Bulgarian Chemical Communications, Volume 46, Number 1 (pp. 85 – 95) 2014

Design, synthesis and pharmacological screening of some [3-benzoyl-5-(4-substituted)-2, 3-dihydro-1,3,4-oxadiazol-2-yl] and [5-(4-substituted)-4*H*-1, 2, 4-triazol-3-yl] derivatives

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Received September 28, 2012; Revised April 15, 2013

A novel series of some substituted [3-benzoyl-5-(4-substituted)-2,3-dihydro-1,3,4-oxadiazol-2-yl] and [5-(4-substituted)-4*h*-1,2,4-triazol-3-yl] derivatives were prepared from benzoic acid hydrazones with the aim to get better antibacterial activity, antifungal activity, antitubercular and anti-inflammatory activity. Chemical 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. QSAR for the tittle compounds had been performed using TSAR 3.3 software and results were found satisfactory. Among the synthesized compounds some compounds found to possess all these activities

Key-words: QSAR**,** antibacterial, antifungal, antitubercular, anti-inflammatory activity.

INTRODUCTION

As the currently marketed drugs like isoniazide offer resistance against tubercle bacilli there is need to develop newer chemical entities which offer least resistance with suitable molecular modifications such as conversion into corresponding aryl Oxadiazoles, 1,2,4-triazole derivatives. This found fruitful in relieving these problems associated with currently marketed antitubercular drugs. Microbial infections have become more dreadful and dangerous so the search of new antibiotics and antibacterial is a continuous process in drug discovery. The 1,3,4-oxadiazole and 1,2,4-triazoles had been reported for various biological activities like antimicrobial activity [1], antitubercular activity[2], anticancer activity[3], anti-inflammatory activity[4] , MAO inhibitors [5] , analgesic activity [6], glycogen synthase kinase-3β inhibitors [7] etc. With reference to above reported medicinal utilities of 5-aryl-1,3,4- Oxadiazoles and 1,2,4-triazole derivatives promote to synthesize new potential 5-aryl-1,3,4- Oxadiazoles and 1,2,4-triazole derivatives and evaluate its possible pharmacological activities like antifungal, antibacterial, anti-HIV, anticancer, antitubercular, antiviral etc. Based on these observations it was planned to synthesize some 5-aryl-1, 3, 4-oxadiazole and 1, 2, 4-triazole derivatives and screened for antimicrobial, antitubercular and anti-inflammatory activities.

EXPERIMENTAL

Materials&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. IR spectra were recorded on Thermo Nicolet IR 200 spectrophotometer using KBr disc method. Biological activity (anti-inflammatory activity) values are reported as inhibitory activity on Carrageenan induced rat paw edema (% inhibition at 2 hr). Pharmacological screening values therein were 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 Chemoffice 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

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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. [8]

Antimicrobial screening

Antibacterial activity

The newly prepared 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 [9].

Anti fungal activity

The newly prepared 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

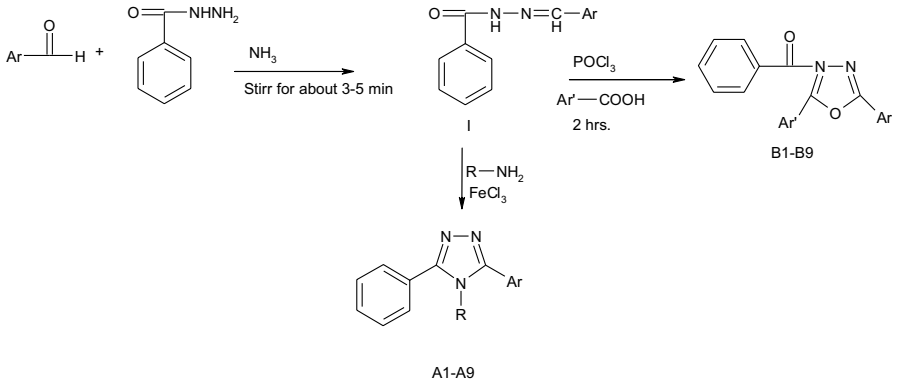
The antitubercular screening was carried out by Middle brook 7H9 agar medium against $H_{37}Rv$. Strain. Middle brook 7H9 agar medium containing different derivatives, standard drug as well as control, Middle brook 7H9 agar medium was inoculated with *Mycobacterium tuberculosis* of $H_{37}Rv$ Strain. The inoculated bottles were incubated for 37°C for 4 weeks. At the end of 4 weeks they were checked for growth. [10]

Anti-inflammatory activity

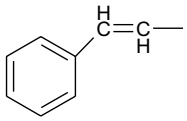
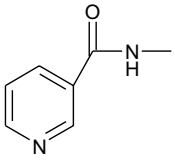
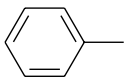
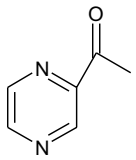
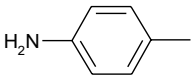
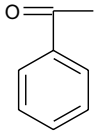
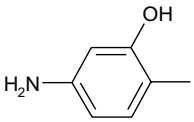
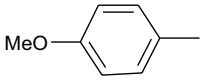
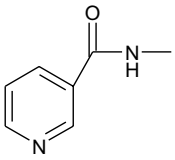
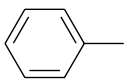
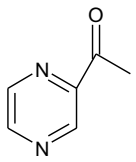
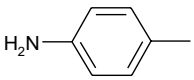
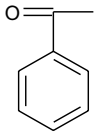
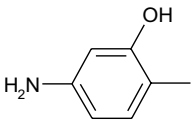
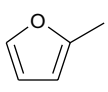
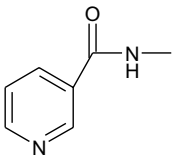
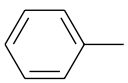
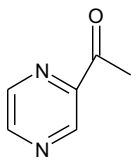
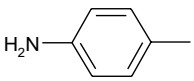
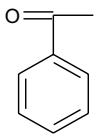
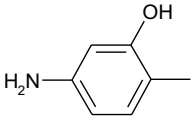
Carrageenan Induced hind Paw Edema: Anti-inflammatory activity was determined by Carrageenan Induced Rat hind Paw method of winter et al. wistar rats (120-150 g) was used for the experiment. The conventional laboratory diet was fed with adequate supply of drinking water. The animals were randomly selected, 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. [11]

Synthesis of [3-benzoyl-5-(4-substituted)-2, 3-dihydro-1, 3, 4-oxadiazol-2-yl] (A_1-A_9)

To a mixture of 0.01 mole of **I_1** and 0.01 mole of benzoic acid was added 10 mole of Phosphorus oxychloride at temp. of -5^{0}c. The reaction mixture refluxed at 100 ^{0} C 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 (**A1**). Similarly **1b-3c** was prepared using **2** and **3** along with Para Amino Benzoic acid and Para amino Salicylic acid respectively [12].



Scheme

Comp. Code	Ar	R	Comp. code	Ar'
A1			B_1	
A2			B_2	
A3			B_3	
A4			B_4	
A5			B_5	
A6			B_6	
A7			B_7	
A8			B_8	
A9			B_9	

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

Mixture of 0.01 mole of I_1, FeCl3.6H2O (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 **(B_1-B_3).** Similarly **B_4-B_9** was prepared using I_2 and I_3 respectively [13].

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:** 7.6-7.8 (4H pyridine), 6.8-7.0 (2H –CH=CH), 6.8-7.2 (10H phenyl), 4.0 (1H –NH), **m/e(100%):** 367.14

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:** 8.1-8.6 (3H pyrazine), 6.8-7.0 (2H –CH=CH), 6.8-7.2 (10H phenyl), **m/e(100%):** 353.13

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:** 6.8-7.0 (2H –CH=CH), 6.8-7.2 (15H phenyl), **m/e(100%):** 366.15

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:** 7.6-7.8 (4H pyridine), 6.8-7.2 (9H phenyl),4.0 (1H NH), 0.8-1.2 (3H –OCH_3), **m/e(100%):** 371.14

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:** 8.1-8.6 (3H pyrazine), 6.8-7.2 (9H phenyl), 0.8-1.2 (3H –OCH_3), **m/e(100%):** 357.12

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:** 6.8-7.2 (15 H phenyl),0.8-1.2 (3H –OCH_3), **m/e(100%):** 355.13

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:** 7.6-7.8 (4H pyridine), 6.8-7.2 (5H phenyl), 5.4-5.8 (3H furyl), 4.0 (1H NH), **m/e(100%):** 331.11

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:** 8.1-8.6 (3H pyrazine), 6.8-7.2 (5H phenyl), 5.4-5.8 (3H furyl), **m/e(100%):** 317.09

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:** 6.8-7.2 (10H phenyl), 5.4-5.8 (3H furyl), **m/e(100%):** 315.10

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), **^{1}H NMR:** 6.8-7.2 (15 H phenyl), 6.0-6.4 (2H –CH=CH), 5.8 (1H 1,3,4-Oxadiazolyl), **m/e(100%):** 354.14

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: 8.2-8.6 (3H pyrazine),** 6.8-7.2 (14H phenyl), 6.0-6.4 (2H –CH=CH), 5.8 (1H 1,3,4-Oxadiazolyl), 4.8-5.2 (2H –NH_2), **m/e(100%):** 369.15

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:** 6.8-7.2 (13H phenyl), 6.0-6.4 (2H –CH=CH), 5.8 (1H 1,3,4-Oxadiazolyl), 5.0 (1H –OH),4.2 (2H –NH_2), **m/e(100%):** 385.14

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:** 6.8-7.2 (14 H phenyl), 6.0-6.4 (2H –CH=CH), 5.8 (1H 1,3,4-Oxadiazolyl),0.8-1.2 (3H –CH_3), **m/e(100%):** 360.15

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:** 6.8-7.2 (13 H phenyl), 5.8 (1H 1,3,4-Oxadiazolyl), 4.8-5.2 (2H –NH_2), 0.8-1.2 (3H –CH_3), **m/e(100%):** 375.16

B_6: 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:** 6.8-7.2 (12 H phenyl), 5.8 (1H 1,3,4-Oxadiazolyl), 5.0 (1H –OH), 4.2 (2H –NH_2), 0.8-1.2 (3H –CH_3), **m/e(100%):** 391.15

B_7: 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:** 6.8-7.2 (10 H phenyl), 6.2-6.6 (3H furyl), 5.8 (1H 1,3,4-Oxadiazolyl), **m/e(100%):** 320.12

B_8: 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:** 6.8-7.2 (9H phenyl), 6.2-6.6 (3H furyl),

5.8 (1H 1,3,4-Oxadiazolyl),408-5.2 (2H –NH_2), **m/e(100%):** 335.13

B_9: 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:** 6.8-7.2 (8 H phenyl), 5.8 (1H 1,3,4-Oxadiazolyl), 5.0 (1H –OH), 4.2 (2H –NH_2), **m/e(100%):** 351.12

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	4.66	19.06
A_2	$C_{21}H_{15}N_5O$	353.38	240-242	74.67	71.38	4.28	19.82
A_3	$C_{23}H_{18}N_4O$	366.42	231-233	68.24	75.39	4.95	15.29
A_4	$C_{21}H_{17}N_5O_2$	371.39	225-257	77.06	67.91	4.61	18.86
A_5	$C_{20}H_{15}N_5O_2$	357.37	250-252	66.95	6.22	4.23	19.60
A_6	$C_{22}H_{17}N_3O_2$	355.39	272-275	72.23	74.35	4.82	11.82
A_7	$C_{18}H_{13}N_5O_2$	331.33	188-190	64.99	65.25	3.95	21.14
A_8	$C_{17}H_{11}N_5O_2$	37.30	210-212	68.82	64.35	3.49	22.07
A_9	$C_{19}H_{13}N_3O_2$	315.33	228-230	75.68	72.37	4.16	13.33
B_1	$C_{23}H_{18}N_2O_2$	354.40	250-253	79.85	77.95	5.12	7.90
B_2	$C_{23}H_{19}N_3O_2$	369.42	230-233	80.12	74.78	5.18	11.37
B_3	$C_{23}H_{19}N_3O_3$	385.42	210-212	72.15	71.67	4.97	10.90
B_4	$C_{22}H_{120}N_2O_3$	360.41	184-186	67.94	73.32	5.59	7.77
B_5	$C_{22}H_{21}N_3O_3$	375.42	230-232	64.72	70.38	4.64	11.19
B_6	$C_{22}H_{21}N_3O_4$	391.42	263-265	71.67	67.51	5.41	10.17
B_7	$C_{19}H_{16}N_2O_3$	320.34	210-212	70.96	71.24	5.03	8.74
B_8	$C_{19}H_{17}N_3O_3$	335.36	233-235	71.67	68.05	5.11	12.53
B_9	$C_{19}H_{17}N_3O_4$	351.36	273-275	71.72	64.95	4.88	11.96

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

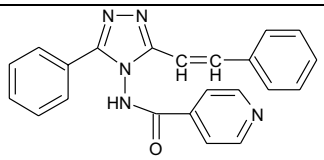
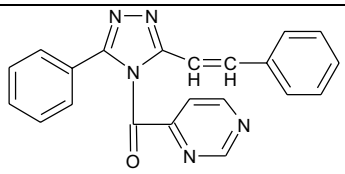
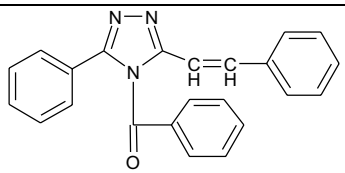
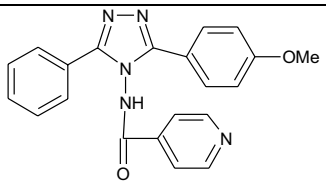
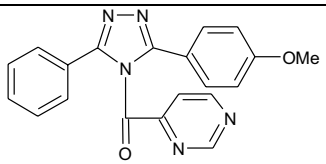
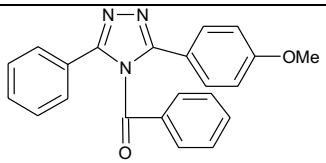
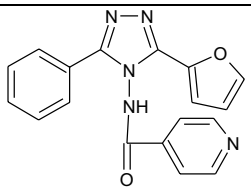
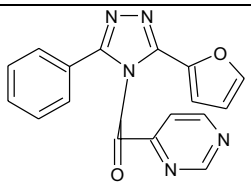
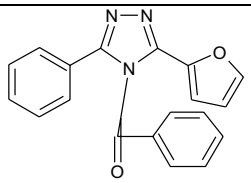
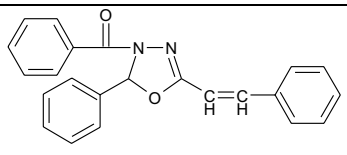
Table 3. Antitubercular activity of the synthesized compounds (A_1-A_9 & B_1-B_9).

Compound	25 µg/mL	50 µg/mL	100 µg/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-A_9 & B_1-B_9)

Treatment	Mean increase in paw volume (ml)±SEM									
	Time in minute									
	0	% inhibition	30	% inhibition	60	% inhibition	90	% inhibition	120	% inhibition
Carrageenen (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	0.34±0.03	29.16	0.35±0.01	55.12	0.33±0.01	61.17	0.30±0.01	66.29
A_2	0.24±0.02	0	0.33±0.03	31.25	0.32±0.01	58.97	0.30±0.01	64.70	0.28±0.02	68.53
A_3	0.23±0.01	4.16	0.34±0.01	29.16	0.38±0.01	51.28	0.38±0.02	55.29	0.32±0.02	64.04
A_4	0.24±0.02	0	0.33±0.01	31.25	0.33±0.02	57.69	0.31±0.02	63.52	0.29±0.01	67.41
A_5	0.23±0.01	4.16	0.32±0.01	33.33	0.34±0.01	56.41	0.32±0.01	62.35	0.30±0.02	66.29
A_6	0.24±0.02	0	0.35±0.01	27.08	0.39±0.02	50	0.38±0.01	55.29	0.32±0.03	64.04
A_7	0.23±0.02	4.16	0.33±0.01	31.25	0.35±0.02	55.12	0.34±0.02	60	0.30±0.01	66.29
A_8	0.24±0.02	0	0.33±0.02	31.25	0.35±0.03	55.12	0.31±0.02	63.52	0.30±0.02	66.29
A_9	0.23±0.03	4.16	0.33±0.02	31.25	0.34±0.01	56.41	0.32±0.02	62.35	0.30±0.02	66.29
B_1	0.24±0.01	0	0.32±0.02	33.33	0.34±0.02	56.41	0.33±0.01	61.17	0.29±0.01	67.41
B_2	0.24±0.02	0	0.34±0.03	29.16	0.34±0.03	56.41	0.35±0.01	58.82	0.31±0.02	65.16
B_3	0.23±0.03	4.16	0.33±0.04	31.25	0.35±0.01	55.12	0.33±0.02	61.17	0.30±0.03	66.29
B_4	0.24±0.01	0	0.36±0.01	25.00	0.35±0.02	55.12	0.35±0.02	58.82	0.33±0.02	62.92
B_5	0.24±0.01	0	0.34±0.01	29.16	0.36±0.01	53.84	0.35±0.02	58.82	0.31±0.01	65.16
B_6	0.24±0.01	0	0.34±0.02	29.16	0.35±0.02	55.12	0.35±0.01	58.82	0.33±0.02	62.92
B_7	0.23±0.01	4.16	0.33±0.02	31.25	0.34±0.02	56.41	0.32±0.02	62.35	0.30±0.01	66.29
B_8	0.24±0.02	0	0.34±0.03	29.16	0.36±0.03	53.84	0.36±0.03	57.64	0.32±0.03	64.04
B_9	0.24±0.02	0	0.34±0.02	29.16	0.37±0.02	52.56	0.36±0.03	57.64	0.33±0.02	62.92

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**		66.29	1.821448
2	**A_2**		68.53	1.835881
3.	**A_3**		64.04	1.806451
4.	**A_4**		67.41	1.828724
5.	**A_5**		66.29	1.821448
6.	**A_6**		64.04	1.806451
7.	**A_7**		66.29	1.821448
8.	**A_8**		66.29	1.821448
9.	**A_9**		66.29	1.821448
10.	**B_1**		67.41	1.828724

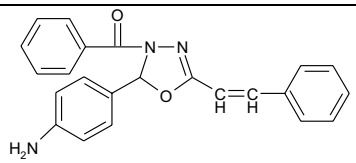
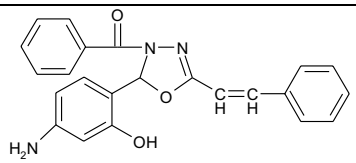
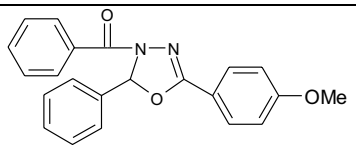
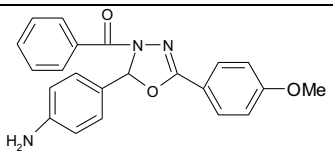
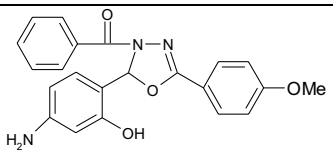
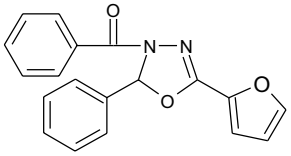
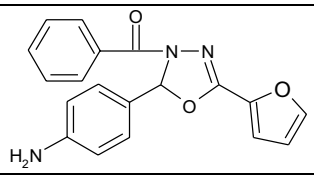
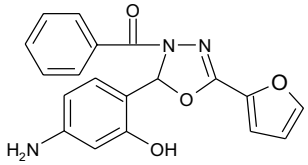
11.	**B_2**		65.16	1.813981
12	**B_3**		66.29	1.821448
13	**B_4**		62.92	1.798789
14	**B_5**		65.16	1.813981
15	**B_6**		62.92	1.798789
16	**B_7**		66.29	1.821448
17	**B_8**		64.04	1.806451
18	**B_9**		62.92	1.798789

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 = -0.199 *X3 - 0.229 * X1 - 1.553 * X2 - 12.575	18	0.361	0.838	0.702	0.538	14.17

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 Fig 1.

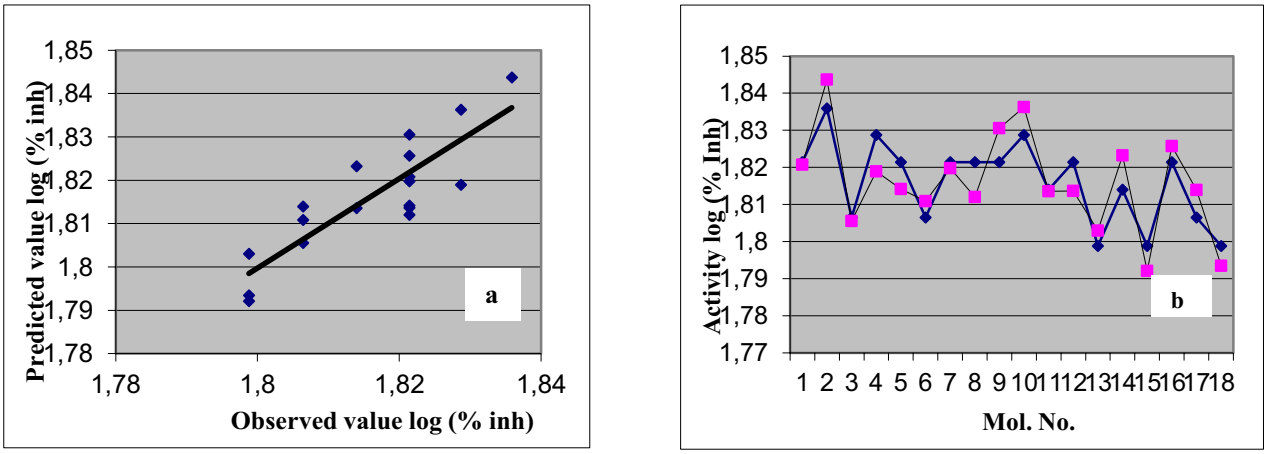


Fig 1. (a) Correlation graph; (b) Histogram of observed and predicted log (% Inh) data for 18 compounds

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

Comp. No.	Observed Value	Predicted Value	Residual Value	Residual Variance
A_1	1.821448	1.820758	0.00069	0.0043
A_2	1.835881	1.843681	-0.0078	0.0027
A_3	1.806451	1.805551	0.0009	0.0090
A_4	1.828724	1.818924	0.0098	0.0009
A_5	1.821448	1.814184	0.007264	0.0049
A_6	1.806451	1.810851	-0.0044	0.0070
A_7	1.821448	1.819752	0.001696	0.0044
A_8	1.821448	1.812048	0.0094	0.0060
A_9	1.821448	1.830548	-0.0091	0.0313
B_1	1.828724	1.836242	-0.00752	0.0019
B_2	1.813981	1.813581	0.0004	0.0035
B_3	1.821448	1.813648	0.0078	0.0006
B_4	1.798789	1.802989	-0.0042	0.0403
B_5	1.813981	1.823181	-0.0092	0.0122
B_6	1.798789	1.7921	0.006689	0.0273
B_7	1.821448	1.825678	-0.00423	0.0135
B_8	1.806451	1.813899	-0.00745	0.0049
B_9	1.798789	1.79345	0.005339	0.0324

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 it is observed that two electronic parameters Dipole Moment Z Component (Whole Molecule) and VAMP HOMO (Whole Molecule) as well as one steric parameter Inertia Moment 2 Length (Whole Molecule) contribute (-0.227, – 1.469 and – 0.414 respectively) negatively for the activity so electron withdrawing and less bulky groups may enhance the activity (%1 Inh).

The synthesized derivatives were screened for anti-bacterial activity using DMF as a solvent against the organisms *S. aureus, B. subtilis* and *E. coli*., 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

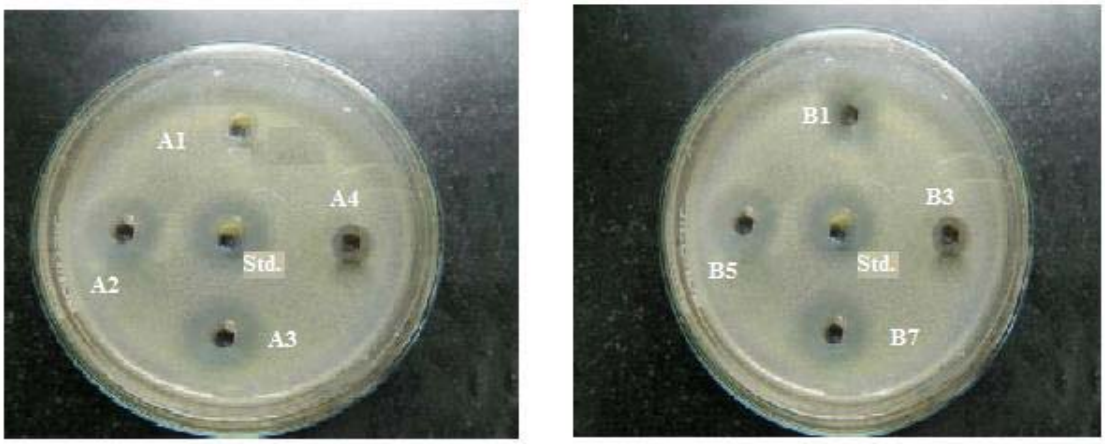


Fig. 2. Anti-bacterial activity of synthesized compounds

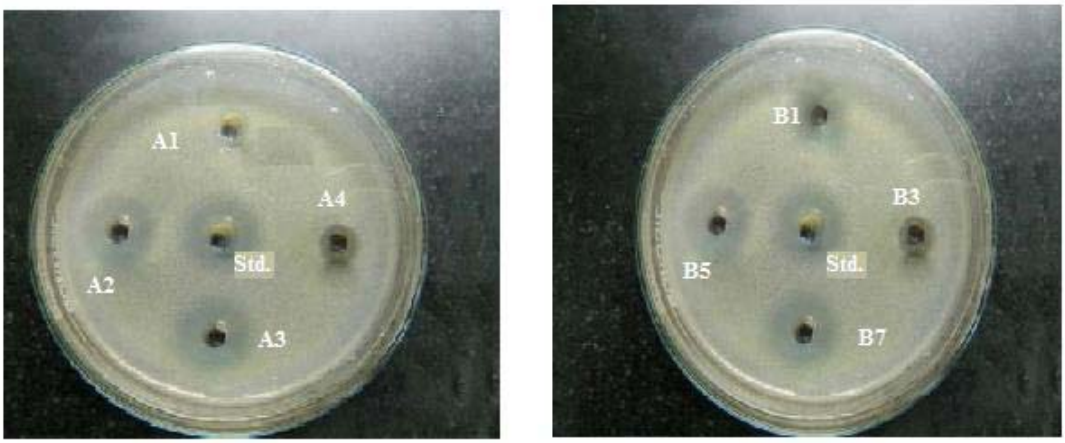


Fig. 3. Antifungal activity of synthesized compounds.

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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ДИЗАЙН, СИНТЕЗА И ФАРМАКОЛОГИЧЕН СКРИЙНИНГ НА НЯКОИ [3-БЕНЗОИЛ-5-(4-ЗАМЕСТЕНИ)-2, 3-ДИХИДРО-1,3,4-ОКСАДИАЗОЛ-2-ИЛ] И [5-(4-ЗАМЕСТЕНИ)-4*H*-1, 2, 4-ТРИАЗОЛ-3-ИЛ] ПРОИЗВОДНИ

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Постъпила на 28 септември, 2012 г.; коригирана на 15 април, 2013 г.

(Резюме)

Синтезирана е нова серия от някои заместени [3-бензоил-5-(4-заместени)-2, 3-дихидро-1,3,4-оксадиазол-2-ил] и [5-(4-заместени)-4*H*-1, 2, 4-триазол-3-ил] производни. Целта е постигането на по-добра антибактериална, противо-гъбична, противотуберкулозна и противо-възпалителна активност. Химичната структура на синтезираните съединения е потвърдена от IR, ^{1}H NMR и мас-спектроскопия. Съединенията са оценени за антибактериална, противо-гъбична, противотуберкулозна и противо-възпалителна активност. Получени са задоволителни резултати за сравнението по метода QSAR с използването на софтуер TSAR 3.3. Някои от съединенията проявяват всички изброени активности.