Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Chemica Sinica, 2012, 3(6):1486-1489

Pelagia Research Library

ISSN: 0976-8505
CODEN (USA) CSHIA5

Synthesis and biological activity of s-bridge heterocyclic compounds

Kishor H. Chikhalia* and Hetal N. Dabhi

Department of Chemistry, School Of Sciences, Gujarat University, Ahmedabad, Gujarat, India

---

ABSTRACT

A series of 2-[{(4-Pyridinyl)-1,3,4-oxadiazole}-5yl]-thio-4-(N,N-diethyl amino)-6-(aryl/alkyl)-amino-s-triazine derivatives is prepared from isoniazide. The synthesized compounds have been characterized by TLC, IR and ^{1}H-NMR spectroscopy. All the compounds were tested for their antibacterial and antifungal activities against S. aureus, S. pyogenus, E-coli, P. aerugin.

Keywords: Antimicrobial activity, s-Triazine, Isoniazide, carbon disulphide, diethyl amine.

INTRODUCTION

The quest for a more reliable and suitable drug is always fascinating and challenging. A number of drugs containing simple heterocyclic or a combination of different heterocyclic moieties have been in use these days. The s-Triazine based 1, 3, 4-oxadiazole-2- thio and their derivatives have their own importance in heterocyclic chemistry due to their good biological activities [1]. S-Triazine derivatives constitute an important class of compounds possessing diverse pharmacological activities including broadly active as herbicidal and antimicrobial [2] . Some are also used for the treatment of HIV infection [3-5]. Several workers investigated the s-triazine nucleus in the scope of potential therapeutic agents for diseases due to cancer [6-8], antitumor [9-10] and malaria [11-12], hypoglycerimic , analgesic, sedative, anti-inflammatory, anthelmintic [13].

On the other hand, five membered 1, 3, 4-oxadiazole heterocycles are also useful intermediates for the development of molecules of pharmaceutical interest where several promising antitumor compounds are found to contain the oxadiazole ring system [14-16]. The 1, 3, 4-oxadiazole are useful in the treatment of analgesic, anticancer and inflammatory[17]. The structures of the various synthesized compounds were assigned on the basis of TLC, IR and ^{1}H-NMR spectral data presented in **Table-I**. These compounds were also screened for their antimicrobial activity presented in **Table-II.**

MATERIALS AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded in KBR on BOMMEN Spectrometer. The ^{1}H –NMR were recorded on HITECHI 300MHz Spectrometer using TMS as an internal standard. The reactions are followed up and the purity of products is carried out on pre-coated TLC plates (Silica gel 60 F254, Merck) of 0.25mm thickness and the spots were rendered visible by expounding to UV light iodine.

Preparation of 2-(4-Pyridinyl)-5-mercapto-1,3,4-oxadiazole (2) : A mixture of isonicotinicacid hydrazide **(1)** (2.7g, 0.02 mol), potassium hydroxide (1.1g, 0.02mol), Then it was monitored by TLC by using toluene : ethyl acetate (7:3) as an eluent. Ethanol was distilled off under reduced pressure, the residue was dissolved in water and then acidified with dilute hydrochloric acid (10%). The solid obtained was filtered, washed, dried and recrystallized from ethanol. M.P. 267°C.

Preparation of 2-[2-{(4-Pyridinyl)-1,3,4-oxadiazole}-5yl]-thio-4,6-dichloro-s-triazine (3) [18-19] : To a stirred solution of 1,3,5-s-triazine (4.00g, 0.02mol), in acetone (40ml) at 0°-5° C the mixture of 2-(4-Pyridinyl)-5-mercapto-1,3,4-oxadiazole(3.58g, 0.02mol), in 10% $NaHCO_3$ (25 ml) was added drop wise in 1 hour. The stirring was continued at 0°-5° C for 6 hours. The P^H was adjusted neutral by addition of 10% Na_2CO_3 solution. The progress of reaction was monitored by TLC by using toluene: ethyl acetate (7:3) as an eluent. After the completation of reaction content was poured into crused ice. Product was filtered, washed with cold water, dried and recrystallized from absolute alcohol. M.P. 180°C.

Preparation of 2-[{(4-Pyridinyl)-1, 3, 4-oxadiazole}-5yl]-thio-4-(N,N-diethyl amino)-6-chloro-s-triazine (4):
A mixture of 2-[{(4-pyridinyl)-1,3,4-oxadiazole}-5yl]-thio-4,6-dichloro-s-triazine (3.27g, 0.01mol), in acetone (50ml) at 35°- 45°C, diethyl amine (0.73ml, 0.01mol) was added drop wise. The PH was adjusted neutral by addition of 10% $NaHCO_3$ solution. The progress of reaction was monitored by TLC by using toluene: ethyl acetate (7:3) as an eluent. After the completation of reaction content was poured into crused ice. Product was filtered, washed with cold water, dried and recrystallized from absolute alcohol. M.P. 230°C.

Preparation of 2-[{(4-Pyridinyl)-1,3,4-oxadiazole}-5yl]-thio-4-(N,N-diethyl amino)-6-(aryl/alkyl)-amino-s-triazine (5):
A mixture of 2-[{(4-Pyridinyl)-1,3,4-oxadiazole}-5yl]-thio-4-(N,N-diethyl amino)-6-chloro-s-triazine (3.64g, 0.01mol) and alkyl or aryl amine in acetone (40 ml) was heated at 70°-80°C on water bath for a 6 hours. The progress of reaction was monitored by TLC by using toluene : ethyl acetate (7:3) as an eluent. After the completation of reaction content was poured into crused ice. Product was filtered, washed with cold water, dried and recrystallized from absolute alcohol.

Similarly other compounds 5a-f and 6a-d were prepared by above method from intermediate (4) and corresponding aryl amine and piperazine respectively, which was purified by crystalizatopn from absolute alcohol. The physical and analytical data are given in **Table – I.**

Preparation of 2-[{(4-Pyridinyl)-1,3,4-oxadiazole}-5yl]-thio-4-(N,N-diethyl amino)-6-(diethyl amine)--s-triazine(5a): IR (cm-1, KBr): 1122(-C-O-C-str. in 1,3,4-oxadiazole ring), 727(-C-S- thil linkage), 825(-C-N- str. in s-triazine),2990(-C-H streching in alkane). ^{1}H NMR (300 MHz, DMF-d6, δ ppm): 2.73(q, 4H, Ar-H), 2.92(t, 6H, Ar-H), 3.31(s, 6H,N-CH_3), 7.74(d, 2H, Ar-H).

Preparation of 2-[{(4-Pyridinyl)-1,3,4-oxadiazole}-5yl]-thio-4-(N,N-diethyl amino)-6-(dimethyl amine)--s-triazine(5b): 1115(-C-O-C-str. in 1,3,4-oxadiazole ring), 727(-C-S- thil linkage), 825(-C-N- str. in s-triazine), 2985(-C-Hstreching in alkane). ^{1}H NMR (300 MHz, DMF-d6, δ ppm): 2.73(q, 4H, Ar-H), 2.92(t, 6H, Ar-H), 3.31(s, 6H,N-CH_3), 7.74(d, 2H, Ar-H), 8.66(d, 2H, Ar-H).

Preparation of 2-[{(4-Pyridinyl)-1,3,4-oxadiazole}-5yl]-thio-4-(N,N-diethyl amino)-6-(aniline)--s-triazine(5c): 1115(-C-O-C-str. in 1,3,4-oxadiazole ring), 727(-C-S- thil linkage), 825(-C-N- str. in s-triazine). ^{1}H NMR (300 MHz, DMF-d6, δ ppm): 2.73(q, 4H, Ar-H),8.67(s, 1H, -NH), 2.92(t, 6H, Ar-H), 3.31(s, 6H,N-CH_3), 7.74(d, 2H, Ar-H)

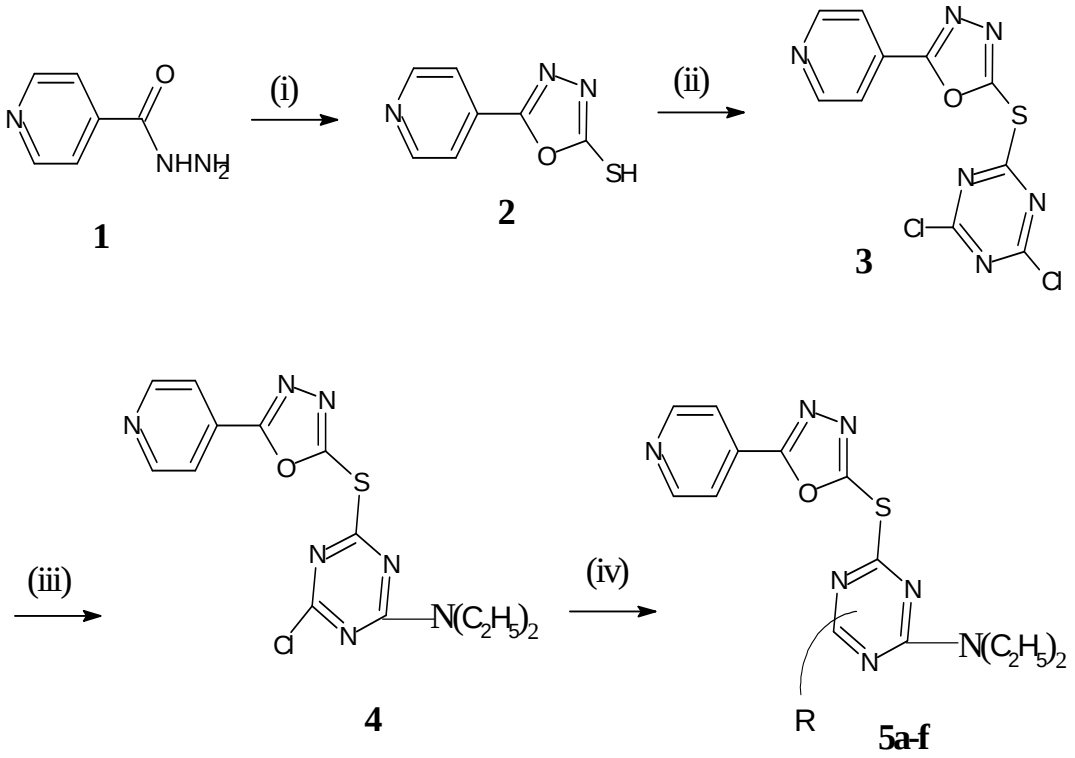
Preparation of 2-[{(4-Pyridinyl)-1,3,4-oxadiazole}-5yl]-thio-4-(N,N-diethyl amino)-6-(3-nitro aniline)--s-triazine(5d): 1115(-C-O-C-str. in 1,3,4-oxadiazole ring), 727(-C-S- thil linkage), 825(-C-N- str. in s-triazine). ^{1}H NMR (300 MHz, DMF-d6, δ ppm): 2.73(q, 4H, Ar-H),8.65(s, 1H, -NH), 2.92(t, 6H, Ar-H), 3.31(s, 6H,N-CH_3), 7.74(d, 2H, Ar-H)**.**

Preparation of 2-[{(4-Pyridinyl)-1,3,4-oxadiazole}-5yl]-thio-4-(N,N-diethyl amino)-6-(2-nitro)--s-triazine(5e): 1115(-C-O-C-str. in 1,3,4-oxadiazole ring), 727(-C-S- thil linkage), 825(-C-N- str. in s-triazine). ^{1}H NMR (300

MHz, DMF-d6, δ ppm): 2.73(q, 4H, Ar-H),8.65(s, 1H, -NH), 2.92(t, 6H, Ar-H), 3.31(s, 6H,N-CH_3), 7.74(d, 2H, Ar-H).

Preparation of 2-[{(4-Pyridinyl)-1,3,4-oxadiazole}-5yl]-thio-4-(N,N-diethyl amino)-6-(4-chloro aniline)--s-triazine(5f): 730(-C-Cl stretching in aromatic ring), 1115(-C-O-C-str. in 1,3,4-oxadiazole ring), 727(-C-S- thil linkage), 825(-C-N- str. in s-triazine). ^{1}H NMR (300 MHz, DMF-d6, δ ppm): 2.73(q, 4H, Ar-H),.8.66 (s, 1H, -NH), 2.92(t, 6H, Ar-H), 3.31(s, 6H,N-CH_3), 7.74(d, 2H, Ar-H).

Reaction Scheme:



Reagents & Conditions: (i) *CS_2/KOH, EtOH, reflux, 5h;* ***(ii)*** *1,3,5-s-triazine, Acetone, 10% $NaHCO_3$, 0-5°C, 6h;* ***(iii)*** *Morpholine, DMF, 10% $NaHCO_3$, 30-45°C, 6h;* ***(iv)*** *Dioxane, 10% $NaHCO_3$, reflux, 6h.* ***(v)*** *aryl aldehyde, EtOH, KOH, reflux, 4h.*

Table-I Analytical data of compounds 5a-f

Compounds	R=alkyl Ar=aryl	Molecular formula	M.P. (°C)	Molecular weight	Yield (%)
5a	R-$(C_2H_5)_2$	$C_{18}H_{24}N_8OS$	196	400.5	69
5b	Ar-H	$C_{20}H_{20}N_8OS$	170	420.4	73
5c	Ar-3-NO_2	$C_{20}H_{19}N_9O_3S$	210	465.4	62
5d	Ar-2-NO_2	$C_{20}H_{19}N_9O_3S$	202	465.4	80
5e	Ar-4-Cl	$C_{20}H_{19}ClN_8OS$	188	454.6	72
5f	R-$(CH_3)_2$	$C_{16}H_{20}N_7OS$	150	328.3	55

RESULTS AND DISCUCCION

Antibacterial activity: The minimum inhibitory concentration (MIC) was determined for each compound along with Gentamycin, Ampicillin, Chlormphenicol, Ciprofloxacin, Norfloxacin as standard control and the results are presented I table-II. All the compounds exhibited moderate to excellent inhibitory effect with MIC values against tested organisms. Among the compound 5b with aniline respectively exhibited significant antibacterial activity Gram negative (E.coil) strains compare to Ampicilin.

Compound 5e with 4-Chloro respectively exhibited significant antibacterial activity Gram positive bacteria (S. Aureus) strains compare to Ampiilin.

Compounds 5c with 3-nitro, 5e with 4-chloro, 5e with dimethyl amine antibacterial activity against gram negative (S. Pyogenus) compare to Ampicili.

Table-II - Antibacterial activities of compounds 5a-f

Compound	R	MIC µg/ml			
		E.coil	*P.aeruginosa*	*S.aureus*	*S.pyogenus*
5a	R-$(C_2H_5)_2$	100	200	250	250
5b	Ar-H	62.5	100	500	500
5c	Ar-3-NO_2	100	150	100	50
5d	Ar-2-NO_2	100	100	250	250
5e	Ar-4-Cl	150	100	62.5	50
5f	R-$(CH_3)_2$	500	500	100	50
	Gentamycin	0.05	1	0.05	0.5
	Ampicillin	100	100	250	100
Standard drugs	Chloramphenicol	50	50	50	50
	Ciprofloxacin	25	25	50	50
	Norfloxacin	10	10	10	10

CONCLUSION

synthesis of 2-[2-{(4-pyridinyl)-1,3,4-oxadiazol}-5-yl}-thio-4-(N,N-diethyl amino)-6-(aryl/alkyl)-amino-s-triazine has been described. The structural variation such as dimethyl amino and 3-nitro phenyl amino substituent against gram negative strain E-coli and P.aeruginosa. While 2-nitro phenyl amino substituent against S.aureus only. Surprisingly unsubstituent, 2-nitro and 4-chloro substituent proves better against S.pyogenus. against C.albicans, dimethyl amino substituent proves beneficial. It concluded that dialkyl amino substituent proved beneficial for antifungal activity.

Acknowledgements
We are very thankful to Prof. Dr. S. K. Menon, Head, Department of Chemistry & Director, School of Sciences, Gujarat University, Ahmedabad, India for his kind cooperation for providing support and research facility & I express my sincere thanks to CSMCRI (Bhavnagar) for extending the facility of the analytical laboratory for NMR spectra.

REFERENCES

[1] N., Santo Y., *Cancer Res.* **1996,** 56, 1512.
[2] Kalpesh S. Parikh, Sandip P. Vyas, *Der Chemica Sinica*, **2012**, 3(2):426-429.
[3] Garmouna M., Blanchoud H., Teil M., Blanchoud M., Chevreuil M., *Water, Air, Soil, Poll*. **2001,** 132, 1.
[4] Jain S., Bhambi D., Sharma R., Talesara L., *Ind. J. Pharm. Sci*. **2007**, 69(1), 28.
[5] Klenke B., Stewart M., Barett M.P., Brun R., Gilbert I.H., *J. Med. Chem.* **2001,** 44, 3440.
[6] Kukla M.J., Janseen P. A., *Eur. Pat.* **1999,** 945, 447.
[7] Patel R. B., Chikhalia K.H., De Clercq E., *J. Braz. Chem. Soc*.**2007,** 18, 2.
[8] Alteramn M., Samulsson B., *J. Med. Chem.* **1998,** 41, 3782.
[9] Ktritzky A. R., Boris V. R., Vladimir Y. V., Normad H., Behranz F. J. *Org. Chem.***2001,** 66, 6797.
[10] Mayumi O., Kawahara**,2006,** 98(8), 545.
[11] Youngyuth Y., Tirayut V., Netnapa C.,Sumalee K., Gordon L., *J. Med. Chem.* **2000**, 43, 2738.
[12] Agrwal A., Srivastava K., Puri S.K., Chauhan M. S. *Bioorg. Med. Chem. Lett.* **2005,** 15, 531.
[13] M. M. Murhekar, P. D. Padghan, S. S. Mhaske, R. E. Khadsan. *Der Pharma Chemica*, **2011**, 3 (6):243-246.
[14] Rostom S. A. F., Shalaby M. A., El- Demellawy M. A. *Eur. J. Med. Chem.* **2003,** 38, 959-974.
[15] Loetchutinat C., Chau F., Mankhetkorn S. *Chem. Pharm, Bull.***2003,** 51, 728-730.
[16] Kumar D., Sundaree S., Johnson E. O., Shah K., *Bioorg. Med. Chem. Lett.* **2009,** 19, 4492-4494.
[17] Pranav.R.Vachharajani, Manish J. Solanki, Gaurang G. Dubal, Viresh H.Shah. Der *Pharma Chemica*, **2011**, 3(1):280-285.
[18] Anjani Solankee, Rajanikant Patel, Kirti Patel, *Der Pharma Chemica*, **2011**, 3 (6):317-324.
[19] A. N. Solankee, G. A. Patel, R. B. Patel, B. K. P. Patel. *Der Pharma Chemica*, **2010**, 2(4):336-341.