SYNTHESIS OF BIOLOGICALLY ACTIVE XANTHENE, CHROMENE, THIAZOLE, THIOPHENE, PYRAZOLE, AND ISOXAZOLE DERIVATIVES FROM CAMPHOR

Ensaf Sultan Alwan* and Rafat Milad Mohareb

1Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences & Pharmaceutical Industries, Future University in Egypt, Cairo, Egypt
2Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

(Received July 4, 2023; Revised September 3, 2023; Accepted September 6, 2023)

ABSTRACT Xanthene, chromene, thiazole, thiophene, pyrazole, and isoxazole derivatives were synthesized from camphor-D monoterpene using multi-component reactions. Camphor has anti-bacterial, anti-fungal and anti-inflammatory properties. It is also used to mitigate pain, treat skin diseases, and improve respiratory functions. In this research, we focus on the effectiveness of the produced compounds from the biologically active camphor. The produced compounds were formed according to various reactions such as a Knoevenagel condensation, Michael adduct, Gewald reaction, a nucleophilic attack, substitution, addition, elimination and cyclization reactions. Furthermore, the novel produced compounds have been tested towards the six cancer cell lines namely A549, MKN-45, U87MG, HT-29, H460 and SMMMC-772. Compounds 5, 11, 15b, 16, 25b and 27b displayed the highest inhibitions compounds toward the mentioned cancer cell lines. In addition, compounds 3, 13, 15a, 22a, 27a and 28 showed moderate inhibitory effects against the cancer cell lines.

KEY WORDS: Camphor, Xanthenes, Pyrimidine, Heterocyclic, Anti-cancer

INTRODUCTION

Xanthene derivatives are an important class of compounds in organic synthesis and in medicinal chemistry. They diverse biological activities like anti-inflammatory [1], antibacterial [2, 3], antifungal [4], insecticidal [5], free radical scavenging activity [6], antiplasmodial [7-9], anticancer [10], antioxidant [11], antimarial [12], antiproliferative [13], apoptotic effects [14], anti-mycobacterial [15] and anti-viral properties [16]. In addition, they are also applied in laser technology [17] and in photodynamic therapy [18]. Xanthenes were used as antagonists for drug-resistant leukemia lines [19] and as pH sensitive fluorescent materials for visualization of biomolecules [20]. These derivatives have received wide attention for their synthesis due to their biological, industrial and therapeutic applications [21]. Xantheme derivatives have been synthesized in a variety of ways [22] in the presence of different catalysts such as, Yb(OTf)3 [23], InCl3 [24], Al(HSO4)3 [25], nano-TiO2 [26], NaHSO4 [27], cyanuric chloride [28], Amberlyst-15 [29], heteropoly acids [30], silica sulfuric acid [31], molecular iodine [32], sulfamic acid [33], P-TSA [34], and AcoH-H2SO4 [35]. Hossein and Oskooie et al. reported the synthesis of 1,8-dioxo-octahydroxanthenes using cellulose sulfonic acid in an excellent yields under solvent-free conditions [21]. Furthermore, Pradeep Paliwal et al. reported the synthesis of xanthenes catalyzed by DABCO in aqueous media [36] and Sami Ullah Bhat et al. reported the synthesis of xanthenes using H-Zeolite as reusable catalyst [37]. Mohareb et al. reported the importance of cyclohexan-1,3-dione in heterocyclic synthesis [38,39]. This compound is an essential compound in xanthenes synthesis. In view of the importance of xanthenes in various fields, our goal in this research was concerned with the synthesis of xanthenes from camphor-D monoterpene based on the multi-component reactions between camphor, benzaldehyde and cyclohexan-1,3-dione. The novel compounds were investigated toward the cancer cell lines mentioned above. Compounds 5,
11, 15b, 16, 25b and 27b displayed the highest inhibitory effect toward the mentioned cancer cell lines. Compounds 3, 13, 15a, 22a, 27a and 28 showed moderate inhibitory effects against the cancer lines.

RESULTS AND DISCUSSION

In this work, we demonstrated use of camphor to produce a bioactive xanthene, chromene, thiazole, thiophene, pyrazole and isoxazole derivatives. Thus, treatment of two-moles of camphor (1) with benzaldehyde (2) in ethanol/piperidine afforded dimethanoxanthene derivative 3. Series of multi-component reactions were done to produce fused chromene derivatives. Thus, the reaction between camphor (1), benzaldehyde (2) and cyclohexanone (4) in ethanol/piperidine gave methanoxanthene derivative 5. Moreover, the reaction between camphor (1), benzaldehyde (2), and cyclopentanone (6) in ethanol/piperidine gave methanocyclopenta[β]chromene derivative 7. Moreover, the reaction between camphor (1), benzaldehyde (2) and ethyl benzoylacetate (8) gave the 5,8-methanochromene-3-carboxylate derivative 9 (Scheme 1). Structures of produced compounds have been proven by (1H, IR, MS, 13C-NMR) spectrums. Thus, 1H NMR of compound 5 displayed two multiplets at 1.63-1.67 ppm for two CH₂ of camphor, two multiplet at 2.41-2.44 equivalent to four CH₂ of cyclohexane, a singlet at δ 6.90 equivalent to H-4 pyran, and a multiplet at δ 7.33-7.64 for C₆H₅.

Scheme 1. Synthesis of compounds 3, 5, 7 and 9.

On the other hand, the reaction between camphor (1), sulfur and phenylisothiocyanate (10) in ethanol/Et3N gave 4,7-methanobenzol[β]thiazole-2(3H)-thione derivative 11. The reaction of camphor (1) with benzaldehyde (2), and cyclohexane-1,3-dione (12) in ethanol containing piperidine gave 3,4,5,6,7,9-hexahydro-1H-1,4-methanoxanthen-8(2H)-one derivative 13. We have chosen compound 13 as a starting point to synthesize of various heterocyclic products by its reaction with different reagents to give biologically active thiophene, pyrimidine-3(2H)-thione, pyrazole, isoxazole, 4,5,6,8,9,10,11,12-octahydro-8,11-methanopyranopyran[2,3-a]xanthene-3-carbonitrile derivatives. Thus, thiophene derivatives 15a,b were synthesized from the reaction between
compound 13. Ethyl cyanoacetate (14a) or malononitrile (14b) and sulfur in ethanol/Et$_3$N according to the Gewald's reaction. Compound 15a or 15b reacted with phenylisothiocyanate (10) to give pyrimidines 16 and 17 (Scheme 2). Structures of produced compounds have been proven by ($^1$H, IR, MS, $^{13}$C-NMR) spectrums. Thus, $^1$H NMR of compound 16 displayed a multiplet at 7.25-7.50 equivalent to the two C$_6$H$_5$ groups and a singlet at $\delta$ 10.88 equivalent to -NH group.

Scheme 2. Synthesis of compounds 11, 13, 15a,b, 16 and 17.

Next, we made additional reactions using compound 13. Thus, compound 13 reacted with diazonium salt 18 in ethanol/NaOAc at (0-5 °C) to give the 3,4,5,6,7,9-hexahydro-1H-1,4-methanoxanthene-8(2H)-one derivative 19. Compound 19 reacted with phenylisothiocyanate (10) to produce the 3,4,5,6,7,9,10,11-octahydro-8,11-methanoxantheno[2,1-c][1,3,4]oxadiazine-2(12H)-thion derivative 20. Also, compound 13 reacted with phenylhydrazine 21a or hydroxylamine hydrochloride 21b to obtain xanthene derivatives 22a,b. In addition, compound 22a or 22b reacted with ethyl cyanoacetate (14a) in ethanol/Et$_3$N to produce pyrazole derivative (23) and isoxazol derivative (24) (Scheme 3). Structures of produced compounds have been proven by ($^1$H, IR, MS, $^{13}$C-NMR) spectrums. Thus, $^1$H NMR of compound 23 displayed a three singlet at 2.30-2.38 confirming for existence of three methyl, a triplet at 3.29 equivalent to camphor-CH, a multiplet at 7.18-7.30 equivalent to two C$_6$H$_5$, a singlet at 4.57 equivalent to amino group.

Moreover, compound 13 reacted with benzaldehyde (2) and ethyl cyanoacetate (14a) or malononitrile (14b) in ethanol/Et$_3$N produced 8,11-methanopyran[2,3-\alpha]xanthene derivatives 25a,b. Compound 13 reacted with triethyl orthoformate (26) and ethyl cyanoacetate (14a) or malononitrile (14b) to afford ethyl 2-amino-4-ethoxy-8,13,13-trimethyl-12-phenyl-4,5,6,8,9,10,11,12-octahydro-8,11-methanopyran[2,3-\alpha]xanthene-3-carboxylate (27a) and 2-amino-4-ethoxy-8,13,13-trimethyl-12-phenyl-4,5,6,8,9,10,11,12-octahydro-8,11-methanopyran...
[2,3-α]xanthene-3-carbonitrile (27b). Finally, compound 13 reacted with phenylisothiocyanate (10) and sulfur in ethanol/Et3N afforded 7,12,12-trimethyl-1,1-diphenyl-4,5,7,8,9,10-hexahydro-1H-7,10-methanoxantheno[1,2-d]thiazole-2(11H)-thione (28) (Scheme 4). Structures of produced compounds have been proven by (1H, IR, MS, 13C-NMR) spectrums. Thus, 1H NMR of compound 27b displayed a three singlet at 2.38-2.49 confirming the existence of three methyl groups, a multiplet at 1.11-1.38 ppm equivalent to four methylene groups, a singlet at 4.45 ppm equivalent to amino group and a multiplet at δ 7.25-7.55 for phenyl group.

![Scheme 3. Synthesis of compounds 19, 20, 22a,b, 23 and 24.](image)

The suggested mechanism to form compound 13 occurred by a Knoevenagel condensation between camphor (1) and benzaldehyde (2), which was followed by Michael adduct with cyclohexan-1,3-dione (12). The nucleophilic attack with the carbonyl of camphor and cyclization was shown in Scheme 5.
Synthesis of xanthene, chromene, thiazole, thiophene, pyrazole, and isoxazole derivatives


Scheme 4. Synthesis of compounds 25a,b, 27a,b and 28.

Scheme 5. Suggested mechanism for the synthesis of xanthene derivative 13.

Cell proliferation assay

The novel compounds have been investigated toward A549, MKN-45, HT-29, U87MG, H460 and SMMC-772 cancer cell lines using foretinib as positive control [40]. The in vitro assay was carried out using standard MTT procedure. IC_{50}'s (inhibitory concentrations 50%) were measured for each compound and determined as the result of the average of three determinations Table 1. The anti-proliferative activity of these products is attributed to various substituent's on heterocyclic and aryl rings.

Table 1. In vitro IC$_{50}$ ± SEM (µM of the produced compounds).

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC$_{50}$ ± SEM (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A549</td>
</tr>
<tr>
<td>3</td>
<td>2.22 ± 1.75</td>
</tr>
<tr>
<td>5</td>
<td>2.26 ± 0.16</td>
</tr>
<tr>
<td>7</td>
<td>8.28 ± 2.26</td>
</tr>
<tr>
<td>9</td>
<td>3.65 ± 1.72</td>
</tr>
<tr>
<td>11</td>
<td>0.38 ± 0.20</td>
</tr>
<tr>
<td>13</td>
<td>2.63 ± 1.11</td>
</tr>
<tr>
<td>15a</td>
<td>2.41 ± 0.90</td>
</tr>
<tr>
<td>15b</td>
<td>0.28 ± 0.12</td>
</tr>
<tr>
<td>16</td>
<td>0.32 ± 0.22</td>
</tr>
<tr>
<td>17</td>
<td>4.94 ± 1.35</td>
</tr>
<tr>
<td>19</td>
<td>6.38 ± 2.43</td>
</tr>
<tr>
<td>20</td>
<td>6.83 ± 2.18</td>
</tr>
<tr>
<td>22a</td>
<td>1.53 ± 0.83</td>
</tr>
<tr>
<td>22b</td>
<td>1.89 ± 0.33</td>
</tr>
<tr>
<td>23</td>
<td>4.25 ± 1.82</td>
</tr>
<tr>
<td>24</td>
<td>5.80 ± 2.31</td>
</tr>
<tr>
<td>25a</td>
<td>6.25 ± 5.52</td>
</tr>
<tr>
<td>25b</td>
<td>5.51 ± 0.14</td>
</tr>
<tr>
<td>27a</td>
<td>2.40 ± 1.36</td>
</tr>
<tr>
<td>27b</td>
<td>0.26 ± 0.08</td>
</tr>
<tr>
<td>28</td>
<td>1.65 ± 1.05</td>
</tr>
<tr>
<td>Foretinib</td>
<td>0.08 ± 0.01</td>
</tr>
</tbody>
</table>

Structure activity relationship

In Table 1 we note that products 5, 11, 15b, 16, 25b and 27b showed the highest inhibitions products against mentioned cancer lines. In addition, compounds 3, 13, 15a, 22a, 27a and 28 were moderate inhibitory effect against cancer lines. The 1,4,5,8-dimethanoxanthene derivative 3 displayed low inhibitory effect against H460, SMMC-7721 and HT29 cancer lines while it exhibited moderate inhibitions toward A549, MKN-45 and U87MG cell lines. Additionally, 1,4-methanoxanthene derivative 5 exhibited high inhibitions against mentioned cancer lines which was referred to existence of chromene moiety with structure of this molecule. Compound 7 showed low inhibitions toward mentioned cancer lines which might be referred to existence of cyclopentene moiety. Considering ethyl methanochromene-3-carboxylate derivative 9 where it displayed low to moderate inhibitions against the mentioned cancer lines. Interestingly, 4,7-methanobenzof[2,3-d]thiazole-2(3H)-thione derivative 11 exhibited high inhibitions toward cancer lines and this was referred to existence of thiazole moiety within the structure of this compound. Considering the methanoxantheno-pyrimidine 13 where it showed the highest inhibitory effect toward HT29, SMMC-7721, MKN-45 and U87MG cell lines with IC$_{50}$ 0.82, 0.62, 0.59 and 0.93 µM, while it expressed moderate inhibitory effect against H460 and A549 cell lines. For the thiophene derivatives 15a,b where compound 15a (R = COOEt) displayed moderate inhibitory effect and compound 15b (R = CN) displayed high inhibitory effect against the mentioned cancer line. The dihydrothieno[2,3-d]pyrimidine derivative 16 expressed high inhibition inhibitions while the dihydrothieno[2,3-d]pyrimidine 17 showed weak inhibitions. The high inhibitions of compound 16 referred to existence of CO group. Both of compounds 19 and 20 showed low inhibitory effect against all cancer lines mentioned above, while compounds 22a and 22b exhibited moderate inhibitions. In addition, products 23 and 24 displayed low inhibitory effect against mentioned cancer lines. Interestingly, the tetrahydropyran[2,3-f]chromens 25a,b where...
compound 25a (R = COOEt) showed low inhibitory effect while compound 25b (R = CN) exhibited high inhibitions against cancer lines. Furthermore, for compounds 27a,b where compound 27a (R = COOEt) expressed moderate inhibitions and compound 27b (R = CN) with high inhibitions. Surprisingly, the 7,10-methanoxanthene[1,2-d]thiazole-2(1H)-thione derivative 28 exhibited moderate inhibitions toward H460 and A549 cell lines with IC₅₀'s 1.35 and 1.65 μM, while it showed low inhibitions against U87MG, SMMC-7721 and MKN-45.

**EXPERIMENTAL**

**Chemistry**

Melting points of produced compounds have been measured and that were uncorrected. Pye Unicam SP-1000 or FTIR plus 460 spectrophotometer was used to measure IR spectra (KBr discs). Jeol AS 500 MHz and Varian Gemini-300 (300 MHz) instruments were used to measure ¹H NMR or (75 MHz) for ¹³C NMR using TMS as internal standard and DMSO-d₆ as solvent, and the δ expressed as ppm. GCMS-QP 1000 Ex Shimadzu and Hewlett Packard 5988 A GC/MS system instruments were used to measure MS (EI) spectra. Vario EL III Elemental analyzer was used to obtain the microanalytical data at Cairo University. Testing of produced compounds against the cancer lines mentioned above was carried.

4,5,11,12,16-hexamethyl-9-phenyl-2,3,4,5,6,7,8,9-octahydro-IH-1,4:5,8-dimethanoxanthene (3). Camphor 1 (3.04 g, 0.02 mol) has been added to benzaldehyde (1.06 g, 0.01 mol) in ethanol/piperidine. The combination has been refluxed for 4 h, and it has been poured over small pieces of ice, then the product has been filtrated. White powder from alcohol, yield (2.70 g, 72%), mp 86-87 °C. IR νmax cm⁻¹: 3050 (aromatic CH), 1640 (C=C), 2890, 2766 (CH₂, CH₃). ¹H NMR: δ 2.22-7.31 (m, 5H, C₈H₈), 2.39-2.46 (3s, 18H, 6CH₃), 1.73-1.87 (2m, 8H, camphor 4CH₂), 6.10 (s, 1H, H-4 pyran), 3.38 (t, 2H, 2camphor CH). ¹³C NMR: 22.5, 22.6 (4CH₃), 23.3 (2CH₃), 27.7, 28.2 (camphor 4CH₃), 39.6, 39.5, 40.3 (camphor CH, camphor 2C), 40.6 (pyran C-4), 125.1, 126.2, 127.3, 128.6 (CH₃), 135.3, 135.8, 136.2, 136.4 (pyran 2C=). Anal. calcd. for C₂₈H₄₅O: C, 86.58; H, 9.15%. Found: C, 86.20; H, 8.92 %. MS: m/z 374.

4,11,11-Trimethyl-9-phenyl-2,3,4,5,6,7,8,9-octahydro-IH-1,4-methanoxanthene (5). Each of cyclohexanone (0.98 g, 0.01 mol) and benzaldehyde (1.06 g, 0.01 mol) have been added to camphor 1 (1.5 g, 0.01 mol) in ethanol/piperidine. The combination has been refluxed for 4 h, and it has been poured over small pieces of ice, then the product has been filtrated. Yellow powder from alcohol, yield (2.90 g, 91%), mp 102-104 °C. IR νmax cm⁻¹: 3054 (aromatic CH), 1643 (C=C), 2890, 2768 (CH₃, CH₂). ¹H NMR: δ 2.39-2.40 (3s, 9H, 3CH₃), 1.63-1.67 (2m, 4H, camphor 2CH₂), 2.41-2.44 (2m, 8H, cyclohexane 4CH₂), 3.38 (t, 1H, camphor CH), 7.33-7.64 (m, 5H, C₈H₈), 6.90 (s, 1H, H-4 pyran). ¹³C NMR: δ 22.5, 22.6 (2CH₂), 23.3 (2CH₃), 27.9, 28.5 (camphor 2CH₂), 38.9, 39.3 (cyclohexane 2CH₂), 39.5, 39.8, 40.1 (camphor CH, camphor 2C), 40.4 (pyran C-4), 128.4, 128.5, 128.6, 128.8 (CH₃), 135.3, 135.8, 136.2, 136.4 (pyran 2C=). Anal. calcd. for C₃₅H₃₇O: C, 86.20; H, 8.81%. Found: C, 85.82; H, 8.43%. MS: m/z 320.

5,10,10-Trimethyl-9-phenyl-1,2,3,5,6,7,8,9-octahydro-5,8-methanocyclopenta-f[b]chromene (7). Each of cyclopentanone (0.84 g, 0.01 mol) and benzaldehyde (1.06 g, 0.01 mol) have been added to camphor 1 (1.52 g, 0.01 mol) in ethanol/piperidine. The combination has been refluxed for 4 h, and it has been poured over small pieces of ice, then the product has been filtrated. Yellowish green powder from alcohol, yield (2.50 g, 82%), mp 102-104 °C. IR νmax cm⁻¹: 3056 (aromatic CH), 1642 (C=C), 2893, 2769 (CH₃, CH₂). ¹H NMR: δ 2.40-2.43 (3s, 9H, 3CH₃), 1.65-1.69 (2m, 4H, camphor 2CH₂), 2.44-2.46 (2m, 6H, cyclopentane 3CH₂), 3.33 (t, 1H, camphor CH), 7.45-

Ethyl 8,9,9-Trimethyl-2,4-diphenyl-5,6,7,8-tetrahydro-4H-5,8-methanochromene-3-carboxylate (9). Each of ethyl benzoylecetate (1.92 g, 0.01 mol) and benzaldehyde (1.06 g, 0.01 mol) have been added to camphor (1.52 g, 0.01 mol) in ethanol/piperidine. The combination has been refluxed for 4 h, and it has been poured over small pieces of ice, then the product has been filtrated. Brown powder from alcohol, yellow (3.80 g, 92%), mp 103-104 °C. IR νmax cm⁻¹: 3053 (aromatic CH), 1688 (CO), 1640 (C=C), 2893, 2772 (CH₃, CH₂). ¹H NMR: δ 2.36-2.41 (3s, 9H, 3CH₃), 1.13-1.46 (2m, 4H, 2CH₂), 3.35 (t, 1H, camphor CH), 1.07 (t, 3H, CH₃), 4.19 (q, 2H, CH₂), 7.32-7.95 (m, 10H, 2CH₃), 7.22 (s, 1H, H-4 pyran). ¹³C NMR: δ 16.3 (OCH₂CH₃), 22.2, 22.5 (3CH₃), 27.9, 28.6 (camphor 2CH₂), 50.3 (OCH₂CH₃), 39.0, 39.6, 40.8 (pyran CH), 27.9, 40.8 (pyran 2CH₂), 125.0, 125.1, 125.0 (2CH₃), 133.3, 134.8, 136.0, 137.2 (pyran 2CH=CH), 166.3 (CO). Anal. calcd. for C₉₃H₈₉O₇N: C, 81.13; H, 7.29%. Found: C, 80.89; H, 6.94%. MS: m/z 414.

4,8,8-Trimethyl-3-phenyl-4,5,6,7-tetrahydro-4,7-methanobenzof[a]thiazole-2(3H)-thione (11). Each of phenylisothiocyanate (1.35 g, 0.01 mol) and sulfur (0.32 g, 0.01 mol) have been added to camphor (1.52 g, 0.01 mol) in ethanol/Et₃N. The combination has been refluxed for 4 h, and it has been poured over ice/water, then the formed product has been filtrated. Yellow powder from alcohol, yellow (2.90 g, 96%), mp 103-104 °C. IR νmax cm⁻¹: 3056 (aromatic CH), 1210 (C=S), 1642 (C=C), 2893, 2772 (CH₃, CH₂). ¹H NMR: δ 2.44-2.46 (3s, 9H, 3CH₃), 1.06-1.36 (2m, 4H, 2CH₂), 3.30 (t, 1H, camphor CH), 7.30-7.51 (m, 5H, CH₃). ¹³C NMR: δ 18.2, 18.8 (3CH₃), 26.8, 27.2 (camphor 2CH₂), 56.1, 65.3, 66.9 (camphor CH, camphor 2C), 121.6, 123.0, 124.9, 125.9 (C₆H₅), 137.4, 138.2 (thiazole C=C), 179.6 (C=S). Anal. calcd. for C₁₇H₁₃N₅S₂: C, 67.73; H, 6.35; N, 4.65; S, 21.27%. Found: C, 67.45; H, 5.95; N, 4.34; S, 20.88%. MS: m/z 301.

4,11,11-Trimethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1H-1,4-methanoxanthen-8(2H)-one (13). Cyclohexan-1,3-dione (1.12 g, 0.01 mol) and benzaldehyde (1.06 g, 0.01 mol) have been added to camphor (1.52 g, 0.01 mol) in ethanol/piperidine. The combination has been refluxed for 4 h, and it has been poured over ice/water, then the product has been filtrated. Beige powder from alcohol, yellow (2.90 g, 87%), mp 181-182 °C. IR νmax cm⁻¹: 3053 (aromatic CH), 1640 (C=C), 1689 (CO), 2893, 2772 (CH₃, CH₂). ¹H NMR: δ 2.41-2.47 (3s, 9H, 3CH₃), 1.68-1.71 (2m, 4H, camphor 2CH₂), 2.44-2.47 (2m, 6H, cyclohexane 3CH₂), 3.40 (t, 1H, camphor CH), 7.35-7.73 (m, 5H, CH₃), 7.10 (s, 1H, H-4 pyran). ¹³C NMR: 18.0, 18.7 (3CH₃), 26.4, 26.8, 28.2, 28.4, 28.6 (5CH₃), 50.9 (pyran C-4), 56.2, 65.6, 66.9 (camphor CH, camphor 2C), 121.8, 122.6, 124.5, 125.3 (C₆H₅), 166.3 (CO), 134.2, 134.4, 135.4, 135.6 (pyran 2CH=CH). Anal. calcd. for C₁₇H₁₃N₅S₂: C, 82.60; H, 7.84%. Found: C, 82.43; H, 7.44%. MS: m/z 334.

Synthesis of methanothieno[3,2-a]xanthe derivatives 15a,b. Ethyl cyanoacetate (1.13 g, 0.01 mol) or malononitrile (0.66 g, 0.01 mol) and sulfur (0.32 g, 0.01 mol) have been added to compound 13 (3.34 g, 0.01 mol) in ethanol/ Et₃N. The combination has been refluxed for 4 h, and it has been poured over small pieces of ice, then the product has been filtrated.

Ethyl 2-amino-7,12,12-trimethyl-11-phenyl-5,7,8,9,10,11-hexahydro-4H-7,10 methanothieno-[3,2-a]xanthe-1-carboxylate (15a). Yellowish white powder from alcohol, yellow (4.00 g, 87%), mp 160-162 °C. IR νmax cm⁻¹: 3055 (aromatic CH), 1643 (C=C), 1698 (CO), 3338 (NH₂), 2890, 2776 (CH₃, CH₂). ¹H NMR: δ 2.29-2.43 (3s, 9H, 3CH₃), 1.37-2.44 (2m, 8H, 4CH₂), 3.25 (t, 1H, camphor CH), 1.10 (t, 3H, CH₃), 4.30 (q, 2H, CH₂), 4.57 (s, 2H, NH₂), 7.12 (s, 1H, H-4 pyran),
Synthesis of xanthene, chromene, thiazole, thiophene, pyrazole, and isoxazole derivatives

7.35-7.50 (m, 5H, 2CH), 1.35 NMR: 16.6 (OCH<sub>2</sub>CH<sub>3</sub>), 18.0, 18.9 (3CH), 50.3 (OCH<sub>2</sub>CH<sub>3</sub>), 51.2 (pyran C-4), 26.6, 26.8, 27.8, 28.0 (4CH), 56.0, 65.6, 66.9 (camphor CH, camphor 2C), 121.3, 122.6, 124.5, 125.6 (C(S)), 132.8, 133.2, 133.4, 134.2, 136.2, 137.5, 138.6, 140.6 (thiophene C, pyran 2C=C), 166.4 (CO). Anal. calcd. for C<sub>25</sub>H<sub>34</sub>NOS: C, 72.85%; H, 6.77%; N, 3.03%; S, 6.95%. Found: C, 72.46; H, 6.53; N, 2.97; S, 6.65%. MS: m/z 461.

2-Amino-7,12,12-trimethyl-11-phenyl-5,7,8,9,10,11-hexahydro-4H-7,10-methanothieno[3,2-a]-xanthene-1-carbonitrile (15b). Yellow powder from alcohol, yield (3.90 g, 94%), mp 218-220 °C. IR ν<sub>max</sub> cm<sup>-1</sup>: 3054 (aromatic CH), 1642 (C=C), 2224 (CN), 2893, 2772 (CH<sub>3</sub>, CH<sub>2</sub>), 3345 (NH). 1H-NMR: δ 2.30-2.44 (3s, 9H, 3CH), 1.39-2.47 (2m, 8H, 4CH), 3.22 (t, 1H, camphor CH), 4.53 (s, 2H, NH<sub>2</sub>), 7.10 (s, 1H, H-4 pyran), 7.35-7.50 (m, 5H, 2C<sub>6</sub>H<sub>5</sub>). 13C NMR: 18.0, 18.9 (3CH<sub>3</sub>), 26.6, 26.8, 28.2, 28.6 (4CH), 56.0, 65.6, 66.9 (camphor CH, camphor 2C), 50.9 (pyran C-4), 121.3, 122.6, 124.5, 125.6 (C<sub>6</sub>H<sub>5</sub>), 133.2, 134.0, 135.4, 135.8, 136.1, 136.4, 138.4, 140.6 (thiophene C, pyran 2C=C), 116.4 (CN). Anal. calcd. for C<sub>25</sub>H<sub>32</sub>NOS: C, 75.33; H, 6.32; N, 6.76; S, 7.73 %. Found: C, 74.93; H, 5.96; N, 6.46; S, 7.47 %. MS: m/z 441.

The combination has been refluxed for 4 h, and it has been poured over small pieces of ice, then the product has been filtered.

Synthesis of methanoxantheno[1',2':4,5]thieno[2,3-d]pyrimidine derivatives 16 and 17. Phenylisothiocyanate (1.35 g, 0.01 mol) or 15 (4.61 g, 0.01 mol) in ethanol/Et<sub>3</sub>N. The combination has been refluxed for 4 h, and it has been poured over small pieces of ice, then the product has been filtered.
The product has been added to compound 3.96 1.68 (2m, 4H, camphor 2CH(N, 6.60%. Found: C, 81.96; H, 7.44; N, 6.37%. MS: m/z 424.

13,13-Trimethyl-3,12-diphenyl-4-(phenylamino)-3,4,5,6,8,9,10,11-octahydro-8,11-methanoxanthene derivative1(21-c)].1,4-oxadiazine-2(12H)-thione (20). Phenylisothiocyanate (1.35 g, 0.01 mol) has been added to compound 19 (4.38 g, 0.01 mol) in ethanol/ Et3N. The combination has been refluxed for 4 h, and it has been poured over small pieces of ice, then the product has been filtered. Beige powder from alcohol, yield (5.15 g, 90%), mp 65-66 °C. IR v max cm\(^{-1}\): 3335 (NH), 3053 (aromatic CH), 1215 (C=S), 1657 (C=C), 2784, 2899 (CH\(_2\), CH\(_3\)). \(^1\)H NMR: \(\delta\) 2.46-2.48 (3s, 9H, 3CH\(_3\)), 1.06-1.36 (2m, 8H, 4CH\(_2\)), 3.39 (t, 1H, camphor CH), 7.12 (s, 1H, H-4 pyran), 7.18-7.42 (m, 15H, 3CH\(_3\)), 11.02 (s, 1H, NH). \(^13\)C NMR: \(\delta\) 18.52, 19.8 (3CH\(_3\)), 26.4, 26.8, 30.8, 36.3 (4CH\(_3\)), 56.0, 65.2, 67.1 (camphor CH, camphor 2C), 50.1 (pyran C-4), 115.5, 121.6, 122.9, 123.5, 124.6, 125.8, 127.9, 128.6, 129.8, 130.0, 130.2, 130.4 (3CH\(_3\)), 134.3, 135.7, 136.5, 140.2 (pyran 2C=C), 140.4, 140.6 (oxadiazine C=C) 187.2 (C=S). Anal. calcd. for C\(_{36}\)H\(_{28}\)N\(_2\)O\(_2\): C, 75.36; H, 6.15; N, 7.32; S, 5.59%. Found: C, 74.96; H, 5.77; N, 6.92; S, 5.21%. MS: m/z 573.

Synthesis of the 1,4-methanoxanthene derivatives 22a,b. Phenylhydrazine (0.93 g, 0.01 mol) or hydroxylamine hydrochloride (0.69 g, 0.01 mol) has been added to compound 13 (3.34 g, 0.01 mol) for 22a the combination added in ethanol/Et3N, but for 22b added in ethanol/sodium acetate (1.00 g). The mixture has been refluxed for 4 h, and it has been poured over small pieces of ice, then the product has been filtered.

1-Phenyl-4,11,11-trimethyl-9-phenyl-3,4,6,7-tetrahydro-1H-1,4-methanoxanth-8(2H,5H,9H)-ylidene hydrzone (22a). Orange powder from alcohol, yield (4.00 g, 94%), mp 70-71 °C. IR v max cm\(^{-1}\): 3327 (NH), 3056 (aromatic CH), 2785, 2920 (CH\(_2\), CH\(_3\)). \(^1\)H NMR: \(\delta\) 2.36-2.41 (3s, 9H, 3CH\(_3\)), 1.59-1.63 (2m, 4H, camphor 2CH\(_2\)), 2.38-2.40 (2m, 6H, cyclohexane 3CH\(_2\)), 3.28 (t, 1H, camphor CH), 9.80 (s, 1H, NH), 6.80 (s, 1H, H-4 pyran), 7.12-7.93 (m, 10H, 2CH\(_3\)). \(^13\)C NMR: \(\delta\) 18.54, 20.2 (3CH\(_3\)), 28.4, 28.8, 32.8, 37.3, 39.5 (5CH\(_3\)), 56.2, 65.4, 67.3 (camphor CH, camphor 2C), 50.3 (pyran C-4), 115.5, 121.6, 122.9, 123.5, 124.6, 125.8, 127.9, 128.6, 130.0, 130.2, 130.4 (3CH\(_3\)), 134.1, 135.3, 136.5, 140.5 (pyran 2C=C), 163.2 (C=N). Anal. calcd. for C\(_{36}\)H\(_{28}\)N\(_2\): C, 81.96; H, 7.44; N, 6.60%. Found: C, 81.96; H, 7.44; N, 6.67%. MS: m/z 424.

4,11,11-Trimethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1H-1,4-methanoxanth-8(2H)-one oxime (22b). Yellow powder from alcohol, yield (3.10 g, 89%), mp 166-168 °C. IR v max cm\(^{-1}\): 3537 (OH), 3057 (aromatic CH), 2787, 2923 (CH\(_2\), CH\(_3\)). \(^1\)H NMR: \(\delta\) 2.33-2.35 (3s, 9H, 3CH\(_3\)), 1.66-1.68 (2m, 4H, camphor 2CH\(_2\)), 2.45-2.48 (2m, 6H, cyclohexane 3CH\(_2\)), 3.35 (t, 1H, camphor CH), 10.80 (s, 1H, OH), 7.07 (s, 1H, H-4 pyran), 7.10-7.23 (m, 5H, C\(_6\)H\(_5\)). \(^13\)C NMR: \(\delta\) 18.54, 20.2 (3CH\(_3\)), 28.4, 28.8, 32.8, 37.3, 39.5 (5CH\(_3\)), 56.2, 65.4, 67.3 (camphor CH, camphor 2C), 50.3 (pyran C-4), 122.8, 123.5, 124.3, 125.7 (C\(_6\)H\(_5\)), 134.5, 135.3, 136.5, 140.9 (pyran 2C=C), 163.2 (C=N). Anal. calcd. for C\(_{36}\)H\(_{26}\)NO\(_2\): C, 79.05; H, 7.79; N, 4.01%. Found: C, 78.87; H, 7.42; N, 3.96%. MS: m/z 349.

Synthesis of pyrazole and isoxazole derivatives 23 and 24. Ethyl cyanoacetate (1.13, 0.01 mol) has been added to compound 22a (4.24 g, 0.01 mol) or 22b (3.49 g, 0.01 mol) in ethanol/Et3N. The combination has been refluxed for 4 h, and it has been poured over small pieces of ice, then the product has been filtered.

5-Amino-2-phenyl-4,11,11-trimethyl-9-phenyl-2,3,4,5,6,9-hexahydro-1H-1,4-methanoxanthene-8-yl)-1H-pyrazol-3(2H)-one (23). Reddish brown powder from alcohol, yield (4.30 g, 88.0%), mp

Synthesis of xanthene, chromene, thiazole, thiphen, pyrazole, and isoxazole derivatives

79–80 °C. IR νmax cm⁻¹: 3339 (NH₂), 3053 (aromatic CH), 2787, 2890 (CH₃, CH₂), 1648 (C=C), 1765 (C=O). ¹H NMR: δ 2.30–2.38 (3s, 9H, 3CH₃), 1.17–1.49 (2m, 8H, 4CH₂), 3.29 (t, 1H, camphor CH), 4.57 (s, 2H, NH₂), 7.10 (s, 1H, H-4 pyran), 4.55, 5.22 (2t, 2H, 2CH=C), 7.18–7.30 (m, 10H, 2CH₃). Anal. calcd. for C₃₂H₃₅N₂O₇: C, 78.18; H, 6.77; N, 8.55%. Found: 77.98; H, 6.59; N, 8.36%. MS: m/z 491.

3-Amino-4,11,11-trimethyl-9-phenyl-2,3,4,5,6,9-hexahydro-1H-1,4-methanoxanthene-8-yliisoxazo-[5(2H)-one (24). Yellow crystals from alcohol, yield (3.80 g, 91%), mp 104–106 °C. IR νmax cm⁻¹: 3340 (NH₂), 3053 (aromatic CH), 2789, 2891 (CH₃, CH₂), 1658 (C=C), 1766 (C=O). ¹H NMR: δ 2.29–2.33 (3s, 9H, 3CH₃), 1.11–1.45 (2m, 8H, 4CH₂), 3.28 (t, 1H, camphor CH), 4.58 (s, 2H, NH₂), 7.09 (s, 1H, H-4 pyran), 4.00, 5.27 (2t, 2H, 2CH=C), 7.12–7.23 (m, 5H, CH₃). Anal. calcd. for C₃₂H₃₅N₂O₇: C, 74.97; H, 6.78; N, 6.73%. Found: C, 74.76; H, 6.39; N, 6.33%. MS: m/z 416.

Synthesis of methanopyrano[2,3-a]xanthene derivatives 25a,b. Benzaldehyde (1.06 g, 0.01 mol) and ethyl cyanoacetate (1.13 g, 0.01 mol) or malononitrile (0.66 g, 0.01 mol) have been added to compound 13 (3.34 g, 0.01 mol) in ethanol/Et₃N. The combination has been refluxed for 4 h, and it has been poured over small pieces of ice, then the product has been filtrated.

Ethyl 2-amino-8,13,13-trimethyl-4,12-diphenyl-4,5,6,8,9,10,11,12-octahydro-8,11-methano-pyrano[2,3-a]xanthene-3-carboxylate (25a). White powder from alcohol, yield (5.10 g, 95%), mp 156–158 °C. IR νmax cm⁻¹: 3349 (NH₂), 3055 (CH aromatic), 2791, 2893 (CH₃, CH₂), 1657 (C=C), 1690 (CO). ¹H NMR: δ 2.40–2.48 (3s, 9H, 3CH₃), 1.06–1.36 (2m, 8H, 4CH₂), 3.39 (t, 1H, camphor CH), 1.05 (t, 3H, CH₃), 3.93 (q, 2H, CH₂), 4.55 (s, 2H, NH₂), 7.04, 7.10 (2s, 2H, 2pyran H-4), 7.18–7.51 (m, 10H, 2CH₃). ¹³C NMR: δ 14.2, 19.8, 26.3 (3CH₃), 14.8 (ester CH), 33.1, 36.1, 36.3, 38.6 (4CH₂), 38.2 (ester CH₂), 39.7, 40.0, 40.3 (camphor CH, camphor 2C), 125.9, 127.6, 127.9, 128.1, 129.3, 124.2, 124.3, 124.9 (2CH₃), 128.3, 130.6, 131.8, 132.2, 134.5, 135.6, 137.3, 145.8 (2pyran 4C-C), 58.7, 77.8 (2pyran C-4), 196.1 (C=O). Anal. calcd. for C₃₁H₃₃N₂O₂: C, 78.48; H, 6.96; N, 2.61%. Found: C, 78.22; H, 6.63; N, 2.29%. MS: m/z 535.

2-Amino-8,13,13-trimethyl-4,12-diphenyl-4,5,6,8,9,10,11,12-octahydro-8,11-methanopyrano-[2,3-a]xanthene-3-carboxonitrile (25b). Yellow powder from alcohol, yield (4.50 g, 92%), mp 222–224 °C. IR νmax cm⁻¹: 3348 (NH₂), 3055 (aromatic CH), 2790, 2892 (CH₃, CH₂), 1654 (C=C), 2220 (CN). ¹H NMR: δ 2.38–2.40 (3S, 9H, 3CH₃), 1.07–1.35 (2m, 8H, 4CH₂), 3.33 (t, 1H, camphor CH), 4.19 (s, 2H, NH₂), 7.04, 6.95 (2s, 2H, 2pyran), 7.14–7.30 (m, 10H, 2CH₃). ¹³C NMR: δ 14.4, 19.6, 26.7 (3CH₃), 34.3, 36.4, 36.6, 38.8 (4CH₂), 38.9, 40.2, 40.4 (camphor CH, camphor 2C), 124.8, 126.5, 127.8, 128.3, 128.8, 128.6, 129.3, 129.9 (2CH₂), 128.3, 130.6, 131.8, 132.4, 134.2, 135.3, 137.0, 145.8 (2pyran 4 C=C), 57.7, 76.8 (two pyran C-4), 115.8 (CN). Anal. calcd. for C₃₁H₃₃N₂O₂: C, 81.12; H, 6.60; N, 5.73%. Found: C, 80.98; H, 6.33; N, 5.45%. MS: m/z 488.

Synthesis of methanopyrano[2,3-a]xanthene derivatives 27a,b. Triethyl orthoformate (1.48 g, 0.01 mol) and ethyl cyanoacetate (1.13 g, 0.01 mol) or malononitrile (0.66 g, 0.01 mol) have been added to compound 13 (3.34 g, 0.01 mol) in ethanol/Et₃N. The combination has been refluxed for 4 h, and it has been poured over small pieces of ice, then the product has been filtrated.

Ethyl 2-amino-4-ethoxy-8,13,13-trimethyl-12-phenyl-4,5,6,8,9,10,11,12-octahydro-8,11-methanopyrano[2,3-a]xanthene-3-carboxylate (27a). Light brown powder from alcohol, yield (3.10 g, 62%), mp 166–167 °C. IR νmax cm⁻¹: 3352 (NH₂), 3056 (aromatic CH), 2793, 2895 (CH₃, CH₂), 1658 (C=C), 1692 (CO). ¹H NMR: δ 2.38–2.49 (3S, 9H, 3CH₃), 1.11–1.38 (2m, 8H, 4CH₂), 3.40 (t, 1H, camphor CH), 1.20–1.28 (2t, 6H, 2CH₃), 4.15–4.30 (2q, 4H, 2CH₂), 4.47 (s, 2H, NH₂).
3. 2.52; Anal. (2C CH, camphor 2C), 56.0 (pyran 2C), 2897, 2775 (CH CH), 2223 (CN). 1H NMR: δ 2.38-2.49 (3s, 9H, 3CH3), 1.11-1.38 (2m, 8H, 4CH2), 3.40 (t, 1H, camphor CH), 1.15 (t, 3H, CH3), 4.13 (q, 2H, CH2), 4.45 (s, 2H, NH3), 7.14, 7.13 (2s, 2H, 2pyran H-4), 7.25-7.55 (m, 5H, C6H5). Anal. calcd. for C29H35N3O6: C, 76.29; H, 7.06; N, 6.14%. Found: C, 75.89; H, 6.86; N, 5.94%. MS: m/z 456.

Xanthene, chromene, thiazole, thiophene, pyrazole, and isoxazole derivatives have been synthesized from camphor-D monoterpane. The synthesized compounds were formed according to various reactions such as a Knoevenagel condensation, Michael adduct, Gewald’s reaction, a nucleophilic attack, substitution, addition and elimination reactions followed by cyclization. Furthermore, the new compounds have been investigated against the mentioned cancer cell lines. Compounds 5, 11, 15b, 16, 25b and 27b exhibited the highest inhibitory effect against the six cancer cell lines. Furthermore, compounds 3, 13, 15a, 22a, 27a and 28 displayed moderate inhibitory effect toward all cancer cell lines.

REFERENCES


Synthesis of xanthene, chromene, thiazole, thiophene, pyrazole, and isoxazole derivatives


