Vidyabharati International Interdisciplinary Research Journal 10(1) **124-128** **ISSN 2319-4979**

SYNTHETIC STUDY OF 1-(3-HYDROXY PHENYL IMINO-4-HYDROXY PHENYL-5-IMINO-1,2,4- THIADIAZOLIDINE)-3-PHENYL THIOCARBAMIDES

K.N. Puri* **and U.W. Karhe**
[1]Department of Chemistry, Shri Shivaji Science College, Amravati, MS, India
[2]Department of Chemistry, Anuradha Engineering College, Chikhli, MS, India
knpuri2008@rediffmail.com

ABSTRACT

Several 1-(3-Hydroxy phenylimino -4- hydroxy phenylimino-1, 2, 4-thiadiazolidine) – 3 – phenyl thiocarbamides **3** were synthesized by the interaction of Phenyl isothiocyanate with 3-Hydroxy phenylimino-4-hydroxyphenyl-5- imino 1, 2, 4 thiadiazolidines **2**.The identities of these new compounds have been established on the basis of chemical transformations and spectral studies. In the present investigation the *In-vitro* bacterial assay of compounds has been evaluated by using several bacteria such as *Staphylococcus aureus, S. Typhi* and *Pseudomonas aeruginosa.* All compounds studied shows satisfactory antibacterial activity.

Keywords: *synthesis, thiocarbamide, 1, 2, 4 thiadiazolidine, Phenyl isothiocyanate, antibacterial activity.*

Introduction

The thiazolidones and thiadiazolidine have drawn considerable attention due to their varied biological and physiological activities, e.g., local anaesthetic[1], anti-bacterial[2], anti-fungal selective Muscarinie Agonists[3] and anti-inflammatory[4]. 1,3,4-thiadiazole derivatives have also been shown to possess anti-microbial[5], anticonvulsant[6], carbonic anhydrase inhibitory[6] and tumor associated isozyme IX inhibitory activities, 3-oxo-1,2,4-thiadizolidines have been shown to possess promising anti-fungal[7], anti-bacterial and plant growth regulator[8] activities. 1, 2, 4-Triazole derivatives have been shown to possess promising eosinophilia inhibitory[9] activities. The oxidative debenzylation and cyclisation[10-13] technique has been reported as a standard technique for the synthesis of *N* and *S* containing 1, 2, 4-thiadiazolidines. A perusal of the synthetic routes followed by earlier workers for the synthesis of 1, 2, 4-thiadiazolidines, oxidative dealkylation and cyclization of isodithiobiurets and related systems, enhanced anti-fungal activities associated with certain 3-oxo-1, 2, 4-thiadiazolidines, prompted us to synthesize newer 1,2,4-thiadiazolidines by employing oxidative debenzylation technique and study their biological activities.

The pharmacological and biochemical aspect of Alkyl/Aryl ureides, thioureides and guinidines have been very extensively investigated and many compounds of these series have been described in the literature. They have been found to posses marked biological activity and are used as bacteriostatic agents and diuretic, analgesic and antithyroid drugs.

One of the most interesting reactions in organic chemistry is the oxidation of thioureas. Depending on the substitution pattern of the thiourea, the oxidizing agent, the polarity of the medium variety of products are formed.

As a part of research work being undertaken in the synthesis of nitrogen and sulfur containing heteroacycles and heterocycles having various application in drug chemistry, pharmaceutical, medicinal, agricultural, industrial and biotechnological sciences. Therefore, it was thought to investigate the following reactions.

Experimental

All the melting points recorded were found to be uncorrected. The structures of newly synthesized compound were confirmed on the basis of elemental and IR spectral analysis[12-13]. IR spectra were recorded in KBr on a FTIR Perkin-Elmer (4000-450cm^{-1}) spectrophotometer and in KBr disks on SHIMADZU IR affinity-1 FTIR spectrometer. Specific rotations were measured on Equip-Tronics EQ-801 Digital Polarimeter. Thin layer chromatography (TLC) was performed on

silica gel G for TLC (Merck) and spots were visualized by iodine vapours.

Result and Discussion

Preparation of 3-Hydroxy phenylimino-4-hydroxy phenyl-5-imino-1,2,4-thiadiazolidines (Hector's base):

To an ethanolic suspension of hydroxy phenyl thiocarbamides acidified with about conc. Hydrochloric acid was added gradually with proper stirring hydrogen peroxide. Reaction was exothermic and thiocarbamide went in to solution and a clear solution was obtained. After complete addition of hydrogen peroxide reaction mixture was allowed to stand for 15 minute. Sulfur was liberated. The liberated sulfur was removed by filtration. On further treatment with dil. Ammonium hydroxide produce white products. It was purify from ethanol.

Synthesis of 1-(3-*o*-Hydroxy phenylimino -4-*o*-hydroxy phenylimino-1, 2, 4-thiadiazolidine) – 3 – phenyl thiocarbamide (3a):

The mixture of Phenyl isothiocyanate and 3-*o*-Hydroxy phenylimino-4-*o*-hydroxyphenyl-5-imino 1, 2, 4 thiadiazolidine was refluxed in acetone medium for 2 hr. The reaction was monitored by TLC. After the completion of the reaction, the solvent was evaporated and product obtained as solid with m. p. 140-142°C.

Similarly when the reaction of Phenyl isothiocyanate were extended to other 3-Hydroxy phenylimino-4-hydroxyphenyl-5-imino 1, 2, 4 thiadiazolidines 2b-c the related 1-(3-Hydroxy phenylimino -4- hydroxy phenylimino-1, 2, 4-thiadiazolidine) – 3 – phenyl thiocarbamides 3b-c were obtained. The structures of the product were confirmed by the spectral[14-16] and elemental analysis (Table 1).

Spectral analysis

2a:- **IR(KBr cm^{-1}):** 3477 (O-H str), 3309 (N-H str), 3010 (Aromatic C-H str), 1504 (C=N str), 1454 (C-N str), 1251 (C-O str), 761 (C-S str), 781 (Monosub. benzene), 715 (disub. benzene). (Found: C, 55.82; H, 3.96; O, 10. 55; N, 9.10; S, 10.49 %, $C_{14}H_{12}O_2N_4S$ Required: C, 56; H, 4; O, 10. 66; N, 9.33; S, 10.66 %).

2b:- **IR(KBr cm^{-1}):** 3412 (O-H str), 3311 (N-H str), 3022 (Aromatic C-H str), 1539 (C=N str), 1446 (C-N str), 1228 (C-O str), 759 (C-S str), 698 (Monosub. benzene), 783 (disub. benzene). (Found: C, 55.90; H, 3.86; O, 10. 56; N, 9.20; S, 10.52 %, $C_{14}H_{12}O_2N_4S$ Required: C, 56; H, 4; O, 10. 66; N, 9.33; S, 10.66 %).

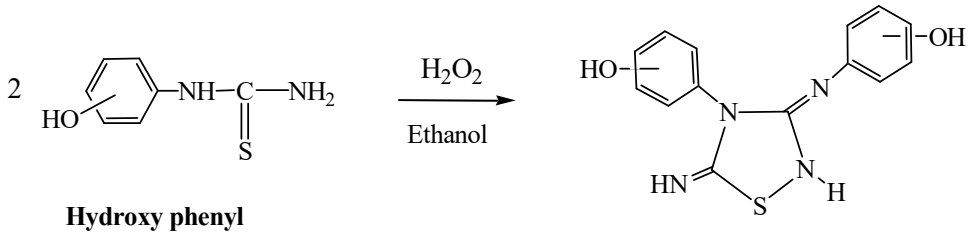
2c:- **IR(KBr cm^{-1}):** 3412 (O-H str), 3311 (N-H str), 3022 (Aromatic C-H str), 1539 (C=N str), 1446 (C-N str), 1228 (C-O str), 759 (C-S str), 698 (Monosub. benzene), 783 (disub. benzene). (Found: C, 55.95; H, 3.86; O, 10.46; N, 9.25; S, 10.56 %, $C_{14}H_{12}O_2N_4S$ Required: C, 56; H, 4; O, 10. 66; N, 9.33; S, 10.66 %).

3a:- **IR(KBr cm^{-1}):** 3429 (O-H str), 3313 (N-H str), 3022 (Aromatic C-H str), 1544 (C=N str), 1558 (C-N str), 1253 (C-O str), 1074 (C=S str), 835 (C-S str), 763 (Monosub. benzene), 731 (disub. benzene). (Found: C, 57.82; H, 3.79; O, 7.30; N, 15.98; S, 14.56 %, $C_{21}H_{17}O_2N_5S_2$ Required: C, 57.93; H, 3.90; O, 7.35; N, 16.09; S, 14.71 %).

3b:- **IR(KBr cm^{-1}):** 3412 (O-H str), 3361 (N-H str), 3005 (Aromatic C-H str), 1508 (C=N str), 1456 (C-N str), 1236 (C-O str), 1085 (C=S str), 790 (C-S str), 688 (Monosub. benzene), 761 (disub. benzene). (Found: C, 57.80; H, 3.90; O, 7.25; N, 16.01; S, 14.60 %, $C_{21}H_{17}O_2N_5S_2$. Required: C, 57.93; H, 3.90; O, 7.35; N, 16.09; S, 14.71 %).

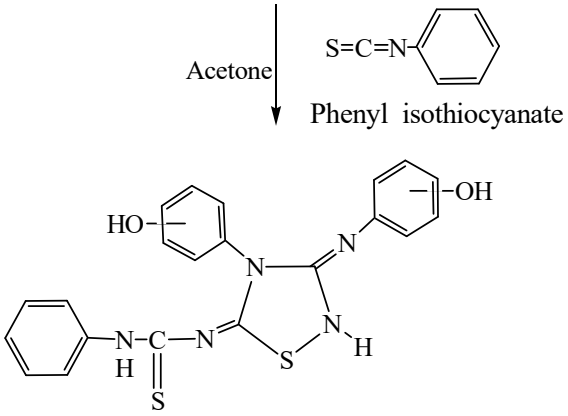
3c:- **IR(KBr cm^{-1}):** 3429 (O-H str), 3313 (N-H str), 3022 (Aromatic C-H str), 1544 (C=N str), 1558 (C-N str), 1253 (C-O str), 1074 (C=S str), 835 (C-S str), 763 (Monosub. benzene), 731 (disub. benzene). (Found: C, 57.83; H, 3.89; O, 7.30; N, 15.98; S, 14.66 %, $C_{21}H_{17}O_2N_5S_2$ Required: C, 57.93; H, 3.90; O, 7.35; N, 16.09; S, 14.71 %)

Reaction Scheme



Hydroxy phenyl thiocarbamides 1

3-Hydroxy phenylimino-4-hydroxy phenyl-5-imino-1, 2, 4-thiadiazolidines 2a-c



1-(3-Hydroxy phenylimino-4-hydroxy phenyl-5-imino-1, 2, 4-thiadiazolidine)-3-phenyl thiocarbamides 3a-c

Where, a) *o*-hydroxy, b) *m*-hydroxy, c) *p*-hydroxy

Table1:- Characterization of 3-Hydroxy phenylimino-4-hydroxyphenyl-5- imino 1, 2, 4 thiadiazolidine 2 and 1-(3-Hydroxy phenylimino -4- hydroxy phenylimino-1, 2, 4-thiadiazolidine) – 3 – phenyl thiocarbamide.

Sr. No.	Compounds	Molecular formula	Mole. wt.	% Yield	M.P in ^{o}C	R_f value Acetone: P.ether (3 : 7)
1	3-*o*-Hydroxy phenylimino-4-*o*-hydroxy phenyl5-imino1,2,4-thiadiazolidine **2a**	$C_{14}H_{12}O_2N_4S$	300	65	249-252	0.50
2	3-*m*-Hydroxy phenylimino-4-*m*-hydroxy phenyl 5-imino 1,2,4-thiadiazolidine **2b**	$C_{14}H_{12}O_2N_4S$	300	63	265-270	0.44
3	3-*p*-Hydroxy phenylimino-4-*p*-hydroxy phenyl 5- imino 1,2,4-thiadiazolidine **2c**	$C_{14}H_{12}O_2N_4S$	300	65	275-280	0.55
4	1-(3-*o*- Hydroxyphenylimino 4-*o*- hydroxy phenyl 5- imino 1,2,4 thiadiazolidine)-3-phenyl thiocarbamide**3a**	$C_{21}H_{17}O_2N_5S_2$	435	61	140-142	0.76
5	1-(3-*m*- Hydroxyphenylimino 4-*m*-hydroxy phenyl 5- imino 1,2,4 thiadiazolidine)-3-phenyl thiocarbamide **3b**	$C_{21}H_{17}O_2N_5S_2$	435	64	160-162	0.40
6	1-(3-*p*- Hydroxyphenylimino 4-*p*- hydroxy phenyl 5- imino 1,2,4 thiadiazolidine)-3-phenyl thiocarbamide **3c**	$C_{21}H_{17}O_2N_5S_2$	435	70	152-155	0.55

Antibacterial activity

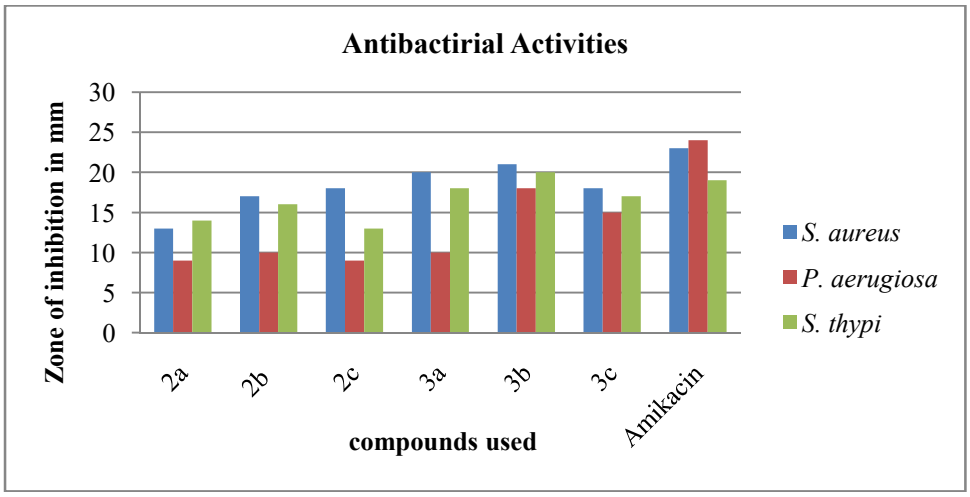
All the compounds have been screened for antibacterial activities using cup plate agar diffusion method[17-18] by measuring the inhibition zone in mm. the compounds were taken at a concentration of 1 mg/mL using dimethyl sulphoxide (DMSO) as solvent. The compounds were screen for antibacterial activity against *Staphylococcus aureus, S. thypi and Pseudomonas* aeruginosa in nutrient agar medium. Amikacin (100 µg/mL) was used as standard for antibacterial activity. The results are presented in Table2.

The study reveals that all compounds show antimicrobial activities. 3a and3b showed more significant activities against Staphylococcus aureus, 3b and 3c showed more significant activities against Pseudomonas aeruginosa Proteus vulgaris and 3b and 3a showed more significant activities against S. thypi respectively.

Table 2: Antibacterial activities of synthesized compounds:

Compounds	*S. aureus*	*P. aerugiosa*	*S. thypi*
2a	13	09	14
2b	17	10	16
2c	18	09	13
3a	20	10	18
3b	21	18	20
3c	18	15	17
Amikacin	23	24	19

Graphical Representation



Conclusion

In this study we have reported the detailed procedure of synthesis of some substituted 1, 2, 4-thiadiazolidines and characterized them on the basis of chemical and spectral study. As heterocyclic compounds may show antimicrobial activities we studied the synthesized compounds against some selected microbes and all compounds show satisfactory results. The method of synthesis and study of the compound in the field of antimicrobial activity is important.

Acknowledgement

Authors are thankful to SAIF/CIL, Panjab University, Chandigarh for providing spectral data. Authors also thankful to Head, Department of Chemistry and Principal, Shri Shivaji College, Amravati for encouragement and providing necessary facilities.

References

1. Bhargawa, P.M. Chourasia, M.R (1969). New local anesthetics. Derivatives of 5-diethylaminoaceto amido-2-arylimino-3-aryl-4-thiazolidones, J. Pharm Sci, 58: 896
2. Abdel-Halin , A.M. Abdel-Aziz , R.M. El-Kafrawy, A.F. (1994). Synthesis and biological activity of some 2-pyrimidine 2-aryl imino-thiazolidine 4-one derivatives. Indian J. Heterocyclic Chem, 4:45
3. Rajeswaran, W. G. Yang, C. Xi-Ping, H. Elizabeth, W. M. Tracy, C. Solina, L. Fenghua, L. Peter, I. N. James, E. Beth, A. L. Karl, H. N. William, S. M. (2001). Design, synthesis and biological characterization of bivalent 1-methyl-1,2,5,6-tetrahydropyridyl-1,2,5-thiadiazole derivatives as selective muscarinic agonists J .Med Chem, 44:4563
4. Geard, C. Bernard, B. Bertin, E. Cristina De, A. Simon, L. C. Dumas, M. Jacques, P. (2003). Synthesis and Biological Activity of Nitro Heterocycles analogous to Megazol , a Trypanocidal lead, J. Med. Chem, 46:427
5. Jag, M. Ashok, K. (2003). Synthesis and Antimicrobial activity of imidazo[2,1-b]-1,3,4-thiadiazolo[2,3-c]-S-triazoles and S-triazolo [3,4,b]-1,3,4-thiadiazoles,. Indian J. Heterocyclic Chemistry, 12:189
6. Srivastava ,A. Kumar, A. (2003). Synthesis of newer indolyl thia-diazoles and their thiazolidnones and formanzans as potential anti-convulsant agents. Indian J. Pharm Sci, 65:358
7. Ilies Marc, A. Daniela, V. Jaromir, P. Andrea, S. Monica, I. Miron, T. C. Silvia, P. Claudie, T. S. (2003). Carbonic anhydrase inhibitions, Inhibition ofTumor Associated Isozyme IX by Halogenosulfanilamide and Halogenophenylaminobenzolamide derivatives. J. Med. Chem, 43: 2187-96.
8. Choubey, A. K. Tripathi, A. K. Singh, R. (1998). Synthesis, antifungal and anti-bacterial activities of Some New 2-benzylideneamino-5-arylimino-3-oxo-1, 2, 4-thiadiazolidines, Indian J. Chem, 37B:145.
9. Singh, R. Choubey, A. K. Tripathi, A. K. (1997). Synthesis of novel 2-p-methoxy-benzylideneimino-5-arylimno-3-oxo-1,2,4-thiadiazolidines, Indian J. Heterocyclic Chem., 6:251.
10. Youichiro, N. Fumihiko, A. Shinji, T. Takehiro, O. Masahiko, K. Hiroko, N. Masanori, S. Chikara, F. Yoshio, K. (1996). Synthesis and pharmacologicalactivities of Triazole derivatives inhibiting Eosinophilia, J. Med Chem, 39: 3019
11. Ali, M. R. Verma, V. K. (1985). One-pot Synthesis of 2-aryl-3-phenyl-5-pheny-limino-1,2,4-thiadiazolines using N-Chlorosuccinimide. Synthesis, 691.
12. Pandey, A. K. Singh, R. Verma, V. K. (1986). Synthesis of 2-phynel-3-oxo-4-arylimino-1,2,4-thiadiazolidines, Indian J. Chem, 25B:202.
13. Singh, R. Choubey, A. K. Bhattacharya, A. A. (1998). Novel rout to the synthesis of 2-cyclohexylidene amino-5-arylamino-3-oxo-1,2,4-thiadiazolidines, J. Indian Chem. Soc., 75:430
14. Baeuerle, P. A. Baichwal, V. R. (1997). NF-B as a frequent target for immuno-suppressive and anti-inflammatory molecules, Adv Immunol , 65:111–37.
15. Silverstein, R. M. Webster, F. X. and Kiemle D. J. (2005). Specrometric Identification of organic compounds.7th ed. Wiley/ New York.
16. Buclzikiewicz, H. Djerassi, C. and Williams, D. H. (1964). Structural Elucidation of natural product by mass spectrometry. I Alkaloids Holden Day/ San Francisco.
17. Kawangh, F. (1963). Analytical Microbiology. Academic press/ New York.
18. British Pharmacopeia-(II). (1998). Biological Assay and Testa. The Stationary Office Ltd. London.