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SYNTHESIS, CHARACTERIZATION AND PHARMACOLOGICAL EVALUATION OF SOME ARYL PIPERAZINE COMPOUNDS

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Keywords:

Aryl piperazine, Biological screens, Thin Layer Chromatography (TLC), Zone of inhibition, Minimum inhibitory concentrations (MIC), *In-vitro*, Turbidimetric

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ABSTRACT: In this planed research work, aryl piperazine derivatives will be synthesized because aryl piperazine currently the most important constructive block in drug discovery with positive pharmacological evaluation. A series N- (4- (benzo[d]thiazol-2-yl) phenyl)-2-[4-(aryl-substituted) piperazines-1-yl]acetamide, N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-[4-(arylsubstituted)piperazines-1-yl]acetamide and Synthesis of N-(4-(benzo[d]imidazol-2-yl) phenyl)- 2- (4- (arylsubstituted)piperazin-1-yl) acetamide will be synthesized with their characterization such as melting point determination, Thin-layer chromatography (TLC) and spectral analysis. After that, pharmacological evaluation, such as antibacterial activity, will be performed for synthesized compounds. All the synthesized compounds were reported for determination of zone of inhibition (mm), minimum inhibitory concentrations (MIC) were also calculated for effective derivatives, with an objective to offer some potent antimicrobial agents to human beings. Antimicrobial activity is determined based on their *in-vitro* activity in pure cultures. *In-vitro* susceptibility testing is done by two methods *i.e.*, Turbidimetric/photometric/tube dilution method and agar diffusion/cup-plate/cylinder plate method.

INTRODUCTION: According to present scenario the appearance of multidrug microbial resistance and worldwide warming are among the main challenges that modern scientists have so far been facing in the recent decades [1-6]. From this information that many pathogenic microorganisms accountable for several human being and animal diseases have developed resistance mechanisms to the classical therapies has stimulated intensive investigations in the fields of natural and synthetic chemistry, with the aim of discovering new drug classes having much better therapeutic profiles [7-12].

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Presently, the piperazine moiety is the most important assembled material in new invention with positive pharmacological results [13-16]. A literature survey exposed that substituted piperazine are extensively valuable in the field of medicinal chemistry such as antimalarial, antibacterial, antifungal, antipsychotic, anti-inflammatory, *etc*. with a combination of a heterocyclic compound such as benzothiazole, benzoxazole, benzimiazole, and indole, *etc*. [17-19] Bacterial infections are among the important infectious diseases [20-22].

All reports are confident to synthesize some newer aryl piperazine derivatives combined with heterocyclic moieties such as benzothiazole, benzoxazole, and benzimiazole in three different series and studied antimicrobial activity for all these new compounds such as antibacterial activity and antifungal activity.

MATERIALS AND METHODS: The substituted aryl piperazines, standard drugs, and other chemicals that were used in the synthetic scheme purchased from a chemical lab. All chemicals used were of analytical grades and purified before used.

The glassware's used were properly cleaned and dried before use and suitably calibrated. Melting points were determined by an open capillary method and are uncorrected. The purity of derivatives was checked by thin-layer chromatography (TLC) by using silica gel G coated glass plates taking mobile phase Hexane: Ethyl acetate (1:1). The spots were visualized in UV chamber or exposure to iodine vapors.

General Procedure: In this planed work aryl piperazine compounds were prepared from three different series. In series 1 benzothiazole derivedin series 2benzoxazole derived and in series 3 benzimiazole derived compounds were used for the preparations of final compounds presented in **Fig. 1.**

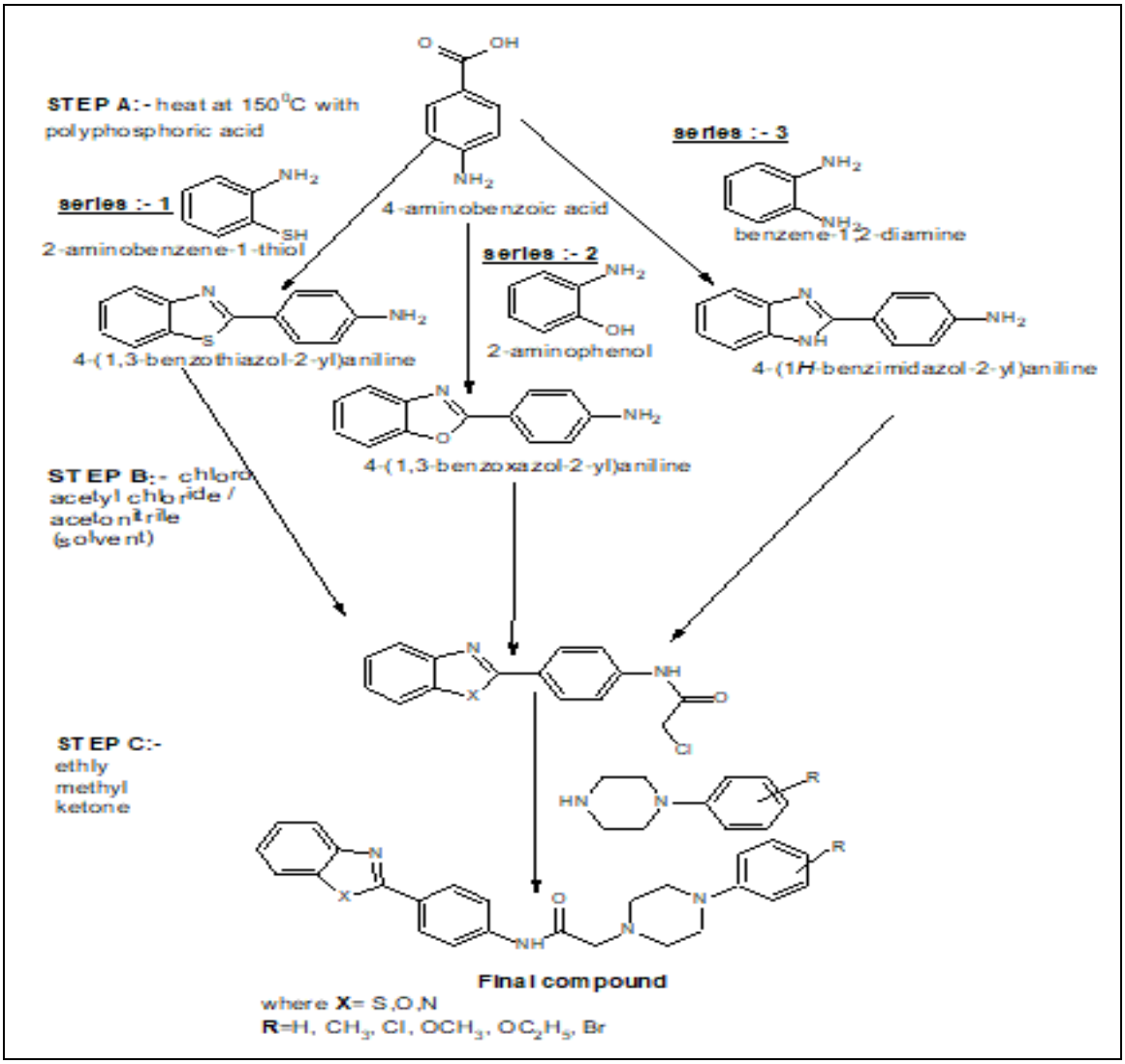


FIG. 1: SYNTHETIC PATHWAY

Step A: Equal moles of 4-aminobenzoic acid and with 2-aminobenzenthiol (series 1)/2-aminophenol (series 2)/benzene-1,2-diamine (series 3) mixed in same mole of polyphosphoric acid. Heat this mixture at 220 °C for 4 h. After cooling of the reaction mixture neutralized with a freshly prepared ice-cold solution of 10% potassium carbonate. The solution was left overnight, and the precipitate was settled down. Finally, filter the solution and crude product obtained, which was recrystallized from methanol to obtain the final compound as 4-(1,3-benzothiazol-2-yl) aniline (series-1) / 4- (1, 3-benzoxazol-2-yl)aniline (series-2)/4-(1*H*benzimid-azol-2-yl) aniline(series-3).

Step B: Dissolved the 0.02 mole of the compound (prepared in step A) in acetonitrile (50 ml) and add 0.02 mole of anhydrous sodium carbonate. The mixture reaction refluxed for two hours with constant stirring. Added dropwise 0.05-mole chloroacetyl chloride solution to this. The complete addition of chloroacetyl chloride refluxed the mixture for 22-24 h. The excess solvent removed by vacuum distillation. Filtered the product and recrystallized from menthol to obtain the final compound.

Step C: Refluxed 0.025 mole of the compound (prepared in step B) in ethyl methyl ketone (25 ml) and add 0.02 mole of anhydrous sodium carbonate for 1 h. Add an N-phenylpiperazine derivative that was added as in series A (D_1-D_6), series B (G_1-G_6), and series C (B_1-B_6) in ethyl methyl ketone with catalytic amount of sodium iodide. Refluxed this mixture for ½ hour. After completion of reaction, excess solvent removed by vacuum distillation and obtained residue wash with an excess of water. Filtered the product and recrystallized from menthol to obtain the final compound.

Physical Characterization of Synthesized Compounds: The thin layer chromatography (TLC) of the compounds was performed on the precoated silica gel G plates. The mobile phase ratio for the synthesized compounds was Hexane: Ethyl acetate (1:1) and using iodine vapors for the detection of the spots.

Pharmacological Activity:

Antimicrobial Activity of Synthesized Compounds (Zone of Inhibition): The synthesized compounds Ia-If, IIa-IIf, and IIIa-IIIf were evaluated for antifungal and antibacterial activity using cup plate method and MIC for potent compounds were calculated by serial dilution method.

Preparation of Media: The nutrient agar medium was used for bacterial strains and sabouraud agar medium for fungi to test the sensitivity of strains against synthesized compounds. 15 ml of freshly prepared nutrient agar medium, sterilized at 121 °C for 15 min was poured and solidified aseptically into sterile petri plates.

Procedure for Inoculation and Incubation of Culture, Standard and Synthesized Compounds (Ia-If, IIa-IIf and IIIa-IIIf): The zones of inhibition concerning the newly synthesized compounds were calculated by the cup plate method. Sterilization procedure for the petri dishes applied by washing thoroughly with clean water and kept in a hot air oven at a temperature of 160 °C for one hour. 25 ml of sterile nutrient agar media for bacteria and sabouraud agar media for fungi was poured into petri dishes (sterile) and placed the petri dishes (sterile) at room temperature till to solidify. The presence of microorganism checked in plates that incubated at 37 °C for 24 h. To seed the medium with the organism with sterile cotton swabs. Sterile borer was used to make the bores on the medium, and 1000 µg/ml of ampicillin for bacteria and 1000 µg/ml ketoconazole for fungi were taken as a standard reference while the sample preparation was also made in same concentrations in Dimethyl sulfoxide (DMSO). Petri dishes placed in the refrigerator for 15 min at 4 °C and allowing diffusion. At 37 °C, the incubation period was 48 h and zone of inhibition noted by measurement of the diameter in millimeter (mm) with a scale after 24 h for bacteria and after 72 h for fungi. Preliminary screening was carried out at a fixed concentration of 1000 µg/ml.

RESULTS AND DISCUSSION: The melting points of the synthesized compounds were determined by open capillary methods and are uncorrected. The report of physical characterization was present in **Table 1.**

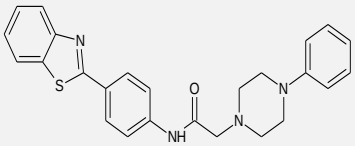
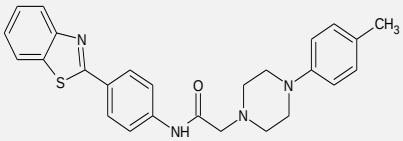
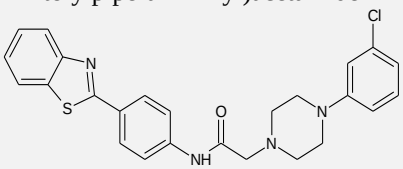
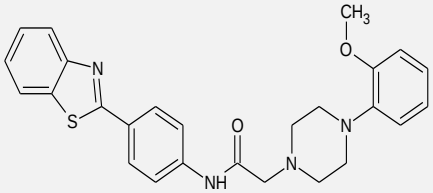
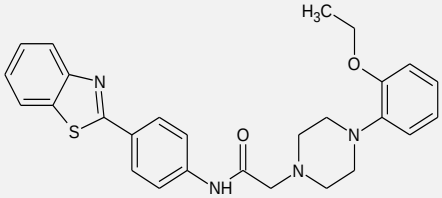
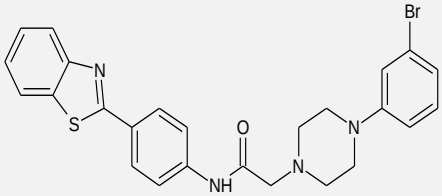
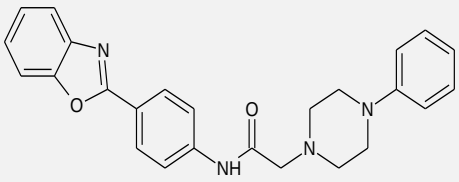
Spectral Data: The Infrared spectroscopy (IR) was carried out by using potassium bromide (KBr) pellet method Shimadzu F.T.I.R Spectrophotometer 8300. The NMR spectra were recorded with Bruker N.M.R. Spectrophotometer AV 400. The spectral data of synthesized compounds shown in **Table 2.**

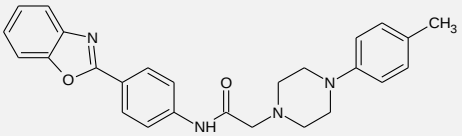
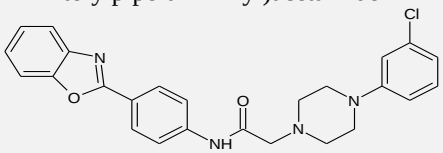
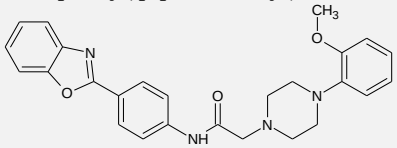
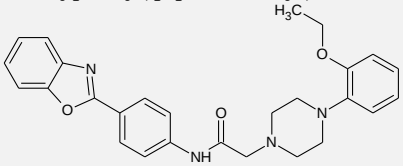
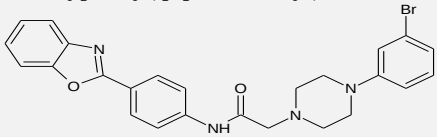
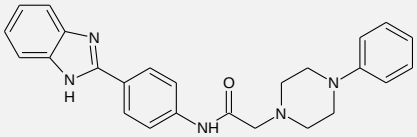
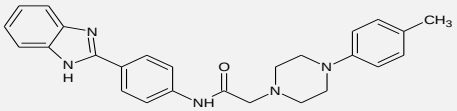
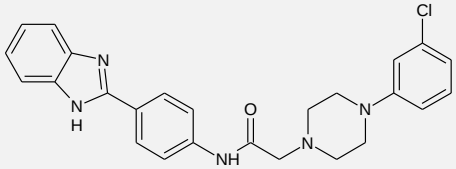
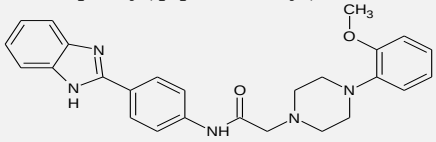
Pharmacological Activity: The synthesized compounds Ia-If, IIa-IIf, and IIIa-IIIf were evaluated for antifungal and antibacterial activity using cup plate method and MIC for potent compounds were calculated by serial dilution method. The compositions of agar media were presented in **Table 3.**

Sub-culturing of Microorganisms: Micro-organisms such as bacteria and fungi used for the culture media are presented in **Table 4**. The zones

of inhibition concerning the newly synthesized compounds were calculated by the cup plate method and compared with the standard, which was presented in **Table 5.**

TABLE 1: PHYSICAL CHARACTERISTICS DATA OF SYNTHESIZED COMPOUNDS

S. no.	Compound	Structure and Name	Molecular Formula	State	R_f value
1	Ia	 N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-phenylpiperazin-1-yl)acetamide	$C_{25}H_{24}N_4OS$	Solid	0.42
2	Ib	 N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-p-tolylpiperazin-1-yl)acetamide	$C_{26}H_{26}N_4OS$	Solid	0.47
3	Ic	 N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-(3-chlorophenyl)piperazin-1-yl)acetamide	$C_{25}H_{23}ClN_4OS$	Solid	0.38
4	Id	 N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-(2-methoxyphenyl)piperazin-1-yl)acetamide	$C_{26}H_{26}N_4O_2S$	Solid	0.45
5	Ie	 N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-(2-ethoxyphenyl)piperazin-1-yl)acetamide	$C_{27}H_{28}N_4O_2S$	Solid	0.50
6	If	 N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-(3-bromophenyl)piperazin-1-yl)acetamide	$C_{25}H_{23}BrN_4OS$	Solid	0.37
7	IIa	 N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-(4-phenylpiperazin-1-yl)acetamide	$C_{25}H_{24}N_4O_2$	Solid	0.41

8	IIb	 N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-(4-p-tolylpiperazin-1-yl)acetamide	$C_{26}H_{26}N_4O_2$	Solid	0.44
9	IIc	 N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-(4-(3-chlorophenyl)piperazin-1-yl)acetamide	$C_{25}H_{23}ClN_4O_2$	Solid	0.39
10	IIId	 N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-(4-(2-methoxyphenyl)piperazin-1-yl)acetamide	$C_{26}H_{26}N_4O_3$	Solid	0.49
11	IIe	 N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-(4-(2-ethoxyphenyl)piperazin-1-yl)acetamide	$C_{27}H_{28}N_4O_3$	Solid	0.50
12	IIf	 N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-(4-(3-bromophenyl)piperazin-1-yl)acetamide	$C_{25}H_{23}BrN_4O_2$	Solid	0.36
13	IIIa	 *N*-(4-(1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(4-phenylpiperazin-1-yl)acetamide	$C_{25}H_{25}N_5O$	Solid	0.43
14	IIIb	 *N*-(4-(1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(4-(*p*-tolyl)piperazin-1-yl)acetamide	$C_{26}H_{27}N_5O$	Solid	0.48
15.	IIIc	 *N*-(4-(1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(4-(3-chlorophenyl)piperazin-1-yl)acetamide	$C_{25}H_{24}ClN_5O$	Solid	0.38
16	IIId	 *N*-(4-(1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(4-(2-methoxyphenyl)piperazin-1-yl)acetamide	$C_{26}H_{27}N_5O_2$	Solid	0.43

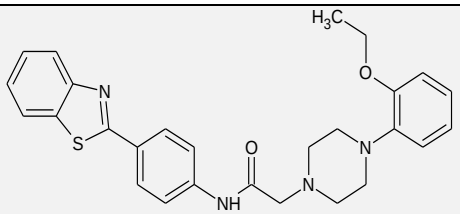
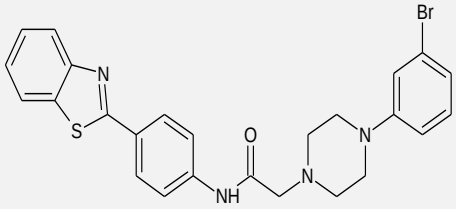
17	IIIe	 N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-(2-ethoxyphenyl)piperazin-1-yl)acetamide	$C_{27}H_{28}N_4O_2S$	Solid	0.40
18	IIIf	 N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-(3-bromophenyl)piperazin-1-yl)acetamide	$C_{25}H_{23}BrN_4OS$	Solid	0.36

TABLE 2: SPECTRAL DATA OF SYNTHESIZED COMPOUNDS

Ia:- N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-phenylpiperazin-1-yl)acetamide	
IR (KBr cm^{-1})	3219(Ar C-H), 2925(Ali C-H), 1687(C=O), 1310(C-N), 730(C-S)
^{1}HNMR (δppm)	7.38(Ar-H), 5.65(-NH), 4.04(CH=CH), 3.3 (N-H)
Ib:- N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-p-tolylpiperazin-1-yl)acetamide	
IR (KBr cm^{-1})	3438 (Ar C-H), 2940 (Ali C-H), 1680(C=O), 1320(C-N), 728(C-S)
^{1}HNMR (δppm)	8.65(Ar-H), 5.45(-NH), 4.34(CH=CH), 3.25 (N-H)
Ic:- N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-(3-chlorophenyl)piperazin-1-yl)acetamide	
IR (KBr cm^{-1})	3360(Ar C-H), 2840(Ali C-H), 1620(C=O), 1310(C-N), 845(C-Cl)
^{1}HNMR (δppm)	8.55(Ar-H), 5.45(-NH), 4.32(CH=CH),
IIa:- N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-(4-phenylpiperazin-1-yl)acetamide	
IR (KBr cm^{-1})	3435 (Ar C-H), 2885(Ali C-H), 1640(C=C), 1565(N-H bend)
^{1}HNMR (δppm)	8.32(Ar-H), 5.21(-NH), 4.39(CH=CH), 3.20 (N-H)
IIb: N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-(4-p-tolylpiperazin-1-yl)acetamide	
IR (KBr cm^{-1})	3425(Ar C-H), 2918(Ali C-H), 1675(C=O), 1313(C-N)
^{1}HNMR (δppm)	7.28(Ar-H), 5.65(-NH), 4.04(CH=CH), 3.3 (N-H)
IId: N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-(4-(2-methoxyphenyl)piperazin-1-yl)acetamide	
IR (KBr cm^{-1})	3405 (Ar C-H), 2865(Ali C-H), 1640(C=C), 1555(N-H bend)
^{1}HNMR (δppm)	7.26(Ar-H), 5.18(-NH), 4.24(CH=CH), 3.22 (N-H)
IIIa: *N*-(4-(1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(4-phenylpiperazin-1-yl)acetamide	
IR (KBr cm^{-1})	3332(Ar C-H), 2940(Ali C-H), 1645(C=O), 1310(C-N)
^{1}HNMR (δppm)	7.31(Ar-H), 5.68(-NH), 4.02(CH=CH), 3.1 (N-H)
IIIe: N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-(2-ethoxyphenyl)piperazin-1-yl)acetamide	
IR (KBr cm^{-1})	3320(Ar C-H), 2980(Ali C-H), 1735(C=O), 1318(C-N)
^{1}HNMR (δppm)	7.29(Ar-H), 5.74(-NH), 4.22(CH=CH), 3.28 (N-H)

TABLE 3: COMPOSITIONS OF AGAR MEDIA

Composition for Nutrient agar media		**Composition for Sabouraud agar media**	
Chemical name	**Quantity**	**Chemical name**	**Quantity**
Beef extract	04gm	Dextrose	40 gm
Peptone	05gm	Mycological peptone	10 gm
Agar	20 gm	Agar	15 gm
Sodium chloride	05 gm	pH (25 °C)	5.6
Distilled water	10000 ml		
pH (25 °C)	7.2 ± 0.2		

TABLE 4: SUB-CULTURING OF MICROORGANISMS

Test organism fungi	**Test organism gram-positive bacteria**	**Test organism gram-negative bacteria**
Aspergillus niger	*Staphylococcus aureus*	*Salmonella typhimurium*
Candida albicans	*Bacillus subtilis*	*Escherichia coli*
Trichoderma viridae	*Streptococcus pyrogens*	*Klebsiella pneumoniae*

TABLE 5: ZONE OF INHIBITION OF SYNTHESIZED COMPOUNDS AGAINST DIFFERENT BACTERIAL AND FUNGAL STRAINS

Compound	Zone of inhibition (mm) @1000µg/ml								
	Fungi			Gram positive bacteria			Gram negative bacteria		
	A. n	***T. v***	***C. a***	***S. a***	***S. p***	***B. s***	***S. t***	***K. pn***	***E. coli***
Ia	35±1.2	32±1.8	40±1.2*	34±1.5	41±2.1	39±1.4	42±1.4*	36±1.3	33±1.9
Ib	33±1.6	32±1.8	36±1.3*	29±1.6	30±2.5	35±2.1	38±1.7	28±1.4	31±2.2
Ic	40±2.4*	36±2.3*	33±1.9	33±1.6	32±2.8	41±2.1*	39±1.4	42±1.4*	39±2.3*
Id	21±1.6	27±1.8	24±1.4	22±1.6	28±2.3	25±1.2	21±2.5	29±1.3	23±1.6
Ie	23±2.2	25±1.4	22±2.2	27±1.3	23±2.6	21±1.6	23±1.8	22±1.2	27±1.6
If	32±1.8	40±2.2*	34±1.5	35±1.2	33±1.6*	32±1.8	36±2.5	40±1.2*	36±1.2
IIa	25±2.2	19±2.3	24±2.3	22±1.5	25±2.7	23±2.2	20±1.6	24±1.6	23±1.2
IIb	24±2.3	29±1.2	23±1.5	26±1.8	21±1.6	27±1.8	22±1.7	25±1.4	27±1.1
IIc	39±1.6	36±1.9*	41±3.1	35±1.2	38±1.9*	32±2.3	36±2.2	40±3.2	32±1.8
IId	28±1.7	25±2.1	23±2.2	22±1.2	24±1.6	21±1.5	29±1.3	26±1.8	22±1.4
IIe	11±3.1	13±1.7	17±1.5	14±1.8	12±1.9	11±1.3	16±2.1	13±2.4	19±2.1
IIf	39±1.2	32±1.5	36±2.2	40±1.3*	33±1.6	35±1.1	42±1.8	36±1.3*	41±2.2*
IIIa	21±1.9	25±2.2	26±1.6	23±2.0	29±1.2	24±1.9	23±1.2	21±2.1	29±1.1
IIIb	33±1.8	39±1.1	34±1.5	31±1.3	37±2.4*	40±1.4	42±1.3*	34±1.6	38±1.5
IIIc	34±1.5	35±1.2	41±2.1*	40±1.2	36±1.3	33±1.9	40±1.2*	36±1.3	41±2.2*
IIId	12±1.9	15±1.3	19±2.2	11±1.4	17±1.5	18±2.1	21±1.6	16±2.1	23±1.1
IIIe	27±1.2	22±1.5	32±1.8	29±1.4	25±1.7	31±1.6	28±1.2	24±1.1	21±1.5
IIIf	25±2.0	19±1.3	24±1.1	22±1.5	25±1.2	27±1.9	28±2.1	25±2.2	24±1.4
Std.	43±2.5[a]	41±3.1[a]	39±2.8[a]	40±2.6[b]	41±1.8[b]	44±2.1[b]	42±1.6[b]	39±2.4[b]	40±3.1[b]

[a]Ketoconazole, [b]Ampicillin

Value are mean ± SD, n=3, [a]P<0.05 versus synthesized compound, [b]P<0.05 versus synthesized compound * Results were compared to standard indicating non-significant difference, left overall were significantly different from standard.

CONCLUSION: Newly aryl piperazine compounds were prepared from three different series. In series 1, benzothiazole derived in series 2, benzoxazole derived and in series 3, benzimiazole derived compounds used and evaluated their pharmacological activity, which was successfully done for all the compounds. On the basis of the result, it be able to concluded that the newly aryl piperazine compounds showed remarkable antibacterial activity and antifungal activity and prospective to more study.

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