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SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL SCREENING OF NOVEL SCHIFF BASE AND THIAZOLIDINONE DERIVATIVES INCORPORATED BY TRIAZOLE MOIETY

Deepak Nagargoje*, Mohammad Shaikh

Dept. of Chemistry, Dr. B.A. Marathwada University, Chh. Sambhajinagar, Maharashtra, India

Abstract

A series of novel 2-(4-(1*H*-1,2,4-triazol-1-yl)phenyl)-3-phenylthiazolidin-4-one derivatives have been synthesized from (Z)-N-(4-(1*H*-1,2,4-triazol-1- yl)benzylidene)benzenamine and thioglycollic acid in dry toluene at reflux temperature. The synthesized compounds were screened for antibacterial activity against gram positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*; and gram-negative bacteria *Escherichia coli* and *Salmonella typhi* respectively. ^{1}H NMR, IR, Mass spectral data and elemental analyses elucidated the structures of the all newly synthesized compounds. Some of the tested compounds showed significant antibacterial activity.

Keywords: Schiff base, thiazolidinone, triazole, antibacterial activity

1. INTRODUCTION

Azoles are found widely in natural sources and there are several drugs available which contain azole ring as a part of their structure. Triazoles are important five membered heterocyclic rings containing three nitrogen atoms. The chemistry of triazole was studied in detail and discussed in literature since last 30-40 years. The major reason behind this is the activities exhibited by triazole moiety. Most of the compounds containing triazoles are potent P450 inhibitors, particularly; Itraconazole is potent inhibitor of human CYP3A4 whereas F luconazole is known to inhibit human CYP2C9 and CYP2C19 isoform. Recently, an attention has been focused on 1 *H*-1,2,4-triazole derivatives for their broad-spectrum of activities, such as fungicidal, herbicidal, anticonvulsant and plant growth regulatory activities [1-3].

In medicinal and pharmaceutical field, schiff bases as well as azo compounds are biologically important compounds [4-6]. It has been suggested that the azomethine linkage might be responsible for biological activities displayed by schiff bases. In addition to this, schiff bases are precursors for the synthesis of some pharmacologically important compounds like azetidinone and thiazolidinone derivatives.

Furthermore, they are reported to show a variety of interesting biological actions including antibacterial [7-12], antifungal, anti-mouse hepatitis virus (MHV) [13], inhibition of herpes simplex virus type 1 (HSV-1) and adenovirus type 5 (Ad 5) [14], anti- cancer [15-19], anti-mosquito larvae [20] and herbicidal activities [21]. In agricultural chemistry, it is known that the presence of a chloro and azo moiety in different types of azomethine compounds can exhibit pesticidal activity [22].

4-thiazolidinones are derivatives of thiazolidine ring with a carbonyl group at 4-position. In 4-thiazolidinone, substituent at 2, 3 and 5 positions may be varied, but the significant and drastic difference in structure and properties is exerted by the group attached to carbon atom at 2- position. Several examples of compounds with substitutions at these positions and with desired properties were synthesized and tested for pharmacological activities. It was observed that these molecules exhibit activities ranging from anticonvulsant [23,24], anti-tubercular [25,26], anthelmintic [27,28], antibacterial [29,30] to anticancer activities [31,32]. The variations in the 3-positions are particularly popular as antimicrobial [33, 34] and as cardiovascular affecting agents.

Therefore, in view of these important biological activities of both the Schiff bases and 4-thiazolidinone derivatives and in continuation of our research program [35], we herein report the synthesis of some new Schiff bases and 4-thiazolidinone derivatives incorporated by triazole moiety. The newly synthesized compounds were tested for the antibacterial activity against representative gram-positive and gram-negative bacteria. Out of which some of them have been found to possess an interesting profile of pharmacological activity.

2. Experimental

2.1 General information

The melting points of all synthesized compounds were determined in open capillary tubes and are uncorrected. The purity of all compounds was checked by TLC. IR spectra were recorded on Jasco FT-IR-4100 in KBr disc. ^{1}HNMR spectra were recorded on a Varian As 400 MHz spectrometer in DMSO-d_6; chemical shifts (δ) were in ppm relative to TMS and coupling constant (J) were expressed in hertz (Hz). Mass spectra were recorded on a Macro mass spectrometer (Water) by electron-spray method (ES). Elemental analysis was performed on Perkin-Elmer EAL-240 elemental analyzer.

2.2 General procedure for the synthesis of (Z)-N-(4-(1*H*-1,2,4-triazol-1- yl)benzylidene)benzenamine (3a)

An equimolar mixture of 4-(1*H*-1,2,4-triazol-1-yl) benzaldehyde **2** (1.0gm, 5mmol) and aniline **1a** (0.53ml, 5mmol) in 10ml ethanol containing few drops of cat. sulphuric acid was refluxed for 5h. After completion of reaction (checked by TLC), the excess of solvent was removed on rotary evaporator to yield solid which was washed with petroleum ether followed by crystallization from ethanol.

The compounds **3(a-j)** were prepared by the above procedure. Their structures have been confirmed by IR, ^{1}H NMR, mass spectra and elemental analyses.

2.3 General procedure for the synthesis of 2-(4-(1*H*-1,2,4-triazol-1-yl)phenyl)-3- phenylthiazolidin-4-one (5a)

To a solution of imine **3a** (0.5 gm, 1.5 mmol) in dry toluene was added thioglycollic acid (0.28 gm, 3 mmol). The contents were refluxed for 6h until completion of the reaction. Excess solvent was removed under reduced pressure and the residue treated with saturated solution of $NaHCO_3$, extracted with ethyl acetate, dried with Na_2SO_4 and solvent distilled off. The residue on recrystallization gave 4-thiazolidinone. The compounds **5(a-j)** were prepared by using the above procedure. Their structures have been confirmed by IR, ^{1}H NMR and Mass spectra.

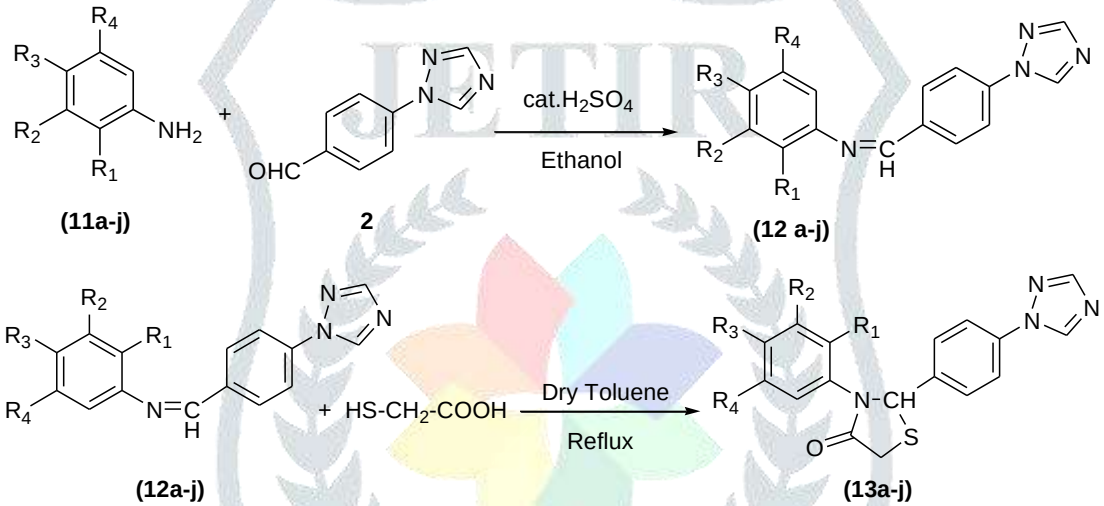

Table 1: Physical data of compounds 12(a-j) and 13(a-j)

Comp. No.	R1	R2	R3	R4	Yield %	M.P.
12a	H	H	H	H	80	141-143
12b	H	F	F	H	81	154-156
12c	F	F	F	H	60	126-128
12d	F	H	F	H	42	153-155
12e	F	Cl	Cl	H	82	149-151
12f	H	H	F	H	79	137-139
12g	H	H	NO2	H	68	145-147
12h	H	H	Br	H	70	187-189
12i	H	NO2	H	H	64	144-146
12j	H	H	I	H	65	172-174
13a	H	H	H	H	75	130-141
13b	H	F	F	H	72	150-151
13c	F	F	F	H	44	136-138
13d	F	H	F	H	70	159-160
13e	F	Cl	Cl	H	72	145-147
13f	H	H	F	H	56	138-139
13g	H	H	NO2	H	55	155-157
13h	H	H	Br	H	69	187-189
13i	H	NO2	H	H	61	148-150
13j	H	H	I	H	60	178-180

2.4 Biological assay

Some of the synthesized compounds were screened for *in vitro* antibacterial activities against gram positive and gram-negative bacteria. In gram positive bacteria, *Staphylococcus aureus* (*S. aureus*) and *Bacillus subtilis* (*B. subtilis*) were used and in gram–negative *Escherichia coli* (*E. coli*) and *Salmonella typhi* (*S. typhi*) were used against standard drugs Tetracycline and Ampicillin. The antibacterial activities were carried out on nutrient agar with standard composition and by standard procedure of paper disc method [36]. Petri dishes and necessary glasswares were sterilized in hot air oven (190°C, 45 min). The nutrient agar and saline (0.82% NaCl) were sterilized in autoclave (121°C, 15psi, 20min). Inoculum was prepared in sterile saline and optical density of all pathogens was adjusted to 0.10 at 625nm on hemito Spectrascan UV 2600 Spectrophotometer which is equivalent to 0.5 McFarland standards. The nutrient agar plates were prepared by pour plate method [37]. The sensitivity of the compounds was tested by disc diffusion method (paper disc method). All the bacterial cells were cultured in nutrient plates and the compounds to be tested were dissolved in DMSO solvent and were soaked on paper discs.

The discs were placed into the plates and incubated at 37ºC for 24h. The diameter in mm of Zone of inhibition around each disc was measured by scale and the observed data of antimicrobial activity of compounds and the standard drugs is given in **Table 2**. Among all the compounds screened **3a, 3c, 3e, 5a** and **5b** showed good antibacterial activity against *gram positive* bacteria and compound **3e, 3h, 5a, 5d** and **5f** showed good activity against *gram–ve* bacteria as comparable with that of standard drug tested. So, result of all preliminary study indicated that the substituted (Z)-N-(4-(1*H*-1,2,4-triazol-1-yl)benzylidene)benzenamine **3(a-j)** and 2-(4-(1*H*-1,2,4- triazol-1- yl)phenyl)-3-phenylthiazolidin-4-one **5(a-j)** moiety represent a new class of pharmacophore for broad spectrum antimicrobial activity.

Table 2: Antimicrobial activities of compounds 3(a-j) and 5(a-j)

	Antimicrobial Activity			
	Gram positive		Gram negative	
	S. aureus	*B. subtilis*	*E. coli*	*S. typhi*
3a	21	23	20	21
3b	20	20	18	15
3c	23	21	19	18
3d	21	22	21	18
3e	25	23	22	24
3f	11	13	08	11
3g	12	10	16	09
3h	21	18	25	27
3i	10	08	11	14
3j	15	11	14	12
5a	18	21	23	27
5b	21	20	17	15
5c	18	13	11	04
5d	15	17	24	26
5e	04	06	10	05
5f	20	18	25	27
5g	06	08	07	05
5h	12	10	06	08
5i	08	11	10	12

5j	05	06	11	12
Tetracycline	**35**	**30**	**27**	**25**
Ampicillin	**33**	**35**	**30**	**31**

2.5 Conclusion

In summary, we have synthesized a series of triazole incorporated (Z)-N-(4-(1*H*-1,2,4-triazol-1-yl)benzylidene)benzenamine and 2-(4-(1*H*-1,2,4-triazol-1-yl)phenyl)-3-phenylthiazolidin-4-one derivatives and their antimicrobial activities have been evaluated. All the compounds demonstrated potent inhibition against all the tested strains.

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References

1. Toyabe, K.; Nezu, M.; Shimazu, H.; Jpn Kokai Tokkyo Koho Jp, *0641086*; *Chem. Abstr.*, **1989**, *121*, 9409q.

2. Shaber, S. J.; Flyn, K. E.; Fujimoto, T. T.; Eur Pat Ep, 529, 973, *Chem. Abstr.*, **1993**, *119*, 72612z.

3. Stankovsky, S.; Jedlovska, E.; Spirkova, K., *Collect Czech Chem. Commun.* **1993**, *58*, 2211.

4. Venturini, A.; Gonzalez J. *J. Org. Chem.* **2002**, *67*, 9089.

5. Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626.

6. Delpiccolo, C. M. L.; Mata, E.G. *Tetrahedron: Asymmetry*, **2002**, *13*, 905.

7. More, P.G.; Bhalvankar, R. B.; Pattar S. C. *J. Ind. Chem. Soc.* **2001**, *78*, 474.

8. Pandeya, S. N.; Sriram, D.; Nath, G.; De Clercq, E. *Farmaco*, **1999**, *54*, 624.

9. Baseer, M. A.; Jadhav, V. D.; Phule, R. M.; Archana, Y. V.; Vibhute, Y. B. *Orient J. Chem.* **2000**, *16*, 553.

10. El-Masry, A. H.; Fahmy, H. H.; Abdelwahed, S. H. A. *Molecules*, **2000**, *5*, 1429.

11. Karia, F. D.; Parsania, P. H. *Asian J. Chem.* **1999**, *11*, 991.

12. Kabeer, A. S.; Baseer, M. A.; Mote, N. A. *Asian J. Chem.* **2001**, *13*, 496-500.

13. Singh, W. M.; Dash, B.C. *Pesticides*, **1988**, *22*, 33-37.

14. Wang, P. H.; Keck, J. G.; Lien, E. J.; Lai, M. C. *J. Med. Chem.* **1990**, *33*, 608.

15. Das, A.; Trousdale, M. D.; Ren, S.; Lien, E. *J. Antiviral Res.* **1999**, *44*, 201.

16. Desai, S. B.; Desai, P. B.; Desai, K. R. *Het. Commun.* **2001**, *7*, 83.

17. Pathak, P.; Jolly, V. S.; Sharma, K. P. *Orient J. Chem.* **2000**, *16*, 161.

18. Kuz'min, V. E.; Lozitsky, V. P.: Kamalov, G. L.; Lozitskaya, R. N.; Zheltvay, A. I.; Fedtchouk, A. S.; Kryzhanovsky, D. N. *Acta. Biochim. Polon.* **2000**, *47*, 867.

19. Phatak, P.; Jolly, V. S.; Sharma, K.P. *Orient J. Chem.* **2000**, *16*, 493.

20. Das, B. P.; Choudhary, R.T.; Das, K.G.; Choudhury, D. N.; Choudhury, B. *Chem. Environ. Res.* **1994**, *3*, 19.

21. Samadhiya, S.; Halve, A. *Orient J. Chem.* **2001**, *17*, 119.

22. (a) Jolly, V. S.; Pathak, P.; Jain, R. *J. Ind. Chem. Soc.* **1993**, *70*, 505. (b) Jarrahpour, A. A.; Motamedifar, M.; Pakshir, K.; Hadi, N.; Zarei, M. *Molecules*, **2004**, *9*, 815.

23. Shyam, R.; Tiwari, R.C. *Bull. Chem. Soc. Jpn* **1972,** *49*, 171.

24. Kumar, R.; Gupta, T. K.; Parmar S. S. *J. Prakt. Chem.* **1970**, *312*, 201.

25. French Patent, **1972**, 1,604,530; *Chem Abstr.* **1973**, *79*, 32038.

26. Litvinchuk, M. D. *Farmakol. Toxicol.* **1963**, *26*, 725; *Chem. Abstr.* **1964**, *60*, 13761.

27. Aries R., French Patent, **1974**, 2,186,245; *Chem. Abstr.* **1974**, *81*, 140869.

28. Aries R., French Patent, **1975**, 2,190,431; *Chem. Abstr.* **1976**, *84*, 35329.

29. Mandlik, J. V.; Patwardhan, V.A.; Nargund, K. S. *J. Univ. Poona Sci. Technol.* **1996**, *32*, 43-45; *Chem Abstr.* **1968**, *68*, 87228.

30. Mohan, L.; Chadha, V. K.; Choudhary, H. S.; Sharma, B. D.; Pujari, H. K.; Mohapatra, L. N. *Indian J. Exp. Biol.* **1972**, *10*, 37.

31. Gududuru, V. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5289.

32. Ottana, R. *Bioorg. Med.Chem. Lett.* **2005**, *15*, 3930.

33. Bondock, S.; Khalifa, W.; Fadda, A. A. *Eur. J. Med. Chem.* **2007**, *42*, 948.

34. Bondock, S.; Khalifa, W.; Fadda, A. A. *Synth. Commun.* **2006**, *36*, 1601.

35. a) Gill, C. H., Jadhav G. R., Shaikh M. U., Kale R. P., Nagargoje D. R., Shiradkar M. R., *Bioorg. and Med. Chem. Lett.* **2008**, 18, 23, 6244 (b) Jadhav G. R., Shaikh M. U., Kale R. P., Shiradkar M. R., Gill, C. H., *Eur. J. Med. Chem.* **2009,** 44, 7, 2930 (c) Kale R. P., Jadhav G. R., S haikh M. U., Gill C. H. *Tetrahedron Lett.* **2010,** 50, 16, 1780 (d) Nagargoje D. R., Mandhane P. G., Shingote S. K., Badadhe P. V., Gill C. H. *Ultrasonics Sonochemistry* **2012,** 19, 1, 94.

36. Godkar, P. B. In *Text Book of Medical Laboratory Technology*, Bhalani P ublishing House, Bombay, India, **1996,** pp-232-245.

37. Kilic, A.; Baysallar, M.; Besirbellioglu, B.; Salih, B.; Sorkun, K.; Tanyuksel, M. *Annals of Microbiology*, **2005**, *55*, 113.