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Synthesis and biological evaluation of some newer triazole based Schiff's bases

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Abstract

Synthesis of some newer Schiff's bases from 1, 2, 4-triazole were achieved. 1, 2, 4-triazole was converted to ethyl-5-N'-(1, 2, 4-triazolyl)-acetate **1** using ethyl bromoacetate. It was then converted to corresponding hydrazide **2**, which upon further treatment with various aromatic aldehydes afforded Schiff's bases **3a-3h**. Structures of various Schiff's bases **3a-3h** were established on the basis of elemental analyses and spectral data. The targeted compounds were obtained in good yields and subjected to antibacterial activity test against pathogenic bacteria at two different concentrations compounds **3b** and **3e** showed promising antibacterial activity compared to other analogues.

Key words: 1, 2, 4-triazole, Schiff's bases, antibacterial activity.

Introduction

The success of antibiotics after World War II led to the impression that bacterial infections could be easily cured. However, infectious diseases still remain a leading cause of global disease burden with high morbidity and mortality especially in the developing world. Hence it is clear that there is still an urgent need for new anti-bacterial agents to be developed [1].

Heterocyclic compounds have been on the forefront to supply varieties of molecules for efficiently battling these diseases. Among these heterocycles azoles like triazole are proven antifungal [2], but structural modifications have shown that triazoles derivatives also exhibit a wide spectrum of activities like antibacterial [3,4], anthelmentic [5], anticancer [6,7], anti-

neoplastic [8], anti-inflammatory [9], anti-convulsant [10], anti-viral [11], anti-malarial [12], anti-TB [13] etc. These facts prompted us to synthesize newer Schiff's bases of 1, 2, 4-triazole and to evaluate them for antibacterial activity.

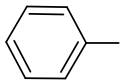
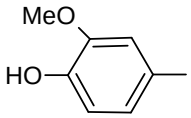
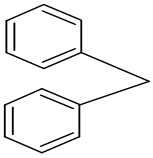
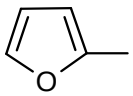
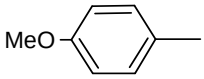
In the present work, 1, 2, 4-triazole was converted to ethyl-5-N'-(1, 2, 4-triazolyl)-acetate **1** using ethyl bromoacetate. It was then converted to corresponding hydrazide **2** by hydrazine hydrate, which upon further treatment with various aromatic aldehydes under acidic condition afforded Schiff's bases **3a-3h**. Structures of these compounds were characterized by means of spectral data and elemental analysis.

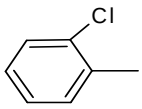
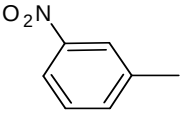
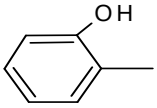
Results and Discussion

The various Schiff's bases were obtained in quantitative yields using known procedure. The structures of the synthesized compounds were established by spectroscopic methods. Antibacterial screening of newly synthesized compounds was carried out against *S. aureus*, *P. aeruginosa* and *E. coli* using cup-plate method. From the results obtained in the biological activity, it was observed that, the para substituted compound like **3e** and di-substituted compound like **3b** showed good activity against all organisms at both concentrations. However, for unsubstituted compounds like **3a** very weak activity was observed.

The physicochemical data for synthesized Schiff's bases is given in following **Table 1**.

Table 1: The physicochemical data for synthesized Schiff's bases

Compound	Ar	Mol. Formula (Mol wt.)	Yield (%)	m.p. (^{0}C)
3a		$C_{11}H_{11}N_5O$ (229)	55	138-140
3b		$C_{12}H_{13}N_5O_3$ (275)	60	227-230
3c		$C_{17}H_{15}N_5O$ (305)	53	156-159
3d		$C_9H_9N_5O_2$ (219)	44	>245
3e		$C_{12}H_{13}N_5O_2$ (259)	48	177-180

3f		$C_{11}H_{10}N_5OCl$ (263.5)	61	130-133
3g		$C_{11}H_{10}N_6O$ (264)	58	186-190
3h		$C_{11}H_{11}N_5O_2$ (245)	68	160-162

Biological evaluation

Cup-plate agar diffusion method [14, 15] was employed for *in vitro* study of antibacterial efficacy of the target compounds against *S. aureus, P. aeruginosa and E. coli* at two different concentrations viz. 50 and 100 µg/mL using streptomycin as the standard. Inhibitory activity was measured (in mm) as the diameter of the observed inhibition zones [16, 17]. The tests were repeated twice to confirm the findings and the average is reported in **Table 2.** The para substituted compound like **3e** and disubstituted compound like **3b** showed good activity against all organisms at both concentrations. However, for unsubstituted compounds like **3a** very weak activity was observed. Other compounds showed moderate activity.

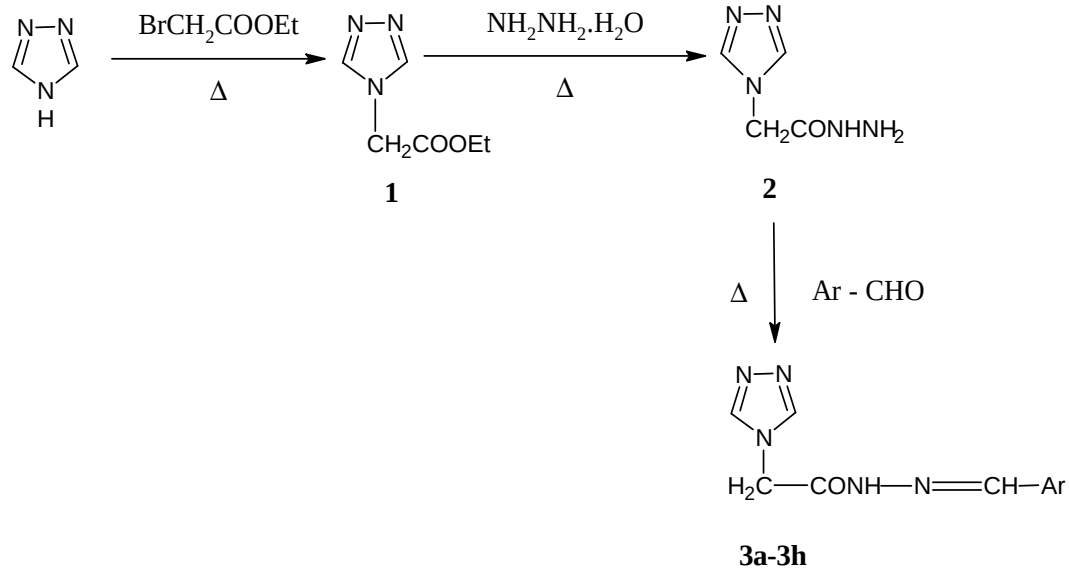
Table 2: Anti-bacterial activity of compounds 3a-3h

Compounds	**Diameter of zone of inhibition/mm**					
	P.aeuroginosa		***S. aureus***		***E. coli***	
	50	100	50	100	50	100
3[a]	09	16	12	18	08	18
3b	17	28	19	29	15	27
3c	11	21	11	17	09	13
3d	13	22	13	19	10	15
3e	16	31	19	30	16	29
3f	12	23	09	23	10	17
3g	10	21	15	19	11	20
3h	11	22	11	19	10	18
Streptomycin	20	30	18	31	17	26

Materials and Methods

Experimental

All the melting points were determined on 'Veego' VMP-D apparatus and are uncorrected. Silica gel G plates of 3x8 cm (Sigma-Aldrich) were used for TLC and spots were located by UV or in iodine chamber. The IR spectra were recorded in the 4000-400 cm^{-1} range using KBr discs on FT-IR 8400 SHIMADZU spectrometer. ^1H NMR spectra were recorded on Varian Mercury (300MHz) spectrometer in $CDCl_3$ as solvent using TMS as an internal standard and values are expressed in δ ppm. The elemental analyses were performed for C, H, N and were within ±0.4 of theoretical values.



1 **2** **3a-3h**

Scheme of Synthesis of Schiff's bases (3a-3h)

Synthesis of ethyl-4-N′-(1,2,4-triazolyl)-acetate (1): In a solution of 1,2,4-triazole (0.1 mole, 6.9 g) in dry methanol, ethylbromoacetate (0.1 mole,16.7 g) was slowly added under constant stirring in the presence of 5 g of anhydrous K_2CO_3. The resulting solution was then refluxed on a water bath for about 15-16 h. Then the reaction mixture was cooled and filtered. The filtrate was distilled to obtain a light yellow color liquid which was utilized in next reaction without further purification, yield 95%, IR(KBR)cm^{-1}: 3416 (NH), 1746 (CO), 1648 (C=N), 1514 (NH) [1].

Synthesis of ethyl-4-N′-(1, 2, 4-triazolomethyl)-hydrazide (2): Ethyl-5-N′-(1,2,4-triazolyl)-acetate **1** (0.1 mole, 15.5 g) was dissolved in methanol (25 ml) and hydrazine hydrate (0.15 mole) was added to this solution slowly. The mixture was refluxed on a water bath for about 10-12 h. The removal of excess of solvent afforded a dark red color liquid which was used as such, yield 80%, IR(KBR)cm^{-1}: 3261 (NH), 1694 (CO), 1602 (C=N), 1547 (NH) cm^{-1}.

General procedure for synthesis of Schiff's bases (3a-3h): To ethyl-4-N′-(1, 2, 4-triazolomethyl)-hydrazide **(2)** (1.4 g, 0.01 mole) was added appropriate aromatic aldehyde (0.015 mole). To it small quantity of glacial acetic acid was added. The mixture was refluxed for about 8-10 h, cooled and solvent was distilled off and solid thus obtained was dried. All these compounds were recrystallized from chloroform or methanol.

*N'-benzylidene-2-(4H-1,2,4-triazol-4-yl)acetohydrazide (***3a) :**
Yield: (55%), m.p.:138-140 ^{0}C, IR (KBR)cm^{-1}: 3114(-Ar C-H), 1697(-CO), 1596(C=N), ^{1}H NMR (DMSO-d_6) : δ 11.64 (s, 1H, NH), 8.65 (s, 1H, N=CH), 8.65-7.39 (m, 7H, Ar), 2.15 (s, 2H, CH_2), Anal Calcd: C, 57.64; H, 4.80; N, 30.57; Found: C, 57.69, H, 4.98; N, 30.99.

N'-(3-hydroxy-4-methoxybenzylidene)-2-(4H-1,2,4-triazol-4-yl)acetohydrazide **(3b) :**
Yield: 60%, m.p.: 227-230 ^{0}C, IR (KBR)cm^{-1} : 3043(-Ar C-H),1683(-CO), 1587(C=N), Anal Calcd: C, 52.36; H, 4.73; N, 25.45; Found: C, 52.76; H, 4.63; N, 25.98, ^{1}H NMR ($CDCl_3$) : δ 9.79(s, 1H, NH), 8.61(s, 1H, N=CH), 7.79-6.64(m, 6H, Ar), 4.00-3.85(s, 3H, OCH_3), 2.16(s, 2H, NCH_2).

N'-(diphenylmethylene)-2-(4H-1,2,4-triazol-4-yl)acetohydrazide (**3c) :**
Yield: 53%, m.p.: 156-159 ^{0}C, IR (KBR)cm^{-1} : 3068(-Ar C-H), 1676(-CO), 1581(C=N), Anal Calcd: C, 66.89; H, 4.92; N, 22.95; Found: C, 66.98; H, 4.11; N, 22.46.

N'-(2-furylmethylene)-2-(4H-1,2,4-triazol-4-yl)acetohydrazide **(3d) :**
Yield: 44%, m.p.: >245 ^{0}C, Anal Calcd : C, 49.32; H, 4.11; N, 31.96; Found: C, 49.65; H, 4.69; N, 31.33;

N'-(4-methoxybenzylidene)-2-(4H-1,2,4-triazol-4-yl)acetohydrazide (**3e) :**
Yield: 48%, m.p. : 177-180 ^{0}C, IR (KBR)cm^{-1} : 3085(-Ar C-H), 1676(-CO), 1558(C=N), Anal Calcd : C, 55.60; H, 5.02; N, 27.03 Found: C, 55.51; H, 5.19; N, 27.11.

N'-(2-chlorobenzylidene)-2-(4H-1,2,4-triazol-4-yl)acetohydrazide (**3f):**
Yield: 61%, m.p: 130-133 ^{0}C, IR (KBR)cm^{-1} : 3066(-Ar C-H), 1684(-CO), 1593(C=N), ^{1}H NMR ($CDCl_3$) : δ 9.09 (s, 1H, NH), 8.23-7.26(m, 7H, N=CH, Ar)2.17 (s, 2H, NCH_2). Anal Calcd : C, 50.09; H, 3.80; N, 26.57; Found: C, 51.01; H, 4.23; N, 25.98;

N'-(3-nitrobenzylidene)-2-(4H-1,2,4-triazol-4-yl)acetohydrazide (**3g) :**
Yield: 58%, m.p.: 186-190 ^{0}C, IR (KBR)cm^{-1} : 3075(-Ar C-H), 1683(-CO), 1577(C=N), Anal Calcd: C, 50.00; H, 3.79; N, 31.82; Found: C, 50.71; H, 4.29; N, 31.00;

N'-(2-hydroxybenzylidene)-2-(4H-1,2,4-triazol-4-yl)acetohydrazide **(3h) :**
Yield : 68%, m.p. : 160-162 ^{0}C, IR (KBR)cm^{-1} : 3114(-Ar C-H), 1697(-CO), 1596(C=N), ^{1}H NMR ($CDCl_3$) : δ 11.39(s, 1H, NH), 8.71(s,1H, N=CH), 7.41-6.95(m, 6H, Ar), 2.17(s, 2H, NCH2), 1.57 (s, 1H, OH), Anal Calcd : C, 53.88; H, 4.49; N, 28. ; Found: C, 52.99; H, 4.23; N, 28.77.

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References

[1] T. D. Chugh, *J. Biosci***., 2008,** 33(4), 549–555.
[2] Shigematsu, Taichiro, Tomita, Masayuki, Shibahara, Tetsuya, *Chem. Abstr* 88:6891g.
[3] A. Spassou, E. Golovinsky, *Chem. Ber.*, **1966,** 99, 3734.
[4] H. A Burch, W.O.Smith, *J. Med. Chem.*, **1966,** 9, 405.
[5] M.A. Ei-Dawy, A.Omarm M. Mohsen, A.M. Ismail, A. B. Hazza, *J. Pharm.Sci*., **1983**, 72, 45.
[6] M. S. Chande, K. Singh-Jathar., *Ind. J Chem*., **1995,** 34B, 654.
[7] J. H. Boyer in *"Heterocyclic Compounds"*, **1961**, Editor R.C. Elderfield, Weissberger, N.Y., 7, 525.
[8] A. Passannanti, P. Diana, P. Barraja, F. Mingoia, A. Lauria, G. Cirrincione, *Heterocycles.* **1998,** 48, 1229.
[9] M. S. Hosur, R. Talwar, *Ind J. Pharm Sci*. **1993**, 55 (3), 86.
[10] K. Ilkay, R. Sevim, *Farmaco*. **2004**, 55 (11), 893.
[11] G. D. Diana, J. J. Nitz, *EP 566199*, **1993**.
[12] M. Jilino, Stevens, F.G. Malcolm., *J. Chem. Soc, Perkin Trans1*. **1998**, 1677.
[13] R. H. Udupi, V. M. Kulkarni, P. Purushottamachar, N. *J.* Srinivasalu, *Ind. Chem. Soc*. **2002**, 79, 381.
[14] H. W. Seely, P. J. Van Denmark In; *Microbes in action: A Lab. Manual of Microbiology*, 2nd ed, **1975**, 55.
[15] A. L. Barry In; *The Antimicrobial Susceptibility Test: Principle and practice*,Lea and Febiger, Philadelphia, **1976,** 180.
[16] F. E. D. Amour, D. L. Smith, *J. Pharmacol Exp. Ther.*, **1941**, 72, 74.
[17] A. W. Bauer, M. Turck, *Am. J. Clin.Pathol.*, **1966**, 45, 493.