



## Synthesis and spectroscopic study of 1,2-thiazine system incorporating various ester groups

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### ARTICLE INFO

#### Article History:

Received: 7/08/2017

Accepted: 15/01/2018

Published: 18/04/2018

#### Keywords:

1, 2- Thiazine,  
Carboxylate ion,  
Nucleophilic Substitution,  
Ester

### ABSTRACT

A series of 3-substituted-methyl-1,2-thiazines (4 a-g) was exclusively obtained in high yields for the first time through nucleophilic substitution reaction of 4,6-dibromo-2-phenyl-5-methyl-3-bromomethyl-1,1-dioxo-1,2-thiazines (3) with each of sodium Formate, acetate, propanoate, glycinate, benzoate, glycolate and salicylate as nucleophilic reagents in a highly polar aprotic solvent at room temperature. The IR, <sup>1</sup>H- and <sup>13</sup>C-NMR and MS spectra of the prepared compounds were conformed to their proposed structures

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## 1. INTRODUCTION

The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of multi-drug resistant microbial

pathogens. In spite of a large number of antibiotics and chemotherapeutics available for medical use, at the same time the emergence of old and new antibiotic resistance created in the last decades revealed a substantial medical need for new classes of antimicrobial agents

and is very important to explore additional sources for substances with potential antimicrobial activity, which could possibly have different modes of activity or affect different sites in the bacterial and fungal cells [aras 2016]. Compounds incorporating ester moiety play an important role in modern drug discovery and medicinal chemistry, and have long been used as anti-cancer [Claudriana et al 2013, Azmat et al 2013 and Shima et al 2013], anti-bacterial [Bartzatt et al 2004 and Bartzatt et al 2003], anti-fungal [Boussalah et al 2013, Martin et al 2012 and HUHTANEN and GUY], anti-viral [Nothias et al 2015 and Hisashi et al 2011], anti-inflammatory [Bassem et al 2013 and Mounir et al 1985], anti-convulsant [Mariia et al 2016 and Waters et al 1986], anti-diabetic [Vaiyapuri and Shruthi 2014] And also as stimulate hair growth agents [Joseph and Gregory 2001]. Looking to the diversified biological activities an attempt was made on the way to synthesis a series of new 1,2-thiazine system incorporating various ester moieties as outlined in Scheme 1.

## 2. MATERIALS AND METHODS

Uncorrected melting points were determined in open capillaries on a Gallen Kamp electrothermal apparatus. IR spectra were recorded on a Thermo-Mattson-300 Spectrophotometer, as KBr disc (Chemistry Department, College of Science, Salahadden University/Erbil), <sup>1</sup>H and <sup>13</sup>C-NMR spectra were measured using a Bruker ultra shield 300 MHz with internal TMS (Central Lab., Al-al-Bayt University/ Jordan), chemical shifts are given in ppm. MS were recorded on a GCMS, shimadzu, QP505 and Lc/MS/API5000 (Pharmaceutical research Unit, Amman-Jordan).

### 2.1. Synthesis of 3,5-dimethyl-2-phenyl-1,1-dioxo-1,2-thiazine (2) :-

A mixture of (200 mmol) of 3,5-dimethyl 1,1-dioxo-1,2-oxathine (1) ( which prepared by [Fanghanel et al 1982] from the reaction of mesityl oxide, acetic anhydride and sulfuric acid at 0 °C for 48h ) and (210 mmol ) of aniline was heated at 130-135 °C for about 1-1.5 h. Then the reaction mixture was cooled to room temperature and 100 mL of 10% cold HCl solution was added, the obtained product was collected by filtration, washed several times with cold water then air-dried and recrystallized from methanol. Pale yellow; yield 47%; m.p.: 112-114; FT-IR (KBr) cm<sup>-1</sup>: 1152.2s, 1384.0s (SO<sub>2</sub>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): 1.894 (s, 3H, 5-CH<sub>3</sub>); 2.115(s, 3H, 3-CH<sub>3</sub>); 5.654 (s, 1H, 4-CH); 6.210 (s, 1H, 6-CH); 7.363-7.4 (m, 2H, **HBz**); 7.445-7.478(m, 3H, **HBz**); <sup>13</sup>C- NMR (CDCl<sub>3</sub>, 300 MHz): 144.002 (C3), 106.874 (C4), 145.196 (C5), 111.936 (C6), 21.452 (C3-CH<sub>3</sub>), 21.888 (C5-CH<sub>3</sub>), 134.120 (C7), 129.464 (C8,8-), 129.928 (C9,9-), 129.516 (C10). MS (m/z, (relative abundance, %): 235.3(81.5), 236.3(24.1), 237.3(8.1), 170.2(100), 171.2(82.8), 156.2(48.2), 129.1(52.9), 115.1(37.9), 77.2(97.1), 67.1(), 51.1(79.5).

### 2.2. Synthesis of 4,6-dibromo-2-phenyl-5-methyl-3-bromomethyl-1,1-dioxo-1,2-thiazine (3):-

4,6-dibromo-2-phenyl-5-methyl-3-bromomethyl-1,1-dioxo-1,2-thiazine (3) was prepared according to the method of [Fanghanel et al 1983]. Pale yellow; yield 55.3%; m.p.: 160-162 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): 2.487(s, 3H, 5-CH<sub>3</sub>); 4.174(s, 2H, 3-CH<sub>2</sub>Br); 7.282-7.322 (m, 2H, **HBz**); 7.473-7.494 (m, 3H, **HBz**); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 300 MHz): 137.469 (C3), 109.887 (C4), 141.603 (C5), 113.198 (C6), 29.026 (C3-CH<sub>2</sub>Br), 24.08 (C5-CH<sub>3</sub>), 134.431 (C7), 128.592 (C8,8-), 130.037 (C9,9-

), 129.77( C10). MS (m/z, (relative abundance, %): 471.1(15.1), 473.1(40.2), 475.1(40.5), 477.1(15.7), 326.2(66.6), 328.2(100), 330.2(683), 246.2(17.1), 248.2(18.2), 168.2(82.4), 167.2(34), 117.1(18.5), 83.7(87.7), 63(30), 51.1(74).

### 2.3. General procedure for the synthesis of esters (4a-g):-

To a stirred solution of (1.5 mmol) of tribromo-1,2-thiazine (3) in 25mL of dimethyl sulfoxide was added (2 mmol) of dry sodium carboxylate (Formate, acetate, propanoate, N-acetyl glycinate, benzoate, glycolate and salicylate) in one portion, and then the resulting pale-yellow mixture was further magnetically stirred at room temperature. The progress of the reaction was monitored by thin layer chromatography using dichloromethane until the disappearance of starting material. After completion of the reaction, the mixture was poured into 60 mL of ice-cold water, stirred for 20 minutes and the corresponding 1,2-thiazinyl carboxylate (4a-g) was extracted from the obtained milky solution using 30 mL of diethyl ether (twice). The ethereal solution was washed with water, dried over anhydrous sodium sulphate, then the diethyl ether was evaporated under rotary evaporator, and the residue was purified by recrystallization from 95% ethanol to yield

#### 2.3.1 (4,6-dibromo-5-methyl-2-phenyl-1,1-dioxo-1,2-thiazine-3-yl methyl) formate (4 a):

Pale yellow crystal with yield 85.7%; m.p.: 138-140 °C; FT-IR (KBr): 1176.4s & 1360.7 (SO<sub>2</sub>), 1719.1s (CO); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): 2.502 (s, 3H, 5-CH<sub>3</sub>); 4.940 (s, 2H, 3-CH<sub>2</sub>-O); 7.977 (s, 1H, -CHO); 7.216-7.248 (m, 2H, HBz); 7.437-.458 (m, 3H, HBz); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 300 MHz): 135.772 (C3), 111.730 (C4), 141.512 (C5), 113.462 (C6), 61.879 (C3-CH<sub>2</sub>O), 24.18 (C5-CH<sub>3</sub>), 134.532 (C7), 128.146 (C8,8-), 129.821(C9,9-), 129.602 (C10), 159.419 (C11). MS (m/z, (relative abundance, %): 473.1(14.3),

475.3(30.3), 441.1(16.4), 326.2(76.6), 328.2(100), 330.2(72.3), 264.1(10.6), 266.1(8.9), 246.2(17.1), 248.2(21.2), 168.2(73.4), 167.2(34), 100(86.1), 77.1(96.8), 51.1(86.1).

#### 2.3.2. (4,6-dibromo-5-methyl-2-phenyl-1,1-dioxo-1,2-thiazine-3-yl methyl) acetate (4 b):

Pale yellow crystal with yield 88.3%, m.p.: 129-131°C; FT-IR (KBr): 1176.2s & 1363.7 (SO<sub>2</sub>), 1733.5s (CO); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): 2.001(s, 3H, CO-CH<sub>3</sub>); 2.486(s, 3H, 5-CH<sub>3</sub>); 4.852 (s, 2H, 3-CH<sub>2</sub>-O); 7.207-7.226 (m, 2H, HBz); 7.419-7.439 (m, 3H, HBz); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 300 MHz): 136.542 (C3), 111.069 (C4), 141.607( C5), 112.950 (C6), 62.586 (C3-CH<sub>2</sub>O), 24.233 (C5-CH<sub>3</sub>), 134.714 (C7), 128.133 (C8,8-), 129.693 (C9,9-), 129.469 (C10), 169.706 (C11), 20.34 (C12). MS (m/z, (relative abundance, %): 449.2(22.3), 451.2(44.9), 453.2(16.4), 326.2(63.6), 328.2(100), 330.2(61.3), 264.1(50.1), 266.1(46.5), 246.2(25.1), 248.2(26.7), 168.2(50.6), 167.2(24), 104.1(33.8), 77.1(54.2), 51.1(37.2), 43.1(73.1).

#### 2.3.3. (4,6-dibromo-5-methyl-2-phenyl-1,1-dioxo-1,2-thiazine-3-yl methyl) propanoate (4 c):

Pale yellow crystal with yield 88.6; m.p.: 87-88 °C; FT-IR (KBr): 1180.0s & 1365.2 (SO<sub>2</sub>), 1743.9s(CO); <sup>1</sup>H- NMR (CDCl<sub>3</sub>, 300 MHz): 1.108 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>); 2.299(q, 2H, OCH<sub>2</sub>CH<sub>3</sub>); 2.5 (s, 2H, 3-CH<sub>2</sub>); 7.197-7.259 (m, 2H, HBz); 7.415-.449 (m, 3H, HBz); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 300 MHz): 136.622(C3), 111.095 (C4), 141.589 (C5), 112.910 (C6), 62.528 (C3-CH<sub>2</sub>O), 24.264 (C5-CH<sub>3</sub>), 134.699 (C7), 128.127 (C8,8-), 129.659 (C9,9-),

129.447 (C10), 173.239 (C11), 27.114 (C12), 9.002 (C13). MS (m/z, (relative abundance, %): 463(18.2), 456(39.5), 467(19.9), 326.2(73.5), 328.2(100), 330.2(72.1), 264.1(60.1), 266.1(58.5), 246(30.3), 248(29.8), 168.2(69.1), 167.2(35.6), 104(29.6), 77.1(76.2), 51.1(85.1).

**2.3.4. (4,6-dibromo-5-methyl-2-phenyl-1,1-dioxo-1,2-thiazine-3-yl methyl) N-acetyl glycinate(4 d):**

Pale yellow crystal with yield 80.%, m.p.: 105-106 °C; FT-IR (KBr): 1182.9s & 1363.9s (SO<sub>2</sub>), 1760.5s & 1640.5s(CO), 3290.6s (NH); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): 2.046 (s, 3H, CO-CH<sub>3</sub>); 2.497 (s, 3H, 5-CH<sub>3</sub>); 4.015 (d, 2H, OCO-CH<sub>2</sub>-NH); 4.943 (s, 2H, 3-CH<sub>2</sub>-O); 5.955(s, 1H, NH); 7.195-7.214 (m, 2H, HBz); 7.439-7.459 (m, 3H, HBz); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 300 MHz): 135.732 (C3), 111.936 (C4), 141.434 (C5), 113.711(C6), 63.228 (C3-CH<sub>2</sub>O), 24.160 (C5-CH<sub>3</sub>), 134.569 (C7), 127.992 (C8, 8-), 129.783 (C9, 9-), 129.609 (C10), 170.175 (C11), 41.047 (C12), 168.926 (C14), 22.868 (C15). MS (m/z, (relative abundance, %): 506.1(18.5), 508.1(38.3), 510.1(19.1), 326.2(56.6), 328.2(100), 330.2(54.3), 264.1(40.6), 266.1(38.9), 246.2(22.1), 248.2(24.2), 168.2(65.2), 167.2(33.2), 100(86.1), 77.1(66.8), 65(18.1) 51.1(86.1), 41(85).

**2.3.5. (4,6-dibromo-5-methyl-2-phenyl-1,1-dioxo-1,2-thiazine-3-yl methyl) benzoate (4 e):**

Pale yellow crystal with yield 89.3%; m.p.: 120-121 °C; FT-IR (KBr): 1181.6s & 1368.4s (SO<sub>2</sub>), 1728.0s (CO); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): 2.52(s, 3H, 5-CH<sub>3</sub>); 5.118(s, 2H, 3-CH<sub>2</sub>O); 7.24-7.271(m, 2H, HBz); 7.383-7.490(m, 3H, HBz); 7.464(t, 2H, H-benzoate); 7.604 (t, 1H, Hbenzoate); 7.991(d, 2H,

Hbenzoate); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 300 MHz): 136.634(C3), 111.349 (C4), 141.608 (C5), 113.238 (C6), 63.081 (C3-CH<sub>2</sub>O), 24.269 (C5-CH<sub>3</sub>), 134.70 (C7), 128.130 (C8,8-), 129.70 (C9,9-), 129.541(C10), 165.369 (C11), 129.793 (C12), 129.077 (C13,13-), 128.512 (C14,14-), 133.435 (C15). MS (m/z, (relative abundance, %): 511(7.1), 513(14.1), 515(8.1), 326.1(16.1), 328.1(32), 330.1(15.6), 246(8.2), 248(9.1), 168.2(18.2), 167.2(8.1), 105(100), 77.1(57.2), 51.1(21).

**2.3.6. (4,6-dibromo-5-methyl-2-phenyl-1,1-dioxo-1,2-thiazine-3-yl methyl) glycolate (4 f):**

Pale yellow crystal with yield 77.1%; m.p.: 144-145 °C; FT-IR (KBr): 1168.9s & 1346.2s (SO<sub>2</sub>) 1740.16s (CO) 3514.0s (OH); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): 2.256(s, 1H, OH); 2.495(s, 3H, 5-CH<sub>3</sub>); 4.126(s, 2H, CO-CH<sub>2</sub>-OH); 4.979(s, 2H, 3-CH<sub>2</sub>-O); 7.196-7.227(m, 2H, HBz); 7.435-7.456(m, 3H, HBz); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 300 MHz): 135.699 (C3), 111.803 (C4), 141.485(C5), 113.563 (C6), 63.246 (CH<sub>2</sub>O), 24.173 (C5-CH<sub>3</sub>), 134.594 (C7), 128.020 (C8,8-), 129.815 (C9,9-), 129.588 (C10), 172.130 (C11), 60.281(C12). MS (m/z, (relative abundance, %): 465.1(13.3), 467.1(27.9), 469.1(14.4), 407.1(8.3), 409(16.1), 411.1(8.2), 326.2(77.6), 328.2(100), 330.2(76.1), 264.1(22.1), 266.1(20.5), 246.2(13.1), 248.2(15.2), 168.2(66.6), 167.2(27.1), 104.1(42.7), 86(22), 85(47.2), 77.1(93.2), 65(13.5), 51.1(58.2).

**2.3.7. (4,6-dibromo-5-methyl-2-phenyl-1,1-dioxo-1,2-thiazine-3-yl methyl) salicylate (4 g):**

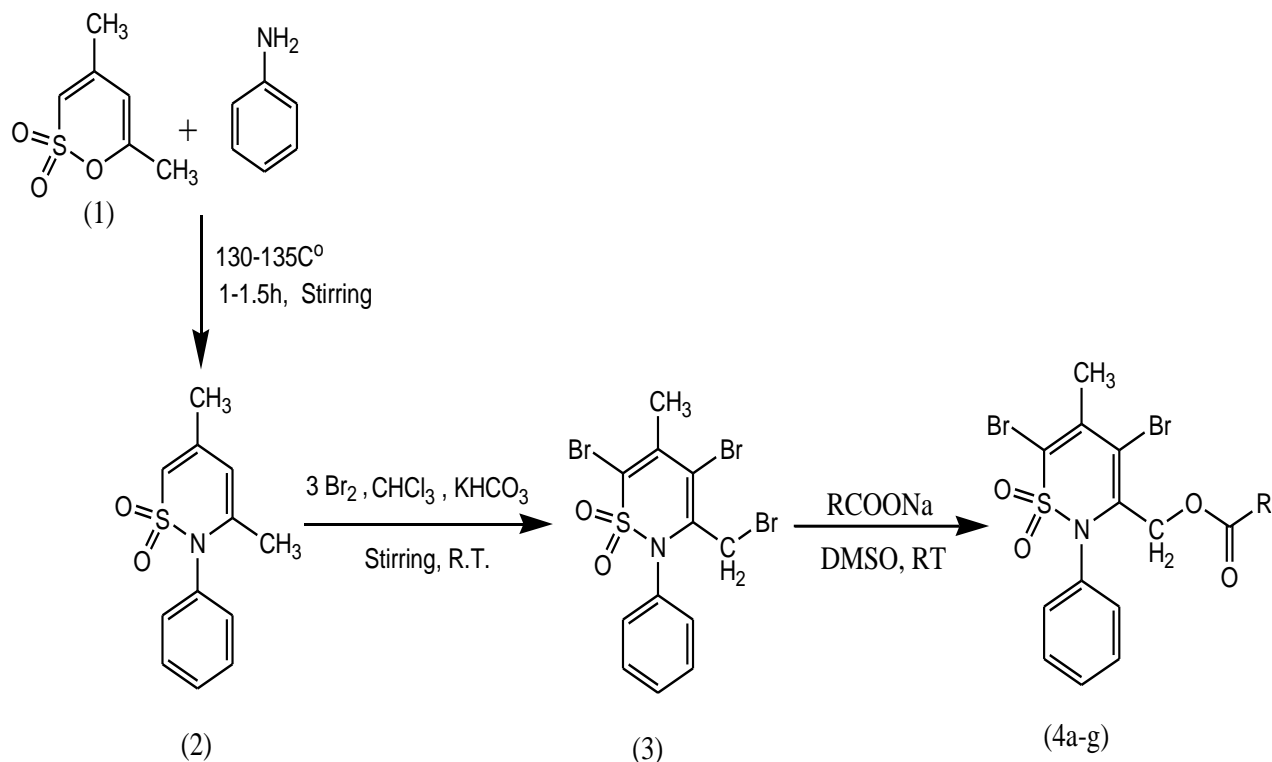
Pale yellow crystal with yield 73.9%; m.p.: 116-117 °C; FT-IR (KBr): 1158.3s & 1362.1s

(SO<sub>2</sub>), 1680.1s (CO), 3126.3w (OH); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): 2.527 (s, 3H, 3-CH<sub>3</sub>); 5.144 (s, 2H, 3-CH<sub>2</sub>O); 6.952 (m, 2H, H salicylate); 7.502 (m, 1H, H-salicylate); 7.769,7.8 (dd,1H, H-salicylate); 7.227-7.284 (m, 2H-, HBz); 7.384-7.434 (m, 3H, HBz); 10.305 (s, 1H, OH); <sup>13</sup>C- NMR (CDCl<sub>3</sub>, 300 MHz): 136.271(C3), 111.732 (C4), 141.540 (C5), 113.587 (C6), 63.148 (C3-CH<sub>2</sub>O), 24.283 (C5-CH<sub>3</sub>), 134.565 (C7), 128.054(C8,8-), 129.811(C9,9-), 129.625 (C10), 168.795 (C11), 130.037 (C12), 161.684 (C13), 117.674(C14), 135.931(C15), 119.464(C16), 141.540 (C17). MS (m/z, (relative abundance, %): 527(19.2), 529(38.1), 531(20.3), 326.2(73.5), 328.2(100), 330.2(72.1), 264.1(12.3), 266.1(11.5), 246(24.5), 248(25.1), 168.2(81.1), 167.2(37.6), 121(97.2), 77.1(59.6), 51.1(37.1).

### 3. RESULTS AND DISCUSSION

The first aim of this study was to synthesize and spectroscopic study of some new 1,2 thiazine system incorporating various esters groups. The required 3, 5-dimethyl-2-phenyl-1,1-dioxo-1,2-thiazine (2) for this study was readily prepared through a single-step reaction as outlined in Scheme 1. From the reaction of 3,5-dimethyl-2-phenyl-1,1-dioxo-1,2-oxathine (1) and aniline [Tawada et al 1990]. The formed 3,5-dimethyl-2-phenyl-1,1-dioxo-1,2-thiazine (2) in the presence of

potassium carbonate in chloroform at room temperature reacts with bromine to afford 4,6-dibromo-2-phenyl-5-methyl-3-bromomethyl-1,1-dioxo-1,2-thiazine (3) [Shen and Dryhurst 2001]. In the present study, 3-bromomethyl 1,2-thiazine (3) easily undergoes nucleophilic substitution reaction in dimethyl sulfoxide at room temperature for giving (4,6-dibromo-5-methyl-2-phenyl-1,1-dioxo-1,2-thiazine-3-yl methyl) formate (4a) in high yield. Since at room temperature-condition, the reaction was progressed smoothly and products were obtained in very good yields and in high purity, the esterification process of 3-bromomethyl groups of compound (3) was extended for the preparation of (4,6-dibromo-5-methyl-2-phenyl-1,1-dioxo-1,2-thiazine-3-yl methyl) acetate (4b) propanoate (4c), N-acetyl glycinate (4d) and benzoate (4e) using sodium acetate, propanoate, N-acetyl glycinate and benzoate. To further expand our understanding of esterification-reactions of 1,2-thiazine system, reaction of 4,6-dibromo-2-(substituted phenyl)-5-methyl-3-bromomethyl-1,1-dioxo-1,2-thiazine (3) with sodium glycolate and salicylate in dimethyl sulfoxide at room temperature was carried out to the corresponding (4,6-dibromo-5-methyl-2-phenyl-1,1-dioxo-1,2-thiazine -3-yl methyl) glycolate (4f)

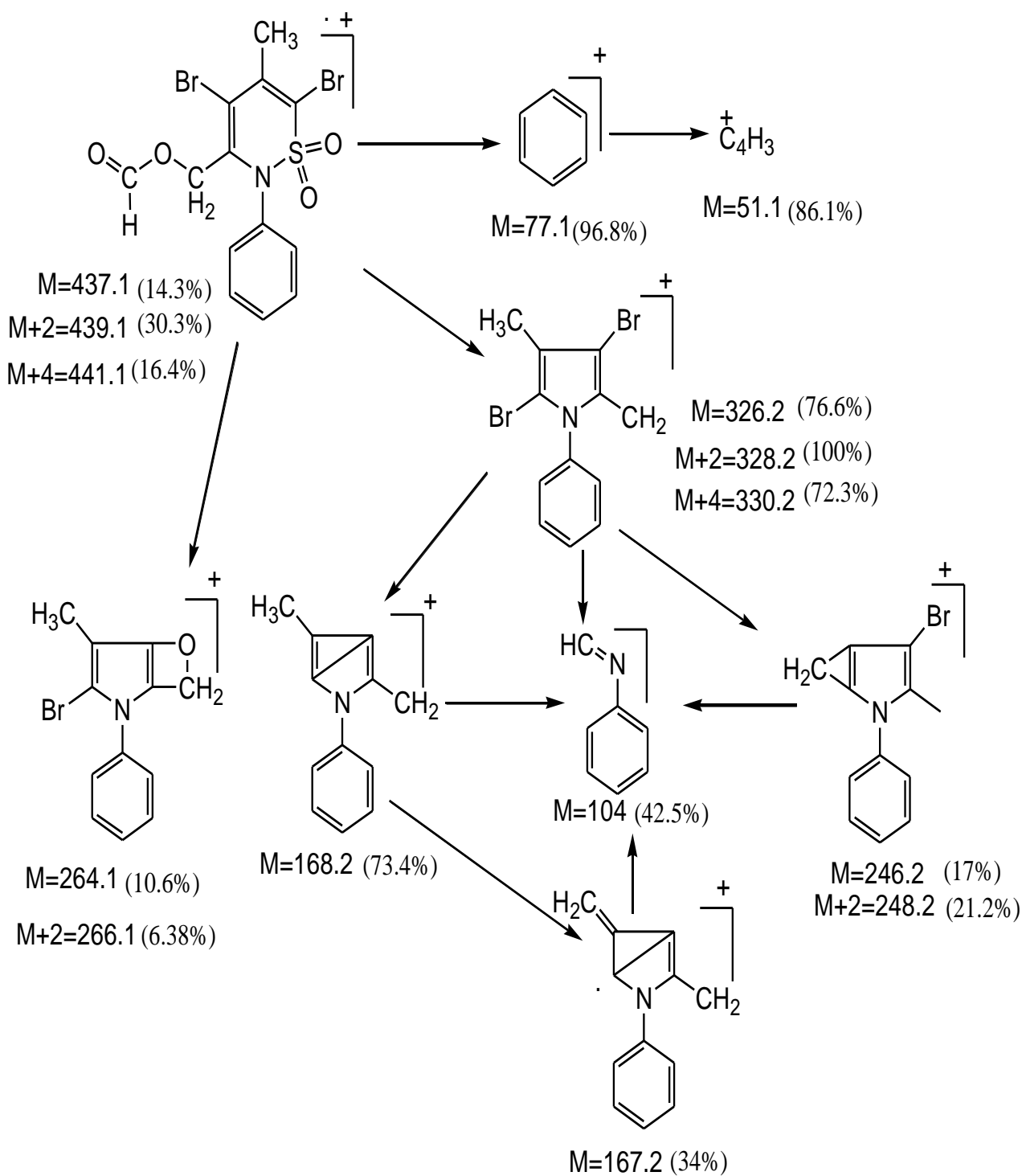


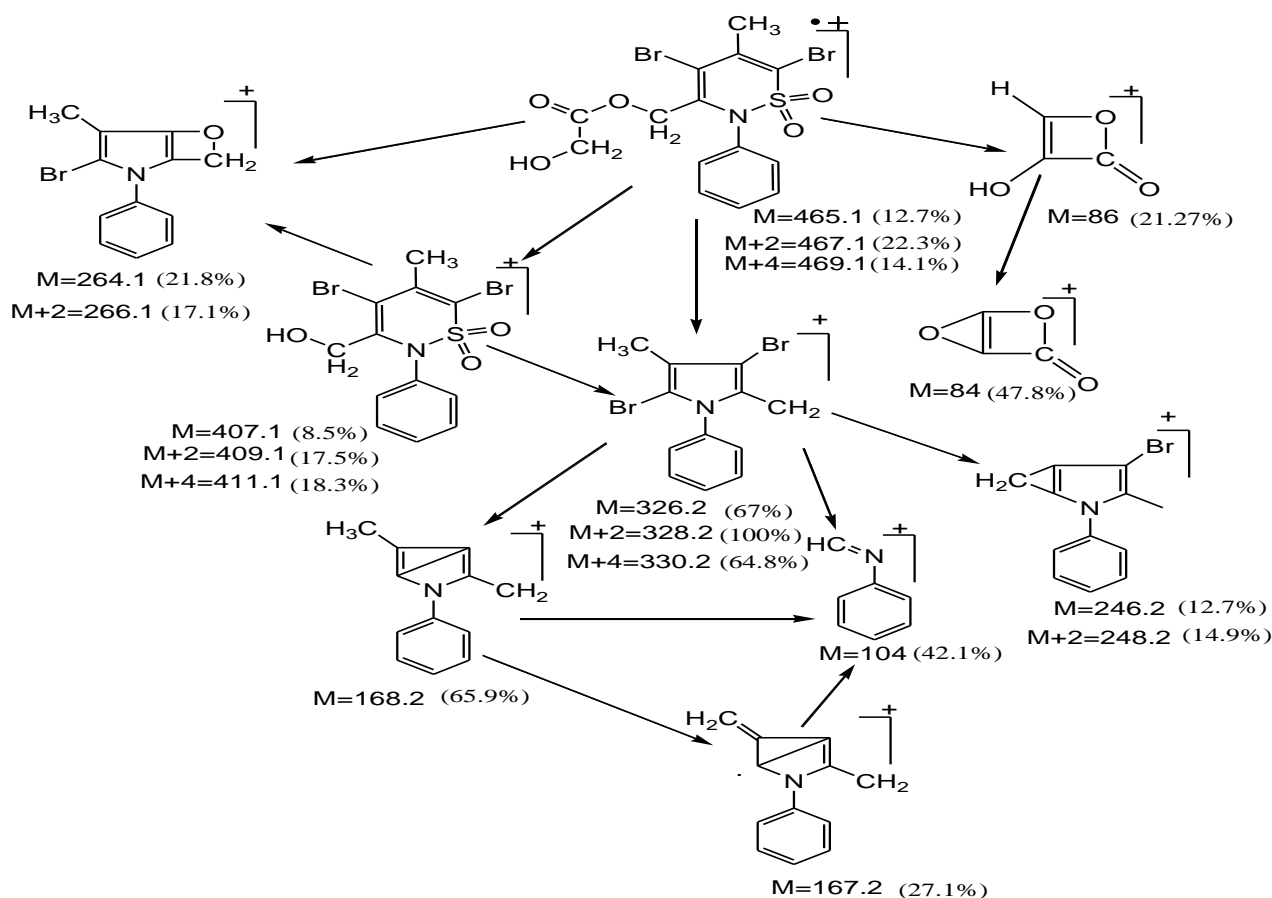
4a R=H, 4b R=CH<sub>3</sub>, 4c R=CH<sub>2</sub>CH<sub>3</sub>, 4d R=CH<sub>2</sub>NHCOCH<sub>3</sub>, 4e R=C<sub>6</sub>H<sub>5</sub>, 4f R=CH<sub>2</sub>OH, 4g R=C<sub>6</sub>H<sub>5</sub>(2-OH)

**Scheme (1):** preparation of compounds (4a-g)

salicylate and (4g) in yields lower than those of (4a-e). Herein, steric effects come into play; the hydroxyl groups of the glycolate and salicylate anions in two modes lowering the product-yield. In the former, the hydroxyl group through its negative inductive effect decreases the nucleophilicity of the glycolate anion, while in the latter; the formed intramolecular hydrogen bond between

carbonyl oxygen atom and the hydroxyl group at ortho position decreases the nucleophilic power of the salicylate anion toward the bromo group of the 3-bromomethyl moiety of (3), and this interpretation was in agreement with their infrared and proton NMR data of the hydroxyl groups and also with the reported data [Hosangadi and Dave 1996].





**Scheme (2):** Mass fragmentation of N-(4,6-dibromo-5-methyl-2-phenyl-1,1-dioxo-1,2-thiazine-3-yl)methyl formate (4a) and glycolate (4f).

signal at 4.174 ppm due to the protons of the 3-methylene group in (3), on esterification process was shifted to around 5 ppm. For our knowledge the depicted molecular ion peak in the mass spectrum of each ester is in covenant with the molecular weight of the obtained esters (4a-g). In addition to that in the mass spectra of ester 4a the base ion peak, which results from the loss of sulfur dioxide molecule and carboxylate radical from its molecular ion appears at  $M/Z = 326.2$ , and the isotope patterns at 328.2 and 330.2 revealed the presence of the two bromo groups in it. Another two prominent peaks at 246.2 with its  $M+2$  at 248.2 were due to 4-bromo-2-phenyl-

2-azabicyclo [3.1.0] hexa-1(5)-3-diene-2-methylene cation and it could be seen in the mass spectra of all ester compounds. The ions at  $M/Z$  at = 264.2 and its  $M+2$  at 266.2 due to formation of 3-bromo-4-methyl-2-phenyl-6-oxa-2-azabicyclo[3.2.0]hepta-1-,3-diene cation and at 168 due to 4-methyl-2-methylene-1-phenyl-2H-pyrrolium cation were shown in the mass spectra of all ester compounds. Herein, we can say that the mass fragmentation of the ester compounds were similar to each other except for showing some different ions which were references to the carboxylate moiety.



#### 4. CONCLUSIONS

In this work a series of new 1,2-thiazine system incorporating various ester groups was prepared through a classical, convenient and practical method. In this method, the products can be separated conveniently from the reaction mixture in high purity and no chromatographic method

needed for their isolation. Another notable advantage of this method is that the reaction condition was mild and the products were obtained in very good yields in suitable time. The present approach has the ability to synthesize a variety of 1,2-thiazines bearing various group.

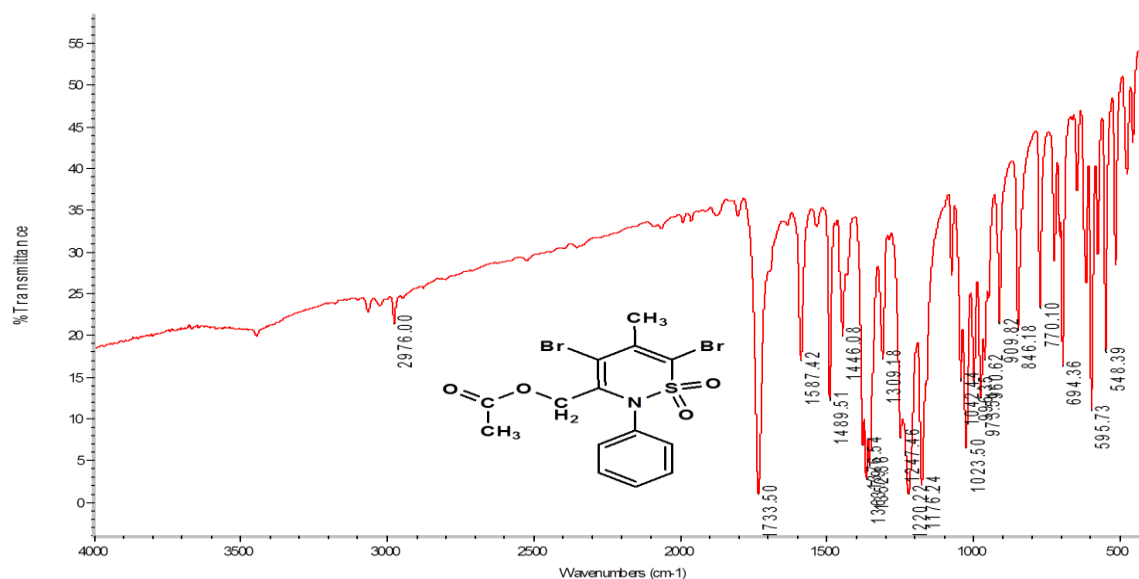


Figure (1): Infrared spectrum of compound (4b)

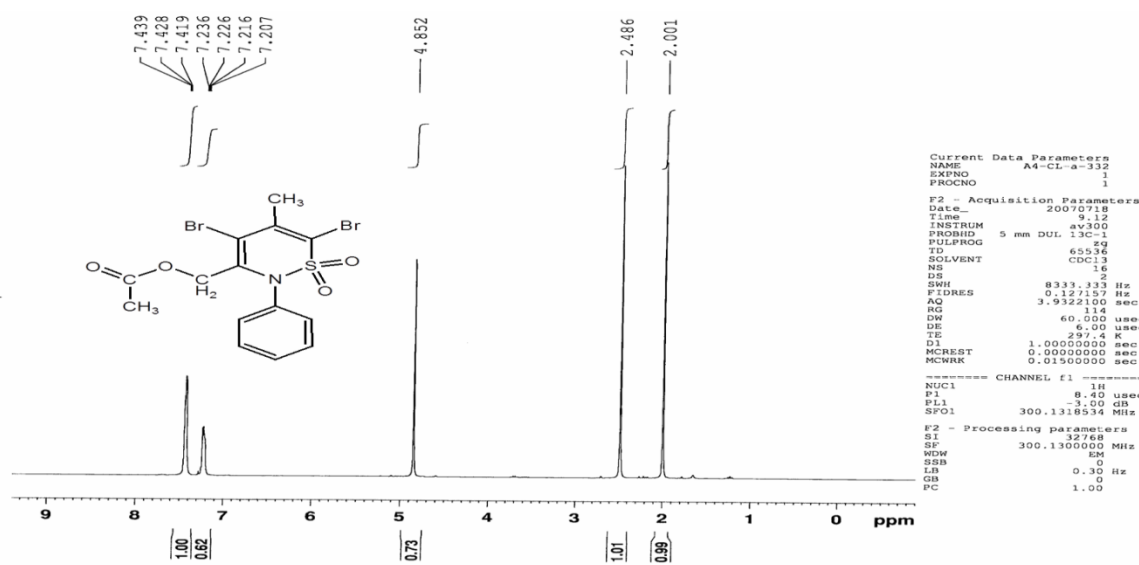


Figure (2): <sup>1</sup>H - NMR spectrum of compound (4b)

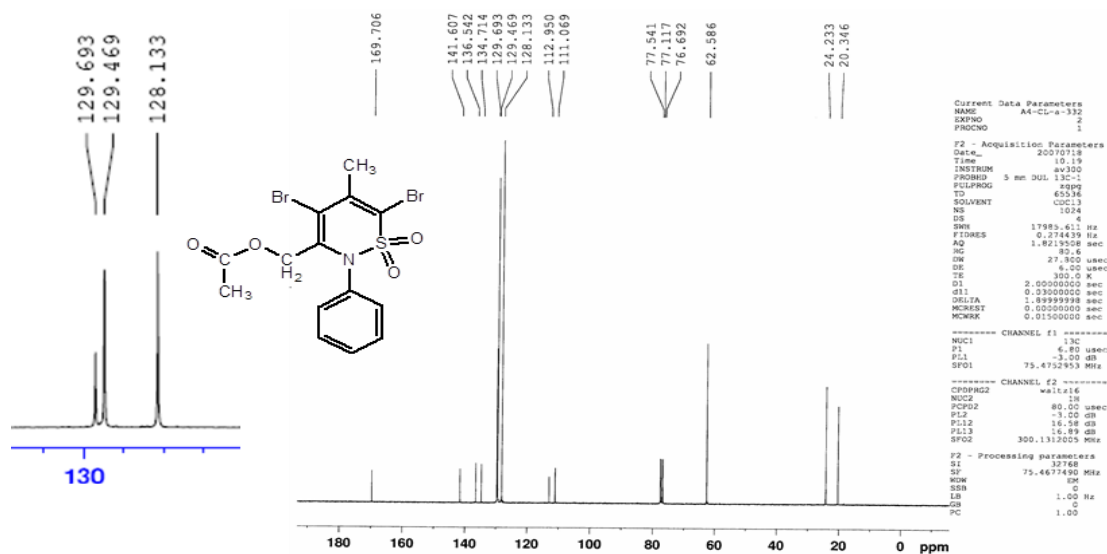
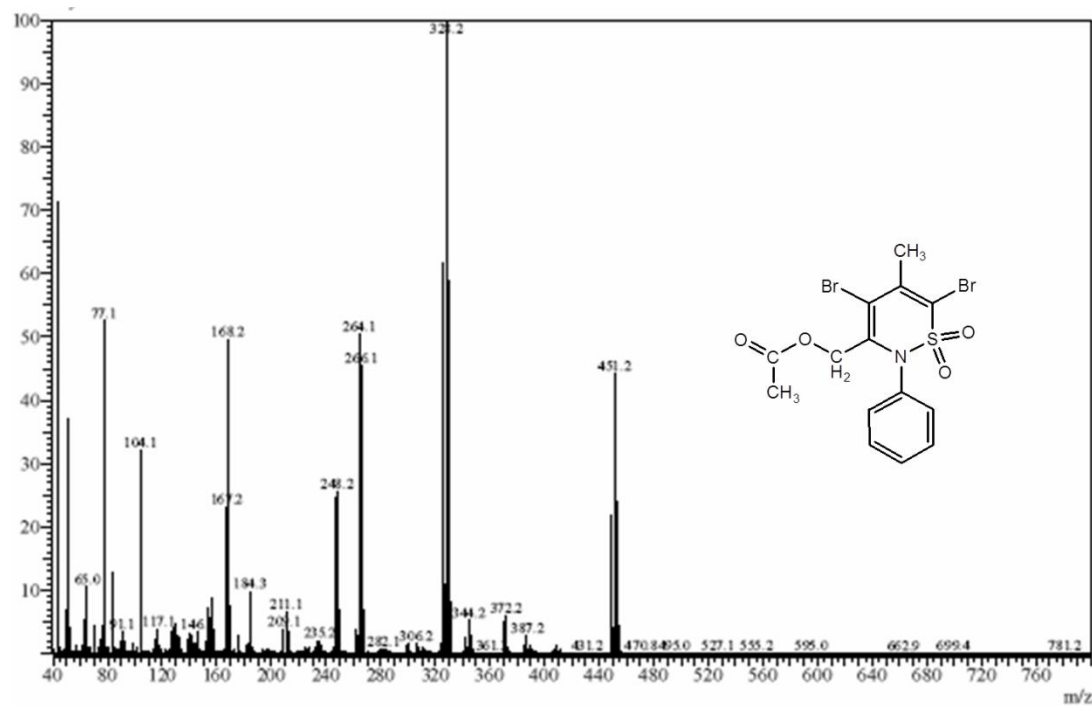
Figure (3): <sup>13</sup>C - NMR spectrum of compound (4b)

Figure (4) : Mass spectrum of compound (4b)

## REFERENCES

- Aras, N., H.; Synthesis and preliminary evaluation of the antibacterial activity of some new compounds from nucleophilic acyl substitution and ring opening reactions
- of 5(4H)-oxazolones , ZANCO Journal of Pure and Applied Sciences, **2016**; 28 (3), 175-185.
- Bartzatt, R.; Malesa, C.; Synthesis, structural analysis and antibacterial activity of a butyl ester derivative of ampicillin, Chemotherapy, **2003**; 49(5), 213-21.
- Bartzatt, R.; Cirillo, S. L.; Cirillo, J. D.; Molecular properties and antibacterial activity of the methyl and ethyl ester derivatives of ampicillin, Physiological Chemistry and Physics and Medical NMR, **2004**; 36, 2, 85-94.
- Bassem, S.; Amar, M. H.; and Abdu, A.; Anti-inflammatory agents of the carbamoylmethyl ester class: synthesis, characterization, and pharmacological evaluation, Journal of Inflammation Research., **2013**; 6: 35–43.
- Boussalah, N., Touzani, R., Souna, F., Himri, I., Bouakka, M., Hakkou, A., Ghalem, S., El Kadiri, S. Hide details, Antifungal activities of amino acid ester functional pyrazolyl compounds against Fusarium oxysporum f.sp. albedinis and Saccharomyces cerevisiae yeast, Journal of Saudi Chemical Society, **2013**, 17, 1, 17-21.
- Claudriana, L.; Fabíola, B. F.; Tânia, B. C.; Alkyl esters of gallic acid as anticancer agents: A review, European Journal of Medicinal Chemistry, **2013**; 60, 233-239.
- Fanghanel, E.; Radeglia, R.; and Mohammed, H.; Substituent Effects and <sup>13</sup>C-NMR Chemical Shifts of para Substituted N-Phenyl-2,4-Dimethyl-buta-1,3-diene-Sultames-1,4; Journal für praktische Chemie, **1983**, 325, 1030.
- Fanghanel, E.; Mohammed, H.; Radeglia, R.; and Keita, Y.; Structure Elucidation of Bromination Products of N-Aryl-2, 4-dimethyl-buta-1,3-diene-sultames-1, 4; Journal für praktische Chemie, **1982**, 324, 353.
- Hisashi Y.; Kazuko T.; Keiko I.; Yukiko S.; Tsutomu A.; Hajime, K.; Antiviral and Virucidal Activities of N-Cocoyl-L-Arginine Ethyl Ester, Advances in Virology, **2011**, 6 -12.
- Hosangadi, B. D.; and Dave, R. H.; An efficient general method for esterification of aromatic carboxylic acids ; Tetrahedron Lett. **1996**, 37(35), 6375.
- Huhtanen, C, N.; Guy, E. J.; Antifungal Properties of Esters of Alkenoic and Alkynoic Acids, journal of food science, **1984**, 49, 1, 281- 285.
- Joseph, P. S.; Gregory, S. H., , heterocyclic ester and amide hair growth compositions and uses,2001, US 6,274,617 B1.
- Khan, A. A.; Alanazi, A. M.; Jabeen, M.; Chauhan, A.; Abdelhameed, A. S.; Design, Synthesis and In Vitro Anticancer Evaluation of a Stearic Acid-based Ester Conjugate, Anticancer Research, **2013**; 33, 6, 2517-2524.
- Mariia. N.; and Iryna, K.; Synthesis and Pharmacological Properties of Novel Esters Based on Monocyclic Terpenes and GABA, Pharmaceuticals (Basel). **2016**; 9(2): 32.
- Martin, K.; Jarmila, V.; Antifungal Activity of Salicylanilides and Their Esters with 4-(Trifluoromethyl)benzoic Acid, Molecules, **2012**, 17(8), 9426-9442.
- Mounir, A. K.; John, C. L.; Henry J. L.; Synthesis of a new anti-inflammatory steroidal acid ester: Methyl 11β-hydroxy-3,20-dioxo-1,4-pregnadien-21-oate, Journal of Pharmaceutical Sciences, **1985**, 74, 2, 180–183.
- Nothias-Scaglia, L. F.; Pannecouque, C.; Renucci, F.; Delang, L.; Neyts, J.; Roussi, F.; Costa, J.; Leyssen, P; Litaudon, M.; Paolini. J.; Antiviral Activity of Diterpene Esters on Chikungunya Virus and HIV Replication., Journal of Natural Products, **2015**, **78** (6), **1277–1283**.
- Shen, X. M.; Dryhurst, G.; Influence of glutathione on the oxidation chemistry of 5-S -cysteinyl dopamine: potentially neuroprotective reactions of relevance to arkinson's disease. Tetrahedron, **2001**, 57, 2, 393–405.
- Shima, H. E. K.; Mohsen, A.; Mohsen, V., Abbas, S.; Ebrahim, A.; and Farzad, K.; Synthesis, Evaluation of Anticancer Activity and QSAR Study of

Heterocyclic Esters of Caffeic Acid, Iranian Journal of Pharmaceutical Research, **2013**; 12, 4, 705–719.

Tawada, H.; Sugiyama, Y.; Ikeda, H.; Yamamoto, Y.; Meguro, K.; Studies on antidiabetic agents. IX. A new aldose reductaseinhibitor, AD-5467, and related 1,4-benzoxazine and 1,4-benzothiazine derivatives: synthesis and biological activity, Chemical and Pharmaceutical Bulletin, **1990**; 38, 1238–45.

Vaiyapuri, S.; Shruthi S. D.; In vitro and in silico antidiabetic activity of pyran ester derivative isolated from *Tragia cannabina*, Asian Pacific Journal of Tropical Biomedicine, **2014**, 4, 1, S455-S459.

Waters, J. A.; Hollingsworth, E. B.; Daly, J. W.; Lewandowski, G.; Creveling C. R.; Anticonvulsant activity of piperidinol and (dialkylamino) alkanol esters., J Medical Chemistry, **1986** ;29(8):1512-6.