SYNTHESIS AND STRUCTURE ELUCIDATION OF SOME BIOLOGICAL ACTIVE 3H-IMIDAZO[1,2-b]PYRAZOLE DERIVATIVES

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***Abstract*— Due to marvelous biological activity of 3H-imidazo[1,2-b]pyrazole heterocyclic compounds, in the preset work some new 3H-imidazo[1,2-b]pyrazole derivatives have been synthesized by multi step process. For the structure elucidation of all these synthesized compounds was carried out by different analytical techniques such as ^{1}H nuclear magnetic resonance, infrared and mass spectrometry. The antibacterial activity of these synthesized compounds was also tested against some gram positive and gram negative bacterial strains in *N,N*-dimethyl formamide and dimethyl sulphoxide solvents. The antifungal activity was also tested against some selected fungal strains in same solvents.**

***Keywords*—3H-imidazo[1,2-b]pyrazole, antibacterial activity, antifungal activity, *N,N*-dimethyl formamide and dimethyl sulphoxide etc.**

I. INTRODUCTION

The heterocyclic compounds contain nitrogen as heteroatom shows marvelous activities in field of medical (Chaudhari *et al*., 2016). Many naturally occurring compounds possess five/ six member ring having one or more nitrogen atoms present in the ring (Mermer *et al*., 2021). Pyrazoles are one of them five member heterocyclic compounds which show some marvelous biological and pharmaceutical activities (Faria *et al*., 2017, Iglesias *et al*., 2019). It is one of the nitrogen based heterocyclic compounds occur in the nature as well as synthesized in laboratories (Tingting *et al.,* 2018). A huge variety of synthesis methods and synthesis analogus of pyrazole derivatives has been reported over the year. The presence of the pyrazole nucleus in different structures leads to diversified applications in different areas such as technology, medicine and agriculture (Mohd *et al*., 2016, Prasanna *et al*., 2015, Hira *et al*., 2020).

The biological activities are further enhanced when two or more than two heterocyclic rings fused with each other (Nagaraju *et al*., 2020, Verma *et al*., 2013). Imidazo[1,2-b]pyrazole is one of the heterocyclic compounds of two fused ring pyrazole and imidazole. Both rings are five members and bearing two nitrogen atoms as heteroatoms.

Last few decades, an Imidazo[1,2-b]pyrazole scaffold has been attracting much attention of many scientists due to their considerable biological and pharmaceutical activities. In the present work, some novel imidazo[1,2-b]pyrazole have been synthesized by multi step process and the structure conformation was carried out by different spectroscopic techniques. Further, anti microbial activity of imidazo[1,2-b]pyrazole derivatives was checked against some selected bacterial and fungal strains in two different solvents.

II. METHODS

A. Spectroscopy study

For the structure confirmation of all the synthesized compounds, some analytical spectroscopic techniques such as infra red (IR), Proton magnetic resonance (^{1}H NMR) and mass analysis were used. For the Infra red spectrum, furrier transport infrared spectrophotometer (IRaffinity-1S SHIMADZU) was used. The IR spectrum was done in moisture free atmosphere. The proton spectrum of all the synthesized compounds was recorded on a Bruker AVANCE III (working over 400 MHz frequencies). For the ^{1}H NMR spectrum, solution of compounds was prepared in Deuterated dimethyl sulphoxide (DMSO-d6) solvent and tetra methylsilane was used as reference material. Mass spectra were determined using direct inlet probe on a SHIMADZU GC-MS (Model-QP2010) mass spectrometer.

B. Chemicals

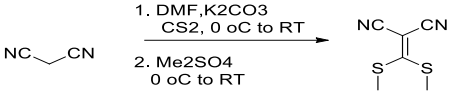
The chemicals used for the synthesis such as different substituted acetophenone, malonitrile, carbon sulphide were purchased from Spectrochem Pvt. Ltd. and were used direct without further any purification. Different solvents such as *N,N*-dimethyl formamide (DMF), dimethyl sulphoxide (DMSO), isopropyl alcohol (IPA) etc., were purchased from Sigma Aldrich Pvt. Ltd.

C. Preparation of 3H-imido[1,2-b]pyrazole derivatives:

(a) *Synthesis of 2-(bis(methylthio)methelene c)malanonitrile (INT-A):*

A 100ml conical flask equipped with magnetic stirrer and septum was charged with a solution of malononitrile (10 mmol) in DMF (10 mL). To this dry K_2CO_3 (10 mmol) was added and the mixture was stirred at room temperature for 2 hours. Then carbon sulphide (CS_2) (30 mmol) was added drop wise and the mixture was stirred for an additional 2 hours at room temperature. Cool the reaction mixture into ice bath 0-5 ^oC and to this methyl iodide (20 mmol) was added drop wise into mixture at 0-5 ^oC. The mixture was stirred for 4 hours at room temperature. The progress of the reaction was monitored by thin layer chromatography using hexane: ethyl acetate (5:5 % v/v) mobile phase. After completion of the reaction, it was

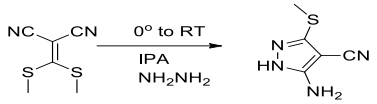
poured into 50ml cold water. The precipitated crude product was purified by filtration followed by crystallization from ethanol (Ajudiya *et al.*, 2019).



INT-A

(b) ***Synthesis of 2-amino-4-(methylthio)-1H-pyrrole-3-carbonitrile (INT-B).***

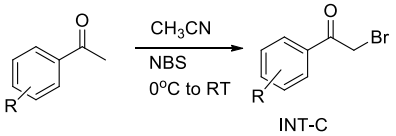
A 100 ml conical flask equipped with magnetic stirrer and septum was charged solution of 2-(bis(methylthio) methelene)malanonitrile (INT-A) (0.1 mmol) in isopropyl alcohol (100mL). Cool the reaction mixture at 0º C temperature and then add hydrazine hydrate (0.1 mmol). The reaction mixture was stirred to room temperature (RT) for 2 hours. After completion of the reaction, it was poured into 50mL cold water. The precipitated crude product was purified by filtration followed by crystallization from ethanol (Ajudiya *et al.*, 2019).



INT-A INT-B

(c) ***General method for the synthesis of 2-bromo-1-phenylethanone derivatives (INT-C)***

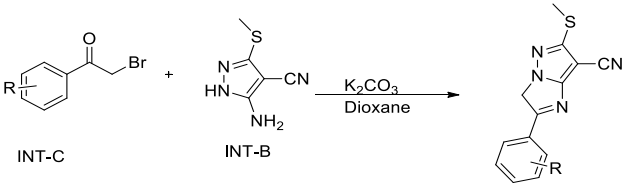
In a round bottom flask, various substituted acetophenon (0.01 mmol), acetonitrile (10 ml) and catalytic amount of p-toluene sulphonic acid was taken. The resulted reaction mixture was cooled up to 0ºC temperature in ice bath and to this solution of N-bromosuccinamide (0.011 mmol) in acetonitrile was added portion wise and stir the reaction mixture for further 15 min. (Borzęcka W *et al*., 2013). After complete addition, raise the temperature of reaction mixture up to room temperature (RT). The reaction progress was checked through the preparative thin layer chromatography using hexane: ethyl acetate (3:7 % v/v) mobile phase. After completion of the reaction, reaction mixture was poured into the crushed ice and extracted with dichloro methane. The organic layer was washed with brine solution, dried over sodium sulphate and concentrated under reduced pressure to get INT-C as a dry solid.



INT-C

(d) ***General synthesis of final compound 3H-imido[1,2-b]pyrazole derivatives:***

Prepare a solution of INT-B (5 mmol) and-bromoacetophenone (5 mmol) in 20 mL of dioxane solvent. To this dry K_2CO_3 (10mmol) was added and mixture was refluxed for 4-6 hours. The reaction progress



INT-C INT-B

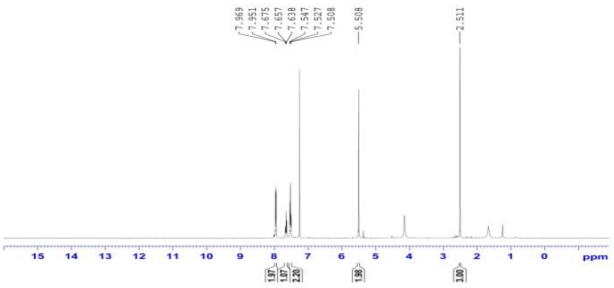


Figure 1: ^{1}H NMR spectrum of JMP-1

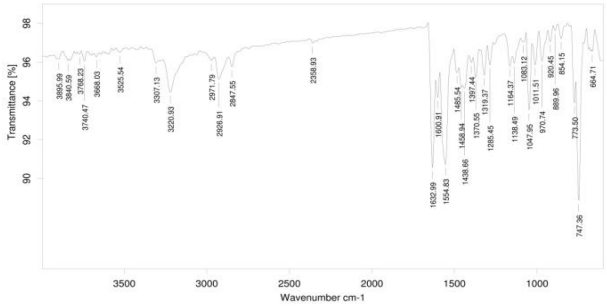


Figure 2: IR spectrum of JMP-1

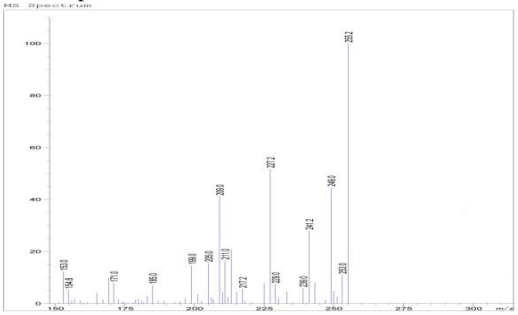


Figure 3: Mass spectrum of JMP-1

was checked through the preparative thin layer chromatography using chloroform: methanol (8:2 % v/v) mobile phase. After completion of the reaction, it was poured into 100 mL cold water. The precipitated crude product was filtered and dried. The purification of desired compounds was carried out by column chromatography using appropriate mobile phase.

(e) Spectral data

JMP-1

^{1}H NMR (DMSO-d6, proton shift value δ ppm): 2.511 (3H, singlet, -SCH_3), 5.508 (2H, singlet, -CH_2-), 7.508-7.547 (2H, triplet, Ar-H), 7.638-6.675 (1H, triplet, Ar-H), 7.951-7.969 (2H, doublet, Ar-H).

IR (cm^{-1}): 2926.91, 2847.51 (C-H stretching alkane), 2358.93 (-CN stretching), 1632.99, 1600.91, 1554.83 (-C=C- stretching cyclic alkenes), 1285.45, 1138.49, 1047.95 (C-N stretching), 970.74 (-C=C- bending alkene).

m/z: 255 (m+1).

Table 1: Some physical data of all the synthesized compounds

Sr. No.	Compound Code	Substitution (R)	Molecular formula	Molecular weight	R_f value	% yield
1	JMP-1	-H	$C_{13}H_{10}N_4S$	254.31	0.56	45
2	JMP-2	2-Br	$C_{13}H_9N_4SBr$	333.21	0.75	58
3	JMP-3	4-Br	$C_{13}H_9BrN_4S$	333.21	0.76	57
4	JMP-4	4-Cl	$C_{13}H_9N_4SCl$	288.76	0.79	62
5	JMP-5	2-Cl	$C_{13}H_9N_4SCl$	288.76	0.80	61
6	JMP-6	2,4-diCl	$C_{13}H_8N_4SCl_2$	323.60	0.84	64
7	JMP-7	4-CH_3	$C_{14}H_{12}N_4S$	268.34	0.48	43
8	JMP-8	2-CH_3	$C_{14}H_{12}N_4S$	268.34	0.51	47
9	JMP-9	2,4-Di CH_3	$C_{15}H_{14}N_4S$	282.36	0.52	45
10	JMP-10	4-OCH_3	$C_{14}H_{12}N_4SO$	284.34	0.59	51

*Mobile phase= chloroform: methanol (8:2 % v/v)

JMP-2

^{1}H NMR (DMSO-d6, proton shift value δ ppm): 2.505 (3H, singlet, -SCH_3), 5.512 (2H, singlet, -CH_2-), 7.514-7.529 (1H, doublet, Ar-H), 7.601-6.637 (2H, triplet, Ar-H), 7.829-7.847 (1H, doublet, Ar-H).

IR (cm^{-1}): 2923.57, 2851.46 (C-H stretching alkane), 2353.78, 2312.88 (-CN stretching), 1629.56, 1605.22, 1551.03 (-C=C- stretching cyclic alkenes), 1281.48, 1132.87, 1045.39 (C-N stretching), 972.68 (-C=C- bending alkene).

m/z: 334 (m+1).

JMP-3

^{1}H NMR (DMSO-d6, proton shift value δ ppm): 2.487 (3H, singlet, -SCH_3), 5.448 (2H, singlet, -CH_2-), 7.511-7.527 (2H, doublet, Ar-H), 7.856-7.877 (2H, doublet, Ar-H).

IR (cm^{-1}): 2928.92, 2848.03 (C-H stretching alkane), 2352.73, 2316.02 (-CN stretching), 1622.99, 1604.72, 1550.67 (-C=C- stretching cyclic alkenes), 1283.92, 1134.69, 1042.59 (C-N stretching), 975.84 (-C=C- bending alkene), 757.38, 710.57, 633.84 (C-Br stretching).

m/z: 334 (m+1).

JMP-4

^{1}H NMR (DMSO-d6, proton shift value δ ppm): 2.516 (3H, singlet, -SCH_3), 5.478 (2H, singlet, -CH_2-), 7.539-7.557 (2H, doublet, Ar-H), 7.689-7.711 (2H, doublet, Ar-H).

IR (cm^{-1}): 2911.46, 2837.49, 2802.93 (C-H stretching alkane), 2351.59, 2312.69 (-CN stretching), 1623.69, 1603.59, 1553.82 (-C=C- stretching cyclic alkenes), 1283.79, 1131.40, 1041.47 (C-N stretching), 974.39 (-C=C- bending alkene), 756.67, 750.37 (C-Cl stretching).

m/z: 289 (m+1).

JMP-5

^{1}H NMR (DMSO-d6, proton shift value δ ppm): 2.521 (3H, singlet, -SCH_3), 5.483 (2H, singlet, -CH_2-), 7.489-7.517 (1H, doublet, Ar-H), 7.595- 7.631 (2H, doublet, Ar-H), 7.821-7.842 (1H, doublet, Ar-H).

IR (cm^{-1}): 2917.39, 2846.29 (C-H stretching alkane), 2357.29, 2311.49 (-CN stretching), 1627.27, 1604.52, 1555.19 (-C=C- stretching cyclic alkenes), 1282.98, 1137.29, 1046.30 (C-N stretching), 972.68 (-C=C- bending alkene), 753.78, 753.07 (C-Cl stretching).

m/z: 289 (m+1).

JMP-6

^{1}H NMR (DMSO-d6, proton shift value δ ppm): 2.523 (3H, singlet, -SCH_3), 5.521 (2H, singlet, -CH_2-), 7.616-7.635 (1H, doublet, Ar-H), 7.711-7.729 (1H, doublet, Ar-H), 8.104 (1H, singlet, Ar-H).

IR (cm^{-1}): 2922.46, 2842.58 (C-H stretching alkane), 2352.59, 2314.92 (-CN stretching), 1624.94, 1608.39, 1554.19 (-C=C- stretching cyclic alkenes), 1285.39, 1134.68, 1044.29 (C-N stretching), 972.32 (-C=C- bending alkene), 750.38, 752.49, 710.95 (C-Cl stretching).

m/z: 324 (m+1).

JMP-7

^{1}H NMR (DMSO-d6, proton shift value δ ppm): 1.178 (3H, singlet, -CH_3), 2.511 (3H, singlet, -SCH_3), 5.518 (2H, singlet, -CH_2-), 7.114-7.132 (1H, doublet, Ar-H), 7.204- 7.223 (1H, doublet, Ar-H), 7.431-7.468 (2H, triplet, Ar-H).

IR (cm^{-1}): 2917.38, 2840.33, 2810.47 (C-H stretching alkane), 2353.58, 2313.59 (-CN stretching), 1623.59, 1605.69, 1552.40 (-C=C- stretching cyclic alkenes), 1282.06, 1132.49, 1045.04 (C-N stretching), 971.48 (-C=C- bending alkene).

m/z: 269 (m+1).

JMP-8

^{1}H NMR (DMSO-d6, proton shift value δ ppm): 1.238 (3H, singlet, -CH_3), 2.482 (3H, singlet, -SCH_3), 5.477 (2H, singlet, -CH_2-), 7.315-7.337 (2H, doublet, Ar-H), 7.454- 7.481 (2H, doublet, Ar-H).

IR (cm^{-1}): 2250.76, 2921.03, 2844.28, 2805.41 (C-H stretching alkane), 2355.29, 2315.20 (-CN stretching), 1625.20, 1607.82, 1554.38 (-C=C- stretching cyclic alkenes), 1281.49, 1135.93, 1047.26 (C-N stretching), 976.29 (-C=C- bending alkene).

m/z: 269 (m+1).

JMP-9

^{1}H NMR (DMSO-d6, proton shift value δ ppm): 1.167 (3H, singlet, -CH_3), 1.201 (3H, singlet, -CH_3), 2.489 (3H, singlet, -SCH_3), 5.493 (2H, singlet, -CH_2-), 7.198 (1H, singlet, Ar-H), 7.441-7.459 (1H, doublet, Ar-H), 7.711-7.732 (1H, doublet, Ar-H).

IR (cm^{-1}): 2255.26, 2923.29, 2844.01, 2802.46 (C-H stretching alkane), 2353.67, 2317.71 (-CN stretching), 1623.87, 1608.28, 1551.38 (-C=C- stretching cyclic alkenes), 1286.29, 1134.44, 1041.30 (C-N stretching),

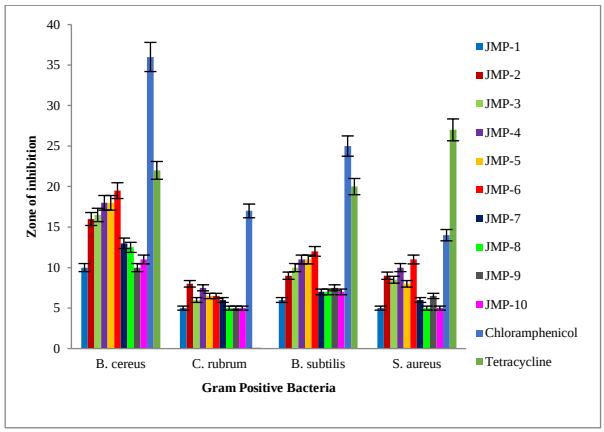


Figure 4: Zone of inhibition against gram positive bacterial strains in *N,N*-dimethyl formamide

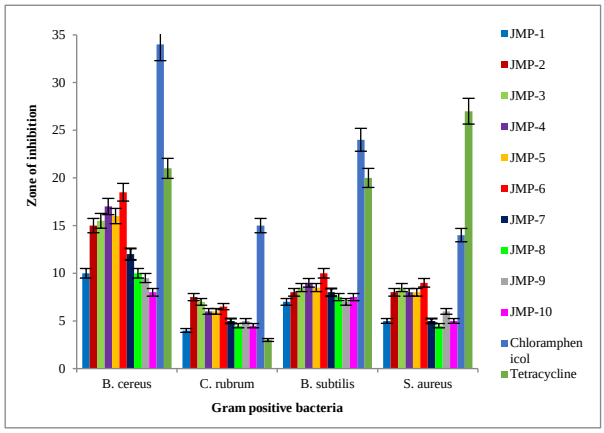


Figure 5: Zone of inhibition against gram positive bacterial strains in dimethyl sulphoxide

972.48 (-C=C- bending alkene).
m/z: 283 (m+1).

JMP-10

^{1}H NMR (DMSO-d6, proton shift value δ ppm): 2.487 (3H, singlet, -SCH_3), 2.614 (3H, singlet, -OCH_3), 5.502 (2H, singlet, -CH_2-), 7.399-7.421(2H, doublet, Ar-H), 7.471-7.494 (2H, doublet, Ar-H).
IR (cm^{-1}): 2251.37, 2922.92, 2846.29, 2803.68 (C-H stretching alkane), 2352.49, 2318.29 (-CN stretching), 1626.20, 1602.98, 1554.87 (-C=C- stretching cyclic alkenes), 1285.66, 1133.28 (C-N stretching), 979.28 (-C=C- bending alkene).
m/z: 285 (m+1).

III. ANTIMICROBIAL ACTIVITY

(a) ***Microorganisms tested:***

The antimicrobial activity of all the synthesized compounds was tested against some selected fungal and bacterial strains into two different solvents, *N,N*-dimethyl formamide and dimethyl sulphoxide. The antimicrobial activity was tested through Agar well diffusion method, in which microorganisms were maintained at 4°C temperature for testing. The microorganisms were maintained on nutrient agar and MGYP medium.

The solution of the synthesized compounds was prepared into *N,N*-dimethyl formamide and dimethyl sulphoxide solvent of 20 mg/ml concentration. For each compound in each selected solvent for a particular one strain, the experiment was repeated three times. The average of these three values is graphically represented in Figs. 4 to 9 along with appropriate uncertainty values.

For the better understanding of antimicrobial activity of all the synthesized compounds, the standard antibiotic compounds were also tested via same method. For the antibacterial study, chloramphenicol and tetracycline were used as reference. For the antifungal strains, nystatin and itraconazole antibiotics are used.

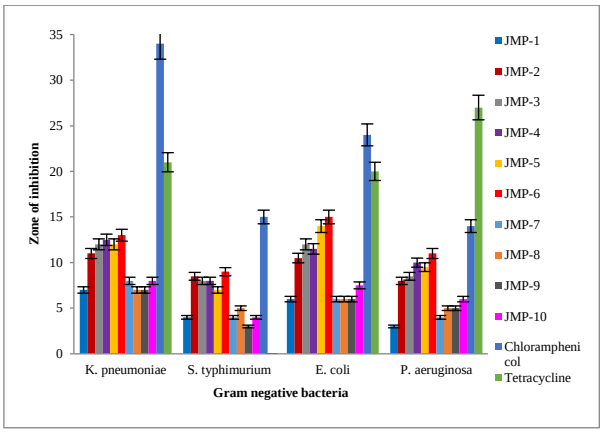


Figure 6: Zone of inhibition against gram negative bacterial strains in *N,N*-dimethyl formamide

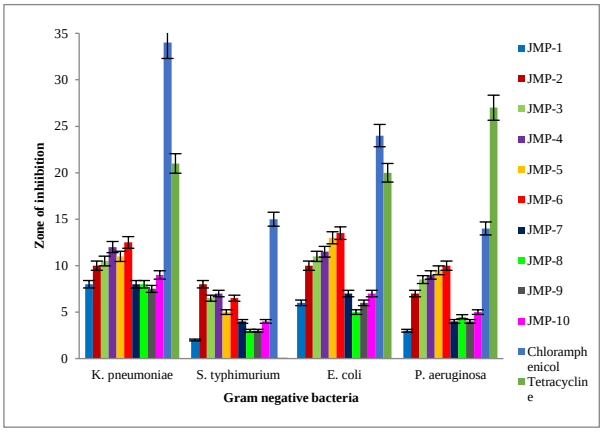


Figure 7: Zone of inhibition against gram negative bacterial strains in dimethyl sulphoxide

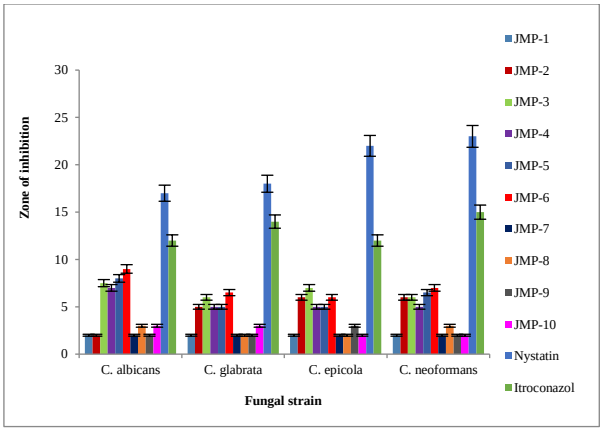


Figure 8: Zone of inhibition against fungal strains in *N,N*-dimethyl formamide

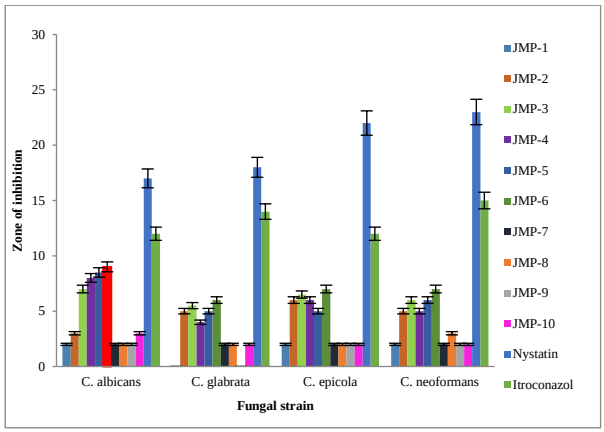


Figure 9: Zone of inhibition against fungal strains in dimethyl sulphoxide

The Gram positive bacteria studied were *Bacillus cereus* (BC), *Corynebacterium rubrum* (CR), *Bacillus subtilis* (BS) and *Staphylococcus aureus* (SA). Gram negative bacteria were *Klebsiella pneumoniae* (KP), *Staphylococcus typhimurium* (ST), *Escherichia coli* (EC), *Pseudomonas aeruginosa* (PA) and fungi were *Candida albicans* (CA), *Candida glabrata* (CG), *Candida epicola* (CE) and *Cryptococcus neoformans* (CN).

IV. RESULTS AND DISCUSION

Some physical constants such as substitution, molecular formula, molecular weight and retention factor is given in Table 1. Further, % yield of all the synthesized compounds was also given in Table 1. % yield was calculated from the reference of theoretical yield and practical yield.

The structure characterization was carried out by different spectroscopic techniques and the various spectrums of JMP-1 compounds are given as Fig. 1 to 3. Figure 2 shows ^{1}H NMR spectrum of JMP-1 compound. Infra red and mass spectrum is given as Fig. 2 and Fig. 3 respectively.

The antibacterial activity of all the synthesized compounds along with two standard antibiotics in *N*,*N*-dimethyl formamide was represent as graph in Figure 4. From the Figure 4, it is observed that that against *Bacillus cereus* in DMF, all the tested compounds showed inhibition and out of them JMP-6 showed maximum inhibition. However, JMP-1 and JMP-9 showed minimum inhibition. All the synthesized compounds have same scaffolds imidazo[1,2-b]pyrazole with different side substitutions. JMP-6 having 2,4-dichloro substitution whereas JMP-1 and JMP-9 having no substitution and 2,4-dimethyl respectively. Hence, from the study it is revealed that the 2,4-dichloro substituted compound was showed more inhibition then alkyl group. Rest of the compounds showed good to moderate biological activity against *Bacillus cereus* in DMF. In DMF against *Corynebacterium rubrum*, JMP-2 (containing 2-bromo substitution) showed maximum inhibition. In DMF, against *Bacillus subtilis*, 2,4-dichloro substitution (as JMP-6) showed maximum inhibition whereas no substituted compound (as JMP-1) showed minimum inhibition. Against *Staphylococcus aureus*, again JMP-6 showed maximum inhibition. However, *Staphylococcus aureus* found to be more resistive against JMP-1, JMP-8 and JMP-10 compounds. From the results, it was revealed that the inhibition is not depending only heterocyclic scaffolds but also depend on side substitution present in molecule.

Figure 5 showed zone of inhibition of all the synthesized compounds along with two standard compounds in dimethyl sulphoxide. From this Figure, it is cleared that the all the synthesized compounds showed good to moderate inhibition against selected bacterial strains. Against *Bacillus cereus*, JMP-6 showed maximum inhibition whereas JMP-10 showed minimum inhibition. In DMSO solvent, against *Corynebacterium rubrum*, 2-bromo substituted compound (as JMP-2) found to be more effective whereas no substituted compound (as JMP-1) show low inhibition. Against *Bacillus subtilis*, all tested compounds showed good inhibition but not any one showed more than standard antibiotics. In DMSO, against *Staphylococcus aureus*, JMP-6 showed maximum inhibition and JMP-8 showed minimum inhibition.

Figure 6 and 7 showed zone of inhibition against some selected negative bacterial strains in DMF and DMSO solvents respectively. Against *Klebsiella pneumonia*, JMP-6 (having 2,4-dichloro substitution) showed maximum inhibition whereas rest of the compounds showed good inhibition but not more than standard antibiotics. Again JMP-6 showed maximum inhibition against *Staphylococcus typhimurium*, *Escherichia coli* and *Pseudomonas aeruginosa* in DMF solvent. Hence, from the results it is cleared that the dichloro substituted compound found to be more effective in DMF solvent.

From the Fig. 7, it is observed that the 2,4-dichloro substituted compound (as JMP-6) possess maximum inhibition against *Klebsiella pneumoniae*, *Staphylococcus typhimurium* and *Pseudomonas aeruginosa* in DMSO solvent. Against *Staphylococcus typhimurium*, JMP-3 and JMP-6 compounds are found to be more effective and almost up to same extent. In DMSO, no one showed inhibition more than standard antibiotics drug.

Figure 8 and 9 show the zone of inhibition for the studied compounds and two antibiotics against some selected fungal strain in DMF and DMSO respectively. From the Figure, it is observed that the most of the compounds showed good inhibition but not more than that of standard reference drugs. 2,4-dichloro substituted compound (as JMP-6) showed maximum inhibition against *Candida albicans*, *Candida epicols* and *Cryptococcus neoformans* in DMF and DMSO solvents.

V. CONCLUSION

In the present work, some new nitrogen based heterocyclic compounds have been synthesized by multi step process. The conformation of the synthesis of 3H-imidazo[1,2-b]pyrazole derivatives by different spectroscopic techniques. The antimicrobial activity of all these synthesized compounds was also tested against some selected bacterial and fungal strains in two different solvents. Form the result; it was revealed that the all synthesized compounds showed good to moderate biological activity against selected strains. However, some halogen

substituted compounds are showed higher inhibition then alkyl or without substituted compounds. Hence form the study, it is clear that the halogen substitution increases antimicrobial activity of 3H-imidazo[1,2-b]pyrazole derivatives.

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