

Original Article

DESIGN, SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME MANNICH BASE DERIVATIVE OF 2-(SUBSTITUTED)-5-AMINO-THIADIAZOLES

K BALAJI¹, PRIYANKA BHATT¹, D. MALLIKA², ANJALI JHA^{1*}

¹Department of Chemistry, GIS, GITAM University, Rushikonda, Visakhapatnam, 530045, India, ²Department of Chemistry, Dr L Bullayya College, Visakhapatnam, 530013, India
Email: anjalimanishjha@yahoo.com

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ABSTRACT

Objective: The major objective of the present study was to design, synthesize some Mannich base derivative of 2-substituted-5-amino thiadiazoles with primary amines/phthalimide and formaldehyde anticipating effective as antimicrobial agents.

Methods: The efficient syntheses of substituted thiadiazole were done simply by reaction of substituted benzoic acid with thiosemicarbazide in presence of only conc. sulphuric acid. The isolated products were further subjected for Mannich reaction and evaluated for antibacterial activity.

Results: Three substituted thiadiazoles (BA-1 to BA-3) were synthesized by solvent less efficient synthesis and their Mannich base derivatives were also prepared with phthalimide, *p*-nitro/methyl/chloro-aniline. All characterized products were screened for antibacterial and antifungal activities. Among these compounds having nitro group (3,7,13) showed maximum activity followed by phthalimide, chloro and methyl groups.

Conclusion: Thiadiazole-Mannich bases derivatives exhibited better antimicrobial activities than their starting components (BA-1 to BA-3) indicating joining different pharmacophore in the same molecule have increased activity.

Keywords: Thiadiazole Mannich bases derivatives, Characterization, Antimicrobial activities.

INTRODUCTION

Heterocycles are widely used in the development of several pharmaceutically important compounds. The nitrogen and sulphur heterocyclic systems are very interesting because of their physicochemical properties with relevance to the design of new drugs. The compounds containing thiadiazole ring play a prominent role in natural processes and also found in numerous biologically active natural and synthetic compounds. According to the literature survey, thiadiazoles were reported to possess various pharmacological activities [1-7]. Anti-microbial activities of substituted thiadiazoles are well established because it possesses (S-C=N) toxophoric unit. They have enhanced lipid solubility with hydrophilicity and can be easily metabolized by routine biochemical reactions.

Mannich reaction is one of the versatile and convenient approaches to powerful C-C bond formation. It has wide application in organic synthesis and many drug molecules. However, the classical Mannich reaction has some limitations and to overcome these limitations, modern variants of this reaction came into the form of various publications [8-9]. Several medicinally useful Mannich base has been reviewed by various scientist [10-12]. Fascinated by various bioactivity of above mentioned compounds along with structure-based pharmacophore approaches in drug discovery and design, we have planned to design and synthesize thiadiazole-Mannich base analogues by using substituted aminothiadiazole, phthalimide, *p*-nitro/methyl/chloro-aniline in presence of formaldehyde with a hope to develop new, potent, less toxic antimicrobial agents. In continuation of our research we studied the antimicrobial action of the resultant molecules against gram negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa* and gram positive bacteria *Staphylococcus aureus*, *Bacillus subtilis* and along with a fungus *Candida albicans*.

MATERIALS AND METHODS

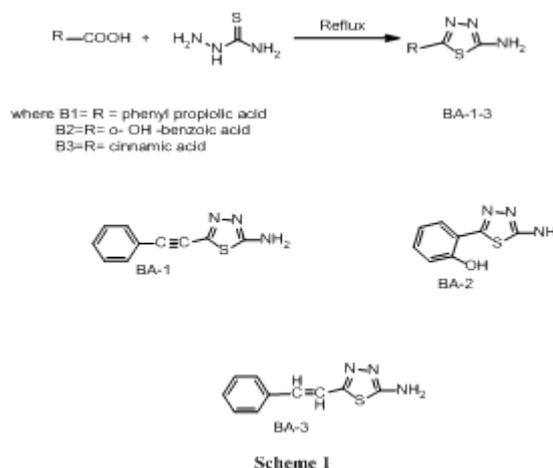
Chemicals and instrumentation

Reagents such as thiosemicarbazide, phenyl propiolic acid/*o*-hydroxy benzoic/cinnamic acid, phthalimide, *p*-nitro aniline, *p*-methyl aniline, *p*-chloro aniline and formaldehyde were purchased from Across Ltd and used as it is. All the solvents were of analytical grade and were distilled before use. Melting points are uncorrected. The solid IR

spectra were recorded in KBr on Perkin Elmer FTIR spectrophotometer at GITAM University, Visakhapatnam; however ¹H and ¹³C NMR spectra were taken on Bruker 400 MHz NMR at Biocon Limited electronic city Bangalore, in DMSO-d₆ using TMS as internal reference. Elemental analysis and mass spectra were recorded at Micro Analytical centre at Andhra University, Visakhapatnam.

Synthesis of 2-amino-5-substituted thiadiazole (BA-1 to BA-3)

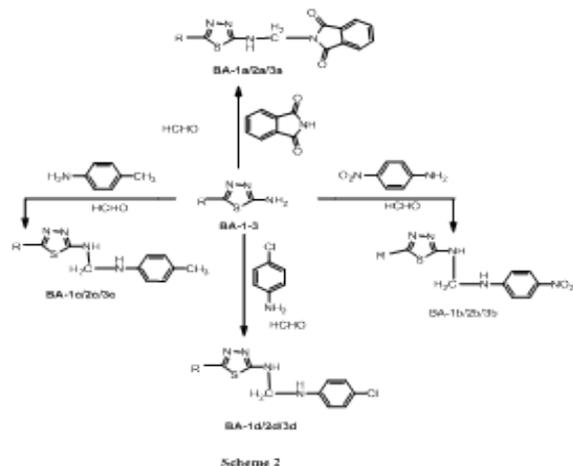
Substituted amino thiadiazoles were prepared by the conventional method as outlined in Scheme 1. A mixture of carboxylic acid (phenyl propiolic/*o*-OH-benzoic/cinnamic acid, 0.01 moles, in separate reactions) and thiosemicarbazide (0.012 mole) was mixed thoroughly. The reaction mixture was heated under reflux (Scheme 1) in the presence of only conc. H₂SO₄ without any solvent for 6-8 h [13]. The reaction mixture was cooled to room temperature and neutralized with ammonia solution. The solid was filtered and washed with water followed by few drops of ether. The products were re-crystallized from ethanol and characterized by various spectral methods.



Scheme 1

Synthesis of BA1a/1b/1c to BA-3a/3b/3c

A methanolic solution of BA-1/BA-2/BA-3 (0.01 mol) was taken (in separate reaction) in a round bottom flask equipped with a stirred and dropping funnel. The solution was stirred to dissolve it completely. To this methanolic solution of formaldehyde (3.0 ml) was added drop wise during 15-20 min. The resulting mixture was stirred during half an hour to complete the reaction. To this reaction mixture the methanolic solution of phthalimide/*p*-NO₂/*p*-CH₃/*p*-Cl aniline (0.01 mol) was added drop wise with stirring in about half an hour at 30 °C temperature and refluxed for 2 h at 65-75 °C (Scheme-2). It was allowed to cool and poured in cold water. The solid obtained was filtered off washed thoroughly with hot water and air dried. All products were characterized by IR, NMR and were found consistent with an expected structure as shown in table 1.



Scheme 2

2-[5-amino-1,3,4-thiadiazol-2-yl] phenyl acetylene (BA-1)

(C₁₀H₇N₃S): IR(Vmax cm⁻¹): 3465,3369 (NH₂), 3104(Ar-H), 2106(C≡C),1627, 1519 (C=N); ¹HNMR (δppm): 7.5-7.9 (Ar-H), 3.5(NH₂), ¹³CNMR(δppm): 86, 77 (C≡C), 126, 128,129, 130 (Ar-C), 157.7, 152.5 (thiazole carbons); m/e: 201; Analysis: Calcd C, 59.70; H, 3.48; N, 20.89; Found: C, 59.75; H, 3.520; N, 20.83.

2-([5-phenyl acetylene)-1,3,4-thiadiazol-2-yl] amino} methyl)-1-H-isoindole-1,3 (2H)-dione (BA-1a)

(C₁₉H₁₂N₄O₂S): IR(γmax cm⁻¹): 3460 (NH), 3100 (Ar-H), 2102 (C≡C), 1625, 1517 (C=N); ¹HNMR (δppm): 7.4-7.8 (Ar-H), 3.8 (NH), ¹³CNMR(δppm): 85, 76(C≡C), 126.5, 128.8,129.7, 130.6 (Ar-C), 157.5, 152.3 (thiazole carbons); m/e: 360; Analysis: Calcd C, 63.33; H, 3.33; N, 15.55; Found: C, 63.29; H, 3.38; N, 15.51.

2-[5-(((4-nitro phenyl)amino)methyl)amino]-1,3,4-thiazol-2-yl] Phenyl acetylene (BA-1b)

(C₁₇H₁₃N₅O₂S), IR(γ max cm⁻¹): 3455, 3365 (NH), 3108 (Ar-H), 2100 (C≡C), 1623, 1515 (C=N); ¹HNMR (δppm): 7.46-7.84 (Ar-H), 3.8.5 (NH), ¹³CNMR (δppm): 84, 75 (C≡C), 126.3, 128.6,129.5, 130.4 (Ar-C), 157.3, 152.1 (thiazole carbons); m/e: 351; Analysis: Calcd C, 58.11; H, 3.70; N, 19.94; Found: C, 58.15; H, 3.66; N, 19.97.

2-[5-(((4-methyl phenyl) amino) methyl) amino)-1,3,4-thiazol-2-yl] Phenyl acetylene (BA-1c)

(C₁₇H₁₆N₄S) IR(γ max cm⁻¹): 3450 (NH), 3105 (Ar-H), 2095 (C≡C), 1621, 1513 (C=N); ¹HNMR (δppm): 7.4.2-7.8.2 (Ar-H), 3.9 (NH), ¹³CNMR(δppm): 84.5, 75.5 (C≡C), 126.1, 128.3,129.3, 130.2 (Ar-C), 157, 152 (thiazole carbons); m/e: 308; Analysis: Calcd C, 66.23; H, 5.19; N, 18.18; Found: C, 66.29; H, 5.14; N, 18.14.

2-[5-(((4-choloro amino) methyl) amino)-1,3,4-thiazol-2-yl] Phenol (BA-1d)

(C₁₇H₁₅N₄SCl): IR(γ max cm⁻¹): 3445 (NH), 3105 (Ar-H), 2095 (C≡C), 1621, 1513 (C=N); ¹HNMR (δppm): 7.4.2-7.8.2 (Ar-H), 3.95 (NH),

¹³CNMR(δppm): 84, 75 (C≡C), 125, 127, 128, 131 (Ar-C), 157, 152 (thiazole carbons); m/e: 342.5; Analysis: Calcd C, 59.56; H, 4.37; N, 16.35; Found: C, 59.61; H, 4.33; N, 16.39.

2-(5-amino-1,3,4-thiadiazol-2-yl) phenol (BA-2)

(C₈H₇N₃O₂): IR(γ max cm⁻¹): 3469 (OH), 3206 (NH₂), 3006 (Ar-H), 1627, 1519 (C=N); ¹HNMR(δ ppm): 9.9 (O-H); 6.6-7.4 (Ar-H), 3.5(NH₂); ¹³CNMR(δppm): 116, 118, 130,134 (Ar-C), 158, 152 (thiazole carbons); m/e: 193; Analysis: Calcd C, 49.74; H, 3.62; N, 21.76; Found: C, 49.68; H, 3.59; N, 21.72.

2-([5-2-hydroxy phenyl)-1,3,4-thiadiazol-2-yl] amino}methyl)-1-H-isoindole-1,3(2H)-dione (BA-2a)

(C₁₇H₁₂N₄O₃S): IR(γ max cm⁻¹): 3465 (OH), 3335 (NH), 3004 (Ar-H), 1625, 1517 (C=N); ¹HNMR(δ ppm): 9.8(O-H); 6. 8-7.5 (Ar-H), 3.8 (NH); ¹³CNMR (δppm): 115, 117, 129,133 (Ar-C), 157, 151 (thiazole carbons); m/e: 352; Analysis: Calcd C, 57.95; H, 3.40; N, 19.94; Found: C, 57.92; H, 3.43; N, 15.95.

2-[5-(((4-nitro phenyl) amino) methyl) amino)-1,3,4-thiazol-2-yl] Phenol (BA-2b)

(C₁₅H₁₃N₅O₃S): IR(γ max cm⁻¹): 3463(OH), 3333 (NH), 3002 (Ar-H), 1624.5, 1516.7 (C=N); ¹HNMR(δppm): 9.76 (O-H); 6.6-6.7-3.7 (Ar-H), 3.9 (NH); ¹³CNMR (δppm): 115.4, 118.6, 128.5,132.7 (Ar-C), 156, 151.6 (thiazole carbons); m/e: 343; Analysis: Calcd C, 52.47; H, 3.79; N, 20.40; Found: C, 52.52; H, 3.75; N, 20.36.

2-[5-(((4-methyl phenyl) amino) methyl) amino)-1,3,4-thiazol-2-yl] Phenol (BA-2c)

(C₁₆H₁₆N₄O₂S): IR(γ max cm⁻¹): 3462(OH), 3330 (NH), 3001 (Ar-H), 1624, 1515.6 (C=N); ¹HNMR(δppm): 9.74 (O-H); 6.6-7.3 (Ar-H), 3.94 (NH); ¹³CNMR (δppm): 115, 118, 128,132 (Ar-C), 155, 151 (thiazole carbons); m/e: 312; Analysis: Calcd C, 61.53; H, 5.12; N, 17.94; Found: C, 61.49; H, 5.16; N, 17.95.

2-[5-(((4-choloro phenyl) amino) methyl) amino)-1,3,4-thiazol-2-yl] Phenol (BA-2d)

(C₁₅H₁₃N₄O₂SCl): IR(γ max cm⁻¹): 3460(OH), 3328 (NH), 3000 (Ar-H), 1623, 1515 (C=N); ¹HNMR(δppm): 9.72 (O-H); 6.8-7.6 (Ar-H), 3.92 (NH); ¹³CNMR (δppm): 114, 117, 127,131 (Ar-C), 154.8, 150.7 (thiazole carbons); m/e: 332.5; Analysis: Calcd C, 54.13; H, 3.90; N, 16.84; Found: C, 54.17; H, 3.86; N, 16.81.

2-(5-amino-1,3,4-thiadiazol-2-yl) phenyl ethylene (BA-3)

(C₁₀H₉N₃S): IR(γ max cm⁻¹): 3360 (NH₂), 3104 (Ar-H), 1673 (HC=CH), 1519, 1459 (C=N); ¹HNMR (δ ppm):7.2-7.5 (Ar-H), 4.8-5.3 (=C-H), 3.5 (NH₂); ¹³CNMR (δppm): 118, 126, 128, 130 (Ar-C), 154 (C=C), 152, 159 (thiazole carbons); m/e: 203; Analysis: Calcd C, 59.11; H, 4.43; N, 20.68; Found: C, 59.15; H, 4.48; N, 20.73.

2-([5-phenyl ethylene)-1,3,4-thiadiazol-2-yl] amino}methyl)-1-H-isoindole-1,3(2H)-dione (BA-3a)

(C₁₉H₁₄N₄O₂S): IR(γ max cm⁻¹): 3358 (NH), 3103 (Ar-H), 1672 (HC=CH), 1518, 1458 (C=N); ¹HNMR (δppm):7.1-7.6 (Ar-H), 4.8-5.5 (=C-H), 3.7 (NH);¹³CNMR (δppm): 117, 125, 127, 129 (Ar-C), 153 (C=C), 151, 158 (thiazole carbons); m/e: 362; Analysis: Calcd C, 62.98; H, 3.86; N, 11.60; Found: C, 62.95; H, 3.91; N, 11.56.

2-[5-(((4-nitro phenyl) amino) methyl)amino)-1,3,4-thiadiazol-2-yl] phenyl ethylene (BA-3b)

(C₁₇H₁₅N₅O₂S), IR(γ max cm⁻¹): 3355 (NH), 3102 (Ar-H), 1671 (HC=CH), 1517, 1457 (C=N); ¹HNMR (δppm):7.0-7.7 (Ar-H), 4.7-5.6 (=C-H), 3.8 (NH);¹³CNMR (δppm): 116, 124, 126, 128 (Ar-C), 152 (C=C), 150.8, 157.6 (thiazole carbons); m/e: 353; Analysis: Calcd C, 57.79; H, 4.24; N, 19.83; Found: C, 57.75; H, 4.28; N, 19.86.

2-[5-(((4-methyl phenyl) amino) methyl)amino)-1,3,4-thiadiazol-2-yl] phenyl ethylene (BA-3c)

(C₁₈H₁₈N₄S): IR(γ max cm⁻¹): 3353 (NH), 3100 (Ar-H), 1670 (HC=CH), 1516, 1456 (C=N); ¹HNMR (δppm):6.9-7.8 (Ar-H), 4.7-5.7 (=C-H), 3.9 (NH);¹³CNMR (δppm): 115, 123, 125.6, 127.4 (Ar-C), 151 (C=C), 149, 157.36 (thiazole carbons); m/e: 322; Analysis: Calcd C,67.08; H, 5.59; N,17.39; Found: C, 63.51; H, 4.12; N, 21.85.

2-[5-(((4-chloro phenyl) amino) methyl) amino]-1,3,4-thiadiazol-2-yl] phenyl ethylene (BA-3d)

(C₁₇H₁₅N₄SCl): IR(ν max cm⁻¹): 3350(NH), 3090 (Ar-H), 1669 (HC=CH), 1515, 1455 (C=N); ¹HNMR (δ ppm):7.0-7.9 (AR-H), 4.8-5.8 (=C-H), 3.9.5 (NH);¹³CNMR (δ ppm): 114.7, 122.6, 125, 127 (Ar-C), 150 (C=C), 147, 157 (thiazole carbons); m/e: 342.5; Analysis: Calcd C, 59.56; H, 4.37; N, 16.35; Found: C, 59.59; H, 4.34; N, 16.38.

Antimicrobial assay

The synthesized compounds (1-15) were assessed for antimicrobial assay against gram positive bacteria BS-*Bacillus*

subtilis (MTCC 441), SA-*Staphylococcus aureus* (MTCC 96), and gram negative bacteria EC-*Escherichia coli* (MTCC 1687), PA-*Pseudomonas aeruginosa* (MTCC 424) along with a fungal strain CA-*Candida albicans* using the well diffusion method[14]. The compounds were dissolved in DMSO and activity was determined using serial dilution method. The whole procedure was carried out as reported by us earlier [15]. Ciprofloxacin and ketaconazole were used as antibacterial and antifungal reference drugs, respectively. The minimum inhibitory concentration (MIC, 10 μ g ml⁻¹) was determined for each compound in triplicate experiments; the values were averaged and are presented in table 2.

Table 1: Structure and physical properties of synthesized compounds

S. No.	Cmpds.	Structure	M. pt °C/Yield (%)	Colour
1	BA-1		174/69	White
2	BA-1a		120/72	Pale brown
3	BA-1b		148/68	Pale yellow
4	BA-1c		156/70	white
5	BA-1d		80/69	Pale yellow
6	BA-2		168/69	white
7	BA-2a		138/71	Brown
8	BA-2b		152/70	Light yellow
9	BA-2c		92/69	Pale white
10	BA-2d		168/72	White
11	BA-3		172/70	Pale brown
12	BA-3a		88/69	Brown
13	BA-3b		196/70	Light yellow
14	BA-3c		134/69	White
15	BA-3d		128/71	Pale yellow

Table 2: The MIC* values of the synthesized compounds for antibacterial and antifungal activity at 10 µg/ml concentration

S. No.	Compound	Bacteria				Fungus
		EC	PA	BS	SA	CA
1	BA-1	12	10	10	9	7
2	BA-1a	17	17	10	11	16
3	BA-1b	21	15	NA	13	10
4	BA-1c	12	10	17	15	22
5	BA-1d	14	16	12	NA	15
6	BA-2	10	6	9	13	11
7	BA-2a	13	9	15	9	9
8	BA-2b	16	12	10	15	17
9	BA-2c	12	8	NA	12	19
10	BA-2d	9	11	12	14	NA
11	BA-3	12	NA	9	8	12
12	BA-3a	15	12	12	NA	NA
13	BA-3b	19	7	10	12	10
14	BA-3 c	12	9	11	7	17
15	BA-3d	10	8	14	9	14
16	Cephaloflaxin	25	18	20	19	-
17	Ketoconazole	-	-	-	-	26

* MIC =minimum inhibitory concentration (Mean of triplicate experiments)

NA-Not active, EC-*Escherichia coli*, PA-*Pseudomonas aeruginosa*, BS-*Bacillus subtilis*, SA-*Staphylococcus aureus*, CA-*Candida albicans*

RESULTS AND DISCUSSION

Synthesis of 1, 3, 4-thiadiazole analogs

Synthesis of novel 1, 3, 4-thiadiazole analogs were achieved by following the procedure as depicted in Scheme 1 and 2. The stoichiometric ratio of thiosemicarbazide and (phenyl propiolic/o-OH-benzoic/cinnamic acid was grinded thoroughly in the mortar and pestle. The reaction mixture was further refluxed [14] in the presence of only conc. H₂SO₄, which was used as cyclising agent. The isolated and characterized substituted thia diazoles (BA-1 to BA-3) were further condensed with phthalimide/*p*-NO₂/*p*-CH₃/*p*-Cl aniline in the presence of formaldehyde to get Mannich base derivatives. TLC was run throughout the reaction to optimize the reaction for purity and completion.

Designed series of molecules (1-15: BA-1 to BA-3, BA-1a/b/c/d to BA-3a/b/c/d) was characterized by spectral techniques before evaluating for antimicrobial studies. Two strong absorption bands appeared in the range between 3340 and 3200 cm⁻¹ in the IR spectra of compounds (1,6,11) was attributed to NH₂ group[16] of substituted thiadiazole, while C-S-C absorption stretches (thiadiazole ring)[17] from 1150 to 1180 cm⁻¹ and C=N absorptions (thiadiazole ring) from 1604 to 1623 cm⁻¹. The other major peaks observed in the IR of these compounds are 3130–3050; 1550-1520 cm⁻¹ could be assigned to aromatic hydrogen and C=C of the ring. The additional peak observed in the IR of 16: BA-3 at 1623 cm⁻¹ was attributed to CH=CH of cinnamic acid. The disappearance of NH₂ peaks of substituted thia diazoles (compound no.1,6,11) in the IR of target compounds (2-5, 7-10 and 12-15) are clearly indicated the condensation of it with formaldehyde and various substituted aniline/phthalimide which was further confirmed by their NMR spectra. The additional peak observed at the range of 1770-1735 cm⁻¹ in compound no.2,7,12 was attributed to C=O of phthalimide ring[18]. Other peaks observed in the IR spectrum of all the compounds were fitted well as expected structure shown in table 1.

The major proton NMR spectral peaks appeared at δ 3.2-3.9 and 6.7-7.8 ppm in the compounds (1, 6, 11) was assigned to NH₂ and aromatic. In the ¹³C NMR spectra, the signals in the range δ 110-135 ppm are due to aromatic carbons and signals in the region δ 150-170 ppm are due to thia diazole carbons[19]. The disappearance of NH₂ and carbonyl peak in the ¹H NMR spectra of compounds (2-5,7-10,12-15) were further supportive of condensation of amino thia diazoles with formaldehyde and various substituted aniline/phthalimide. The additional peaks at δ 4.2-4.5 ppm were assigned to CH₂ of Mannich base derivatives [20]. The observed signals in ¹³C NMR spectra of compounds (2-5,7-10 and 12-15) in the range of δ 33.41-38.55 ppm are due the formation of-N-CH₂-N-of derivatives [21] of thiadiazole. Other proton and carbon peaks were found to be well consistent with

the expected structures. All the compounds showed a single peak in their mass spectra suggesting their purity.

All synthesized and characterized compounds (1–15) were evaluated for their antibacterial activity against gram positive bacteria-*Bacillus subtilis*, *Staphylococcus aureus* and gram negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa* together with a fungus *Candida albicans* using well diffusion method, and compared with well-known antibacterial/antifungal drug, Ciprofloxacin/ketaconazole. The minimum inhibitory concentration (MIC, 10µg ml⁻¹) was determined for each compound in triplicate experiments. The values were averaged and reported in table 2 while graphically shown in fig. 1.

The observed values reveal that type of substituent directly attached to 1, 3, 4-thiadiazole ring has a significant impact on the antibacterial/antifungal activities of these novel analogs. In particular, compound no.3, 7, 13 showed the activity to a greater extent due to the presence of nitro group [22]. However, the chloro [23] containing compounds 5, 10, and 15 showed significant activity against all five microorganisms. In light of the various available literature describing biological activities of compounds containing phthalimides, we also noticed the compounds 2,7,12 showed appreciable activity. Additionally, unsaturation [24] plays some role in activity since compounds having triple bond (1-5) showed better activity then compound having the double bond (11-15). However, the trend observed in all synthesized compounds containing nitro, chloro and methyl is in decreasing order (BA-1, BA-2, BA-3) and well consistent with literature.

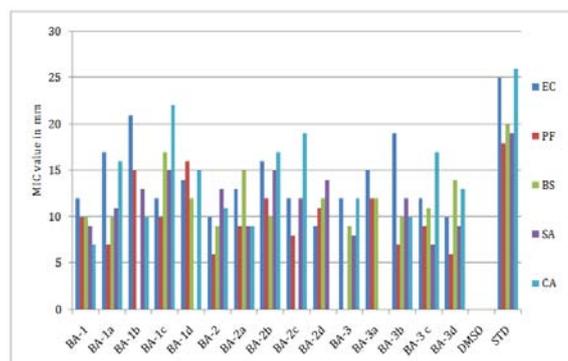


Fig. 1: Graphical representation of antimicrobial activity of synthesized compounds (1-15)

CONCLUSION

The present work provides a convenient and efficient route for the preparation of new substituted thiadiazole (BA-1, BA-2, BA-3) and their Mannich base derivatives. All the newly synthesized compounds have been screened for their antimicrobial activities. Most of the tested compounds exhibited activities against the strains used. Our present results demonstrated that the presence of nitro group has the significant effect on activity, which was followed by chloro, methyl groups. However, phthalimide had showed appreciable activity in all three cases.

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CONFLICT OF INTERESTS

The authors have no conflict of interest in publication of this article.

REFERENCES

- Küçükgülzel G, Kocatepe A, Clercq ED, Şahin F, Güllüce M. Synthesis and biological activity of 4-thiazolidinones, thiosemicarbazides derived from diflunisal hydrazide. *Eur J Med Chem* 2006;41:353-9.
- Karegoudar P, Karthikeyan MS, Prasad DJ, Mahalinga M, Holla BS, Kumar NS. Synthesis of some novel 2,4-disubstituted thiazoles as possible antimicrobial agents. *Eur J Med Chem* 2008;43:261-7.
- Basavaraja KM, Somasekhar B, Appalaraju S. Synthesis and biological activity of some 2-[3-substituted-2-thione-1,3,4-thiazole-5-yl]aminobenzothiazoles. *Indian J Heterocycl Chem* 2008;18:69-72.
- Agarwal T, Gupta P, Asthana S, Khursheed A. *In silico* analysis to access the antibacterial effect of thiazides on pdrfs: molecular docking approach. *Int J Pharm Pharm Sci* 2014;6:387-91.
- Verma A, Saraf SK. 4-Thiazolidinone-Abiologically actives caffold. *Eur J Med Chem* 2008;43:897-905.
- Jiang B, Gu X. H Syntheses and cytotoxicity evaluation of bis (indolyl) thiazole, bis (indolyl) pyrazinone and bis (indolyl) pyrazine: analogues of cytxic marine bis (indole) alkaloid. *Bioorg Med Chem* 2000;8:363-71.
- Pawar S, Sawant S, Nerkar A, Bhosale A. *In silico* design, synthesis and pharmacological screening of novel 2-(6-substituted benzo [d] thiazol-2-yl) isoindoline-1, 3-diones as potential cox-2 inhibitors for anti-inflammatory activity. *Int J Pharm Pharm Sci* 2014;6:353-7.
- Ravichandran V, Mohan S, Kumar KS. Synthesis and antimicrobial activity of Mannich bases of isatin and its derivatives with 2-[(2,6-dichlorophenyl)amino]phenylacetic acid (07-2496LP). *ARKIVOC J* 2007;14:51-7.
- Syamala M. Recent progress in three-component reactions. *Organic Preparations and Procedures International: Journal Organic Synthesis* 2009;41:1-68.
- Bala S, Sharma N, Kajal A, Kamboj S, Saini V. Mannich bases: an important pharmacophore in present scenario. *Int J Med Chem* 2014. Available from: URL: <http://dx.doi.org/10.1155/2014/191072>. [Last accessed on 10 Jun 2015]
- Subramaniapillai SG. Mannich reaction: A versatile and convenient approach to bioactive Skeletons. *J Chem Sci* 2013;125 : 467-82.
- Meenakshi K, Gopal N, Sarangapani M. Synthesis, characterization and antimicrobial activity of some novel Schiff and mannich bases of isatin. *Int J Pharm Pharm Sci* 2014;6:318-22.
- Pandey VK, Negi HS, Joshi MN, Bajpai SK. Synthesis and biological activity of some new benzophenothiazines. *Indian J Chem* 2003;42B:206-10.
- Rahman A, Choudhary MI, Thomsen WJ. *Bioassay techniques for drug development*. Harwood Academic Publishers, The Netherlands; 2001. p. 16
- Jha A, Murthy YLN, Sanyal U, Durga G. Rapid synthesis, characterization, anticancer and antimicrobial activity studies of substituted thiadiazoles and their di nucleating ligand metal complexes. *Med Chem Res* 2012;21:2548-56.
- Ghatolea AM, Lanjewarb KR, Gaidhane MK. Synthesis and antimicrobial activity of some substituted bis[2-((e)-2-(4-benzylideneamino)thiazol-4-yl)-4-methylphenol] metal complexes. *Int J Pharm Pharm Sci* 2014;6:142-6.
- Vishnuvardhanaraj G, Tamilvendan D, Amaladasan M. Synthesis, characterization and biological activities of cinnamaldehyde's Mannich bases. *Int J Pharm Pharm Sci* 2013;5:821-5.
- Bannela R, Shrivastava SP. Synthesis and evaluation of some N-Mannich base of isoindol-1,3(2H-dione) derivatives as potential antimicrobial, anthelmintic and in septicidal agents. *Indian J Chem* 2014;53B:1128-35.
- Sahin D, Bayrak H, Demirbas A, Demirbas N, Karaoglu SA. Design and synthesis of new 1, 2, 4-triazole derivatives containing morpholine moiety as antimicrobial agents. *Turk J Chem* 2012;36:411-26.
- Kanchana SN, Burra V, Nath KR. Novel synthesis and antimicrobial activity study of innovative mannich bases containing 2-phenoxy-1,3,2-dioxaphospholanes and indole systems. *Orient J Chem* 2014;30:1349-60.
- Al-Azzawi AM, Al-Razzak MSA. Synthesis, characterization and antibacterial screening of new Schiff bases linked to phthalimide. *Int J Res Pharm Chem* 2013;3:682-90.
- Desai NC, Pandya DD, Kotadiya GM, Desai P. Synthesis and characterization of novel benzimidazole bearing pyrazoline derivatives as potential antimicrobial agents. *Med Chem Res* 2014;23:1474-87.
- Moger M, Satam V, Govindaraju DRC, Paniraj AS, Gopinath VS, Hindupur RM, et al. Synthesis and antimicrobial properties of 1,3,4-oxadiazole analogs containing dibenzosuberane moiety. *J Braz Chem Soc* 2014;25:104-11.
- De P, Baltas M, Bedos-Belval F. Cinnamic acid derivatives as anticancer agents-a review. *Curr Med Chem* 2011;18:1672-703.