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DESIGN, SYNTHESIS, ANTIMICROBIAL AND ANTI – INFLAMMATORY CTIVITIES OF SOME N-{3-[2-(SUBSTITUTED SULFANYL) –1H- ENZIMIDAZOL-1-YL]-4H (SUBSTITUTED)-1, 2, 4 – TRIAZOLE AND 2-(SUBSTITUTED SULFANYL)-1-[5-SUBSTITUTED -1, 3, 4 – OXADIAZOL -2-YL]-1H-BENZIMIDAZOLE DERIVATIVES

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ABSTRACT

A Novel Series of Some substituted *N*-{3-[2-(substituted sulfanyl)-1*H*-benzimidazol-1-yl]-4*H (substituted)*-1,2,4-triazole and 2-(substituted sulfanyl)-1-[5-substituted -1, 3, 4-oxadiazol-2-yl]-1*H*-benzimidazole derivatives (A_1-A_9 & B_1-B_9) were prepared with the aim to get better antibacterial activity, antifungal activity, antitubercular and anti-inflammatory activity. The structures of synthesized compounds were supported by means of IR, ^{1}H NMR and Mass spectroscopy. Title compounds were evaluated for antibacterial activity, antifungal activity, antitubercular and anti-inflammatory activities. Among the synthesized compounds ,some compounds found to possess all these activities. The QSAR study for anti imflamatory activity shows good results.

KEYWORDS: QSAR, Antibacterial, antifungal, anti-inflammatory activity, *N*-{3-[2-(substituted sulfanyl) -1*H*-benzimidazol-1-yl]-4*H (substituted)* -1, 2, 4-triazole and 2 - (substituted sulfanyl) -1-[5-substituted -1, 3, 4-oxadiazol-2-yl]-1*H*-benzimidazole.

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INTRODUCTION

The diverse biological activities of benzimidazole derivatives made an impact to direct the attention of medicinal chemist as a promising class of a heterocyclic compounds with profound biological activities. Specifically, this nucleus is a constituent of vitamin-B_{12}. This ring system is present in numerous antioxidant, antiparasitic, antihelmintics, antiproliferative, anti-HIV, anticonvulsant, anti - inflammatory, antihypertensive, antineoplastic and antitrichinellosis activities. Varied bioactivities exhibited by benzimidazoles, efforts have been made from time to time to generate libraries of these compounds and screened them for potential biological activities. Also it is well documented that oxadiazole nucleus is associated with a variety of pharmacological actions. It displays pronounced anticonvulsant, antifungal and antimycobacterial activities. Extensive biochemical and pharmacological studies have confirmed that benzimidazoles molecules are effective against various strains of microorganisms. Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities. Looking at the importance of benzimidazoles and oxadiazole nucleus, it was thought that it would be worthwhile to design and synthesize some new benzimidazoles derivatives bearing oxadiazole moiety and screen them for potential biological activities. On the other hand, five-membered 1, 3, 4-oxadiazole heterocycles are also useful intermediates for the development of molecules of pharmaceutical interest where several promising antitumor compounds are found to contain the oxadiazole ring system. 1, 3, 4-Oxadiazole heterocycles are good bioisosteres of amides and esters, which can contribute substantially in increasing pharmacological activity by participating in hydrogen bonding interactions with the receptors.

MATERIALS AND METHODS

Melting points were determined in open capillary method and are uncorrected. The ^{1}H-NMR spectra were recorded on sophisticated multinuclear FT-NMR Spec-trometer model Advance-II (Bruker) using dimethylsulfoxide-d_6 as solvent and tetramethylsilane as internal standard. The FTIR spectra are recorded on the Thermo Nicolet spectrophotometer using KBr disc method.Biological activity (anti-inflammatory activity) values are reported as inhibitory activity on Carrageenan induced rat paw oedema (% inhibition at 2 hr). Pharmacological screening values were by converted into Log (% Inh) were used for multiple correlation analysis with descriptors generated using TSAR 3.3 software.

QSAR METHODOLOGY

All molecules were drawn in Chem draw ultra 8.0 module in Chem office 2004 software and imported into TSAR software. Charges were derived using Charge 2-Derive charges option and optimized by using Cosmic-optimize 3 D option in the structure menu of the project table. Substituents were defined and descriptors were calculated for whole molecule as well as for the Substituents. Several equations were generated correlating both Log (% Inh) with physicochemical parameters (descriptors) by multiple linear regression analysis (MLR) method. Data was standardized by range and leave one out method was used for cross validation. Models were excluded if correlation was exceeding 0.9 for more rigorous analysis. Correlation matrix was generated to find any Intercorrelation between the descriptors. Intercorrelation between the descriptors in the final equation is less than 0.2.[1]

ANTIMICROBIAL SCREENING

Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli* (MTCC 443), *Bacilus subtilis* (ATCC12228) and *Staphylococcus aureus* (ATCC25923) bacterial strains by disc diffusion method. In all the determinations tests were performed in triplicate and the results were taken as a mean of three determinations. Levofloxacin was used as a standard drug[2].

Anti fungal activity

The newly synthesized compounds were screened for their antifungal activity against *C.*

albicans and *A. niger* in DMSO by agar diffusion method. In all the determinations tests were performed in triplicate and the results were taken as a mean of three determinations. Amphotericin B was used as a standard drug.

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[3].

Anti-inflammatory activity

Carrageenan Induced hind Paw Edema

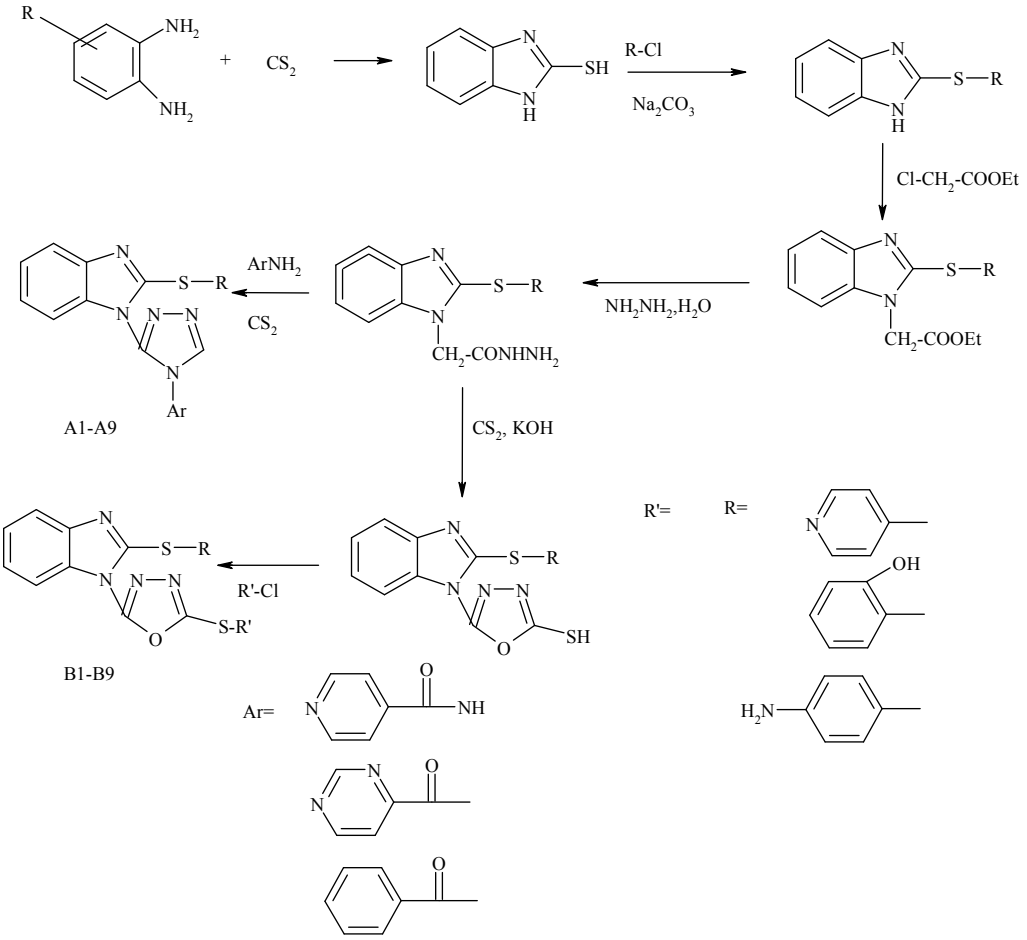
Anti-inflammatory activity was carried out by Carrageenan Induced Rat hind Paw method of winter *et al.* wistar rats (120-150 g) was used for the experiment. The conventional laboratory diet was fed with adequate supply of drinking water. The animals were randomly selected, marked to permit individual identification and kept in polypropylene cages for one week prior to dosing to allow acclimatization of them to laboratory conditions. The drugs were prepared as a suspension by triturating with water and 0.5% sodium CMC. The standard group received 50mg/kg body weight of Ibuprofen, test group received 200mg/kg body weight of synthesized compounds and the control group received 1% w/v of CMC[4].

Synthesis of N-{3-[2-(substituted sulfanyl) -1H-benzimidazol-1-yl]-4H (substituted)-1, 2, 4-triazole (A_1-A_9)

To a Mixture of 0.01 mole of hydrazide, $FeCl_3.6H_2O$ (0.02 mole) & 0.01 mole of INH / Pyrazinamide/ Benzamide was ground by pestle & mortar at room temp. After complete conversion as indicated by TLC. The reaction mixture was digested with water. The resultant solid was filtered, washed with water. The crude material is purified by recrystallization from methanol to afford corresponding triazoles (A_1-A9)[5].

Synthesis of 2-(substituted sulfanyl)-1-[5-substituted -1, 3, 4-oxadiazol-2-yl]-1H-benzimidazole (B_1-B_9)

To a mixture of 0.01 moles (1.38) of 1,3,4-MERCAPTO-OXADIAZOLE, 0.01 mole of aryl chloride were taken in 250 ml round bottom flask attached to a refluxed condenser and refluxed with 50 ml of 95% abs. ethanol for 10 hrs. The resultant mixture was concentrated in 250 ml beaker and cooled at room temperature. Then it was acidified with dilute HCl. The solid mass thus separated out was filtered, dried. The same was recrystallized from ethanol to offer final product. (B_1-B_9)



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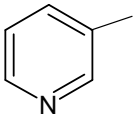
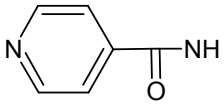
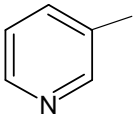
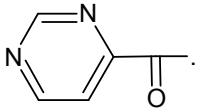
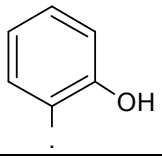
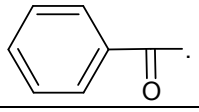
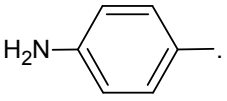
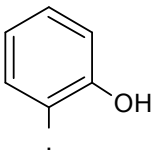
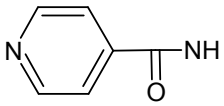
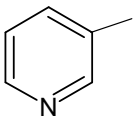
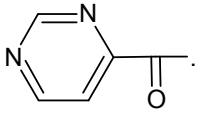
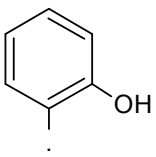
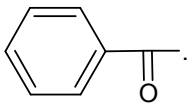
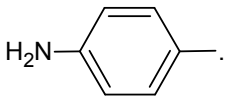
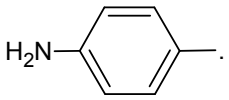
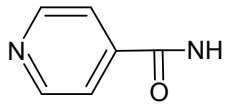
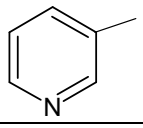
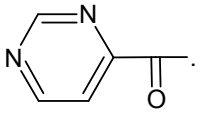
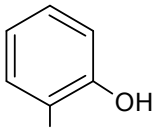
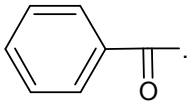
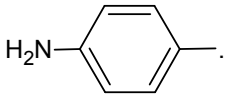
A_1			B_1	
A_2			B_2	
A_3			B_3	
A_4			B_4	
A_5			B_5	

A_6			B_6	
A_7			B_7	
A_8			B_8	
A_9			B_9	

SPECTRAL DATA

A_1- IR (KBr) cm^{-1}

3310.43 (-CH=CH str.), 3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str). ^{1}H NMR: (δ ppm): 9.06 (CH, 4-pyridine), 8.0 (NH, sec. amide), 7.26 (CH, Benz-imidazole), m/e (100%) - 414.10

A_2- IR (KBr) cm^{-1}

3310.43 (-CH=CH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str). ^{1}H NMR-(δ ppm): 8.3 (CH, 1, 2, 4 triazole), 7.26 (CH, Benz-imidazole), 7.04 (CH,4-pyridine), m/e (100%)-400.09

A_3- IR (KBr) cm^{-1}

3310.43 (-CH=CH str.), 3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str). ^{1}H NMR-(δ ppm): 8.8 (CH, 1, 2, 4 triazole), 7.26 (CH, Benz-imidazole), 7.54 (CH, 1-Benzene), m/e (100%) - 398.09

A_4- IR (KBr) cm^{-1}

3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str). ^{1}H NMR- (δ ppm): 8.3 (CH, 1, 2, 4 triazole), 7.26 (CH, Benz-imidazole), 7.96 (CH,4-pyridine), m/e (100%) – 429.10

A_5- IR (KBr) cm^{-1}

3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str). ^{1}H NMR-(δ ppm): 8.3 (CH, 1, 2, 4 triazole), 7.26 (CH, Benz - imidazole), 8.29 (CH, 4-pyridine), m/e (100%) – 415.09

A_6- IR (KBr) cm^{-1}

3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str). ^{1}H NMR-(δ ppm): 8.8 (CH, 1, 2, 4 triazole), 7.26 (CH, Benz-imidazole), 6.66 (CH, 1-Benzene), m/e (100%) - 413.09

A_7- IR (KBr) cm^{-1}

3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 1016.11 (-C-O-C str.). ^{1}H NMR- (δ ppm): 8.3 (CH, 1, 2, 4 triazole), 7.26 (CH, Benz-imidazole), 6.26 (CH, 1-Benzene), 8.0 (NH, sec. amide), m/e (100%) – 428.12

A_8- IR (KBr) cm^{-1}

3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 1016.11 (-C-O-C str.). ^{1}H NMR-(δ ppm): 8.3 (CH, 1, 2, 4 triazole), 7.26 (CH, Benz-imidazole), 6.26 (CH, 1-Benzene), 4.0 (NH2, Aromatic C-NH), m/e (100%) – 414.10

A_9- IR (KBr) cm^{-1}

3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 1016.11 (-C-O-C str.). ^{1}H NMR-(δ ppm): 8.3 (CH, 1, 2, 4 triazole), 7.26 (CH, Benz-imidazole), 6.26 (CH, 1-Benzene), 4.0 (NH2, Aromatic C-NH), m/e (100%) – 412.11

B_1-IR (KBr) cm^{-1}

3310.23 (-CH=CH str.), 3010.23 (Ar-CH str.), 1689.78 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str), 1016.38 cm^{-1}(-C-O-C str), 3210.45 (-OH str.), 3208.13 (-NH_2 str.), 3010.23 (Ar-CH str.), 1689.78 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str), 1016.38 cm^{-1}(-C-O-C str), ^{1}H NMR-(δ ppm): 7.26 (CH, Benz - imidazole), 7.30 (CH,4-pyridine), m/e (100%) – 404.05

B_2- IR (KBr) cm^{-1}

3310.23 (-CH=CH str.), 3208.12 (-NH_2 str.), 3010.23 (Ar-CH str.), 1689.78 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str), 1016.38 cm^{-1}(-C-O-C str), ^{1}H NMR-(δ ppm): 7.26 (CH, Benz-imidazole), 8.29 (CH,4-pyridine), 6.30 (CH, 1-Benzene), 4.0 (NH2, Aromatic C-NH), m/e (100%) – 414.05

B_3- IR (KBr) cm^{-1}

3310.23 (-CH=CH str.), 3208.12 (-NH_2 str.), 3210.45 (-OH str.), 3010.23 (Ar-CH str.), 1689.78 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str), 1016.38 cm^{-1}(-C-O-C str), ^{1}H NMR-(δ ppm): 7.26 (CH, Benz-imidazole), 8.29 (CH,4-pyridine), 6.30 (CH, 1-Benzene), 4.0 (NH2, Aromatic C-NH), m/e (100%) – 417.08

B_4- IR (KBr) cm^{-1}

3010.23 (Ar-CH str.), 2810.23 (-CH_3 str.), 1689.78 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str), 1016.38 cm^{-1}(-C-O-C str), ^{1}H NMR-(δ ppm): 7.26 (CH, Benz-imidazole), 6.66 (CH, 1-Benzene), 5.00 (OH, Aromatic C-OH) m/e (100%) – 419.05

B_5-: IR (KBr) cm^{-1}

3210.45 (-NH_2 str.), 3010.23 (Ar-CH str.), 1689.78 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str), 1016.38 cm^{-1}(-C-O-C str), ^{1}H NMR-(δ ppm): 7.26 (CH, Benz-imidazole), 6.66 (CH, 1-Benzene), 5.00 (OH, Aromatic C-OH), m/e (100%) – 434.05

B_6- IR (KBr) cm^{-1}

3210.45 (-NH_2 str.), 3010.23 (Ar-CH str.), 1689.78 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str), 1016.38 cm^{-1}(-C-O-C str), ^{1}H NMR- (δ ppm): 7.26 (CH, Benz-imidazole), 6.66 (CH, 1-Benzene), 5.00 (OH, Aromatic C-OH), 4.0 (NH2, Aromatic C-NH), m/e (100%) – 433.07

B_7- IR (KBr) cm^{-1}

3210.45 (-OH str.), 3208.13 (-NH_2 str.), 3010.23 (Ar-CH str.), 1689.78 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str), 1016.38 cm^{-1}(-C-O-C str), ^{1}H NMR-(δ ppm): 7.26 (CH, Benz-imidazole), 6.66 (CH, 1-Benzene), 4.0 (NH2, Aromatic C-NH), m/e (100%) – 418.07

B_8- IR (KBr) cm^{-1}

3010.23 (Ar-CH str.), 1689.78 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str), 1016.38 cm^{-1}(-C-O-C str), ^{1}H NMR- (δ ppm): 7.26 (CH, Benz-imidazole), 6.66 (CH, 1-Benzene), 5.00 (OH, Aromatic C-OH), 4.0 (NH2, Aromatic C-NH), m/e (100%) – 433.07

B_9- IR (KBr) cm^{-1}

3210.23 (-NH_2 str.), 3010.23 (Ar-CH str.), 1689.78 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str), 1016.38 cm^{-1}(-C-O-C str), ^{1}H NMR- (δ ppm): 7.26 (CH, Benz-imidazole), 6.66 (CH, 1-Benzene), 4.0 (NH2, Aromatic C-NH), m/e (100%) – 432.08

ANTI-INFLAMMATORY ACTIVITY

Anti-inflammatory activity was carried out using carrageenan - induced hind paw edema method (Winter *et al*.1962). Wistar rats of either sex were divided into ten groups of six animals each. The first group served as control and received only vehicle (10% Tween 80 in distilled water), and the second group was administered standard drug ibuprofen (50 mg/kg, i.p.). The animals of the third to thirty eight groups were treated with A_1-A_9, B_1-B_9, respectively (100 µg/kg, i.p., each). All the prepared compounds were dissolved in the vehicle. After 30 min of the above treatments, 0.05 ml of 1%w/v carrageenan in saline was injected into the sub plantar tissue of the left hind paw of the animals. The degree of paw edema of all the groups was measured plethysmometrically at 0, 30, 60, 90 and 120 min after the administration of carrageenan to each group; 0 min readings are the initial paw volume of animals.

Table 1
Analytical & Physicochemical data of the synthesized compounds (A_1-A_9 & B_1-B_9)

Comp.	Mol. Formula	Mol. Wt.	M.P. ° C	Yield %	Elemental analyses Calcd. (found)		
					C	H	N
A_1	$C_{22}H_{17}N_5O$	367.40	196-198	75.64	71.92 (71.62)	4.66 (4.34)	19.06 (18.86)
A_2	$C_{21}H_{15}N_5O$	353.38	240-242	74.67	71.38 (71.08)	4.28 (3.92)	19.82 (19.68)
A_3	$C_{23}H_{18}N_4O$	366.42	231-233	68.24	75.39 (75.08)	4.95 (4.64)	15.29 (14.98)
A_4	$C_{21}H_{17}N_5O_2$	371.39	225-257	77.06	67.91 (67.61)	4.61 (4.35)	18.86 (18.65)
A_5	$C_{20}H_{15}N_5O_2$	357.37	250-252	66.95	76.22 (75.98)	4.23 (3.98)	19.60 (19.25)
A_6	$C_{22}H_{17}N_3O_2$	355.39	272-275	72.23	74.35 (74.03)	4.82 (4.48)	11.82 (11.70)
A_7	$C_{18}H_{13}N_5O_2$	331.33	188-190	64.99	65.25 (64.98)	3.95 (3.82)	21.14 (19.85)
A_8	$C_{17}H_{11}N_5O_2$	37.30	210-212	68.82	64.35 (63.98)	3.49 (3.15)	22.07 (21.85)
A_9	$C_{19}H_{13}N_3O_2$	315.33	228-230	75.68	72.37 (72.04)	4.16 (3.86)	13.33 (12.98)
B_1	$C_{23}H_{18}N_2O_2$	354.40	250-253	79.85	77.95 (77.65)	5.12 (4.85)	7.90 (7.65)
B_2	$C_{23}H_{19}N_3O_2$	369.42	230-233	80.12	74.78 (74.42)	5.18 (4.89)	11.37 (11.02)
B_3	$C_{23}H_{19}N_3O_3$	385.42	210-212	72.15	71.67 (71.33)	4.97 (4.78)	10.90 (10.68)
B_4	$C_{22}H_{120}N_2O_3$	360.41	184-186	67.94	73.32 (72.98)	5.59 (5.29)	7.77 (7.43)
B_5	$C_{22}H_{21}N_3O_3$	375.42	230-232	64.72	70.38 (70.02)	4.64 (4.25)	11.19 (10.95)
B_6	$C_{22}H_{21}N_3O_4$	391.42	263-265	71.67	67.51 (67.08)	5.41 (5.28)	10.17 (9.87)
B_7	$C_{19}H_{16}N_2O_3$	320.34	210-212	70.96	71.24 (70.98)	5.03 (4.88)	8.74 (8.39)
B_8	$C_{19}H_{17}N_3O_3$	335.36	233-235	71.67	68.05 (67.98)	5.11 (4.87)	12.53 (12.18)
B_9	$C_{19}H_{17}N_3O_4$	351.36	273-275	71.72	64.95 (64.64)	4.88 (4.51)	11.96 (11.65)

Table 2
Antibacterial and antifungal activity of synthesized compounds (A_1-A_9 & B_1-B_9)

Compd.	Zone of inhibition at 200µcg/mL (in mm.)				
	E. coli	*B.* Subtilis	S. aureus	*A.* niger	*C.* albicans
A_1	24	25	26	15	22
A_2	20	23	25	16	21
A_3	20	24	25	19	22
A_4	25	26	23	20	21
A_5	24	23	26	21	22
A_6	20	22	24	18	23
A_7	21	23	22	20	21
A_8	22	24	25	20	22
A_9	23	22	20	18	22
B_1	24	26	23	19	21
B_2	25	23	24	21	23
B_3	26	22	24	20	22
B_4	24	25	26	21	23
B_5	23	25	26	20	22
B_6	26	23	26	20	21
B_7	26	23	25	19	21
B_8	25	24	26	20	21
B_9	25	26	26	21	20
Levofloxacin	26	25	26	-	-
Amphotericin B	-	-	-	22	23

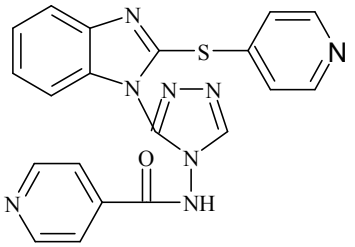
Table 3
Antitubercular activity of the synthesized compounds (A_1-A_9 & B_1-B_9)

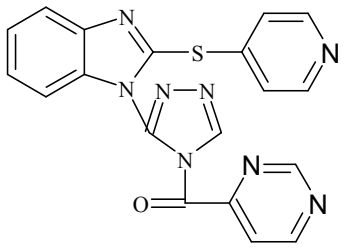
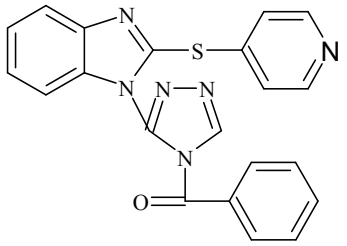
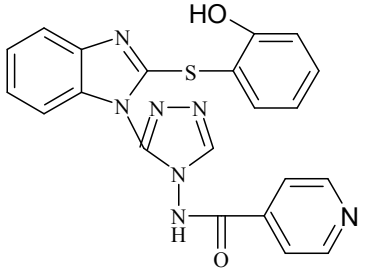
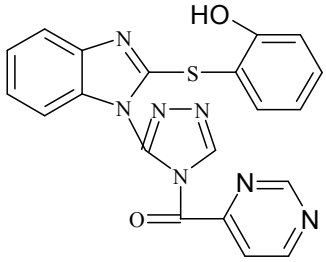
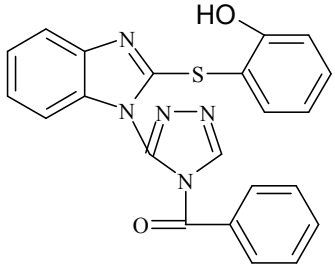
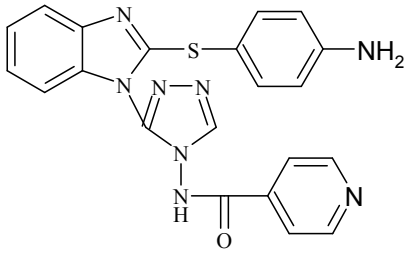
Compd.	25 µcg/mL	50 µcg/mL	100 µcg/mL
A_1	R	S	S
A_2	R	R	S
A_3	R	R	R
A_4	R	S	S
A_5	R	R	S
A_6	R	R	R
A_7	R	S	S
A_8	R	R	S
A_9	R	R	R
B_1	R	S	S
B_2	R	R	S
B_3	R	R	R
B_4	R	S	S
B_5	R	R	S
B_6	R	R	R
B_7	R	S	S
B_8	R	R	S
B_9	R	R	R
Streptomycin	S	S	S

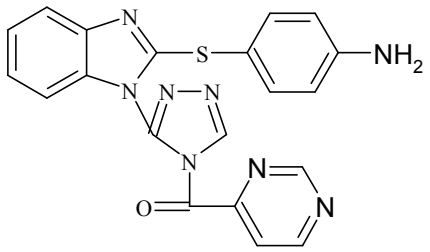
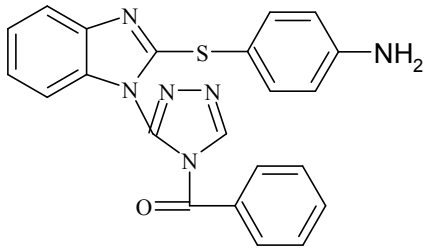
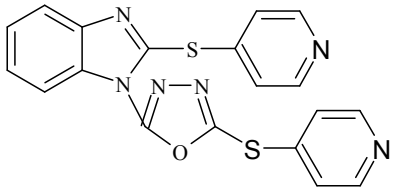
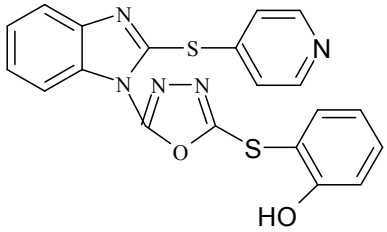
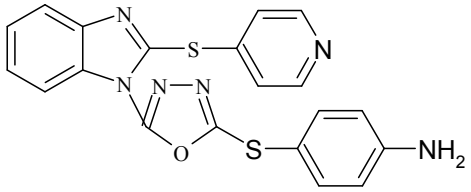
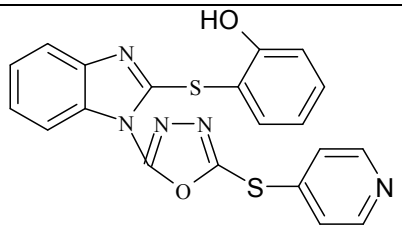
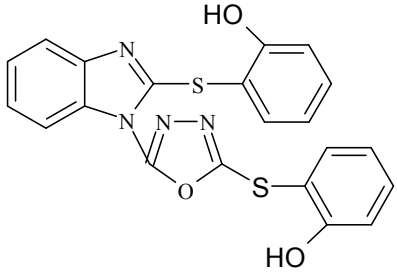
Table 4
Anti-inflammatory activity of synthesized compounds (A_{1-9}) and (B_{1-9})

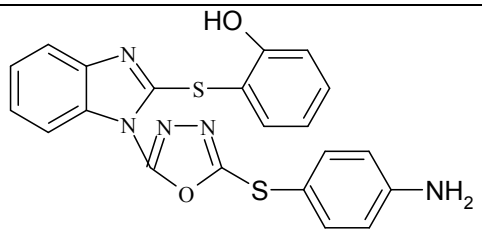
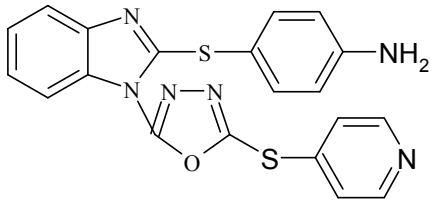
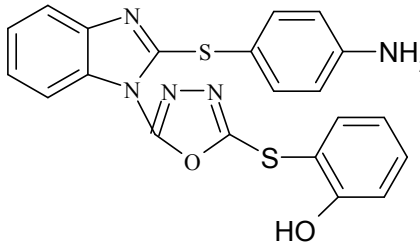
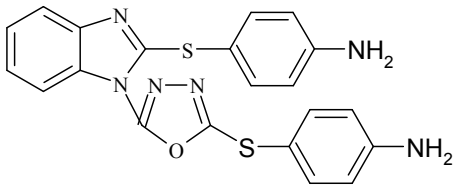
Treatment		Mean increase in paw volume (ml)±SEM Time in minute								
	0	% inhibition	30	% inhibition	60	% inhibition	90	% inhibition	120	% inhibition
Carrageenan(Control)	0.24±0.01		0.48±0.03		0.78±0.09		0.85±0.12		0.89±0.14	
Ibuprofen	0.24±0.03	0	0.31±0.07	35.41	0.30±0.07	61.53	0.27±0.06	68.23	0.26±0.13	70.78
A_1	0.24±0.01	0	0.32±0.03	33.33	0.31±0.01	60.25	0.29±0.01	65.88	0.27±0.01	69.66
A_2	0.24±0.02	0	0.34±0.03	29.16	0.35±0.01	55.12	0.32±0.01	62.35	0.30±0.02	66.29
A_3	0.24±0.01	0	.034±0.01	29.16	0.34±0.01	56.41	0.32±0.02	62.35	0.29±0.02	67.41
A_4	0.24±0.02	0	0.41±0.01	14.58	0.48±0.02	38.46	0.51±0.02	40.00	0.42±0.01	52.80
A_5	0.23±0.01	4.16	0.32±0.01	33.33	0.31±0.01	60.25	0.30±0.01	64.70	0.28±0.02	68.53
A_6	0.24±0.02	0	0.33±0.01	31.25	0.34±0.02	56.41	0.32±0.01	62.35	0.29±0.03	67.41
A_7	0.23±0.02	4.16	0.34±0.01	29.16	0.35±0.02	55.12	0.33±0.02	61.17	0.30±0.01	66.29
A_8	0.24±0.02	0	0.32±0.02	33.33	0.30±0.03	61.53	0.29±0.02	65.88	0.28±0.02	68.53
A_9	0.23±0.03	4.16	0.34±0.02	29.16	0.33±0.01	57.69	0.32±0.02	62.35	0.29±0.02	67.41
B_1	0.24±0.01	0	0.34±0.02	29.16	0.34±0.02	56.41	0.31±0.01	63.52	0.30±0.01	66.29
B_2	0.24±0.02	0	0.34±0.03	29.16	0.35±0.03	55.12	0.31±0.01	63.52	0.30±0.02	66.29
B_3	0.23±0.03	4.16	0.31±0.04	35.41	0.30±0.01	61.53	0.30±0.02	64.70	0.28±0.03	68.53
B_4	0.24±0.01	0	0.33±0.01	31.25	0.34±0.02	56.41	0.32±0.02	62.35	0.30±0.02	66.29
B_5	0.24±0.01	0	0.32±0.01	33.33	0.30±0.01	61.53	0.29±0.02	65.88	0.28±0.01	68.53
B_6	0.23±0.01	4.16	0.33±0.02	31.25	0.34±0.02	56.41	0.33±0.01	61.17	0.32±0.02	64.04
B_7	0.23±0.01	4.16	0.31±0.02	35.41	0.31±0.02	60.25	0.28±0.02	67.05	0.27±0.01	69.66
B_8	0.24±0.02	0	0.33±0.03	31.25	0.34±0.03	56.41	0.33±0.03	61.17	0.32±0.03	64.04
B_9	0.24±0.02	0	0.31±0.02	35.41	0.30±0.02	61.53	0.28±0.03	67.05	0.28±0.02	68.53

Table 5
Structures and Log (% Inh) of A_1-A_9 and B_1-B_9

Sr. No.	Comp. Name	Structure	% Inh	Log (% Inh)
1.	A_1		69.66	1.842983

2	A_2		66.29	1.821448
3.	A_3		67.41	1.828724
4.	A_4		52.80	1.722634
5.	A_5		68.53	1.835881
6.	A_6		67.41	1.828724
7.	A_7		66.29	1.821448

8.	A_8		68.53	1.835881
9.	A_9		67.41	1.828724
10.	B_1		66.29	1.821448
11.	B_2		66.29	1.821448
12	B_3		68.53	1.835881
13	B_4		66.29	1.821448
14	B_5		68.53	1.835881

15	B_6		64.04	1.806451
16	B_7		69.66	1.842983
17	B_8		64.04	1.806451
18	B_9		68.53	1.835881

RESULTS

Intercorrelation between the descriptors in the final equations is less than 0.2. Best Equations correlating Log (% Inh) with descriptors for series (A_1-A_9 and B_1-B_9) generated are presented in Table 6

Table 6
Equations generated between Log (% Inh) and descriptors

Sr. No.	Equation	N	S	R	r^2	r^2_{cv}	F
series (A_1-A_9 and B_1-B_9)	Y = - 0.218 * X3 - 1.576 * X2 - 13.218	18	0.364	0.835	0.697	0.487	13.816

Where
Y = Log (% Inh); X1: ClogP -; X2 = VAMP HOMO (Whole Molecule);
X3 = Dipole Moment Z Component (Whole Molecule);
X4 = Inertia Moment 2 Length (Whole Molecule)

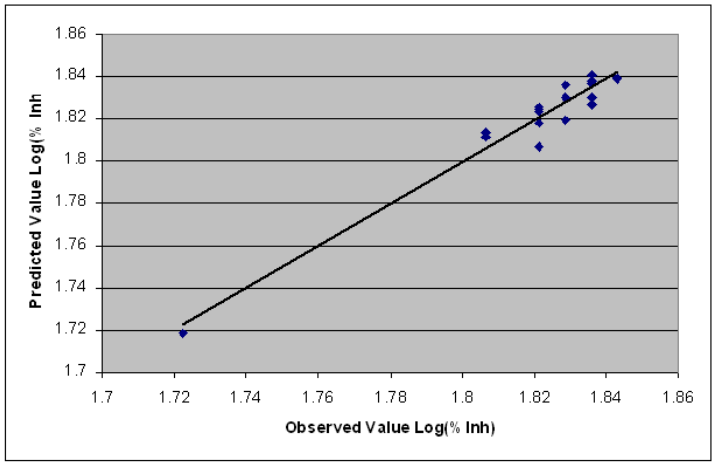
Significance of the terms –

N= No. of Molecules
s = standard error --- less is better
r = correlation coefficient – higher is better > 0.7,
r^2cv = cross validated r^2 - higher is better > 0.5,
F Value = higher is better
Observed and predicted data and graphs are presented in Table 6 and Graph I for Series

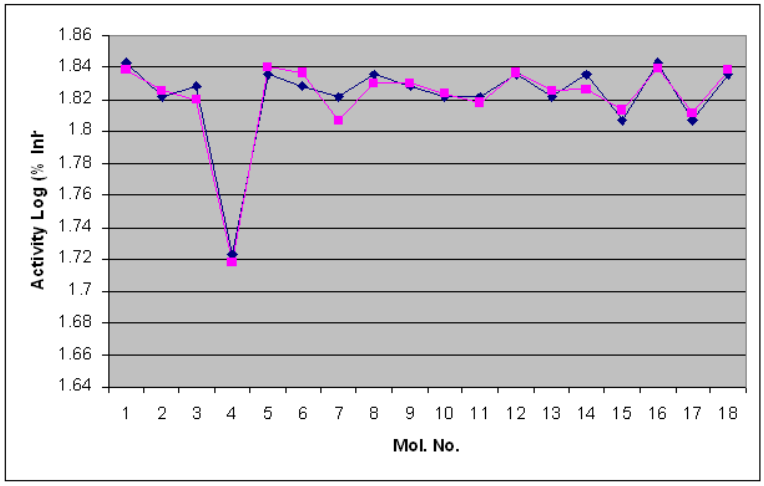
Table 7
Observed and predicted log (% Inh) value data for 18 compounds

Comp. No.	Observed Value	Predicted Value	Residual Value	Residual Variance
A_1	1.842983	1.83868347	-0.0043	0.0057
A_2	1.821448	1.825048019	0.0036	0.0078
A_3	1.828724	1.819724327	-0.009	0.0049
A_4	1.722634	1.718733923	-0.0039	0.0198
A_5	1.835881	1.840780732	0.0049	0.0073
A_6	1.828724	1.836424327	0.0077	0.0044
A_7	1.821448	1.807048019	-0.0144	0.0347
A_8	1.835881	1.829880732	-0.006	0.0184
A_9	1.828724	1.830024327	0.0013	0.0092
B_1	1.821448	1.823348019	0.0019	0.0075
B_2	1.821448	1.817948019	-0.0035	0.0034
B_3	1.835881	1.836480732	0.0006	0.0078
B_4	1.821448	1.825748019	0.0043	0.0042
B_5	1.835881	1.826780732	-0.0091	0.0091
B_6	1.806451	1.813751323	0.0073	0.0066
B_7	1.842983	1.83948347	-0.0035	0.0044
B_8	1.806451	1.811351323	0.0049	0.0087
B_9	1.835881	1.838280732	0.0024	0.0057

a)



b)



Graph I
a) Correlation graph and
b) Histogram of observed and predicted log (% Inh) data for 18 compounds

DISCUSSION

Statistical evaluation of the equations is in accepted range. The correlation coefficient is high with less standard error. The residual value and residual variance for each series also is less indicating good predictive power of models. From equation 1 it is observed that two electronic parameters Dipole Moment Z Component (Whole Molecule) and VAMP HOMO (Whole Molecule) contribute (-0.218 and – 1.576) negatively for the activity so electron withdrawing groups may enhance the activity (% Inh). The synthesized compounds were then screened for their anti bacterial activity using DMF as a solvent against the *E.coli, B.subtilis* and *S.aureus* microorganism. and antifungal activity using *C. albicans* and *A. niger* by disc diffusion method on nutrient agar media. The standard drug used was Levofloxacin and Amphotericin B for antibacterial and antifungal activity respectively.

Antibacterial activity

The compounds A_1, A_2, A_3, A_5, A_8, B_4, B_5 ,B_6, B_7, B_8, B_9 has excellent Antibacterial activity against *S. aureus*, the compounds A_1, B_4, B_5 have shown Antibacterial activity against *B. subtilis,* while A_4, B_2, B_3, B_6, B_7, B_8, B_9 shows Antibacterial activity against *E.coli.,* when compared with standard Levofloxacin

Antifungal activity

The compounds A_5, B_2, B_4, B_9 has excellent antifungal activity against *Aspergillus niger* (NCIM 596), while the compounds A_1, A_3, A_5, A_6, A_8, A_9, B_2, B_3, B_4, have shown Antifungal activity against *Candida albicans* (NCIM 3102) when compared with standard Amphotericin B.

Antitubercular 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_1, A_4, A_7, B_2, B_4 and B_7 has shown promising antitubercular activity.

Anti-Inflammatory Activity

All the compounds were evaluated for Anti-inflammatory activity by Carrageenan Induced Rat hind Paw method. The synthesized compounds A_2,A_4,A_5,A_6,A_8, B_1,B_3,B_7,and B_8 showed better anti-inflammatory activity found comparable with standard drug Ibuprofen (70.78% inhibition) at the same dose (100 µg/kg).

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