A. niger)* where its MIC values are190 and 390µg/mL respectively. Compounds **6** an**d 9** exhibited MIC of 90µg/mLwhenn screened against yeast *S. pyogenus and P. aeruginosa*both. Compound **7** exhibited MIC of 400µg/mL against yeast A. *clavatus.* All of the synthesized compounds are active against the fungal and bacterial stains considered.

3. Conclusion

We have developed an efficient methods one pot synthesis of 2 - thioxo - 1H - imidazole derivatives of four - components coupling reaction of different primary amines, aqueous NH_3, with 3 - chloro - pentane - 2, 4 - dione*via* CS_2/Triton - B system. Thus, we have reported a new method for the synthesis of synthons containing C - S linkage. The synthesized compounds were screened for antimicrobialactivity. The data in this**Table - 2** specify that amongst the synthesized compounds**2**, **4**, **7**and **9** are showing good to excellent antibacterial activity. Compounds **2**, **6** and **7**are showing good to excellent antifungal activity (**Table 2**). All the compounds are result of numerous biological actions that is strong these compounds would be improved usage in drug improvement to contest antimicrobial agents in the future.

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