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ORIGINAL ARTICLE **OPEN ACCESS**

Microwave irradiated efficient synthesis of substituted 1*H*-1,2,4-triazol-3-substituted carboxylic acid and their Schiff bases and comparative study of their microbial activities.

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ABSTRACT
The mild acid catalysed efficient microwave irradiated synthesis of 2-[3-Amino-5-(2-hydroxy-phenyl) – substituted-1,5-dihydro-[1,2,4]triazol-4-yl]-substituted acid and their Schiff bases 2-[3-(substituted Benzylidene-amino)-5-(2-hydroxy-phenyl)–substituted-1,5-dihydro-[1,2,4]triazol-4-yl]-substituted acid derivatives were obtained from the multicomponent insitu or stepwise reaction. Both the synthesized compounds were evaluated for their anti bacterial and anti fungal activities, the intermediate compound triazole moiety found good activities against tested standard drugs molecules.
Keywords: Triazole, Antifungal Drugs, column chromatography

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INTRODUCTION

Now a day the development of newer green, eco-friendly, benign, and more economical or commercial methods is mostly needy to minimize the harmful and hazardous effects of various catalysts and solvents used in conventional synthesis of drug molecules. Generally the use of water as well as mixture of water and ethanol as a important green solvent involved a lot of synthetic chemist [1-2]. Sometimes natural catalysts like extract species of lemon juice, citrus limonium are also used in the organic synthesis [3-5]. Researchers reported the synthesis of triazole compounds using metal catalysis and non metal catalysis, metal-free (3 + 2)-cyclo addition approaches were developed for synthesize diversely functionalized 1,2,3-triazoles [6, 7]. Metals or metal complexes such as CuI [8], Ru [9], Ag [10] and Au [11] catalyst is also used for the synthesis of various functionalized triazole compounds.

Similarly, the heterocyclic compounds containing Nitrogen, Oxygen and Sulphur as heteroatom's showing potent biological activities [12-14]. Various types of Azoles derivatives are also showing broad range of biological activities, out of that the triazole and its different derivatives, are well known as Anti-cancer [15-16], Anti-inflammatory, [17-18] Antitubercular, [19, 20] Antileishmanial as well as antitrypanosomal activity, [21-22] Antimicrobial activity, [23, 24] Antiviral activity, [25, 26] Antibacterial activity, [27, 28] Miscellaneous [29, 30] agents.

Along with the various activities of the synthesized triazole derivatives it is also present in commercial medicinal drugs such as Tazobactum **A** and Cefatrizine**D** (antibiotic), Fluconazole **B** and Isavuconazole**C** (Antifungal) etc (fig. 1).

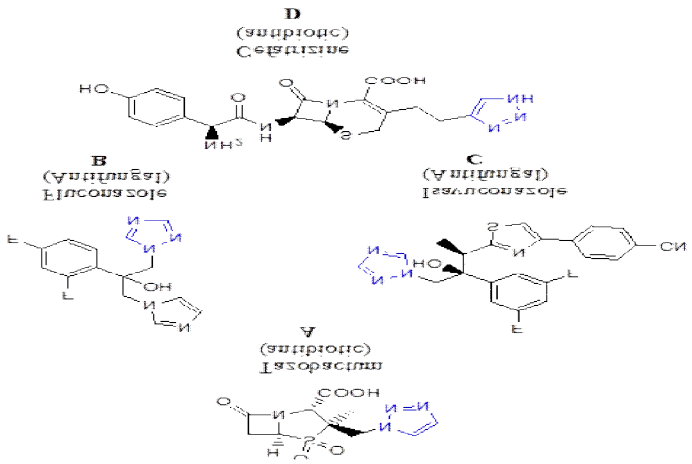


Fig. 1 Marketed drugs containing triazole moiety.

Not only triazole molecules are bioactive but also Schiff bases showing promising biological activities. In general the compounds containing azomethine or imine (–C=N–) functional group are called as Schiff bases. The derivatives of Schiff bases or Schiff base complexes exhibit antifungal,[31-32] antiseptic,[33,34] anti-inflammatory and anticancer etc [35, 36]. Microwave irradiation is a modern technique used for the small scale organic synthesis having lot of advantages. The previous research in the synthesis of various heterocyclic molecules,[37, 38] the present work was done to develop synthetic methodology for the synthesis of 1,2,4-triazole and their Schiff base derivatives with evaluating their anti-microbial activities.

MATERIAL AND METHODS

All the reactions were performed in oven and dried glassware. All reagents and solvents used were in analytical grade (AR) and used as it is received by commercial suppliers. Melting point of products was taken on a precision M.P. apparatus. IR of compounds are obtained in KBr disks on a Nicolet 400D spectrometer, also ^{1}H NMR and ^{13}C spectra was recorded in DMSO or $CDCl_3$ solvent on a Bruker spectrometer. A mass spectrum recorded on a Waters ZQ-4000 spectrometer. Microwave were used for irradiation is of make 'Catalyst microwave synthesizer Sr. No. 130602954'. The give up of products mentioned is for isolated product. Progress of reaction was checked by pre coated Thin Layer Chromatography on silica plates (2 mm) using n-hexane and ethyl acetate as a solvent system. Then plate was poured in iodine chamber as well as in UV chamber.

Synthetic procedures

Procedure - synthesis of triazole derivatives 4a-g.

The equimolar amount of 2-hydroxy acetophenone or 2-hydroxy 1 (0.02 mol) and substituted amino acids 2 (0.02 mol) were added in 250 ml RBF and shake well by adding mixture of 10ml water and 10ml ethanol and 2 ml glacial acetic acid. Then thiosemicarbazide 3(0.02 mol) were addedin previous reaction mixture. Then place the RBF in microwave oven and fitted with water condenser, then start it by adjusting temperature at 80OC for 10-15 min (at power 280 Watt). Progress of reaction was monitored using TLC. Reaction completions observed by TLC, stop irradiation and cool reaction mass to room temperature. The poured on ice cold water and precipitate was separate out by filtration. The product was purified by using chromatography (column) (Scheme 1).

Procedure - synthesis of Schiff base 6a-d.

The equimolar mixture of 2-[3-Amino-5-(2-hydroxy-phenyl)-5-methyl-1,5-dihydro-[1,2,4]triazol-4-yl]-propionic acid **4b** (0.02 mol) and substituted benzaldehyde **5** (0.02 mol) were taken in 250 ml RBF and shake well by adding mixture of 10ml water and 10ml ethanol and 2 ml glacial acetic acid. After that place the RBF in microwave oven and fitted with water condenser, then start it by adjusting temperature at $80^{0}C$ for 10-15 min (at power 280 Watt). Progress of reaction were monitored using TLC. Reaction completions observed by TLC, stop irradiation and cool reaction mass to room temperature. Then poured on ice cold water and precipitate was separated out by filtration. Products were purified by using column chromatography (Scheme 2).

General procedure for synthesis of Schiff base 6a-d (insitu).

The equimolar amount of 2-hydroxy acetophenone**1** (0.02 mol) and alanine / 2-Amino-propionic acid**2** (0.02 mol) were added in 250 ml RBF and shake well by adding mixture of 10ml water and 10ml ethanol and 2 ml glacial acetic acid. Then thiosemicarbazide(0.02 mol) were added in previous reaction mixture. Then place the RBF in microwave oven and fitted with water condenser, then start it by adjusting

temperature at 80^{0}C for 10-15 min. Progress of reaction were monitored using TLC. Reaction completions observed by TLC, stop irradiation and cool the reaction mass to room temperature. Then added substituted benzaldehyde **5** and again place the RBF in microwave oven and forward the reaction. Stop the reaction when completion observed by TLC, cooled at room temperature and poured on ice cooled water and precipitate were separate out by filtration. Products were purified by using column chromatography (Scheme 3).

2-[3-Amino-5-(2-hydroxy-phenyl)-5-methyl-1,5-dihydro- [1,2,4]triazol-4-yl]-propionic acid 4bIR (KBr, cm^{-1}): 3552 (O–H), 3390 (O–H), 3289–3202 (NH2), 3254 (NH), 3010 (C–H) aromatic, 2991 (C–H) aliphatic, 1641 (C=N). ^{1}H NMR (400MHz; d_6-DMSO, δ ppm): 2.22 (s, 3H, CH_3), 2.32 (d, J = 6.12 Hz, 3H, CH_3), 2.97(q, J = 6.40 Hz, 1H, CH–COOH), 6.86–7.54 (m, 4H, ArH), 8.02 (s, 1H, NH, disappeared by D_2O), 10.52(sbroad, 3H, NH_3, exchangeable by D_2O), 12.73 (s, 1H, OH, disappeared by D_2O). ^{13}C NMR (100 MHz; d_6-DMSO, ppm): 15.08 (CH_3), 24.55 (CH_3), 36.42 (CH–COOH), 57.72 (Ctriazole), 117–149.37 (m, ArC), 152.91 (C=N), 157.72 (C-OH), 180.95 (C=O). MS (m/z+): 268 (M+2).**5-(2-hydroxyphenyl)- 3-[(2-methoxy-benzylidene)-amino]- 5-methyl1,5-dihydro [1,2,4]triazol-4-yl} propionic acid 6b**IR (KBr, cm^{-1}): 3403 (OH), 3290 (OH), 3206 (NH), 3104 (C H)aromatic, 2974 (C H)aliphatic. 1H NMR (DMSO-d_6), δ ppm: 2.22 (d, 3H, J = 6.25 Hz, CH_3), 2.33 (s, 3H, CH_3), 3.46 (q, 1H, J = 6.16 Hz, CH COOH), 3.83 (s, 3H, OCH_3), 6.94 (s, 1H, NH, exchangeable by D_2O), 6.96 to 8.11 (m, 8H, ArH),), 8.14 (s, 1H, OH, exchangeable by D_2O), 8.41 (s, 1H, CH N), 11.42 (s, 1H, OH, exchangeable by D_2O).

RESULTS AND DISCUSSION

At the beginning of the synthesis of triazole and their Schiff base derivatives we were study the solvent effect on the percent yield and time required for conversion under microwave irradiation technique.

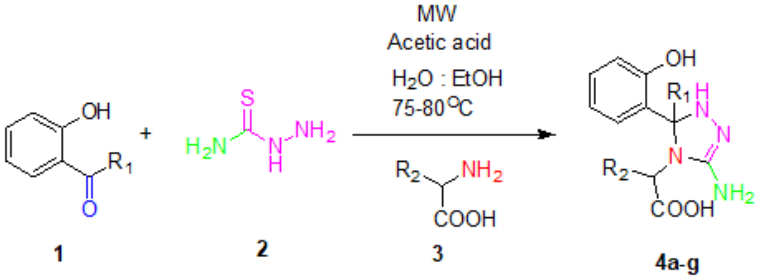
Table 1. Solvent effect on the synthesis of **4a** and **6a**.

Entry	% of H_2O	% of EtOH	Time (min.)[a]	% Yield
4a	80	20	15	46
4a	**50**	**50**	**11**	**92**
4a	20	80	18	52
6a	80	20	14	49
6a	**50**	**50**	**10**	**88**
6a	20	80	15	48

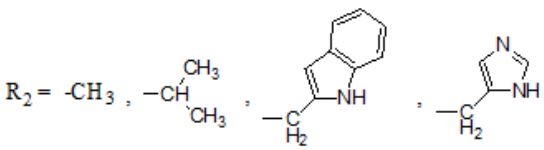
[a]Time required for microwave irradiation.
[b]Percent yield of crude product.

From the study of solvent effect we were found that 50% water and 50% ethanol is most excellent and suitable solvent for the particular synthesis. 100% water or ethanol is also used for the synthesis but it gives unknown inseparable impurities in the final product. Hence, we were decided to synthesize all the product using 50% water and 50% ethanol i.e. 1:1 ratio (Table 1).

In the present synthesis initially 2-hydroxy acetophenone or salicyladehyde**1** were reacted with thiosemicarbazide**2**and mixed well for two min,then the addition of substituted amino acids **3**in the mixture of H_2O : ethanol (1:1) using acetic acid as catalyst at 75-80^{0}C for near about 10-15 min under microwave irradiated condition (Scheme 1).

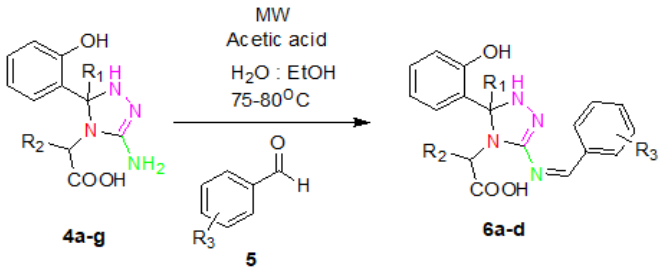


R_1 = -H, -CH_3

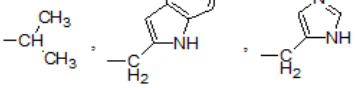


Scheme 1. Microwave irradiated synthesis of triazole derivatives **4a-g** using mixture of **1**, **2** and adding **3**. Pink coloured $-NH_2$ group from thiosemicarbazide**2** is reacted with carbonyl group of acetophenone or salicyladehyde**1** to form intermediate as Schiff base, addition of amino acid **3** and its red colour $-NH_2$ group attacks on the electrophilic carbon of (-C=S) group present in thiosemicarbazide followed by cyclization to form five member cyclic triazole derivative **4a-d** .

The formed triazole derivatives **4a-g** have a three active functional group such as hydroxyl (–OH) group from **1**, free amine ($-NH_2$) group from **2** and carboxylic acid (-COOH) functional group from **3**. All these functional groups having a good reactivity and promising activity, we were decided to convert a free amino group in to Schiff base **6a-d** derivatives using substituted benzaldehyde **5** derivatives. For the synthesis of **6a-d**were used derivatives of **4a-g** and **5** under microwave irradiation condition in presence of 1:1 mixture of water and ethanol at reflux and catalytic amount of acetic acid (Scheme 2).The reaction is also completed in 10-15 min observed on TLC.



R_1 = -H, -CH_3

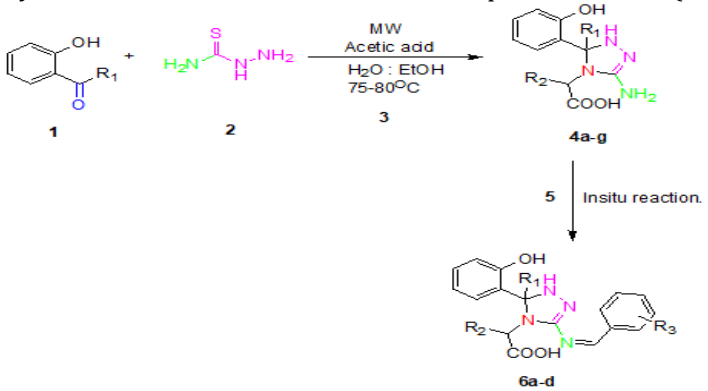
R_2 = -CH_3 , 

R_3 = -H, 4-OCH_3, 4-Cl, 4-F

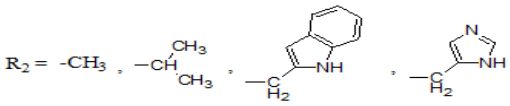
Scheme 2. Microwave irradiated synthesis of triazole bearing Schiff base derivatives **6a-d** using **4a-g** and adding **5**.

We were found that the multicomponent synthesis of triazole derivatives **4a-g**and two step synthesis of Schiff bases **6a-d**using microwave irradiation method is working successful (Fig 1).

Our next step of investigation is to synthesis of final product i.e. **6a-d**using insitu condition and also this synthetic methodology worked efficiently. In the present *In situ* synthesis first step is similar to scheme 1, after completion of first step observed on TLC after 10-15 min without isolation of product **4a-g,** were added substituted benzaldehydes derivatives **5** to afford a final *In situ* product of **6a-d** (Scheme 3).



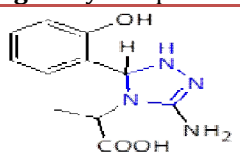
R_1 = -H, -CH_3

R_2 = -CH_3 , 

R_3 = -H, 4-OCH_3, 4-Cl, 4-F

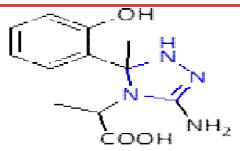
Scheme 3. Microwave irradiated *In situ* synthesis of triazole containing Schiff base derivatives**6a-d**.
In the current synthesis we observed the synthesis of triazole derivatives using scheme 1 required 10-15 min for completion and synthesis of Schiff base derivatives also want 10-15 min for completion in scheme 2 while using scheme 3 it required two half of 10-15 min, first half for the synthesis of triazole and second half for the synthesis of Schiff bases but scheme 3 gives a good percent yield of the synthesized product and no need for the isolation of intermediated triazole derivatives i.e. *In situ* fashion of synthesis (Fig 2).

Fig1. Physical parameters of the synthesized triazole derivatives **4a-g**.



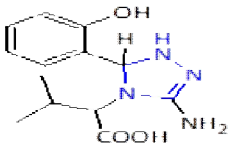
4a

Percent yield – 92 %
Time – 11 min.
M. P. – 240 241^{O}C (238 240^{O}C)



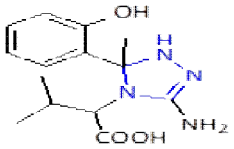
4b

Percent yield = 96 %
Time = 15 min.
M. P. = 190-191^{O}C (189-191^{O}C)



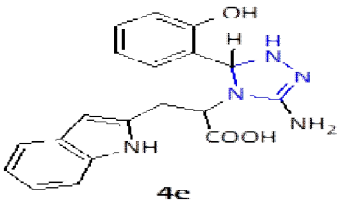
4c

Percent yield = 94 %
Time = 10 min.
M. P. = 248-249^{O}C (247-249^{O}C)



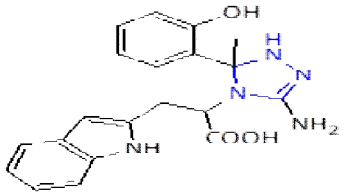
4d

Percent yield = 90 %
Time = 15 min.
M. P. = 196^{O}C (195-197^{O}C)



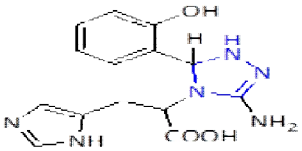
4e

Percent yield = 93 %
Time = 11 min.
M. P. – 230^{O}C (230 232^{O}C)



4f

Percent yield = 91 %
Time = 10 min
M. P. = 220-221^{O}C (220-222^{O}C)

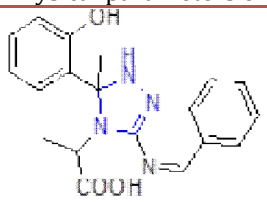


4g

Percent yield = 95 %
Time = 14 min.
M. P. – 230 232^{O}C (232 234^{O}C)

Percent yield = Isolated percent yield
M. P. = Melting point (reported)[39]

Fig 3. Physical parameters of the synthesized Schiff base derivatives **6a-d**.

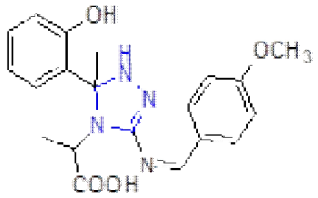


6a

Percent yield – 88 & 90%

Time = 10 & 14 min.

M. P. = 82-83^{O}C (82^{O}C)

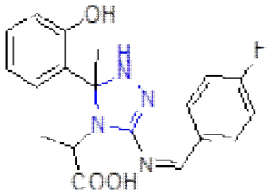


6b

Percent yield – 92 & 95 %

Time = 11 & 15 min.

M. P. = 140-141^{O}C (140^{O}C)

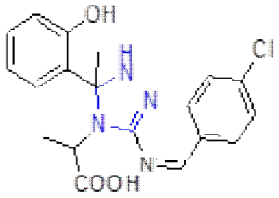


6c

Percent yield = 92 & 96 %

Time – 15 & 15 min.

M. P. = 107-109^{O}C (108^{O}C)



6d

Percent yield = 93 & 96 %

Time – 12 & 15 min.

M. P. = 124-126^{O}C (125^{O}C)

Percent yield = Isolated percent yield (Two step & insitu synthesis).
Time = (required for Two step & insitu synthesis)
M. P. = Melting point (reported)[40]

Micro broth dilution method were used for screening of microbial activities of the synthesized compounds. Anti bacterial activity of compounds were tested in opposition to 2 gram positive as well as 2 gram negative bacteria while antifungal activity in opposition to 3 different fungal spores. Anti bacterial activity was compared with standards drugs like Gentamycin, Ampicilin, Chloramphenicol, Ciprofloxacin and Norfloxacin while anti fungal activity of synthesized product were compared with Nystatin and Greseofulvin as standards (Table 2).

Table 2. *In Vitro* anti-microbial activities of synthesized compounds **4a-g** and **6a-d**.

Entry	**Minimal inhibition concentration (µg mL^{-1})**						
	Bacterial species				**Fungal species**		
	Gram-positive		**Gram-negative**				
	S. a.	*S. p.*	*E. c.*	*P. a.*	*C. a.*	*A. n.*	*A. c.*
4a	250	100	100	50	250	500	100
4b	200	62.5	50	250	500	100	200
4c	50	50	100	500	900	500	100
4d	50	100	25	100	100	250	500
4e	10	200	500	450	500	100	500
4f	250	100	50	250	100	900	100
4g	450	50	150	100	500	450	100
6a	50	250	50	100	100	250	500
6b	250	200	500	450	150	250	500
6c	50	100	50	250	1000	100	1000
6d	75	100	95	100	500	450	100
Gentamyci-n	0.25	0.5	0.05	1	--	--	--
Ampicilin	250	100	100	100	--	--	--
Chloram-phenicol	50	50	50	50	--	--	--
Ciproflox-acin	50	50	25	25	--	--	--
Norfloxa-cin	10	10	10	10	--	--	--
Nystatin	--	--	--	--	100	100	100
Greseofu-lvin	**--**	**--**	**--**	**--**	**500**	**100**	**100**

S. a. = Staphylococcus aureus, S. p. = Streptococcus pyogenus,
E. c. = Escherichia coli, P. a = Pseudomonas aeruginosa,
C. a. = Candida albicans, A. n. = Aspergillusniger, A. c. = Aspergillusclavatus.

Antibacterial activity of synthesized compounds

The synthesized products 4a-g and 6a-d was evaluated for their in vitro anti- microbial activity against two gram positive *S. Aureus* and *S. pyogenus* and two gram negative *E. Coli* and *P. aeruginosa*.

From the b data, some are possessed superb antibacterial activity compared with standard drugs such as Ampicilin entry 4a and 4f active in opposition to gram positive *S. aureus.*Also compounds 4c and 4d active against *S. aureus* compared with standard Chloramphenicol or Ciprofloxacin while 4ewith Norfloxacin. 4a, 4d and 4f were active against *S. Pyogenus* compared with Ampicilin while 4c and 4g compared with Chloramphenicol or Ciprofloxacin.

The entry 4a, 4c, and 4f were potent active against gram negative *E. coli* bacteria compared with Ampicilin while compound 4b and 4f compared with Chloramphenicol and compound 4d with Ciprofloxacin. The compounds active against *P. Aeruginosa* such as 4d and 4g compared with Ampicilin and 4a compared with Chloramphenicol.

The entry 6a, 6b and 6c active in opposition to gram positive *S. aureus* compared with Chloramphenicol, Ampicilin and Ciprofloxacin respectively. Compound 6c and 6d active against *S. pyogenus* compared with Ampicilin. The entry 6a and 6c was found potent active against gram negative *E. Coli bacteria* compared with Chloramphenicol while compound 6a and 6d active against *P. Aeruginosa* compared with Ampicilin standard (Table 4).

Antifungal activity of the synthesized compounds

The 3 fungal species viz. *C. Albicans. A. niger* and *A. clavatus* was used for in vitro antifungal activity and it compared with standard drugs Nystatinin and Greseofulvin. Some synthesized compounds found to potent antifungal such as compound 4b, 4e and 4g comparing with standard Greseofulvin against *Candida albicans*, then the compound 4d, 4f, also active against *Candida albicans* compared with Nystatin.The entry4b, 4e are showing good activity against *Aspergillus niger* compared with both the standards Greseofulvin and Nystatin.Compound4a, 4c,4f and 4gare found very good antifungal activity against *Aspergillus clavatus* compared with the standard Greseofulvin and Nystatin. The compounds 6a and 6d were potent active against *Candida albicans* compared with standard Nystatin and Greseofulvin respectively. The compound 6c showing antifungal activity against *Aspergillus niger* compared with standard Nystatin or Greseofulvin as well as compound 6d are also good active against *Aspergillus clavatus* compared with both the standards used (Table 4).

From the anti microbial activity data, we observed that the maximum triazole 4a-g derivatives were potent active against bacterial as well as fungal strains while only few Schiff base 6a-d derivatives showing potent activity. No anyone compound showing activity comparing or in range of standard drug Gentamycin.

CONCLUSIONS

In the summary, we concluded that the microwave irradiation method is most convenient and superior over the traditional or conventional methods used. We also concluded that the not always final products showing good biological activity but intermediates are also exhibiting excellent activity. Finally we found that insitu synthetic fashion is more suitable and more profitable.

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