International Journal of Applied and Advanced Scientific Research (IJAASR)
Impact Factor: 5.255, ISSN (Online): 2456 - 3080
(www.dvpublication.com) Volume 1, Issue 2, 2016

SYNTHESIS OF SUBSTITUTED BIS-THIAZINE DERIVATIVES OF IMINE COMPOUNDS AND ITS CHARACTERIZATION

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Cite This Article: R. Suganya, M. Ganapathi & A. Ravi, "Synthesis of Substituted Bis-Thiazine Derivatives of Imine Compounds and Its Characterization", International Journal of Applied and Advanced Scientific Research, Volume 1, Issue 2, Page Number 70-74, 2016

Abstract:

The target compound bis-thiazine derivatives of imine were synthesized via three stages of chemical reaction. In a stage 1, a number of substituted chalcone derivatives were prepared by condensing with substituted aldehyde and acetophenone in the presence of sodium hydroxide as base mediated as PEG – 400. In a stage 2, the substituted chalcone derivatives were condensed with thio-urea in the presence of catalytic amount of piperidine yielded as substituted thiazine derivatives. In a stage 3, the various substituted thiazine derivatives were reacted with terephthaldehyde in presence of catalytic amount of acetic acid which yielded as bis-thiazine derivatives of imine compounds. All stages of the synthesized compounds structures were identified and confirmed by various spectral studies like UV-Visible, FTIR and ^{1}H NMR analysis respectively. The purity of the synthesized compounds were monitored by TLC. . The anti-bacterial activities of compounds have also been tested using Minimum Inhibitory Concentration (MIC) method with two different microorganisms like *Staphyloccocous aures* (MTCC3381) and *Escheriochia coli* (MTCC739). The results of the studies infer that the bis-thaizine derivatives imine compounds found to have excellent antibacterial activity against the selected pathogenic organisms.

Key Words: Chalcones, Thio-Urea, Piperidine, PEG-400 & Bis-Thiazines

1. Introduction:

Heterocyclic rings have played an important role in medicinal chemistry, serving as key central to the development of numerous important therapeutic agents [1]. Chalcones are very good intermediate for synthesis of various medicinal oriented compounds [7-8]. Substituted chalcones and their derivatives possess some interesting biological properties such as antibacterial, antifungal [23], insecticidal, anaesthetic [25], analgesic, ulcerogenic [26] etc. Chalcones, considered as the precursor of flavonoids and isoflavonoids, are abundant in edible plants, and have also been shown to display a diverse array of pharmacological activities, such as anti-protozoal, anti-inflammatory [29], anticancer [30] and antihyperglycemic properties [31]. Consequently, the chalcone backbone could be a versatile scaffold for drug design. The heterocyclic compounds which containing the atoms of nitrogen and sulphur compounds found to possess enormous medicinal applications. Thiazines derivatives that exhibit various biological activities such as anti-tubercular, anti-fungal [48], anti-bacterial, analgesic, anti-inflammatory [54], anti mycobacterial activity [51] etc. Imines are referred to as schiff bases or azomethines. Most of the natural products and biologically potent compounds (drugs) contain N-atoms. Therefore, development of new methods for C-N bond formation is important. An imine is a functional group or chemical compound containing a carbon– nitrogen double bond, with the nitrogen attached to a hydrogen atom (H) or an organic group. If this group is not a hydrogen atom, then the compound can sometimes be referred to as a schiff base. Imines substituted compounds found to have lot biological applications such as antifungal [62], antiviral, antimicrobial [63], Anti parassitic activity etc. Based on the careful analysis of literature survey, the well focused and biologically potent bis-thaizines derivatives of imines compounds were synthesized via three stages of reaction.

2. Experimental Section:

A. Methods and Materials: The chemicals 4-hydroxybenzaldehyde (1), 4-methylacetophenone (2), were purchased from Sigma Aldrich, India and thiourea (3), terepthaldehyde (4) Sodium hydroxide, PEG-400, ethanol and piperidine were purchased from Avra, Chemicals, hyderabad. Pre-coated Silica gel plate was purchased from Merck (TLC purpose). The solvents were purified as per the standard procedure. FTIR spectra (KBr pellets) were measured using Alpha Bruker FTIR instrument scanning with the entire region of 4000 - 400 cm^{-1} with typical resolution of 1.0 cm^{-1}. UV-Visible spectra were also recorder using Alpha Bruker UV spectrophotometer. The NMR spectra of the compounds have been recorded on Bruker AV400 spectrometer operating at 400 MHz for recording ^{1}HNMR spectra in DMSO solvent using TMS as internal standard. Melting points of all synthesized compounds have been determined in open glass capillaries on Mettler FP51 melting point apparatus and are uncorrected.

B. Synthesis: The substituted bis-thiazine derivatives of imine compound have been synthesized in three stages.

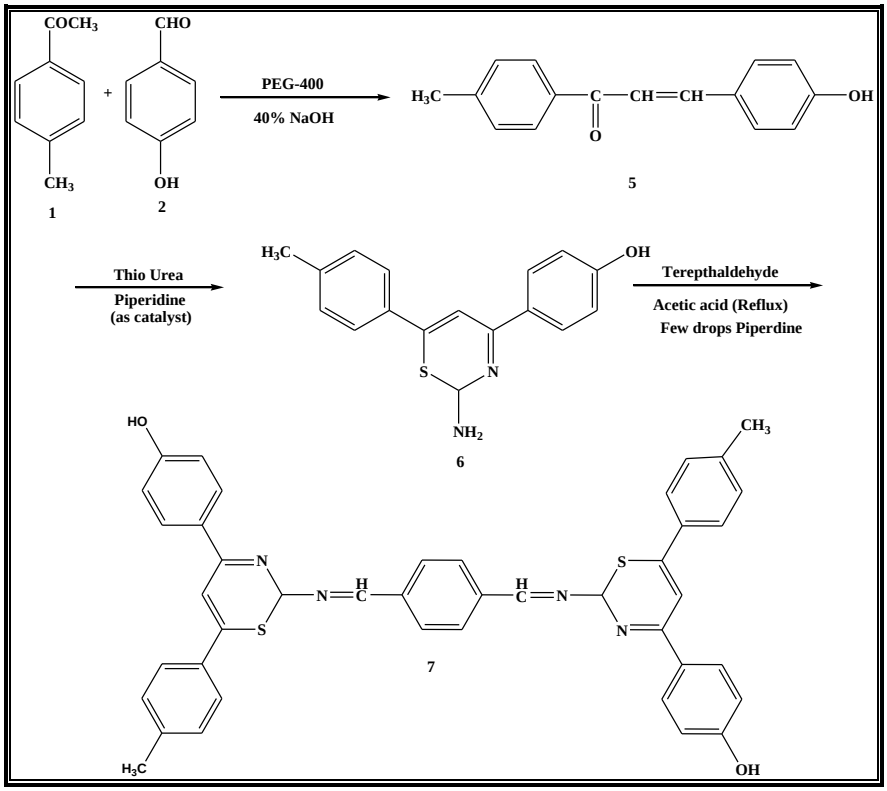
General procedure for synthesis of compounds 5-7

Stage 1: The equimolar quantities of 1 (0.0409 mol, 5g) and 2 (0.0409mol, 5.4879g) and sodium hydroxide (0.0818 mol, 3.272g in 20mL H_2O) was stirred in PEG-400 (20 mL) for 3-4 hours at 70ºC. The progress of the reaction is monitored by TLC. After completion of the reaction, the reaction mixture cooled into room

temperature and neutralized with dilute hydrochloric acid (adjusted to pH=2-3). The reaction mixture was filtered. The sandal solid obtained was then recrystallized with ethanol to get fine sandal crystals of 3-(4-hydroxyphenyl)-1-p-tolylprop-2-en-1-one 5. The filtrate was evaporated to remove water to get PEG-400. The same PEG was reused for further synthesis of substituted chalcones. The melting point of compound 5 found to have 141°C-143°C.

Stage 2: The brown waxy solid of 4-(2-amino-6-p-tolyl-2H-1,3-thiazin-4-yl)phenol 6 was synthesized from equimolar quantities of 5 (0.0088 mol, 2g) and 3 (0.0088mol, 0.66g) was dissolved in 10 mL ethanol. To this 4-5 drops piperidine catalyst were added and the reaction mixture was refluxed at 80°C for 2-3 hours. The progress of the reaction was observed by TLC. Then the reaction mixture was filtered and washed with cold water. The brown waxy solid was obtained then recrystallized with ethanol. The melting point of compound 6 found to have 120°C-122°C.

Stage 3: A mixture of 4-(2-amino-6-p-tolyl-2H-1,3-thiazin-4-yl)phenol 6 (0.0033mol, 1g) and terephthaldehyde 4 (0.0016mol, 0.22g) were dissolved in 20 mL acetic acid placed in a round bottomed flask equipped with a condenser. The reaction mixtures were refluxed at 110°C for 4-5 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice cold water. Then the reaction mixture was extracted with dichloromethane (3x20 mL), washed with brine solution (20 mL) dried over anhydrous sodiumsulphate. The reaction mixture was concentrated under reduced pressure. The brown solid of substituted bis-thiazine derivatives of imine compound 7 was obtained as crude product which is recrystallized using methanol, resulted in a brown solid. The melting point of the compound 3c found to have 133°C-135°C.The formation of the compounds 5, 6 and 7 were confirmed by various spectral techniques like UV, FTIR and ^{1}H NMR.



Scheme: Synthesis of substituted bis-thiazine derivatives of imine compound

3. Results and Discussion:

Spectral details of 3-(4-hydroxyphenyl)-1-p-tolylprop-2-en-1-one (5)

Melting point	**:**	141°C-143°C	
Yield	**:**	92%	
UV-Visible	**:**	206 ($\pi \rightarrow \pi^*$ transition), 302 ($n \rightarrow \pi^*$ transition)	
FTIR (cm^{-1})	**:**	3369 (Ar O-H), 3063 (C-**H str**), 1651(C=O str), 1580(C=C), 1217(C-F), 780 (C-H out plane bending)	(Figure 1)
^{1}H NMR (δ ppm)	**:**	9.62(s, 1H, Ar-OH), 7.22-8.06(m, 8H), 6.85-6.88(d, 2 CH=CH-), 2.50(s, 3H,-CH_3).	(Figure 2)

Spectral details of 4-(2-amino-6-p-tolyl-2H-1,3-thiazin-4-yl)phenol (6)

Melting point	**:**	120°C-122°C	
Yield	**:**	94%	

UV-Visible	**:**	206 ($\pi \rightarrow \pi^*$ transition), 302 ($n \rightarrow \pi^*$ transition)	
FTIR (cm^{-1})	**:**	3203 (Ar O-H), 2960 (C-**H str**), 1022(C=O str), 1596(C=C), 1454(C-N), 781 (C-H out plane bending)	(Figure 3)
^{1}H NMR (δ ppm)	**:**	9.4(s, 1H, Ar-OH), 6.80-7.44(m, 8H), 6.80(s, 1H, -C=CH-), 5.31(s, 1H,-CH), 4.59(s, 2H, $-NH_2$), 2.35(s, 3H, $-CH_3$)	(Figure 4)

Spectral details of substituted bis-thiazine derivatives of imine compound (7)

Melting point	**:**	133°C-135°C	
Yield	**:**	91%	
UV-Visible	**:**	242 ($\pi \rightarrow \pi^*$ transition), 300 ($n \rightarrow \pi^*$ transition)	
FTIR (cm^{-1})	**:**	2926 (Ar C-H), 1645 (C=**N str**), 1594(C=C), 1452(C-N), 1166(C-S str), 828 (C-H out plane bending)	(Figure 5)
^{1}H NMR (δ ppm)			(Figure 6)

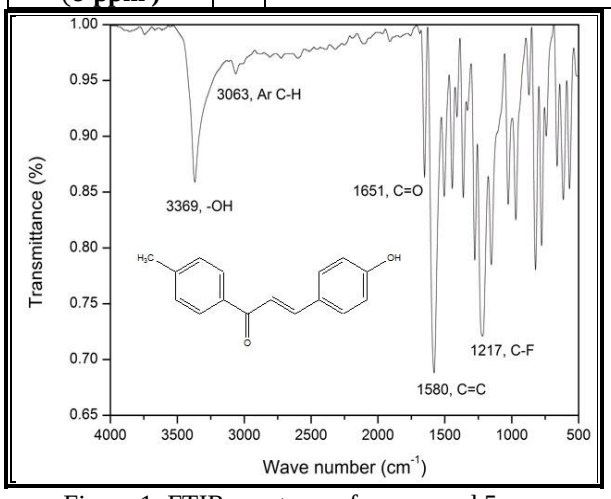


Figure 1: FTIR spectrum of compound 5

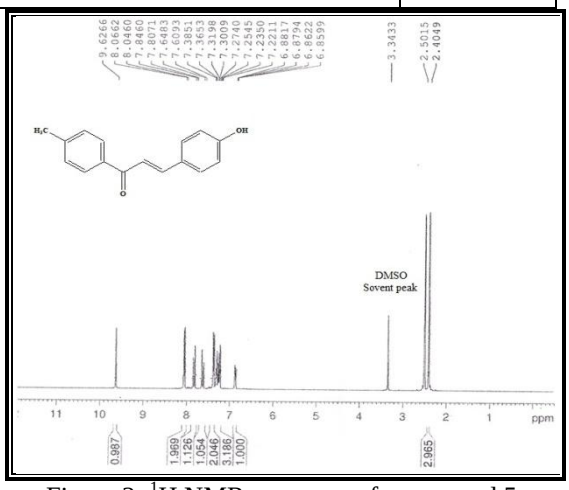


Figure 2: ^{1}H NMR spectrum of compound 5

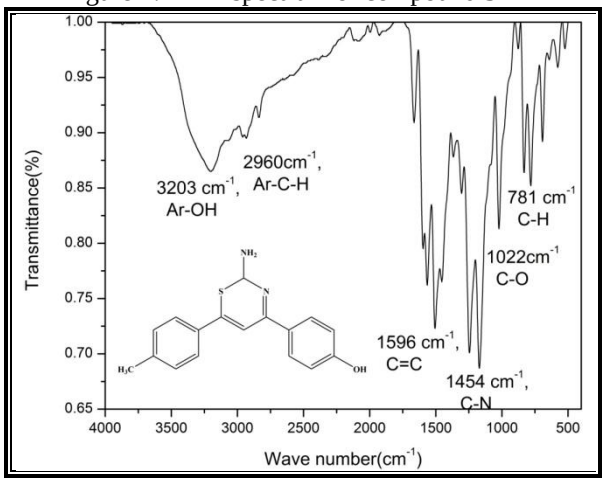


Figure 3: FTIR spectrum of compound 6

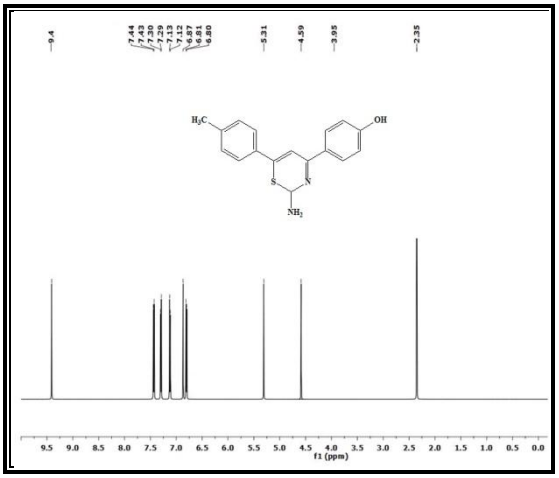


Figure 4: 1H NMR spectrum of compound 6

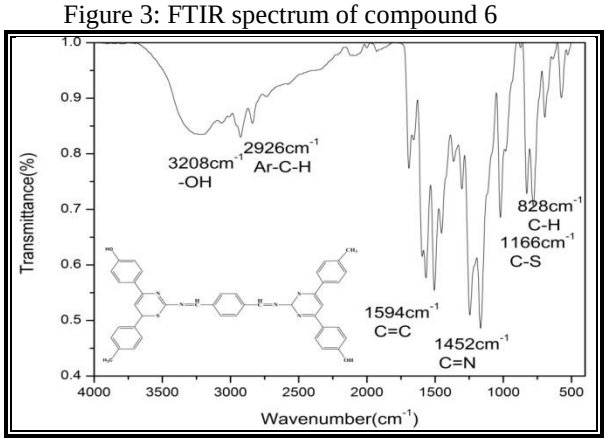


Figure 5: FTIR spectrum of compound 7

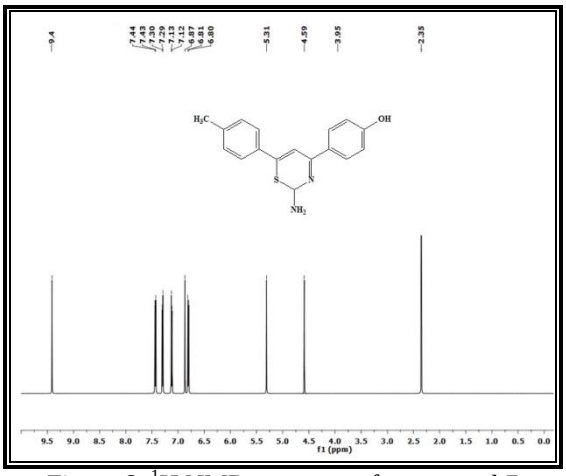


Figure 6: ^{1}H NMR spectrum of compound 7

As first stage, compound 5 have been synthesized via PEG – 400 as solvent successively. The usage of alcohol solvent is not recommended for green chemistry protocol and as well as cannot able to reuse again. But while using PEG-400 as solvent was reusable, eco-friendly and the reaction ends with shorter duration. In a second stage, the compound 6 have been synthesized from substituted chalcone and thiourea in the presence of piperdiene as catalyst. The reaction takes much more time when compared to the absence of piperidine. In a third stage, the substituted thiazine derivatives were condensed with terepthaldehyde in the presence of catalytic amount of acetic acid. Figure (1-2) revealed the FTIR and ^{1}HNMR spectra of 3-(4-hydroxyphenyl)-1-p-tolylprop-2-en-1-one 5 respectively using compound 1 and 2 with PEG-400 as solvent in the presence of sodium hydroxide has been shown in the scheme. Figure (3-4) revealed the FTIR and ^{1}HNMR spectra of 4-(2-amino-6-p-tolyl-2H-1,3-thiazin-4-yl)phenol 6 respectively using compound 5 and 3 with acetic acid in the presence of piperidine as catalyst. Figure (5-6) revealed that FTIR and ^{1}HNMR spectra of substituted bis-thiazine derivatives of imine compound 7 from compounds 6 and 4 in the presence of acetic acid been presented in the Scheme.

UV absorption and FTIR spectra of compound 5 has been provided a preliminary idea for the formation of product. According to the UV spectrum, presence of peaks at 206 and 302 nm clearly showed that the compound 5 has -CH=CH- group and hetero atom respectively. According to the FTIR, the presence of peak at 1580 cm^{-1} has clearly noticed the utilization of starting materials transforms into the product. Further, the corresponding peaks at 3203, 2960, 1596, 1454 and 781 cm^{-1} have been related to –OH, C-H aromatic, C-O, aliphatic C=C, C-N and C-H out plane bending vibration respectively in the compound 6. Similarly, proton NMR strongly empowered for the formation of the product by its δ value at 9.4, 6.80 – 7.44, 5.80 – 5.31, 4.59 and 2.35 ppm corresponding to the O-H, Ar-H, -C=CH, -CH, NH_2,and CH_3 protons. UV absorption and FTIR spectra of compound 7 has provided a preliminary idea in confirmation the formation of product. According to the UV spectrum of compound 7, presence of peaks at 242 and 300 nm has been related to aromatic double bond and hetero atom respectively. According to the FTIR, peaks at 2926, 1645, 1594, 1452, 1166 and 828 cm^{-1} for –Ar-C-H aromatic stretching, C=N, C=C, C-N, C-S stretching and C-H bending vibrations respectively in the compound 7. All such stretching and bending peaks have also been supported for the formation of the product. Similarly, proton NMR strongly empowered for the formation of the product by its δ value at 9.39, 6.55-7.87, 5.42 – 5.48, 3.08-3.87and 2.30 ppm corresponding to the O-H, Ar-H, C-H, CH_2 and $CO-CH_3$ protons of compound 7 were mentioned in Figure (6).

4. Antimicrobial Activity:

The synthesized compounds were evaluated for their antibacterial activity using broth dilution method to find the MIC value were tested against one gram positive and one gram negative bacterial strains namely *staphylococcus aureus* and *Escherichia coli* respectively. The MIC values of synthesized compounds were given in the following Table. 1. From the result, compound 7 found to have better against the *staphylococcus aureus* and *Escherichia Coli* than that of other synthesized compounds of 5 & 6. The better activity due the presence of bis-thiazine containing imine.

Table 1: Minimum Inhibiting Concentration (MIC) (µg/ml) of the synthesized compounds

Compound	Staphylococcus Aureus	Escherichia Coli
5	125.0	125.0
6	250.0	250.0
7	**62.50**	**62.50**

5. Conclusion:

In the present work, the substituted bis-thiazine derivatives of imine compound have been synthesized successfully. In a first stage substituted chalcones were synthesized by using PEG-400 as solvent in presence of

NaOH as catalyst. Using PEG-400 as solvent is non-toxic, inexpensive, water soluble and recyclable. In a second stage, the substituted chalcones were condensed with thiourea in the presence of catalytic amount of piperidine. Use of piperidine as catalyst found to have lesser reaction time (less than an hour) whereas the same the reaction proceeds more than eight hours to complete in the absence of catalyst. In a third stage, the substituted thiazines were condensed with terephthaldehyde dissolved in acetic acid yielded as thiazine derivatives of bis-imine compound. The chemical structures of compounds 5, 6 and 7 have been confirmed using various spectral techniques viz., FTIR, UV-Visible and ^{1}H-NMR spectra and were found to be in agreement with the chemical structures expected. The antibacterial activities chalcone, thiazine and bis-thiazine derivatives of imine compounds substituted chalcones were checked against the two microbes *Staphylococcus aureus* and *Escherichia coli.* The report of antimicrobial activity clearly showed that, the synthesized compounds of 7 has better activities towards the tested bacterial strains of both gram positive and gram negative. This might be due to the presence of nitrogen, sulphur and imine moieties in the molecule.

6. References:

1. C. D. Cox, M. J. Breslin, B. J Mariano, Tetrahedron Lett. 45, 1489 (2004).
2. M. A. El.Hashah; M. El-Kady; M. A. Saiyed and A. A. Elaswy, Egypt. J. Chem., 27, 715 (1985)
3. L. S. Crawley and W. J. Fanshawe, J. Heterocyclic chem., 14, 531 (1977)
4. K. J. Mehta, V. S. Patel and A. R. Parikh; J. Indian Chem. Soc., 50, 241(1978).
5. G. Hosni and S. F. Saad; Acta Chim Acad Sci. Hung, 86, 263 (1995).
6. O. H. Hishmat, H. I. El-Diwani and F. R. Melek; Indian J. Chem., 1996, 35B, 30.
7. M. A. Babu, N. Shakya, P. Prathipati, S. G. Kaskhedikar and A. K. Saxena; Bioorg. Med. Chem., 10, 4035-4041 (2003).
8. S. K. Kumar, E. Hager, C. Pettit, H. Gurulingappa and N. E. Davidson; J. Med. Chem., 46, 2813-2815 (2003).
9. M. Satyanarayana, P. Tiwari, B. K. Tripathi, A. K. Srivastava and R. Pratap, Bioorg. Med. Chem., 12, 883-889 (2004).
10. Ram SG, Rajesh PG and Parhate VV.,Rasayan Journal of Chemistry.;6:65-67(2013)
11. Eleni AR, George NZ, Antonios M Gavalas, Phaedra TE and Panos N.14: 5616–5624. (2006)
12. Sriram, D.; Yogeeswari, P.; Myneedu, N.S; Saraswat, V. Bioorg. Med. Chem. Lett. 2006. 16, 2127-2129.
13. Guo, Z.; Xing, R.; Liu, S.; Zhong, Z.; Ji, X.; Wang, L., Carbohydr. Res. 2007, 342, 1329-1332.
14. Wang, P.H.; Keck, J.G.; Lien, E.J.; Lai, M.M.C. J.Med. chem.1990, 33, 608-614.