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SYNTHESIS AND BIOLOGICAL EVALUATION OF OXADIAZOLYL-1, 4-BENZOTHIAZINES

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ABSTRACT

A series of 2*H*, 4*H*-2-[(substituted) - phenyl-1, 3, 4- oxa-diazol-5-yl]-methyl 3-oxo-1,4-benzothiazine derivatives **5a-f** have been synthesized by the reaction of 2*H*, 4*H* -2- hydrazino carbonyl methyl-3-oxo-1,4-benzothiazine **4** with substituted aromatic acids using ultrasound irradiation in lesser time with higher yields. All the synthesized compounds were investigated for their antibacterial activities. The result indicate that the compounds shows convincing activities against *gram-positive* and *gram- negative* bacteria when compared with standard drug (*ampicillin trihydrate*). These compounds were also synthesized by conventional method and their structures have been elucidated on the basis of spectral and elemental analysis.

Keywords: 2-aminothiophenol, oxadiazoles, antibacterial.

INTRODUCTION

The chemistry of heterocyclic compounds has been an interesting field of study for a long time. The synthesis of novel oxadiazole derivatives and investigation of their chemical and biological behaviour have gained more importance in recent decades for medicinal and agricultural reasons. Different classes of oxadiazole compounds possess an extensive spectrum of pharmacological activities, particularly in compounds bearing 1,3,4-oxadiazole nucleus which are known to exhibit unique antiedema and anti-inflammatory activity[1-2]. Substituted oxadiazole moiety has been found to have important activities such as analgesic[3,4] antimicrobial[5,6], antitumor[7], antimalerial[8] and anti-hepatities[9]. In some cases 1,4-benzothiazines are also known for their utility as dyes, photographic developers, ultraviolet light absorbers and antioxidants[10].

Application of ultrasound (sonochemistry) has become an exciting field of research. The chemical effects of ultrasound are diverse and include substantial improvements in both stoichiometric and catalytic chemical reactions. Ultrasonic irradaiation accelerates the reactivity million fold and many synthetically useful reactions were successfully accomplished. As compared to conventional conditions, viz. strong base and long reaction time, the ultrasonic irradiation procedure is milder and more conventional leading to higher yields in shorter reaction time[11-13].

In view of these reports the synthesis of title compounds **5a-f** is being reported herein.

EXPERIMENTAL

All chemicals were procured by E. Merck (Germany) and S. D. Fine Chemicals (India). Melting points of all synthesized compounds were determined in open capillary tubes using Veego VMP-1 melting point apparatus and are expressed in ºC (uncorrected). The purity of the compounds was monitored by thin layer chromatography on silica gel coated aluminium plates (Merck) as adsorbent and UV light as visualizing agent. IR spectra in KBr pellets were recorded on Perkin-Elmer spectrophotometer in the range of 4000-400 cm^{-1}. ^1H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using DMSO-d_6 as a solvent and TMS as an internal standard (chemical shifts in δ ppm). The mass spectra were taken on a Jeol SX-102/PA-6000 (EI) spectrometer. C, H, N estimations were done on Carlo

Erba 1108 (C H N) Elemental Analyser. Ultrasound irradiation was carried out in 'Probe Ultrasound', manufactured by Dakshin pvt Ltd, Mumbai (Electrical Supply 230V A.C., 50 Hz).

Method A (Ultrasound Method):

3,4-dihydro-2-methoxycarbonylmethyl-3-oxo-2H-1,4-benzothiazine (3):

2-Aminothiophenol (**1**) (1.25 gm, 0.01 mole), maleic anhydride (**2**) (0.98 gm, 0.01 mole), Methanol (25 mL) and Conc. H_2SO_4 (2 mL) were taken in 100 ml round bottom flask and subjected to sonication for 10 mins. After completion of the reaction (monitored by TLC), the reaction mixture was cooled, solid thus obtained was washed with 5% sodium bicarbonate solution and extracted in dichloromethane to obtain **3**. (Yield 84 %, m.p. 138-140°C).

IR (cm^{-1}): *v* 1740 (C=O), *v* 1690 (C=O), *v* 1480 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.88 (d, 2H, CH_2), 3.61 (s, 3H, CH_3), 3.85 (t, 1H, CH), 6.99 – 7.32 (m, 4H, ArH), 10.70 (s, 1H, ring NH).

2-Hydrazinocarbonylmethyl-3, 4-dihydro-3-oxo-2H-1, 4-benzothiazine (4):

Compound **(3)** (2.37 gm, 0.01 mole), hydrazine hydrate (2 gm, 0.02 mole) and dry methanol (20 mL) were taken in 100 ml round bottom flask and subjected to sonication for 8mins. After completion of the reaction (monitored by TLC), the reaction mixture was cooled, poured on crushed ice, solid thus obtained was washed with water and recrystallised from methanol to get **4**. (Yield 80 %, m.p. 190-192°C).

IR (cm^{-1}): *v* 3350 (NH), 1760 (C=O), *v* 1630 (NH-NH_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.69 (d, 2H, CH_2), 3.82 (t, 1H, CH), 4.22 (s, 2H, NH_2), 6.98 – 7.30 (m, 4H, ArH), 9.09 (s, 1H, NH), 10.65 (s, 1H, ring NH).

2H, 4H-2-[(substituted) - phenyl-1, 3, 4- oxa-diazol-5-yl]-methyl 3-oxo-1,4-benzothiazines 5a-f:

Equimolar mixture of compound **4**, substituted aromatic acid (0.01 mole) and phosphorous oxychloride (5mL) was taken in round bottom flask and subjected to ultrasound irradiation. After conclusion of the reaction (monitored by TLC), the reaction mixture was poured onto crushed ice. On neutralization of the contents with sodium bicarbonate solution (20%) a solid mass separated out, which was filtered, washed with water and dried to yield **5**. The physical data of the compounds given in **Table 1**.

Method B (Conventional):

Compound **4** (0.01 mole) was dissolved in phosphorous chloride (15mL) and to it was added substituted aromatic acid (0.01 mole). The reaction mixture, after refluxing for 6 hr, was cooled to room temperature and poured onto crushed ice. The product was isolated in a similar manner as described above to get the desired compound.

2H, 4H-2-[phenyl-1, 3, 4- oxa-diazol-5-yl]-methyl 3-oxo-1,4-benzothiazines 5a:

IR (cm^{-1}): *v* (CH) 2978; *v* (C=O) 1665; *v* (N-N=C) 1245; *v* (C-O-C) 1090. ^{1}H NMR δ (ppm): 10.71 (s, 1H, ring NH); 7.08- 7.54 (m, 9H, Ar-H); 4.01 (t, 1H, CH); 2.68 (d, 2H, CH_2);

^{13} C NMR δ ppm: 168.1 (C=O); 154.2 (C=N); 157.6 (C=N); 122-142 (ArC); 78.5 (CH); 37.3 (CH_2).

2H, 4H-2-[methyl-1, 3, 4- oxa-diazol-5-yl]-methyl 3-oxo-1,4-benzothiazines 5b:

IR (cm^{-1}): *v* (CH) 2984; *v* (C=O) 1675; *v* (N-N=C) 1238; *v* (C-O-C) 1095. ^{1}H NMR δ (ppm): 10.74 (s, 1H, ring NH); 7.18- 7.63 (m, 8H, Ar-H); 4.07 (t, 1H, CH); 2.68 (d, 2H, CH_2); 2.37 (s, 3H, CH_3).

^{13} C NMR δ ppm: 165.4 (C=O); 152.1 (C=N); 157.1 (C=N); 124-140 (ArC); 79.1 (CH); 35.1 (CH_2); 27.4 (CH_3). MS: 338 (M^+)

2H, 4H-2-[methoxy-1, 3, 4- oxa-diazol-5-yl]-methyl 3-oxo-1,4-benzothiazines 5d:

IR (cm^{-1}): *v* (CH) 2994; *v* (C=O) 1690; *v* (N-N=C) 1230; *v* (C-O-C) 1085. ^{1}H NMR δ (ppm): 10.70 (s, 1H, ring NH); 6.84- 7.38 (m, 8H, Ar-H); 4.1 (t, 1H, CH); 3.78 (s, 3H, OCH_3); 2.76 (d, 2H, CH_2). ^{13} C NMR δ ppm: 164.1 (C=O); 151.5 (C=N); 155.7 (C=N); 122-140 (ArC); 79.7 (CH); 55.4 (OCH_3); 37.5 (CH_2). MS: 354 (M^+)

2H, 4H-2-[hydroxy-1, 3, 4- oxa-diazol-5-yl]-methyl 3-oxo-1,4-benzothiazines 5e:

IR (cm^{-1}): *v* (CH) 3010; *v* (C=O) 1680; *v* (N-N=C) 1242; *v* (C-O-C) 1090. ^{1}H NMR δ (ppm): 10.72 (s, 1H, ring NH); 6.90- 7.34 (m, 8H, Ar-H); 5.4 (s, 1H, OH); 4.1 (t, 1H, CH); 2.72 (d, 2H, CH_2).

Antimicrobial evaluation

Representative compounds were evaluated for their antibacterial activity against gram-negative bacteria, *E. coli* and *P. aeruginosa* and gram-positive bacteria, *S. aureus*, and *C. diphtheriae* using disc diffusion method[14]. The zone of inhibition was measured in mm and the activity was compared with standard drug *ampicillin trihydrate*. The results of antibacterial screening studies are reported in Table-2.

RESULTS AND DISCUSSION

2*H*, 4*H*-2-[(substituted) - phenyl-1, 3, 4- oxa-diazol-5-yl)]-methyl 3-oxo-1,4-benzothiazines **5a-f** described in this study are shown in Table 1 and the reaction sequence for the synthesis is outlined in Scheme 1. 2-aminothiophenol **(1)** with an equimolar amount of maleic anhydride **(2)** in presence of ethanol and conc. H_2SO_4 undergoes cyclization to form 3,4-dihydro-2-methoxycarbonylmethyl-3-oxo-2H-1,4benzothiazine **(3)**. The formation of **(3)** was explained on the basis of an IR band at 1740 & 1690 cm^{-1} due to ester and cyclic >C=O respectively. This was also confirmed from ^1H NMR signal at 3.6 ppm due to $–CH_3$. The compound **(3)** underwent hydrazinolysis led to formation of 2*H*, 4*H*-2-hydrazino carbonyl methyl-3-oxo-1,4-benzothiazine **(4)**. The formation of compound **(4)** was ascertained on the basis of IR bands at 3350, 3310 and 1630 cm^{-1} due to $NH\text{-}NH_2$. Disappearance of signal at 3.6 ppm and 2.9 ppm due to $–CH_3$, $–CH_2$ respectively and ppearance of signal at 4.2 ppm and at 9.08 ppm due to NH_2 and -NH respectively in ^1H NMR confirms the formation of compound **(4)**. Further cyclization of **(4)** with aromatic acids in $POCl_3$ yielded 2*H*, 4*H*-2-[(substituted) - phenyl-1, 3, 4- oxa-diazol-5-yl]-methyl 3-oxo-1,4-benzothiazines **(5a-f)**. In the IR spectra two new vibrations at 1090 cm^{-1} (C-O-C) and at 1245 cm^{-1} (N-N=C) were visible, while no bands were seen at 1625 cm^{-1} ($NH\text{-}NH_2$) and 3310-3420 cm^{-1} (NH) regions, indicating the absence of –CONH linkage. Vibration at 1090 cm^{-1} was the characteristic of a cyclic –C-O-C- linkage and 1245 cm^{-1} for –N-N=C group formation, confirming the presence of a 1,3,4-oxadiazole ring. The structures were also supported by ^1H NMR and ^{13}C NMR spectra.

CONCLUSION

Ultrasound irradiation for synthesis of the title compounds offers reduction in reaction time, operation simplicity, cleaner reaction, easy work up and improved yields. The procedure clearly highlights the advantages of ultrasound. The synthesized compounds **5a-f** showed convincing activity against gram positive and gram negative organisms. The data reported in this article may be helpful guide for the medical chemists who are working in this area.

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Table-1: Charactrization of the synthesized compounds

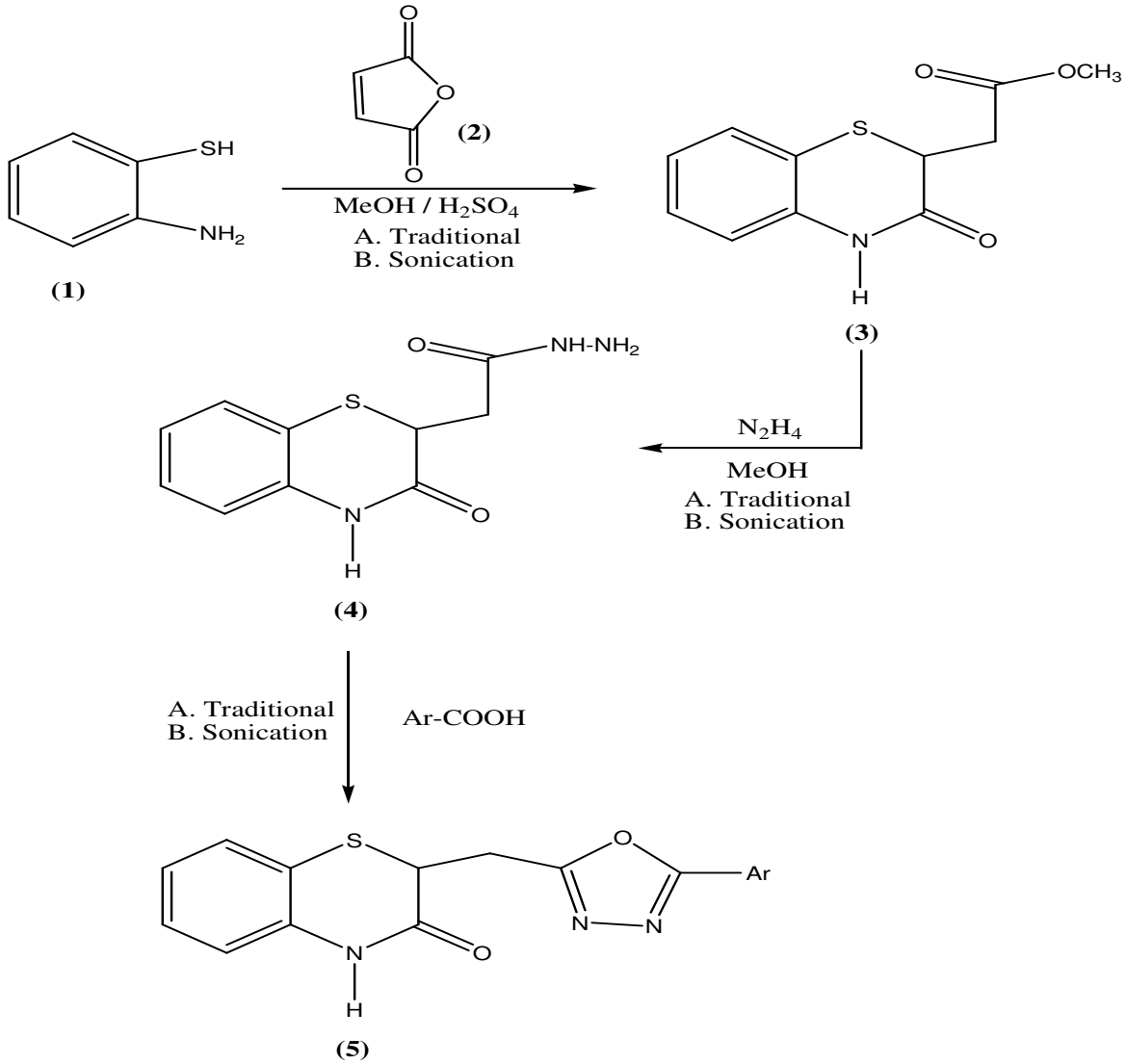
Compd	Ar	Molecular Formula*	Molecular weight	Melting point (°C)	Yield (%)	
					Ultrasound	Conv.
5a	Phenyl	$C_{17}H_{13}N_3O_2S$	323	284-286	85	55
5b	4-methylphenyl	$C_{18}H_{15}N_3O_2S$	337	> 300	84	58
5c	4-chlorophenyl	$C_{17}H_{12}N_3O_2SCl$	357.5	278-280	82	54
5d	4-methoxyphenyl	$C_{18}H_{15}N_3O_3S$	353	> 300	80	52
5e	4-nitrophenyl	$C_{17}H_{12}N_4O_4S$	368	> 300	86	59
5f	4-hydroxyphenyl	$C_{17}H_{13}N_3O_3S$	339	> 300	85	56

*Satisfactory C, H and N analysis were obtained for all the compounds.

Table-2: Antibacterial *in vitro* activity of compounds 5a-f

Compd	Zone of inhibition (in mm)*			
	Gram Positive		Gram Negative	
	S.aureus	*C. diphtheria*	*E. coli*	*P. aeruginosa*
5a	14	16	15	11
5b	23	21	16	12
5c	18	20	21	19
5d	16	17	10	11
5e	23	21	14	15
5f	19	20	20	18
Ampicillin trihydrate	27	25	24	22
DMSO	0	0	0	0

* N.B. Concentration selected was 100 µg/ml and DMSO was used as the solvent



Scheme-1:Synthesis of novel 1,4-benzothiazines

REFERENCES

1. Asif Husain and Priyanka Ahuja, *Acta Poloniae Pharm.*, **65**, 527 (2008)
2. R. Franski, *Asian J Chem.*, **17**, 2063 (2005)
3. B. Narayana, K. K. Vijatraj, B. V. Ashalatha and N. S. Kumari, *Arch Pharm.*, **338**, 373 (2005)
4. M. Amir, S. Kumar, *Acta Pharm.*, **57**, 31 (2007)
5. S. L. Gaonkar and K. M. Rai, *Eur J Med Chem.*, **41**, 841 (2006)
6. P. Mishra, H. Rajak and A. Mehta, *J Gen Appl Microbiol.*, **51**, 133 (2005)
7. N. M. M. Bezerra, S. P. De-oliveria and R. M. Srivastava, *Farmaco.*, **60**, 955 (2005)
8. M. Zareef, R. Iqbal, J. Rodrigues and C. T. Supuran, *J Enzyme Inhib Med Chem.*, **22**, 301 (2007)
9. T. M. Tan, Y. Chen, K. H. Kong, S. G. Lim, T. H. Ang and Y. Lam, *Antiviral Res.*, **71**, 7 (2006)
10. C. Rasmussen, *Chem Abstr.*, **80**, 95987 (1974
11. V. V. Dabholkar and Faisal Ansari, *Phosphorus, Sulfur and Silicon*, **185**, 298 (2010)
12. V. V. Dabholkar and Faisal Ansari, *J Serb Chem Soc*., **74 (11)**, 1219 (2009)
13. Y. J. Bian, J. T. Li and T. S. Li, *Chin J Org Chem.*, **22**, 227 (2002).
14. B. A. Arthington-Skaggs, M. Motley and C. J. Morrison, *J. Clin Microbiology.*, **38**, 2254 (2000).

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