Est. 1984

ORIENTAL JOURNAL OF CHEMISTRY
An International Open Free Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2012, Vol. 28, No. (4):
Pg. 1791-1796

Synthesis, Characterization and Antimicrobial Evaluation of some Schiff Bases and their Thiazolidinone Products

DESTA GEBRETEKLE, ABI TADESSE, R. K. UPADHYAY* and AMAN DEKEBO

Department of Chemistry, College of Natural and Computational Sciences,
Haramaya University, Ethiopia.
*Corresponding author E-mail: rkupadhyay14@gmail.com

(Received: September 29, 2012; Accepted: November 10, 2012)

ABSTRACT

Six isomeric nitro- and methoxy anilines were condensed with vanillin to obtain Schiff's bases. A new series of 2-(4-hydroxy-3-methoxy phenyl)-1-thiazolidinone derivatives were synthesized by the cyclocondensation of Schiff's bases with mercapto acetic acid. The chemical structures of synthesized compounds were confirmed by elemental analysis, molecular weight determination, IR, ^{1}H & ^{13}C and DEPT-135 NMR spectral measurements. Antibacterial and antifungal activities were studied *in vitro* against *staphylococcus aurous* and *Escherichia coli* bacteria and *Aspergillus niger* and *Rhizoctoia bataticola* fungi by using Ampicillin and Bavistin reference drugs respectively.

Key words: Schiff's bases, Amines, Thiazolidinones, Bacteria, Fungi.

INTRODUCTION

Schiff's bases, characterized by the presence of imine or azomethine (-C=N-) group, constitute an important class of organic synthetic compounds. Imines owing to –C=N- linkage are useful as precursors in diverse organic synthesis and exhibit wide spectrum of biological properties, viz. pesticidal[1], fungicidal[2-4], bactericidal[5,6], bacteriostatic[7], anticancer[8,9], antiviral[10,12] etc. They have been reported as novel ligands informing complexes of unusual coordination numbers and isomeric structures with metals[13], as dyes[14] and analytical reagents[15-16]. Vanillin containing Schiff's bases act as a weak inhibitor of tyrosinase and display both antimutagenic and comutagenic properties in *Escherichia coli*[17] in addition to antimicrobial activities against various microbes and several pharmacological properties[1].

Thiazolidinone derivatives were reported to display antitumor[18], antituberculor[19], anti-HIV[20], analgesic[21], anti-inflammatory[20], ulcerogenic[22], and antibacterial[23-24] and antifungal[22] activities. Therefore it was envisaged that compounds containing vanillin and thiazolidinone moieties would result in compounds of interesting biological properties. In the present study vanillin was treated with isomeric nitro-and methoxy anilines to produce Schiff's bases. The Schiff's bases were subjected to cyclocondensation reactions with thioglycolic acid to produce 4-thiazolidinones. The chemical

structures of the synthesized compounds were confirmed by means of elemental analyses, molecular weight determination, and IR, ^{1}H, & ^{13}C and DEPT-135 NMR. All the compounds were screened against Gram-positive and Gram-negative bacteria and fungi.

EXPERIMENTAL

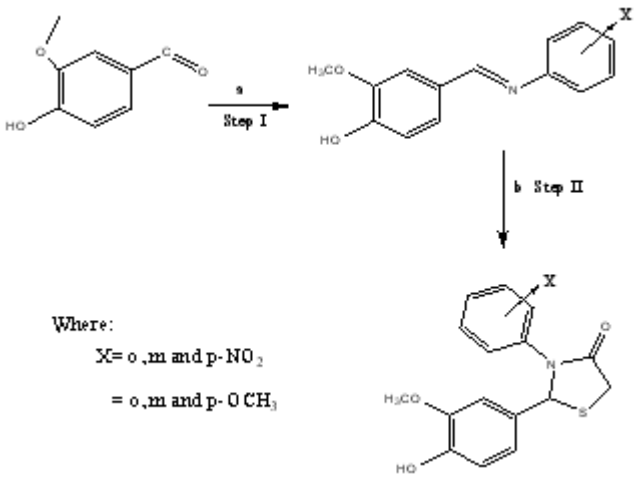
Synthesis Scheme

Synthesis of 1, 4-thiazolidinones involved two steps:

Reagent and conditions

(a) Respective primary amines, dry ethanol, reflux 3h.

(b) Thioglycolic acid, dry acetone, anhydrous CH_3COONa, aqueous Na_2CO_3, reflux 3h



Step I

All the Schiff's bases were prepared by mixing equimolar (0.5 mol) saturated solutions of each of substituted anilines with vanillin in dry ethanol and reaction mixtures were refluxed for 3 h on water bath. The solids precipitated or obtained on evaporation of the solvent as residues were washed with water and ether to remove unreacted vanillin and amine, if any, successively. Products were crystallized from acetone or methanol and dried in oven at 60-70 °C.

Step II

For the synthesis of 1, 4-thiazolidinones, saturated solution of Schiff's bases (0.25 mol) in acetone was mixed with thioglycolic acid in 1:3 molar ratio and 5 gram anhydrous sodium acetate was added to the reaction mixture and refluxed for ~3h. Hot reaction mixtures were filtered, cooled to room temperature and neutralized with aqueous Na_2CO_3 solution to remove unreacted acid; precipitates of products were filtered and washed with water repeatedly to ensure complete removal of sodium salt(s) and dried in air. All the compounds were purified by crystallization from ethanol or ether.

The purity of the synthesized compounds was checked by thin-layer chromatography and the impure samples were purified either by column chromatography or by washing with the solvent as identified by TLC.

Physico-chemical and Microbial analysis

Microanalaytical analyses were performed on a Vario-el III, elemental-R analyzer. Melting points were determined in open glass capillaries using MP-D Mitaruma Rikero Kiygo electro-thermal melting point apparatus. Molecular weights of the compounds were determined by Rast's method with camphor as solvent. IR spectra in 500 cm^{-1} – 4000 cm^{-1} range were recorded in KBr medium on FT-IR Shimadzu spectrometer. ^{1}H spectra, ^{13}C and DEPT-

135 NMR spectra were recorded in $CDCl_3$ on Bruker 400 MHz Advanced spectrometer.

Antimicrobial (antibacterial and antifungal) activities of the azomethines and thiazolidinones, were tested *in vitro* using disc diffusion method against *Staphylococcus aureus* and *Escherichia coli* bacteria in Mueller Hinton Agar (MHA) medium and against *Aspergillus niger* and *Rhizoctoia bataticola* fungi in Potato Dextrose Agar (PDA) medium. The degree of bactericidal and fungicidal activities was determined by measuring diameter of inhibition zone and compared with the standard drugs ampicillin and bavistin, respectively.

RESULTS AND DISCUSSION

Theoretically proposed molecular formulae of the compounds are in conformity of experimental data of molecular weights and elemental analyses (Table 1).

The common characteristic groups of 1a-f and 2a-f of azomethines and thiazolidinones, display ν C-OH & δ C-OH (phenolic), ν C-O-C, aromatic ν C=C & δ C-H, aliphatic ν C-H, ν C-NO_2 (symm.) & ν C-NO_2 (asymm.) and ortho, meta and para substitution vibrations in their infrared spectra in 3215-3482 cm^{-1} & 1029-1154 cm^{-1}, 1265-1378

Table 1: Structure, melting point, yield and analyses data of compounds

Compound	Colour	Yield (%)	m.p. (°C)	M.W Calcd. (Found)	%Analyses: Calcd.(Found)			
					C	H	N	S
1a	Smoky white	51.9	78±1	272 (264.7)	61.76 (62.20)	4.44 (4.90)	10.29 (10.20)	-
1b	Light yellow	96.2	132±1	272 (273.8)	61.76 (61.21)	4.44 (4.62)	10.29 (10.22)	-
1c	White	94.2	103±1	272 (283.6)	61.76 (61.65)	4.44 (4.68)	10.29 (10.17)	-
1d	Yellow	94.0	119±1	257 (248.1)	70.02 (69.76)	5.88 (6.12)	5.44 (5.33)	-
1e	Light yellow	58.4	126±1	257 (256.1)	70.02 (69.26)	5.88 (6.54)	5.44 (5.82)	-
1f	White	99.2	154±1	257 (259.5)	70.02 (69.80)	5.88 (5.46)	5.44 (5.40)	-
2a	Yellow	51.3	116±1	346 (345.2)	55.48 (55.00)	4.07 (4.24)	8.09 (7.73)	9.26 (9.05)
2b	Orange	59.4	113±1	346 (360.9)	55.48 (54.92)	4.07 (4.18)	8.09 (8.16)	9.26 (9.36)
2c	Light yellow	65	166±1	346 (336.4)	55.48 (55.26)	4.07 (4.41)	8.09 (7.84)	9.26 (9.10)
2d	Orange	62.3	119±1	331 (317.6)	61.61 (60.98)	5.17 (5.31)	4.23 (4.28)	9.68 (9.35)
2e	Yellow orange	62.1	134±1	331 (330.8)	61.61 (59.87)	5.17 (5.13)	4.23 (3.98)	9.68 (9.90)
2f	Pale orange	81.5	141±1	331 (354.5)	61.61 (60.69)	5.17 (4.86)	4.23 (3.99)	9.68 (9.29)

Where:

1. $C_7H_7O_2$-CH=N-ArX 2. $C_7H_7O_2$-C_3H_3NOS-ArX

a: *o*-NO_2 b: *m*-NO2 d: *o*-OCH_3 e: *m*-OCH_3 f: *p*-OCH_3

cm^{-1}, 1452-1595 cm^{-1} & 2954-3106 cm^{-1}, 2921-3105 cm^{-1}, 1265-1377 cm^{-1} & 1515-1666 cm^{-1}, and ca.747-727 cm^{-1}, ca.777-789 cm^{-1} and ca.843-836 cm^{-1} regions respectively. A strong band observed in 1a-f at 1592-1668 cm^{-1} range assigned to CH=N clearly indicates formation of the new azomethines owing to condensation of CHO group of vanillin with NH_2 group of primary amine and absence of any peak of CHO group supports the proposed structure of 1a-f. Cyclocondensation of azomethine compounds with thioglycolic acid leads to the formation of thiazolidinones containing C=O, C-S-C, C-N and CH_2 groups of heterocyclic ring with elimination of water. IR spectra of these compounds exhibit ν C=O (cyclic), ν C-S-C(ring) and ν C-N(ring) vibrations in 1608-1667 cm^{-1}, 650-722 cm^{-1} and 1300-1367 cm^{-1} regions respectively whereas heterocyclic ring methylene group (CH_2) displayed its ν C-H symmetric, ν C-H asymmetric and δ C-H bands in 2852-2855 cm^{-1}, 2921-2955 cm^{-1} and 1447-1463 cm^{-1} ranges respectively. The absence of νCH=N peak and presence of these characteristic groups of heterocyclic ring obviously conform the cyclization of the azomethines leading to the formation of thiazolidinones (2a-f)[25].

For the verification of IR results, ^1H and ^{13}C NMR spectra of the compounds have been examined. ^1H NMR spectra of azomethines (1a-f) display singlet in δ 3.80- 4.00, δ 7.70-8.40 and ä 8.40- 9.85 regions characteristics of $–OCH_3$, -OH and –CH=N groups, respectively and multiplet bands of benzene rings in δ 6.27- 8.06 range. ^1H NMR spectra of thiazolidinones however displayed signals in ä 3.85- 4.40, δ 8.10- 9.85, δ 8.10- 8.75 and δ 5.55- 6.20 regions for their OCH_3, OH(phenolic), CH-N (ring) and -S-CH_2 (ring) groups respectively; benzene protons exhibit multiplets in δ 6.10-7.60 ppm region[24]. ^{13}C NMR spectra of 1a-f of carbon containing groups-OCH_3, C-OH, CH=N and C-NO_2 exhibit their characteristic signals in ä 56, δ 147-153, δ 159-191 and δ 136-147, respectively along with benzene ring carbons in ä 107-161 range. ^{13}C NMR spectra of 2a-f display signals of carbon containing groups (Ar)O-CH_3, C-OH (phenolic), C-N (ring), C=O (ring), C-S (ring) and CH_2 (ring) in δ 56-66, δ 139-152, δ 55-56, δ 166-191, δ 55-56 and δ 30-34 ranges respectively and aromatic carbon signals in ä 109-158 region. In NO_2 substituted products C-NO_2 signal is exhibited in δ 136-148 range. Signals corresponding to C-N (ring),

Table 2: Inhibitory zone diameters (%) of azomethines and thiazolidinones against tested bacteria and fungi strains by paper disc diffusion method

Compound	Antibacterial activity				Antifungal activity			
	S. aureus		*E.coli*		*A.niger*		*R.bataticola*	
	10 µL/ disc	20 µL/ disc	10 µL/ disc	20 µL/ disc	10 µL/ disc	20 µL/ disc	10 µL/ disc	20 µL/ disc
1a	32	32	27	27	30	36	39	39
1b	32	36	27	31	65	59	58	65
1c	32	36	23	27	50	73	58	65
1d	32	32	23	27	30	36	65	62
1e	32	36	23	31	40	41	54	65
1f	36	36	23	27	30	32	58	73
2a	32	41	27	31	40	50	50	62
2b	36	45	31	35	45	55	54	50
2c	32	41	27	35	70	64	100	115
2d	32	41	27	31	30	36	23	35
2e	36	45	39	50	45	41	27	35
2f	36	41	31	42	30	27	31	35
DMSO	-	-	-	-	-	-	-	-
Ampicillin	100	100	100	100	-	-	-	-
Bavistin	-	-	-	-	100	100	100	100

C-S (ring) and O-CH_3 group have been seemed to be overlapped. All the NMR inferences are totally in conformity of IR results[25]. DEPT-135 spectra of azomethines also displaying O-CH_3 and CH=N signals at the same ppm as observed in ^{13}C NMR spectra and seven aromatic hydrogen bonded carbons exhibit seven peaks in upward direction as expected. Thiazolidinones also display peaks of OCH_3, CH-N and aromatic hydrogen bonded carbons exhibit peaks at the same ppm as observed in ^{13}C NMR spectra in upward direction as expected[27].

The results of antimicrobial studies reveal less significant antibacterial activity of both series of compounds, against both test bacteria; *m*-methoxy thiazolidinone however exhibits better results against *E.coli* among all others. All the compounds show better antifungal activities than bactericidal properties against both fungi tested. Although several azomethines and thazolidinones exhibit highly significant results, *p*-nitro thiazolidinone has highest antifungal action against *R. bataticola* in both the concentrations used, better than standard drug bavistin (Table 2)[28].

REFERENCES

1. Thorat, B.R., Mandewala, M., Shelke, S., Kamat, P., Atram, R.G., Bhalerao, M., Yamgar, R. *J. Chem. Pharm. Res*., **4**:14 (2012).
2. Singh, H., Yadav, L.D.S., Mishra, S.B.S. *J. Inorg. Nucl. Chem.,* **43**: 1701 (1981).
3. Saravanan, G., Pannerselvam, P., Prakash, C.R. *J. Adv. Pharm. Techn. Res*., **1**: 320 (2010).
4. Panneerselvam, P., Nair, R.R., Vijayalakshmi, G., Subramanian, E.H., Sridhar, S.K. *Eur. J.Med. Chem*., **40**: 225 (2005).
5. Przybylski, P., Huczynski, A., Pyta, K., Brzezinski, B., Bartl, F. *Curr. Org. Chem.,* **13**: 124 (2009).
6. Karthikeyan, M.S., Parsad, D.J., Poojary, B., Bhat, K.S., Holla, B.S., Kumari, N.S. *Bioorg. Med. Chem.,* **14**: 7482 (2006).
7. Yuxia, Z., Tao, Z., Wanshan, M., Haibin, Z., Suifeng, C. *Hauxue Shiji,* **24**: 117 (2002).
8. Sinha, D., Tiwari, A.K., Singh, S., Shukla, G., Mishra, P., Chandra, H., Mishra, A.K. *Eur. J.Med. Chem.,* **43**: 160 (2008).
9. Przybylski, P., Pyta, K., Wicher, B., Gdaniec, M., Brzezinsk, B. *J. Mol. Struct.,* **889**: 332 (2008).
10. Holla, B.S., Akberali, P.M., Shivananda, M.K. *Il Farmaco,* **56**: 919 (2001).
11. Jarrahpour, A., Khalili, D., De Clercq, E., Salmi, C., Brunel, J.M. *Molecules,* **12**: 1720 (2007).
12. B.K. Rai, S.N. Vidyarthi, Amit,Rabindra Singh, Nitish Bhardwaj and Aninush Ojhr, *Orient J. Chem*., **28**(3): 1403-1409 (2012).
13. Upadhyay, R.K., Sharma, V.K., Singh, V.P. *J. Liq. Chromatography* **5:** 1141 (1982).
14. Upadhyay, R.K., Agarwal, N. *Nat. Acad. Sci. Letter*, **14:** 251(1991).
15. Upadhyay, R.K., Bajpai, A.K., Rathore, K. *Chromatographia,* **18:** 618 (1984).
16. Wtanable, K., Ohta,T., Shirasu,Y. *Mutat Res*., **218:** 105 (1989).
17. Mehta, D.S., Shah, V.H. *Indian.J.Heterocyc.Chem*., **11:** 139-144 (2001).
18. Kucukguzel, S.G., Orul, E.E., Rollas, S., Salin, F., Ozbek, A. *Eur.J.Med.Chem.,* **37:** 197-206 (2002).
19. Rawal, R.K., Prabhakar, Y.S., Katti, S.B., DeClercq, E. *Bioorg.Med.Chem*., **13:** 6771 6776 (2005).
20. Vigorita, M.G., Ottana, R., Monforte, F., Maccari, R., Trovato, A., Monforte, M.T., Taviano, M.F. *Bioorg.Med. Chem.Lett*., **11:** 2791-2794 (2001).
21. Shanmugapandiyan, P., Denshing, K.S., Ilavarasan, R., Anbalagan, N., Nirmal R. *International Journal of Pharmaceutical Sciences and Drug Research* **2:** 115-119 (2010).
22. Singh, G.S., Molotsi, B.J. *Il Farmaco*., **60:** 727-730 (2005).
23. Rahman, V. P. M., Mukhtar, S., H.Ansari, W., Lemiere, G. *Eur.J.Med.Chem.,* **40:** 173-184 (2005).
24. M.H. Salunke, Z.A. Filmwala and A.D. Kamble, *Orient J. Chem*., **27**(3): 1243-1248

(2011).
25. Meyers, R.A., Wiley and Sons, Ó J. Interpretation of Infrared Spectra, Ltd a Practical Approach, 10815–10837(2000).
26. Timothy, D.W. High-Resolution NMR Techniques in Organic Chemistry 1st edition (1999).
27. Hore, P.J., Oxford University Press, USA; Nuclear Magnetic Resonance. 1st edition (1995).
28. Yadav, P.S., prakash, D., Senthilkumar, G.P. *Intern. J. Pharm. Sc. Drug Res*., **3:** 01-07(2011).