



## MICROWAVE ASSISTED SYNTHESIS OF SUBSTITUTED THIAZINE BEARING BIS-IMINE DERIVATIVES AND ITS CHARACTERIZATION

S. Manikandan\*, M. Ganapathi\*\* & A. Ravi\*\*\*

PG & Research Department of Chemistry, Government Arts College, Tiruvannamalai, Tamilnadu

**Cite This Article:** S. Manikandan, M. Ganapathi & A. Ravi, "Microwave Assisted Synthesis of Substituted Thiazine Bearing Bis-Imine Derivatives and Its Characterization", International Journal of Applied and Advanced Scientific Research, Volume 1, Issue 2, Page Number 55-60, 2016

### Abstract:

A series of substituted thiazine bearing bis-imine derivatives were synthesized by the following three steps. In a first step substituted acetophenones were condensed with terephthaldehyde through Claisen-Schmidt condensation reaction yielded as substituted bis-chalcones. In a second step substituted bis-chalcones were condensed with thio-urea with sodium hydroxide as base. In a third step have been achieved by condensation between second stage compounds of substituted bis-thiazine with benzaldehyde in presence of catalytic amount of acetic acid. All steps of the reactions were achieved through both conventional and microwave assisted methods. The synthesized compound structures were identified and confirmed by UV-Visible, FT-IR and <sup>1</sup>H NMR spectral analysis respectively.

**Key Words:** Bis-Chalcones, Thio-Urea, Bis-Thiazine & Bis-Imines

### 1. Introduction:

The chemistry of chalcones generated intensive scientific studies throughout the world, especially interesting for their biological and industrial applications. Chalcones are abundantly present in nature starting from ferns to higher plants [1] and a number of them are polyhydroxylated in the aryl rings. The compounds with chalcone as backbone have been reported to possess varied biological and pharmacological activities [2], including antimicrobial [3], anti-inflammatory [4], antitumor [5]. Thiazines are six membered heterocycles that contain in their structure a nitrogen atom and a sulphur atom. Thiazines are very useful units in the fields of medicinal and pharmaceutical chemistry and have been reported to exhibit a variety of biological activities such as anti-inflammatory [6], anti-diabetic activity [7], anticancer activity [8], antimicrobial activity [9]. Imines are valuable functional group or chemical compounds containing a carbon nitrogen double (C=N) bond. Condensation reaction of aldehydes and primary amines resulting imines, commonly called Schiff bases or azomethines are well known in organic synthesis. The accomplishment of antimicrobial agents, ranging from direct killing of invading pathogens to immune response modulation and other complex biological responses, has stimulated research and clinical interest for more than two decades. Biologically, imines show antifungal activity [10], antiviral activity [11] and antimicrobial activity [12]. The synthesized compounds were characterized on the basis of UV-Visible, FT-IR, and <sup>1</sup>H NMR spectral data.

### 2. Experimental:

**A. Methods and Materials:** The chemicals terephthalaldehyde (1), 4-fluoroacetophenone (2), thiourea (3), benzaldehyde (4) and acetic acid, methanol, tetrahydrofuran, sodium hydroxide, hydrochloric acid, ethyl acetate, hexane were purchased in Avra. The purity of compounds were checked by TLC (0.5mm thickness) using Silica gel-G coated aluminium plates (Merck) and were visualized by exposing the dry plates into the iodine vapours and exposing UV light. The synthesised compounds were investigated to FT-IR spectra were recorded on Alpha-Bruker spectrophotometer (KBr pellets) scanning with the entire region of 4000 - 400cm<sup>-1</sup>. UV spectra were recorded on Alpha Bruker UV spectrophotometer. <sup>1</sup>H NMR spectra were recorded on Bruker AV400 spectrometer operating 400 MHz for recording <sup>1</sup>H NMR spectra in DMSO solvent using TMS as internal reference (chemical shift in ppm).

**B. Synthesis:** A series of substituted bis-thiazine bearing imine derivatives have been synthesized through three steps. Three steps have been carried out by both conventional and micro-wave assisted methods.

#### Step 1: General Procedure for Synthesis of Compound 5

**Method A:** An equal molar quantities mixture of compounds 1 (3g, 0.02mol) 2 (6.1mL, 0.04mol) with 30 mL of methanol were stirred for 10 minutes. After the homogeneous mixture attained, sodium hydroxide solution (3.5g, 0.08mol) were added to the above reaction mixture. Then reaction mixture was stirred for 24 hours. The reaction mixture were quenched into ice cold water and neutralized with dilute hydrochloric acid solution. The red colour solid was obtained was recrystallized using methanol get the needles like red crystals of 5. The purity of the product was checked by TLC.

**Method B:** A mixture of compound 1 (3g, 0.02mol) 2 (6.1mL, 0.04mol) and sodium hydroxide (3.5g, 0.08mol) were grinded in to mortar. Then it was mixed with minimum amount of methanol. The mixed compounds were taken in a 100mL beaker and it was irradiated in microwave oven for the 5 to 10 minutes at 110W operating at 2450Hz at 30 seconds of intervals. After completion of reaction as followed by T.L.C examination, chilled

water was added to the reaction mixture and neutralized by an acid. The solid product was obtained, which was filtered, dried and crystallized from methanol. The purity of the product was checked by TLC.

**Step 2: General Procedure for Synthesis of Compound 6**

**Method A:** To a stirred mixture of 5 (3g, 0.008mol) and 3 (1.2g, 0.016mol) with 5mL of methanol and 5mL of tetrahydrofuran were stirred for 10 minutes. After the homogeneous mixture attained, sodium hydroxide solution (1.2g, 0.032mol) were added to the above reaction mixture. Then reaction mixture was refluxed for overnight. The reaction mixture were quenched into ice cold water and neutralized with dilute hydrochloric acid solution. The crimson red colour solid was obtained was recrystallized using acetic acid get the needles like crimson red crystals of product was obtained 6. The purity of the product was checked by TLC.

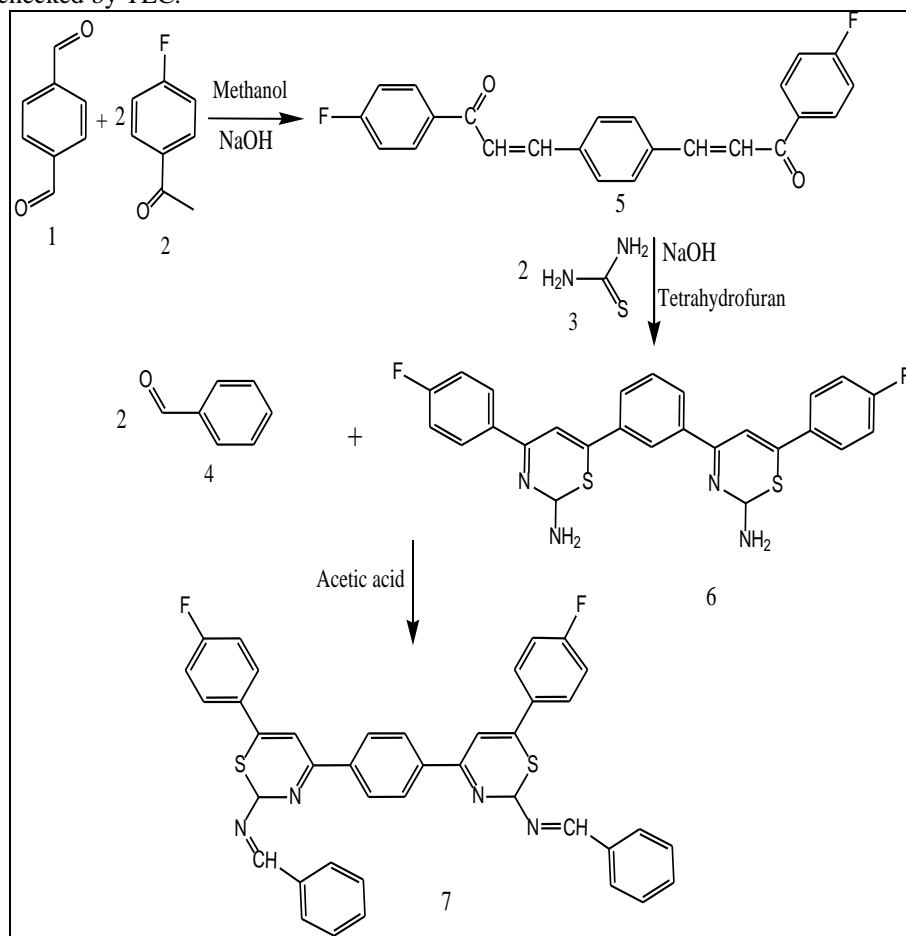
**Method B:**

To a stirred mixture of 5 (3g, 0.008mol) and 3 (1.2g, 0.016mol) and sodium hydroxide (1.2g, 0.032mol) were grinded in to mortar. Then it was mixed with minimum amount 5mL of methanol 5mL of tetrahydrofuran. The mixed compounds were taken in a 100mL beaker and it was irradiated in microwave oven for the 5 to 10 minutes at 110W operating at 2450Hz at 30 seconds of intervals. After completion of reaction as followed by T.L.C examination, chilled water was added to the reaction mixture and neutralized by an acid. The solid product was obtained 6, which was filtered, dried and recrystallized from acetic acid. The purity of the product was checked by TLC.

**Step 3: General Procedure for Synthesis of Compound 7**

**Method A:** To a stirred solution of 6 (3g, 0.006mol) and 4 (1.2mL, 0.012mol) with 5mL of acetic acid were stirred for 10 minutes. Then reaction mixture was refluxed at 6-8 hours. The reaction mixtures were quenched into ice cold water. The red colour solid was obtained was recrystallized using ethanol get the needles like red crystals of product was obtained 7. The purity of the product was checked by TLC.

**Method B:** To a stirred solution of 6 (3g, 0.006mol) and 4 (1.2mL, 0.012mol) were grinded in to mortar. Then it was added with catalytic amount of acetic acid. The mixed compounds were taken in a 100mL beaker and it was irradiated in microwave oven for the 5 to 10 minutes at 110W operating at 2450Hz at 30 seconds of intervals. After completion of reaction as followed by T.L.C examination, chilled water was added to the reaction mixture. The solid product was obtained 7, which was filtered, dried and crystallized from ethanol. The purity of the product was checked by TLC.



Scheme 1: Synthesis of (32)-N-benzylidene-4-(4-((2)-2-(benzylideneamino)-6-(4-fluorophenyl)-2H-1,3-thiazin-4-yl) phenyl)-6-(4-fluorophenyl)-2H-1,3-thiazin-2-amine

### 3. Results and Discussion:

#### Spectral Details of Bis-Chalcone (5):

<b>Melting Point</b>	:	120-121°C	
<b>Yield</b>	:	91 %	
<b>UV –Visible (<math>\lambda_{\text{max}}</math>:nm)</b>	:	220 ( $\pi \rightarrow \pi^*$ transition), 345 ( $n \rightarrow \pi^*$ transition)	
<b>FTIR (<math>\text{cm}^{-1}</math>)</b>	:	3046 (Aromatic C-H str), 1661 (C=O), 1593 (C=C str), 1032 (C-F), 817 (C-H out plane bending)	Figure 1
<b><math>^1\text{H NMR}</math> (<math>\delta</math> ppm) (400 MHz, DMSO-<math>d_6</math>)</b>	:	7.4-8.0 (M, 12H), 6.8-6.9(d, 4H).	Figure 2

#### Spectral details of 6-(3-(2-amino-6-(4-fluorophenyl)-2H-1,3-thiazin-4-yl)phenyl)-4-(4-fluorophenyl)-2H-1,3-thiazin-2-amine (6):

<b>Melting Point</b>	:	145-147°C	
<b>Yield</b>	:	89%	
<b>UV –Visible (<math>\lambda_{\text{max}}</math>:nm)</b>	:	218 ( $\pi \rightarrow \pi^*$ transition), 268 ( $n \rightarrow \pi^*$ transition)	
<b>FTIR (<math>\text{cm}^{-1}</math>)</b>	:	3279 (Aromatic C-H str), 1508(C=N), 1594 (C=Cstr), 1016 (C-F), 816(C-H out plane bending)	Figure 3
<b><math>^1\text{H NMR}</math> (<math>\delta</math> ppm) (400 MHz, DMSO-<math>d_6</math>)</b>	:	6.5-7.6 (m, 12H, Ar-H), 5.4(s, 2H, ethylenic proton), 3.7(s, 2H, methine proton), 3.3(s, 4H, primary amine)	Figure 4

#### Spectral details of (32)-N-benzylidene-4-(4-((2)-(benzylideneamino)-6-(4-fluorophenyl)-2H-1,3-thiazin-4-yl)phenyl)-6-(4-fluorophenyl)-2H-1,3-thiazin-2-amine (7):

<b>Melting Point</b>	:	112 – 113°C	
<b>Yield</b>	:	87%	
<b>UV –Visible (<math>\lambda_{\text{max}}</math>:nm)</b>	:	268 ( $\pi \rightarrow \pi^*$ transition), 342 ( $n \rightarrow \pi^*$ transition)	
<b>FTIR (<math>\text{cm}^{-1}</math>)</b>	:	3050 (Aromatic C-H str), 1675 (C=N), 1569 (C=C str), 1015 (C-F), 824 (C-H out plane bending)	Figure 5
<b><math>^1\text{H NMR}</math> (<math>\delta</math> ppm) (400 MHz, DMSO-<math>d_6</math>)</b>	:	8.4 (s, 2H, imine protons), 7.3-7.32 (m, 22H, Ar-H), 6.8 (s, 2H, ethylenic protons), 5.8 (s, 2H, methine protons).	Figure 6

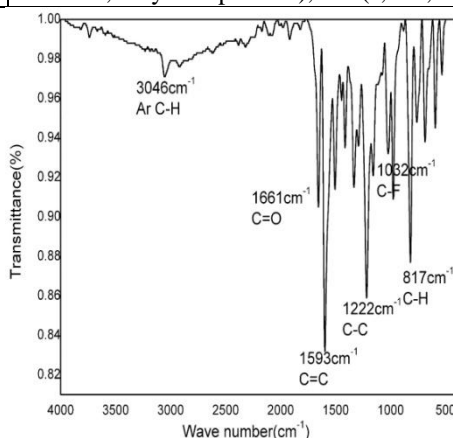


Figure 1: FT-IR spectrum of compound (5)

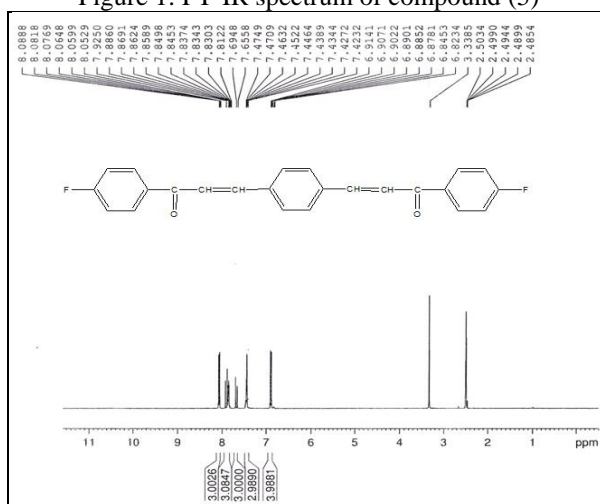


Figure 2:  $^1\text{H NMR}$  spectrum of compound (5)

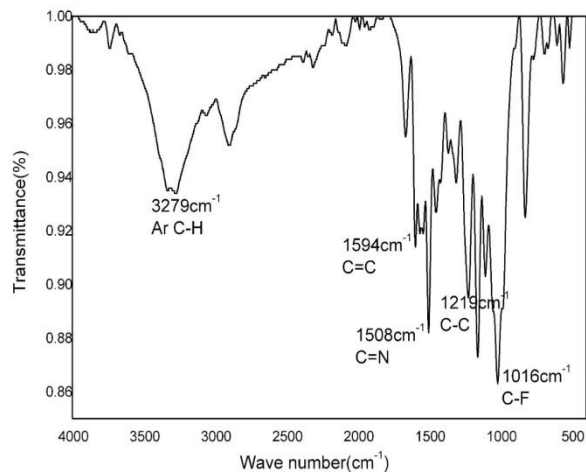


Figure 3: FT-IR spectrum of compound (6)

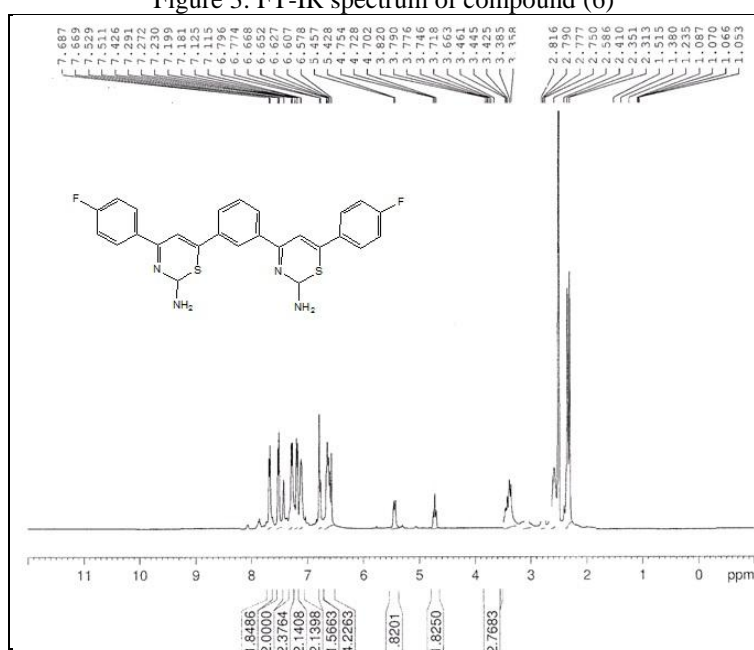


Figure 4: <sup>1</sup>H NMR spectrum of compound (6)

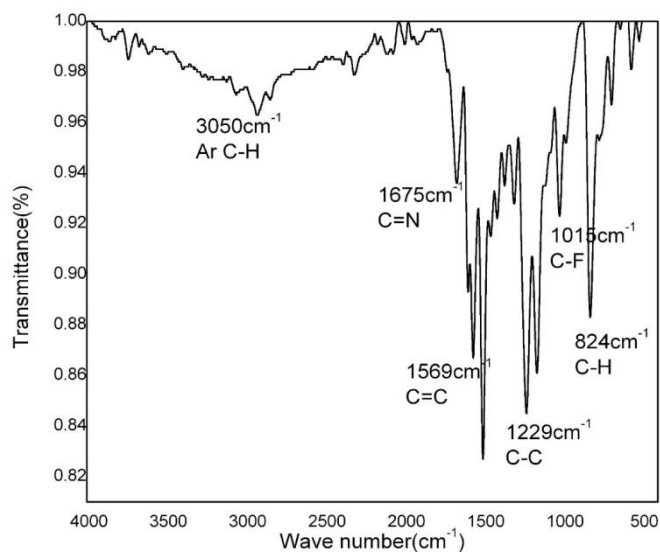


Figure 5: FT-IR spectrum of compound (7)

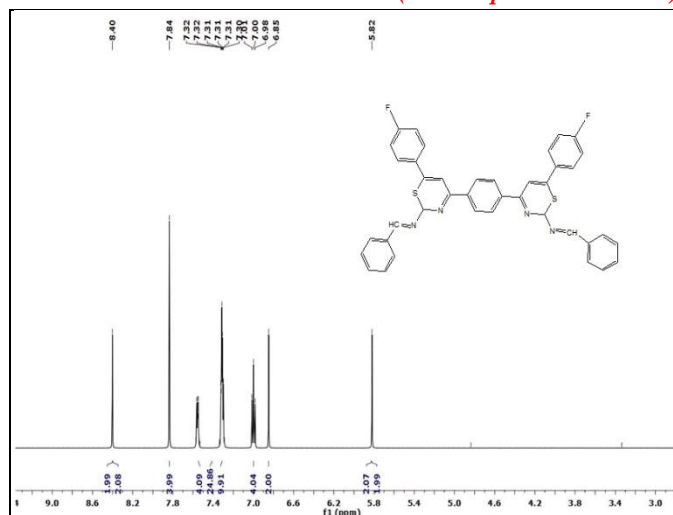


Figure 6: <sup>1</sup>H NMR spectrum of compound (7)

Figure (1-2) revealed the FTIR and <sup>1</sup>H NMR spectra of bis-chalcone respectively using compound 1 and 2 with compound 5 in the presence of sodium hydroxide has been shown in the scheme. Figure (3-4) revealed the FTIR and <sup>1</sup>H NMR spectra of 6-(3-(2-amino-6-(4-fluorophenyl)-2H-1,3-thiazin-4-yl)phenyl)-4-(4-fluorophenyl)-2H-1,3-thiazin-2-amine respectively using compound 5 and 3 with compound 6 in the presence of sodium hydroxide has also been presented in the scheme. Figure (5-6) revealed the FTIR and <sup>1</sup>H NMR spectra of (32)-N-benzylidene-4-(4-((2-(benzylideneamino)-6-(4-fluorophenyl)-2H-1,3-thiazin-4-yl)phenyl)-6-(4-fluorophenyl)-2H-1,3-thiazin-2-amine respectively using compound 6 and 4 with compound 7 in the presence of acetic acid has been shown in the scheme. UV absorption and FTIR spectra of compound (5) has been provided a preliminary idea in confirmation the formation of product. According to the UV spectrum, presence of peaks at 220 and 345 nm clearly showed that the compound (5) has -CH=CH- group respectively. According to the FTIR, represented in Figure (1), presence of peak at 3046, 1222, 1661 and 1593 cm<sup>-1</sup> have been related to C-H aromatic, C-C, C=O stretching and aliphatic C=C stretching respectively in the compound 5. Similarly, proton NMR strongly empowered for the formation of the product by its  $\delta$  value at 7.4-8.0, and 6.8-6.9 ppm corresponding to the Ar-H and -CH=CH- protons of compound (5) were mentioned in Figure (2).

UV absorption and FTIR spectra of compound (6) has provided a preliminary idea in confirmation the formation of product. According to the UV spectrum of compound (6), presence of peaks at 218 and 268 nm has been related to aromatic double bond and hetero atom respectively. According to the FTIR, represented in Figure (3), presence of peak at 3279, 1508, 1594, 1016 and 816 cm<sup>-1</sup> for C-H aromatic stretching, C=N, C=C stretching, C-F and C-H bending vibrations respectively in the compound (6). 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  $\delta$  value at 6.5-7.6, 5.4, 4.7 and 3.3 ppm corresponding to the Ar-H, C=CH, C-H and NH<sub>2</sub> protons of compound (6) were mentioned in Figure (4). 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 268 and 342 nm has been related to aromatic double bond and hetero atom respectively. According to the FTIR, represented in Figure (5), presence of peak at 3050, 1675, 1569, 1015 and 824 cm<sup>-1</sup> for C-H aromatic stretching, C=N, C=C stretching, C-F 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  $\delta$  value at 8.4, 7.3-7.32, 6.8 and 5.8 ppm corresponding to the Ar-H, N=CH, CH=CH and NH<sub>2</sub> protons of compound (7) were mentioned in Figure (6). Similarly, the rest of the compound structures also determined to the above same spectroscopic techniques.

#### 4. Conclusions:

In the present work bis-thiazine substituted bis-imines derivatives were synthesized successfully by Claisen-Schmidt condensation using both conventional and microwave irradiation methods. Generally most of the researchers have been synthesized chalcones using alcohol as solvent and catalyst like NaOH. Synthesis of chalcones by using alcohol has generated vast organic solvent as waste and which cannot reuse again. Use of sodium hydroxide as catalyst in the synthesis the bis-imines is a shorter reaction time process whereas without the catalyst, the reaction was progressed more than 12 hours. Synthesizing of chalcones and imine compounds via microwave assisted method of reaction; it is clean with shorter reaction time, as compared to conventional methods and reduces the use of volatile organic compounds (VOCs) and finally, it is agreement with the green chemistry protocols. The chemical structures of compounds 5, 6 and 7 have been confirmed using various

spectral techniques viz., FTIR, UV-Visible, and <sup>1</sup>H-NMR spectra and were found to be in agreement with the chemical structures expected.

**5. References:**

1. Mark, C. and Nagarathnam, D.; J. Nat. Prod. 1991, 54, 1656.
2. Dhar, D.N.; Wiley Interscience. 1981, 16, 336.
3. Karthikeyan, M. S., Holla, B. S., Kumari, N. S.; Eur J Med Chem. 2007, 42(1), 30-36.
4. Kotra, V., Ganapaty, S. and Adapa, S. R.; Indian J. Chem. 2010, 49, 1109.
5. Nakamura, C., Kawasaki, N., Miyataka, H., Jayachandran, E., Kim, I. H.; et al. Bioorg Med Chem Lett. 2002, 10(3), 699-706.
6. SrikanthJupudi et al. International Journal of Research in Pharmacy and Chemistry. 2013, 3(2), 213-220.
7. Beauchamp, Benardeau., Hilpert., Wang.; world intellectual property organization. 2011, 23, 165.
8. Wei Wang., Bing Zhao., Chao Xu., Wenpeng Wu.; International Journal of Organic Chemistry. 2012, 2, 117-120.
9. Thansu, J., Kanagarajan, V. and Gopalakrishnan, M.; J EnzymInhib Med Chem, 2010, 25 (6), 756-764.
10. Guo, Z., Xing, R., Liu, S., Zhong, Z., Ji, X., Wang, L.; Carbohydr. Res. 2007, 342, 1329–1332.
11. Wang, P. H., Keck, J. G., Lien, E. J., Lai, M. M. C.; J. Med. Chem. 1990, 33, 608–614.
12. Omar M. M., Mohamed, G. G., Ibrahim, A.A.; Chimi. Acta Part A, 2009, 73, 358–369.