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Design, Synthesis and Evaluation of Some Novel Pyrazolidine-3-One, Aryl Oxadiazole and Mercapto Oxadiazole Derivatives of Biological Interest

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HUMAN

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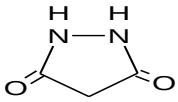
ABSTRACT

A number of substituted pyrazolidin-3-one, aryl oxadiazole and mercapto oxadiazoles are known for their biological importance like anti-bacterial, antitubercular, antioxidant and anti-inflammatory activity. The present investigation is carried for the synthesis of certain substituted pyrazolidin-3-one, aryl oxadiazole and mercapto oxadiazole and carried out their biological activity. The title compounds has been synthesized from diclofenac acid & ofloxacin reacts with ethanol in presence of acid to give hydrazide which on further reaction with Ethylacetoacetate gives substituted pyrazolidin-3-one which undergoes Mannich reaction gives Pyrazolidin-3-one. Acid hydrazide on treatment with Aromatic acids in presence of Phosphorus oxychloride gives aryl oxadiazoles. Mercaptooxadiazoles synthesized using acid hydrazide and carbon disulphide. The newly synthesized compounds have been characterized by IR, ^{1}H NMR and CHN analysis. Selected compounds are screened for antimicrobial, antioxidant, anti-inflammatory and antitubercular activity *in vitro*, Few of them exhibited promising activity.

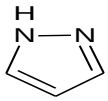
INTRODUCTION

PYRAZOLONE

Pyrazolidine 3,5-dione belongs to NSAIDS class of drugs. These are used as anti-inflmmatory agents. Drugs of this group belong to non-acidic anti-inflammatory agents class of NSAIDS. Pyrazolidine 3,5-dione(I) is the 3,5 dioxo-derivatives of completely hydrogenated pyrazole (II). It is isomeric with hydantoin (III) and is structurally related to barbituric acid.



(I)



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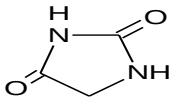

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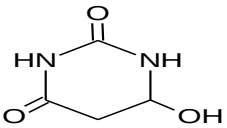
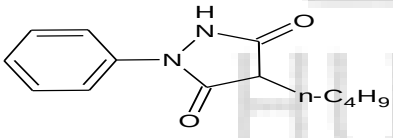


(IV)

1,2 diaryl pyrazolidine-3,5-diones have been recently described as a novel antibacterial class showing potent and specific inhibition of MurB and good activity against some strains of antibiotics resistant bacteria. Earlier studies of these compounds have also resulted in the development of phenyl butazone (V), Oxyphen butazone (VI) sulfin pyrazone (VII) as drugs used for the treatment of fever, inflammation, arthritis and gout.



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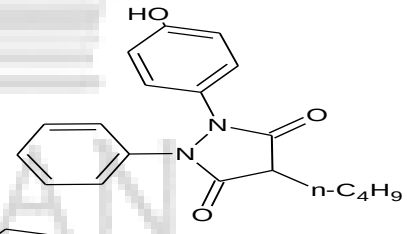

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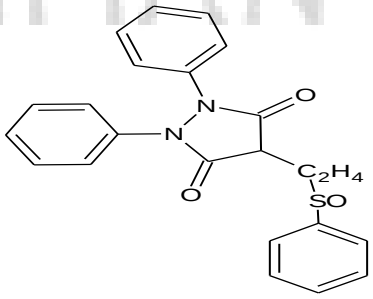
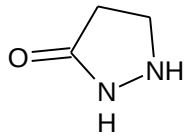


(VII)

The unfolding of these therapeutics properties of the above drugs promoted the development of the chemistry of this group of compounds. As of now, several approaches for the synthesis of pyrazolidine-3.5-diones have been developed and many of their properties have been developed in the literature.

Being a heterocyclic compound, pyrazolone finds use in the research as a starting material for the synthesis of larger, usually bioactive structures.



pyrazolidin-3-one

Its aromaticity makes it relatively stable, although a heterocyclic compound, it has reactive sites which allow for funtionalization.

OXADIAZOLE

General Introduction:

Oxadiazole having a five member heterocyclic ring which has two nitrogen atoms with an oxygen atom are considered to be an important class of compounds in medicinal chemistry because of their interesting diversified biological application.[1] Literature survey revealed that a minor modification in the structure can result in qualitative as well as quantitative changes in the activity, convinced us to begin on the synthesis of various new 1, 3, 4- Oxadiazole derivatives with the aim of having improved activity and lesser toxicity. During the past few years, considerable evidence has been accumulated that demonstrates the efficacy of 1, 3, 4-oxadiazoles having anti-tubercular, and antihypoglycemic activity, anti-inflammatory activity, anticancer activity, antibacterial activity.

MATERIALS AND METHODS

EXPERIMENTAL

The identification and characterization of the prepared compounds were carried out by the following procedure to ascertain that all prepared compounds were of different chemical nature than the respective parent compound.

Physical Constants, Thin Layer Chromatography (TLC), Fourier Transformer Infrared Spectroscopy (FT-IR), Nuclear Magnetic Resonance Spectroscopy (^{1}H-NMR), Elemental Analysis (C, H, N) calculated and found.

Melting Point Determination:

The melting points of the organic compounds were determined by open capillary in a heavy liquid paraffin bath. Melting point is a valuable criterion of purity for an organic compound, as a pure crystal is having definite and sharp melting point.

EXPERIMENTAL WORK COMPRISES OF THE SCHEME

1] General method for Synthesis of Ester (I)

A mixture of 0.3 mole of acid, 0.3 mole of absolute ethanol and 0.15 ml of concentrated sulphuric acid was refluxed for 4 hrs.

2] General method for Synthesis of acid hydrazide (II)

A mixture of 0.1 mole of ester and 0.2 mole (10ml) of Hydrazine hydrate were refluxed in 50 ml of 95% ethanol for 4 hrs. The resultant mixture was concentrated, cooled and poured into crushed ice. The solid mass thus separated out was filtered, dried and purified by recrystallization from ethanol.

3A] General method for Synthesis of 5-methyl-2, 4 dihydro-4H-pyrazolin-3-one (III)

A mixture of 0.01 mole of acid hydrazide and 0.1 mole (13ml) of ethyl acetoacetate were heated on water bath for 2hrs with stirring from time to time with a glass rod. The resultant heavy reddish syrup was allowed to cool to room temperature. It was washed thorouly with ether to remove colored impurities. The solid thus separated out was filtered, dried and purified by recrystallization from ethanol.

3B] Preparation of 5-aryl 1, 3, 4-oxadiazole(IV)

To a mixture of 0.01 mole of acid hydrazide (**II**) was added 10 mole of Phosphorus oxychloride at temp. of -5^0C and 0.01 mole aromatic acid (Benzoic acid) added. The reaction mixture refluxed at 100^0C for 2 hrs. The reaction mixture was cooled to room temperature, the excess of $POCl_3$ was concentrated through high vacuum, the residue was quenched with ice and the solid separated was filtered and dried through pump to afford corresponding aryl oxadiazole.

3C] Preparation of 5-mercapto-1, 3, 4-oxadiazole (V)

A mixture of 0.01mole of acid hydrazide (**II**), 0.01mole of KOH & 10ml of CS_2 were taken in a 250ml RBF attached to a refluxed condenser and were refluxed with 50ml of 95% abs. ethanol for 4 hrs. The resultant mixture was concentrated in 250ml beaker & cooled at room temp. Then it was acidified with dilute HCl acid. The solid mass thus separated out was filtered and dried. The same was recrystallized from ethanol to afford.

4] General method for Synthesis of Pyrazolidine-3-one derivatives (VI)

A mixture of 0.005 mole of **III**, 5ml of formaldehyde and 0.005 mole of primary amine (Pyrazinamide, Sulfanilamide) was refluxed with 25ml of 95% ethanol for 2 hrs. The resultant mixture was concentrated. The solid mass thus separated out was filtered, dried and purified by recrystallization from ethanol.

SCHEME

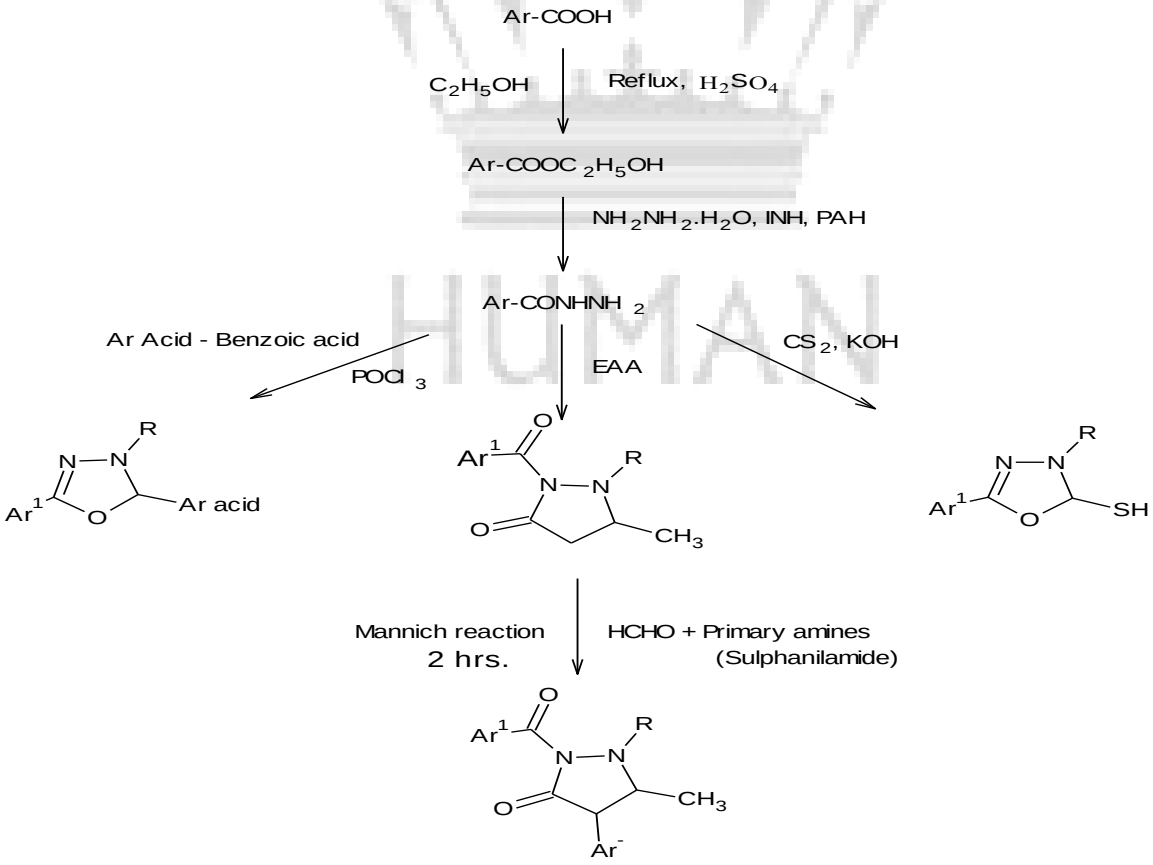
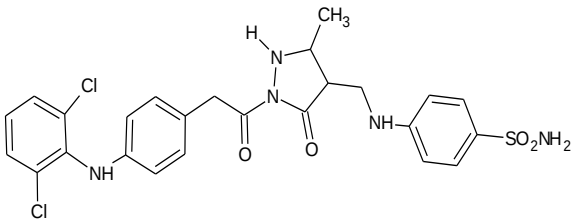
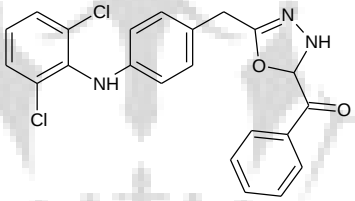
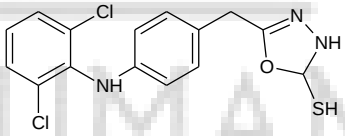
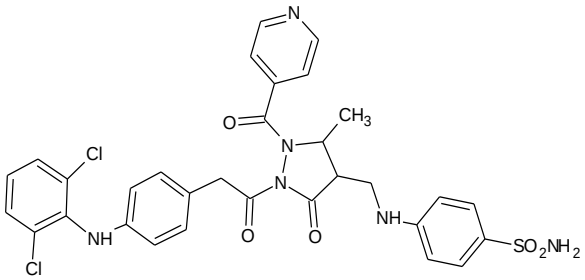
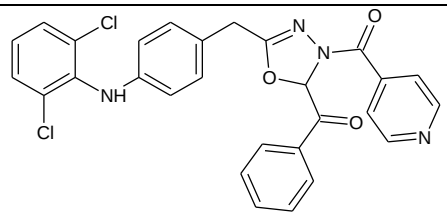
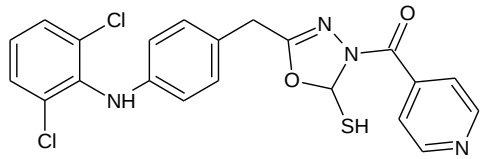
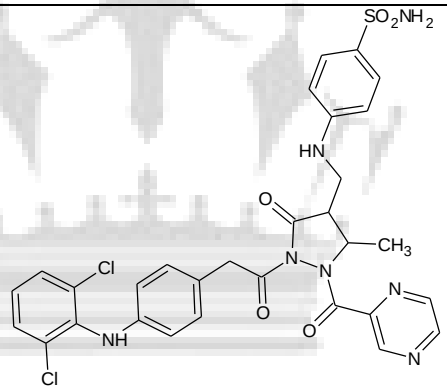
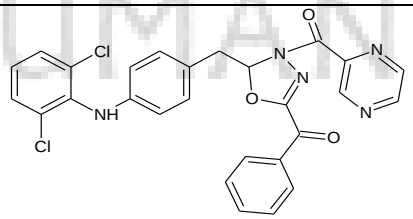
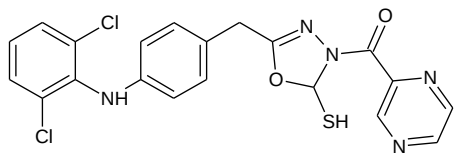
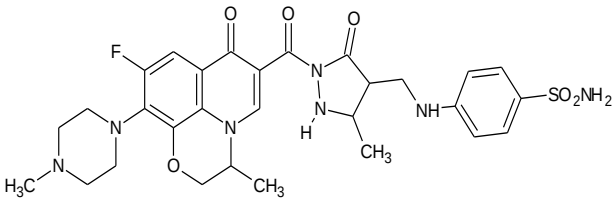
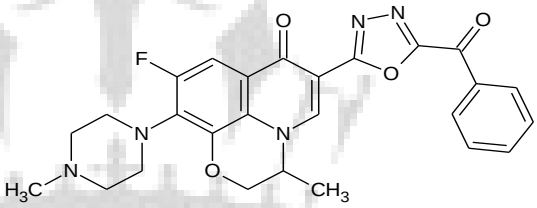
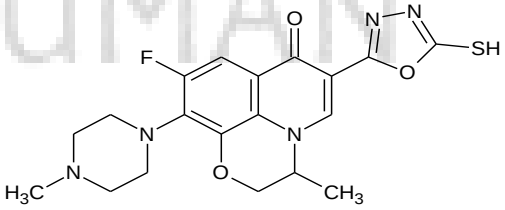
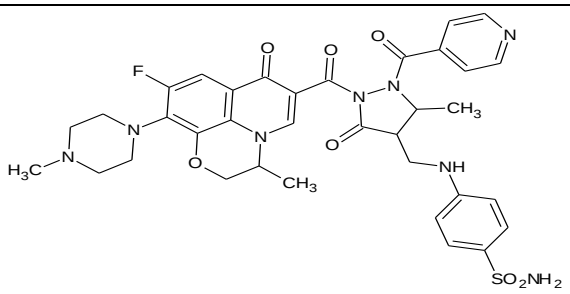
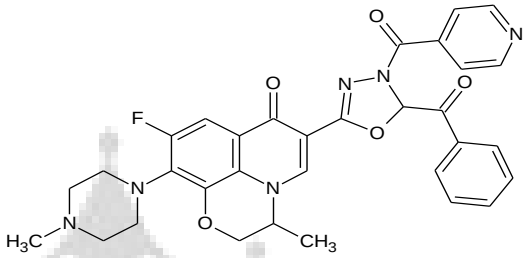
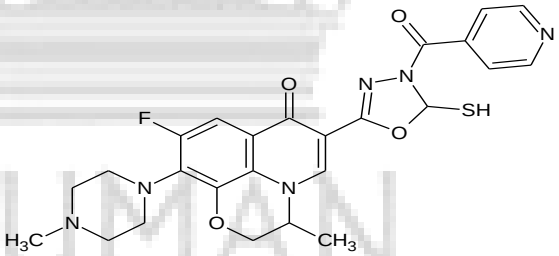
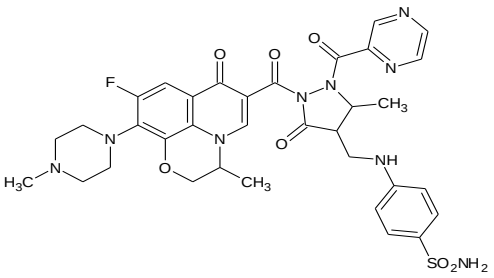


Table 3: List of 1,4(disubstituted) 5,methyl pyrazolidin-3-one and 2,3(disubstituted) 1,3,4-oxadiazole compounds

Comp.	IUPAC name	Molecular Structure
A_1	4-[4methylamino benzenesulfonamide] 2-{4-[(2,6-dichlorophenyl)amino] acetaldehyde, benzyl}-5-methylpyrazolidin-3-one	
A_2	(5-{4-[(2,6-dichlorophenyl)amino]benzyl}-2,3-dihydro-1,3,4-oxadiazol-2-yl)(phenyl)methanone	
A_3	5-{4-[(2,6-dichlorophenyl)amino]benzyl}-2,3-dihydro-1,3,4-oxadiazole-2-thiol	
A_4	1-[pyridine-4 carbaldehyde]4-[4-methylaminobenzenesulfonamide] 2-{4-[(2,6 dichlorophenyl)amino]acetaldehyde, benzyl}-5-methylpyrazolidin-3-one	

A_5	[5-{4-[(2,6-dichlorophenyl)amino]benzyl}-1,3,4-oxadiazol-3(2*H*)-yl](pyridin-4-yl)methanone2-benzyl	
A_6	[5-{4-[(2,6-dichlorophenyl)amino]benzyl}-2-sulfanyl-1,3,4-oxadiazol-3(2*H*)-yl](pyridin-4-yl)methanone	
A_7	2-{4-[(2,6-dichlorophenyl)amino]acetaldehyde, benzyl}-5-methyl -1-(pyrazin-2-ylcarbonyl)pyrazolidin-3-one 4-benzene N-methyl sulphonamide	
A_8	[2-{4-[(2,6-dichlorophenyl)amino]benzyl}-1,3,4-oxadiazol-3(2*H*)-yl](pyrazin-2-yl)methanone2-benzyl.	
A_9	[5-{4-[(2,6-dichlorophenyl)amino]benzyl}-2-sulfanyl-1,3,4-oxadiazol-3(2*H*)-yl](pyrazin-2-	

	yl)methanone	
B_1	2{9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-2,3-dihydro-7*H*-[1,4]oxazino[2,3,4-*ij*]carboxy,quinolin-7-one} 4[4-methylaminobenzenesulfonamide]5-methylpyrazolidin-3-one	
B_2	5{9-fluoro,3-methyl-10-(4-methylpiperazin-1-yl)-2,3-dihydro-7*H*-[1,4]oxazino[2,3,4-*ij*]quinolin-7-one}1,3,4-oxadiazol-2-yl(phenyl)methanone	
B3	9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-6-(5-sulfanyl-1,3,4-oxadiazol-2-yl)-2,3-dihydro-7H-[1,4]oxazino[2,3,4-ij]quinolin-7-one	
	1(pyridine 4- carboxy) 2{9-fluoro,3-methyl-10-(4-methylpiperazin-1-yl)-2,3-dihydro-7H-[1,4]oxazino[2,3,4-	

B4	ij]carboxy,quinolin-7-one}4-[(3-methyl-pyrazolidne-3-one-4 yl4mino]benzeneN-methyl sulfonamide	
B5	3{9-fluoro,3-methyl-10-(4-methylpiperazin-1-yl)-2,3-dihydro-7H-[1,4]oxazino[2,3,4-ij]quinolin-7-one} pyridin-4-yl(2-sulfanyl-1,3,4-oxadiazol-3(2H)-yl)methanone	
B6	5-{9-fluoro,3-methyl-10-(4-methylpiperazin-1-yl)-2,3-dihydro-7H-[1,4]oxazino[2,3,4-ij]quinolin-7-one}pyridin-4-yl(2-sulfanyl-1,3,4-oxadiazol-3(2H)-yl)methanone	
B_7	2{9-fluoro,3-methyl-10-(4-methylpiperazin-1-yl)-2,3-dihydro-7*H*[1,4]oxazino[2,3,4-*ij*]carboxy,quinolin-7-one}4-({[5-methyl-3-oxo-1-(pyrazin-2-ylcarbonyl)pyrazolidin-4-	

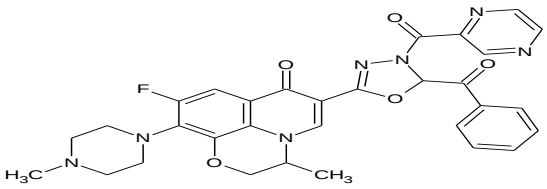
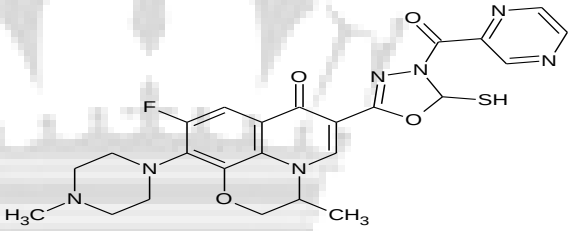
	yl]methyl}amino)benzen esulfonamide	
B_8	5{9-fluoro,3-methyl-10-(4-methylpiperazin-1-yl)-2,3-dihydro-7*H*-[1,4]oxazino[2,3,4-*ij*]quinolin-7-one}phenyl[3-(pyrazin-2-ylcarbonyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl]methanone	
B_9	5{9-fluoro,3-methyl-10-(4-methylpiperazin-1-yl)-2,3-dihydro-7*H*-[1,4]oxazino[2,3,4-*ij*]quinolin-7-one}pyrazin-2-yl(2-sulfanyl-1,3,4-oxadiazol-3(2*H*)-yl)methanone	

Table 2: Analytical data of synthesized compounds (Scheme A_1-B_9)

Comp.	Mol. Formula	Mol. Wt.	M.P ^{0}C	Rf Value	Yield %	Elemental analyses Calcd (Found)		
						C	H	N
A1	$C_{24}H_{25}Cl_2N_5O_3S$	534.45	118-120	0.67	71.90	53.93 (53.90)	4.71 (4.70)	13.10 (13.09)
A_2	$C_{22}H_{15}Cl_2N_3O_2$	424.27	142-144	0.71	67.54	62.28 (62.30)	3.56 (3.57)	9.90 (9.89)

A3	$C_{15}H_{11}Cl_2N_3OS$	352.23	128-130	0.56	54.32	51.15	3.15	11.93
A4	$C_{30}H_{28}Cl_2N_6O_4S$	639.55	136-138	0.61	69.18	56.34 (56.32)	4.41 (4.40)	13.14 (13.13)
A5	$C_{28}H_{20}Cl_2N_4O_3$	531.38	112-114	0.52	62.21	63.29	3.79	10.54
A6	$C_{21}H_{16}Cl_2N_4O_2S$	459.34	126-128	0.59	53.76	54.91	3.51	12.20
A7	$C_{29}H_{27}Cl_2N_7O_4S$	640.53	132-134	0.64	75.07	54.38 (54.40)	4.25 (4.26)	15.31 (15.30)
A8	$C_{27}H_{19}Cl_2N_5O_3$	532.37	148-150	0.67	65.10	60.91	3.60	13.15
A9	$C_{20}H_{15}Cl_2N_5O_2S$	460.33	130-134	0.55	55.64	52.18 (52.22)	3.28 (3.29)	15.21 (15.20)
B1	$C_{20}H_{32}FN_7O_5S$	597.66	230-232	0.48	74.66	56.27	5.40	16.41
B2	$C_{26}H_{24}FN_5O_4$	489.49	212-214	0.56	54.19	63.80 (63.81)	4.94 (4.95)	14.31 (14.30)
B3	$C_{19}H_{20}FN_5O_3S$	417.45	198-200	0.61	65.41	54.67 (54.68)	4.83 (4.82)	16.78 (16.79)
B4	$C_{34}H_{37}FN_8O_6S$	704.77	218-220	0.54	72.45	57.94	5.29	15.90
B5	$C_{32}H_{29}FN_6O_5$	596.60	256-258	0.66	60.81	64.42 (64.40)	4.90 (4.92)	14.09 (14.11)
B6	$C_{25}H_{25}FN_6O_4S$	524.56	244-246	0.72	56.15	57.24	4.80	16.02
B7	$C_{33}H_{36}FN_9O_6S$	705.75	222-224	0.74	73.22	56.16 (56.20)	5.14 (5.15)	17.86 (17.87)
B8	$C_{31}H_{28}FN_7O_5$	597.59	188-190	0.66	67.81	62.30	4.72	16.41

B9	$C_{24}H_{24}FN_7O_4S$	525.55	202-204	0.53	70.43	54.85 (54.84)	4.60 (4.61)	18.66 (18.64)

The combustion analysis of compounds is within the limits (±0.4). **TLC Solvents for Scheme: (A_1-A_9)** Acetone: Ethyl acetate: Methanol (2:4:1), **(B_1-B_9)** Ethyl acetate: Hexane (1:3)

IV. SPECTRAL STUDY

Infrared Spectra.

^{1}H-NMR Spectra: **^{1}H-NMR Spectra.**

UV-visible Spectra.

Mass spectroscopy.

Table 4: Infra Red / ^{1}H-NMR spectral study of the synthesized compounds. (A_1-B_9)

Compd. Code	IR Bands (cm^{-1})	Types of Vibrations	δ Values in ppm	No. of Protons
A_1	3029.90 2870.35 1495.32 3289.23 1680.09 1477.05 1169.21 785.10 1580.23	C-H stretch (Aromatic) CH stretch (Alkane) C-C stretch (Aromatic) N-H stretch (Amine) C=O stretch (Ketone) C-N stretch (Ring) S=O (Ali. Chain) C-Cl (Aromatic) N-N (Aromatic)		
A_2	3045.64 2890.43 1567.37 1480.32 3457.20 1678.43	C-H stretch (Aromatic) CH stretch (Alkane) C-C stretch (Aromatic) C-N stretch (Ring) N-H stretch (Amine) C=O stretch (Ketone)		

	1713.14 734.22	C-O-C stretch (Ester) C-Cl (Aromatic)		
A_3	1540.51 3075.28 2877.65 3470.78 1667.42 1458.91 2565.37 749.74	C-C stretch (Aromatic) C-H stretch (Aromatic) CH stretch (Alkane) N-H stretch (Amine) C=O stretch (Ketone) C-N stretch (Ring) S-H stretch (Ali.Chain) C-Cl (Aromatic)		
A_4	2987.45 3059.44 1530.76 3389.90 1678.21 1440.57 1714.10 1170.42 734.95	C-H stretch (Alkane) C-H stretch (Aromatic) C-C stretch (Aromatic) N-H stretch (Amine) C=O stretch (Ketone) C-N stretch (Ring) C-O-C stretch (Ester) S=O stretch (Ali. Chain) C-Cl (Aromatic)	7.1-7.3 7.7-7.8 8.8-8.9 3.2-3.4 1.3-1.4 7.3 8.0, 9.7	4H(CH, aryl) 4H(CH, aryl) 2H(CH, pyridine) 2H(CH_2, methylene) 3H(CH_3, methyl) 3H(NH, amine) 1H(NH, aromatic amine)
A_5	2876.33 3091.26 1522.43 1364.71 1655.22 3378.31 1712.40 731.28	CH stretch (Alkane) C-H stretch (Aromatic) C-C stretch (Aromatic) C-N- stretch (Ring) C=O stretch (Ketone) N-H stretch (Amine) C-O-C (stretching) C-Cl (Aromatic)		
A_6	3089.35 2883.26 1524.32 3379.54	C-H stretch (Aromatic) CH stretch (Alkane) C-C stretch (Aromatic) N-H stretch (Amine)		

	1650.27	C=O stretch (Ketone)		
	1366.71	C-N stretch (Ring)		
	1729.07	C-O-C (stretching)		
	2564.31	S-H (stretching)		
	732.01	C-Cl (Aromatic)		
	3087.75	C-H stretch (Aromatic)		
	2856.90	CH stretch (Alkane)		
	1370.59	C-N stretch (Ring)		
	1571.37	C-C stretch (Aromatic)		
	1683.38	C=O stretch (Ketone)		
	3410.52	N-H stretch (Amine)		
A_7	1743.21	C-O-C (stretching)		
	1167.32	S=O stretch (Ali. Chain)		
	730.31	C-Cl (Aromatic)		
	3076.26	C-H stretch (Aromatic)		
	2790.87	CH stretch (Alkane)		
	1574.45	C-C stretch (Aromatic)		
A_8	3428.65	N-H stretch (Amine)		
	1678.44	C=O stretch (Ketone)		
	1380.91	C-N stretch (Ring)		
	1742.56	C-O-C (stretching)		
	730.32	C-Cl (Aromatic)		
	3075.45	C-H stretch (Aromatic)	1.5-1.6	1H(SH, thiol)
	2791.67	CH stretch (Alkane)	8.9-9.0	2H(CH,2-pyrazine)
	1573.51	C-C stretch (Aromatic)	7.2-7.3	4H(CH, aryl)
A_9	1382.77	C-N stretch (Ring)	6.9-7.0	3H(CH, aryl)
	3421.40	N-H stretch (Amine)	9.6-9.7	1H(NH,aromatic)
	1684.32	C=O stretch (Ketone)	2.5-2.6	2H(CH_2,methylene)
	1730.76	C-O-C (stretching)		
	2576.52	S-H (stretching)		
	731.04	C-Cl (Aromatic)		

B_1	1546.87	C-C stretch (Aromatic)		
	3078.44	C-H stretch (Aromatic)		
	2786.75	CH stretch (Alkane)		
	3420.09	N-H stretch (Amine)		
	1682.49	C=O stretch (Ketone)		
	1367.54	C-N stretch (Ring)		
	1732.09	C-O-C (stretching)		
	1154.32	S=O stretch (Ali. Chain)		
	1380.20	C-F (Aromatic)		
B_2	2843.74	CH stretch (Alkane)		
	3045.52	C-H stretch (Aromatic)		
	1552.33	C-C stretch (Aromatic)		
	1365.57	-C-N- stretch (Ring)		
	1689.55	C=O stretch (Ketone)		
	3458.52	N-H stretch (Amine)		
	1734.27	C-O-C (stretching)		
	1378.65	C-F (Aromatic)		
B_3	3056.77	C-H stretch (Aromatic)	3.0	1H,(SH, aromatic)
	2844.51	CH stretch (Alkane)	3.3	1H(CH methein)
	1554.32	C-C stretch (Aromatic)	1.2	3H(CH_3 methyl)
	3455.25	N-H stretch (Amine)	3.4	4H(CH_2 methylene)
	1366.43	-C-N- stretch (Ring)	2.3-2.4	4H(CH_2 methylene)
	1684.52	C=O stretch (Ketone)	7.5	1H(CH aryl)
	1733.08	C-O-C (stretching)	7.3	1H(H ethylene)
	2569.34	S-H (stretching)	2.1-2.2	3H(CH_3 methyl)
	1382.05	C-F (Aromatic)		
B_4	3060.63	C-H stretch (Aromatic)		
	2845.32	CH stretch (Alkane)		
	1368.55	C-N stretch (Ring)		
	1555.30	C-C stretch (Aromatic)		
	1673.43	C=O stretch (Ketone)		

	3356.55	N-H stretch (Amine)		
	1745.32	C-O-C (stretching)		
	1157.35	S=O stretch (Ali. Chain)		
	1380.43	C-F (Aromatic)		
	3056.77	C-H stretch (Aromatic)		
	2874.52	CH stretch (Alkane)		
B_5	1552.33	C-C stretch (Aromatic)		
	3464.21	N-H stretch (Amine)		
	1673.22	C=O stretch (Ketone)		
	1367.90	C-N stretch (Ring)		
	1766.89	C-O-C (stretching)		
	1378.70	C-F (Aromatic)		
	3076.81	C-H stretch (Aromatic)		
	2854.47	CH stretch (Alkane)		
	1556.73	C-C stretch (Aromatic)		
B_6	1387.76	C-N stretch (Ring)		
	3465.96	N-H stretch (Amine)		
	1672.30	C=O stretch (Ketone)		
	1765.90	C-O-C (stretching)		
	2568.76	S-H (stretching)		
	1375.32	C-F (Aromatic)		
	1554.57	C-C stretch (Aromatic)		
	3076.55	C-H stretch (Aromatic)		
B_7	2865.43	CH stretch (Alkane)		
	3467.89	N-H stretch (Amine)		
	1673.59	C=O stretch (Ketone)		
	1350.90	C-N stretch (Ring)		
	1766.43	C-O-C (stretching)		
	1158.13	S=O stretch (Ali. Chain)		
	1365.54	C-F (Aromatic)		
	2854.43	CH stretch (Alkane)	9.9	1H(CH, 2-pyrazine)

B_8	3080.64	C-H stretch (Aromatic)	7.5-7.6	4H(C-H aryl)
	1543.40	C-C stretch (Aromatic)	2.2	3H(CH_3 methyl)
	1677.42	C=O stretch (Ketone)	8.9-9.0	2H(CH,2-pyrazine)
	1348.53	C-N stretch (Ring)	3.4,2.3	4H(CH_2 methylene)
	3465.42	N-H stretch (Amine)	8.0	1H(H ethylene)
	1765.30	C-O-C (stretching)	3.3	1H(CH metheine)
	1367.80	C-F (Aromatic)		
B_9	3083.54	C-H stretch (Aromatic)		
	2890.65	CH stretch (Alkane)		
	1554.41	C-C stretch (Aromatic)		
	3470.44	N-H stretch (Amine)		
	1689.42	C=O stretch (Ketone)		
	1352.77	C-N stretch (Ring)		
	1370.23	C-F (Aromatic)		
	2567.34	S-H (stretching)		
	1760.31	C-O-C (stretching)		

IR spectras were taken for all compounds. However, NMR spectra were taken only for prototype of compounds.

ANTI-BACTERIAL ACTIVITY

a) Method: Cup-plate agar diffusion method using Nutrient agar.

b) Materials Used:

Culture: Two G positive and one G negative was chosen for screening.

Gram positive organisms: *Staphylococcus aureus* (ATCC 29737) and *Bacillus subtilis* (ATCC 6633) Gram negative organism: *Escherichia coli* (NCTC 10418)

Media: Nutrient agar media from Hi-Media was used with composition:

Method of testing: Nutrient agar plates were prepared by pouring 15-20 mL of the medium into each sterilized Petri dish and were allowed to set at room temperature. The cell suspension was

standardized to the density of 530nm using spectrophotometer and was inoculated over the surface of agar medium using sterile cotton swab. The cups were scooped in each plate using a sterile cork borer of 6mm diameter. Then the solutions of test compounds (0.10 mL) were added in cups by using micropipettes and these plates were incubated at 37°C for 48 hrs. The zone of inhibition was measured in mm for each organism.

Observation:

Plates were observed within 20 to 24 hours and may be continued to incubate for 48 hours. Zone of inhibition of the compound discs were measured and compared with the standard compound discs.

ANTI-TUBERCULAR ACTIVITY

The antitubercular screening was carried out by Middle brook 7H9 agar medium against $H_{37}Rv$. Strain. Middle brook 7H9 agar medium containing different derivatives, standard drug as well as control, Middle brook 7H9 agar medium was inoculated with *Mycobacterium tuberculosis* of $H_{37}Rv$ Strain. The inoculated bottles were incubated for 37°C for 4 weeks. At the end of 4 weeks, they were checked for growth.

ANTI- INFLAMMATORY ACTIVITY

***In-vitro* anti-inflammatory activity**

Method 1: Inhibition of protein denaturation

The standard drug and synthesized compounds were dissolved in minimum quantity of dimethyl formamide (DMF) and diluted with phosphate buffer (0.2 M, pH 7.4). Final concentration of DMF in all solution was less than 2.5%. Test solution (1mL) containing different concentrations of drug was mixed with 1 mL of 1mM albumin solution in phosphate buffer and incubated at 27 + 1°C in BOD incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 60 + 1°C in water bath for 10 min. After cooling, the turbidity was measured at 660nm (UV-Visible Spectrophotometer). Percentage of inhibition of denaturation was calculated from control where no drug was added. Each experiment was done in triplicate and average is taken.

Ibuprofen was used as standard drug. The percentage inhibition of denaturation was calculated by using following formula:

% of Inhibition = 100 X [1- Vt / Vc]

Where, Vt = Mean absorbance of test sample.

Vc = Mean absorbance of control

ANTIOXIDANT ACTIVITY

Hydrogen peroxide radical scavenging activity

1mL of test drug/standard (Ascorbic acid) was added to 0.6mL of hydrogen peroxide solution in phosphate buffer (pH - 7.4). After incubating for 10 minutes at 37^{o}C the absorbance was measured at 230nm. Corresponding blanks were taken. The experiment was performed in triplicate. The absorbance of hydrogen peroxide in phosphate buffer as control was measured at 230nm. The scavenging effect (%) was measured using following equation. Hydrogen peroxide produces hydroxyl radicals in cells. Scavenging of these radicals by the test drug is used as a test for antioxidant activity. The reduction of these radicals is seen by the decreased absorbance at 230nm with increasing concentration of the test drug.

$$\text{Scavenging Effect (\%)} \quad \frac{\text{Control absorbance} - \text{Test absorbance}}{\text{Control absorbance}} \quad \text{X } 100$$

Control Absorbance- 0.942

The results are expressed as mean ± SEM (n = 3). Significance was calculated by using one-way ANOVA with Dunnet's t- test. The difference in results was considered significant when $p<0.05$. *$p<0.05$ vs. Control.

RESULTS AND DISCUSSION

From the review of literature it is known that substituted pyrazolidine-3-one, aryl oxadiazole and mercapto oxadiazole have been reported for number of pharmacological activities. Here we have synthesized some novel pyrazolidine-3-one, aryl oxadiazole and mercapto oxadiazole and

screened them for their anti-microbial, anti-inflammatory, antioxidant and antitubercular activities and the results are as follows.

The synthesized pyrazolidine-3-one, aryl oxadiazole and mercapto oxadiazole derivatives were screened for antibacterial activity using DMF as a solvent against the organisms, *S. aureus*, and *E. coli*. by disc diffusion method on nutrient agar media. The standard drug used was Ciprofloxacin was used as standard for antimicrobial activity.

ANTIBACTERIAL ACTIVITY:

All the compounds were screened for antibacterial activity at 100 μcg/ml concentration. However, the compounds **A_1, A_2, A_6, A_8, A_9** and **B_1, B_2, B_3, B_4, B_5, B_7, B_8, B_9** have shown promising antibacterial activity against *E. coli* (NCTC 10418), and **A_3, A_5, A_6, A_8 and B_2, B_3, B_5, B_7, B_8, B_9** have shown promising activity against *S. aureus* (ATCC 29737) while the remaining compounds have also shown moderate antibacterial activity, when compared with standard drug Ciprofloxacin against *Staphylococcus aureus* (Gram positive) ATCC 29737, *Bacillus subtilis* and *Escherichia coli* (Gram negative) NCTC 10418.

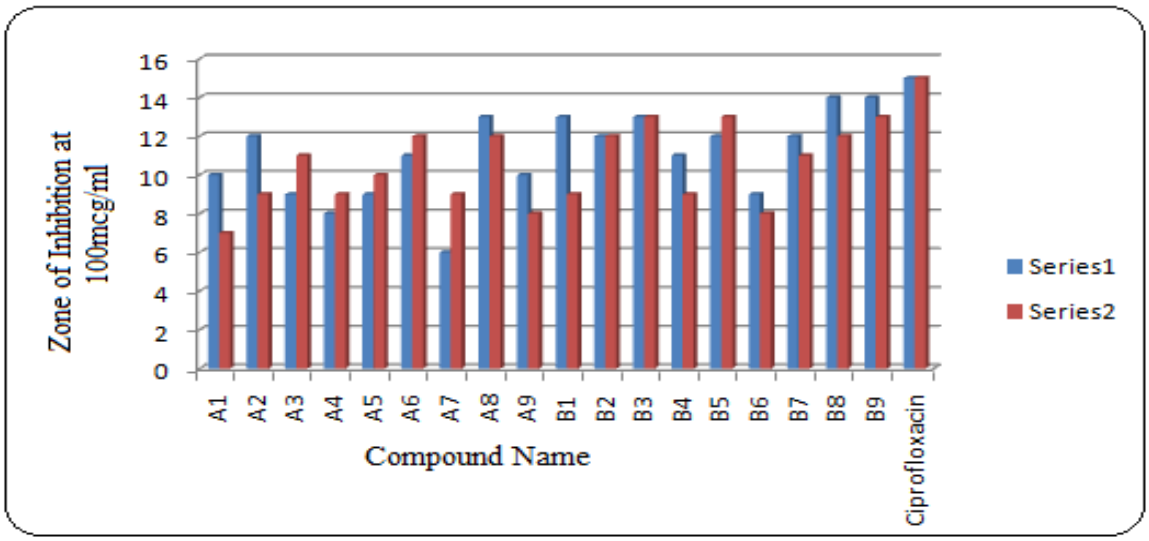
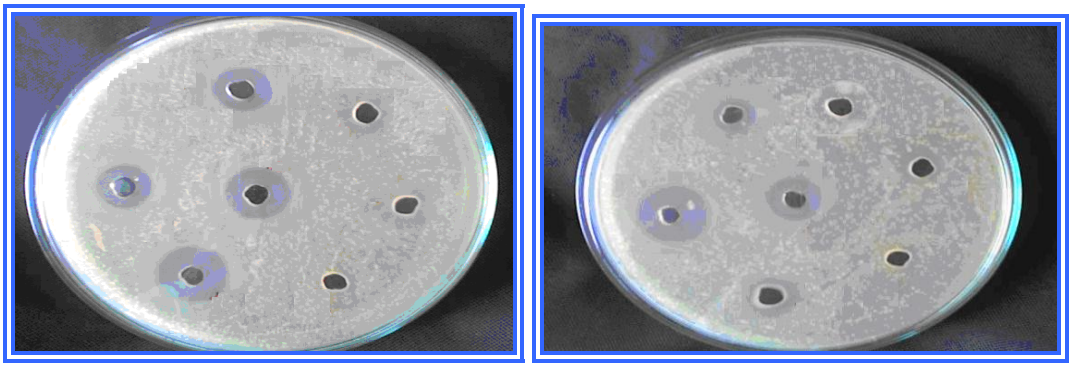


Fig. 1: Bar – Total Anti-bacterial activity of the synthesised compound (A_1-B_9)

Series 1 - *E. coli* (NCTC 10418), Series2 - *S. aureus* (ATCC 29737)

Fig.2: Zone of Inhibtion of anti-bacterial synthesized compounds



Staphylococcus aureus ***Escherichia coli***

ANTI-TUBERCULAR ACTIVITY:

All the compounds were screened for antitubercular activity by Middle brook 7H9 agar medium as described by Elmer WK et al. against $H_{37}Rv$ Strain. Compounds **A_2, A_6, A_7, B_1, B_2, B_3, B_4, B_5 B_7, B_8, B_9** have shown promising antitubercular activity. Streptomycin was used as standard drug. However, Streptomycin has shown antitubercular activity at 25 ucg/ml.

ANTI-INFLAMMATORY ACTIVITY:

All the compounds were screened for *in-vitro* anti-inflamatory activity at different concentration like 100 and 200 µg/mL by inhibition of protein denaturation method. Compounds **A_1, A_3, A_4, A_5, A_7, A_9, B_1, B_4** and **B_5** have shown promising anti-inflammatory activity at 100 µg/mL concentration and **A_1, A_4, A_3, A_5, A_6, A_8, A_9, B_2** and **B_7** have shown promising anti-inflammatory activity at 200 µg/mL concentration. Ibuprofen was used as standard drug. Series 1-100 mcg/ml concentraton, Series 2-200 mcg/ml concentration.

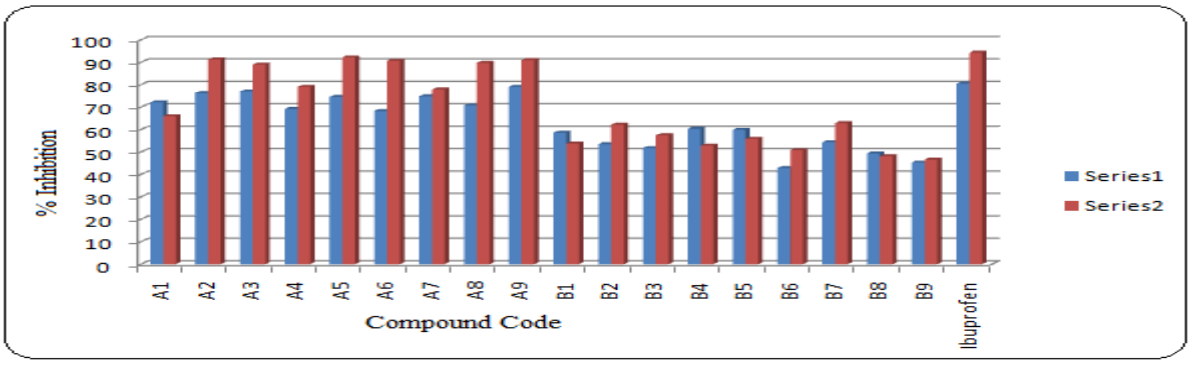


Fig. 3: Bar-Total Anti-inflammatory activity of synthesised compound (A_1-B_9)

ANTIOXIDANT ACTIVITY:

All the compounds were screened for antioxidant activity at different concentration. However Compounds **B_2 & B_9 ,B_9 & A_8** have shown promising antioxidant activity at 50 and 100 µg/mL respectively, **A_2, A_3, A_5, A_6, A_8, A_9, B_2, B_3, B_5, B_6, B_8 and B_9** have shown promising antioxidant activity at 150 µg/mL while the remaining compounds have also shown moderate antioxidant activity, when compared with standard drug ascorbic acid.

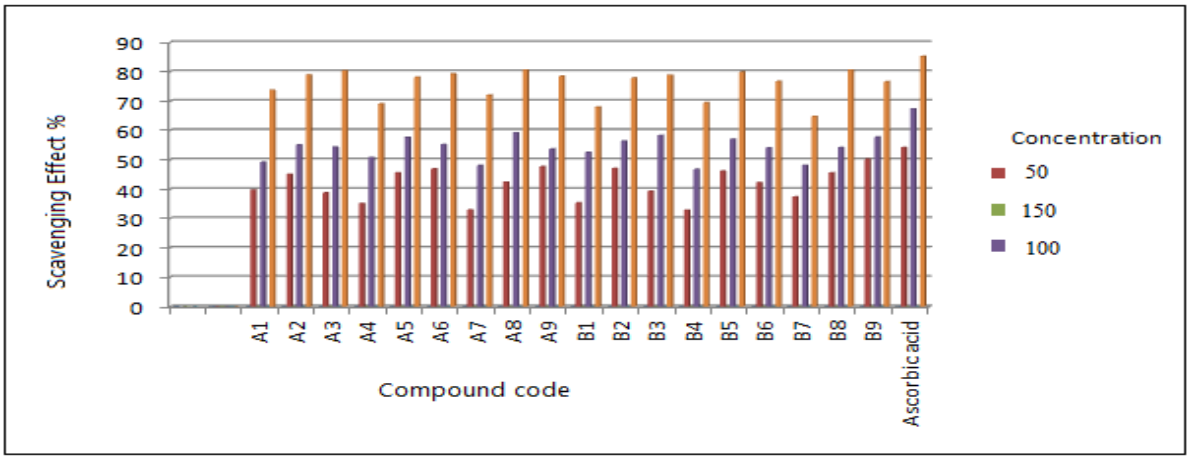


Fig.4: Bar-Total antioxidant capacity of the synthesized compounds A_1-A_9 and B_1-B_9

From the figure all compounds showed antioxidant capacity whereas compounds **A_2, A_3, A_5, A_6, A_8, A_9, B_2, B_3, B_5, B_6, B_8 and B_9** showed good antioxidant capacity.

CONCLUSION

The present work is for the synthesis of derivatives of pyrazolidine-3-one, aryl oxadiazole and mercapto oxadiazole. In this view, we have made extensive review on pyrazolidine-3-one and substituted oxadiazole derivatives for their medicinal values with the help of chemical abstracts. Synthesis of pyrazolidine-3-one, aryl oxadiazole and mercapto oxadiazole were established. Around 18 new derivatives were synthesized, with the standard chemicals and well established procedures. The synthesized compounds were tested for their preliminary tests, physical constants and TLC etc. The structures of the final compounds were confirmed by IR of all, ^{1}H-NMR spectra and CHN analysis were carried out for prototype of compounds. The proposed compounds were screened for their antimicrobial, antitubercular, anti-inflammatory and

antioxidant activities with the standard drugs in the well-equipped microbiology and pharmacology lab by using standard methods.

Compounds **A_1, A_2, A_3, A_5, A_6, A_8, A_9, B_1, B_2, B_3, B_4, B_5, B_6, B_7, B_8,** and **B_9** have shown promising antibacterial activities against *Escherichia coli* and *staphylococcus aureus*.

Compounds **A_1, A_3, A_4, A_5, A_6, A_7, A_8, A_9, B_1, B2, B_4, B_5** and **B_7** have exhibited excellent anti-inflammatory activity. Standard used for anti-inflammatory activity is Ibuprofen.

All the compounds were screened for anti-tubercular activity **A_1-B_9** And **A_2, A_6, A_7, B_1, B_2, B_3, B_4, B_5 B_7, B_8, B_9** showed promising activity as compared to standard drug Streptomycin.

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