Bull. Chem. Soc. Ethiop. **2023**, 37(6), 1539-1552.
DOI: https://dx.doi.org/10.4314/bcse.v37i6.18

ISSN 1011-3924
Printed in Ethiopia
Online ISSN 1726-801X

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

Ensaf Sultan Alwan[1*] and Rafat Milad Mohareb[2]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences & Pharmaceutical Industries, Future University in Egypt, Cairo, Egypt
[2]Department 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 SMMC-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

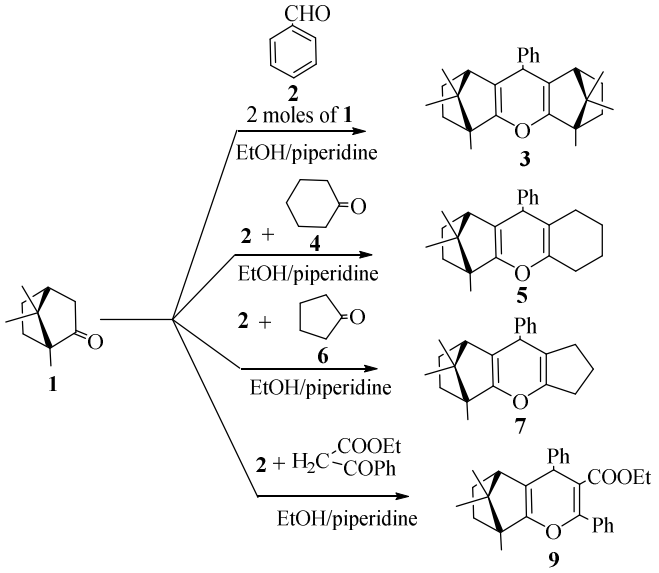
Xanthene derivatives are important class of compounds in organic synthesis and in medicinal chemistry. They diverse biological activities like anti-inflammatory [1], antibacterial [2, 3], antifungal [4], insecticidal [5], free radical scavenging activity [6], antiplasmodial [7-9], anticancer [10], antioxidant [11], antimalarial [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]. Xanthene derivatives have been synthesized in a variety of ways [22] in the presence of different catalysts such as, $Yb(OTf)_3$ [23], $InCl_3$ [24], $Al(HSO_4)_3$ [25], nano-$TIO_2$ [26], $NaHSO_4$ [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-$H_2SO_4$ [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**,

*Corresponding author. E-mail: ensaf.alwan74@yahoo.com

**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

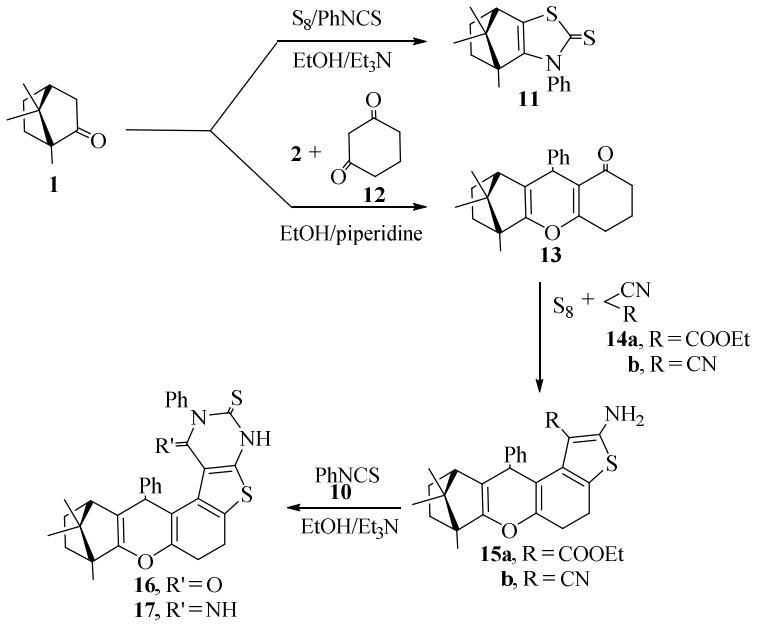
In this work, we demonstrated use of camphor to produce a bioactive xanthene, chromene, thiazole, thiophene, pyrazole and isoxazole derivatives. Thus, treatment of two-moles of camphor (**1**) with benzaldehyde (**2**) in ethanol/piperidine afforded dimethanoxanthene derivative **3**. Series of multi-component 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[*b*]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 ($^1$H, IR, MS, $^{13}$C-NMR) spectrums. Thus, $^1$H NMR of compound **5** displayed two multiplets at 1.63-1.67 ppm for two $CH_2$ of camphor, two multiplet at 2.41-2.44 equivalent to four $CH_2$ of cyclohexane, a singlet at δ 6.90 equivalent to H-4 pyran, and amultiplet at δ 7.33-7.64 for $C_6H_5$.




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/$Et_3N$ gave 4,7-methanobenzo[*d*]thiazole-2(3*H*)-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-1*H*-1,4-methanoxanthen-8(2*H*)-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(2*H*)-thione, pyrazole, isoxazole, 4,5,6,8,9,10,11,12-octahydro-8,11-methanopyrano[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/$Et_3N$ 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 $C_6H_5$ groups and a singlet at δ 10.88 equivalent to -NH group.

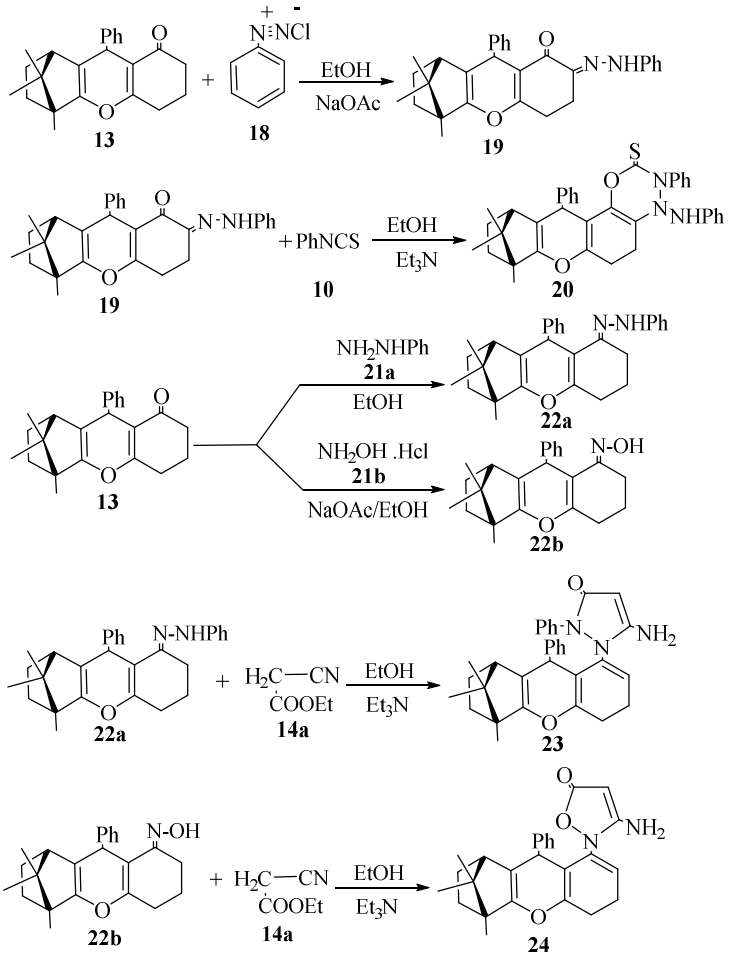



Scheme 2. Synthesis of compounds **11**, **13**, **15a,b**, **16** and **17**.

Next, we made additional reactions using compound **13**. Thus, compound **13** reacted with diazonium salt **18** in ethanol/NaOAc at (0-5 ºC) to give the 3,4,5,6,7,9-hexahydro-1*H*-1,4-methanoxanthen-8(2*H*)-one derivative **19**. Compound **19** reacted with phenylisothiocyanate (**10**) to produce the 3,4,5,6,8,9,10,11-octahydro-8,11-methanoxantheno[2,1-*e*][1,3,4]oxadiazine-2(12*H*)-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/$Et_3N$ 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 $C_6H_5$, a singlet at 4.57 equivalent to amino group.

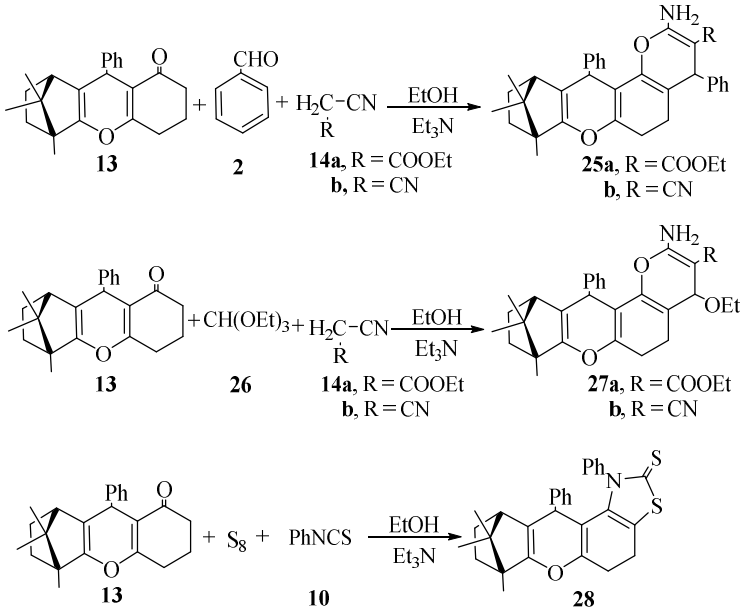
Moreover, compound **13** reacted with benzaldehyde (**2**) and ethyl cyanoacetate (**14a**) or malononitrile (**14b**) in ethanol/$Et_3N$ produced 8,11-methanopyrano[2,3-*a*]xanthene derivatives **25a,b**. Compound **13** reacted with triethyl orthoformate (**26**) and ethyl cyanoacetate (**14a**) or 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-methanopyrano[2,3-*a*]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-methanopyrano

[2,3-*a*]xanthene-3-carbonitrile (**27b**). Finally, compound **13** reacted with phenylisothiocyanate (**10**) and sulfur in ethanol/$Et_3N$ afforded 7,12,12-trimethyl-1,11-diphenyl-4,5,7,8,9,10-hexahydro-1*H*-7,10-methanoxantheno[1,2-*d*]thiazole-2(11*H*)-thione (**28**) (Scheme 4). Structures of produced compounds have been proven by ($^1$H, IR, MS, $^{13}$C-NMR) spectrums. Thus, $^1$H 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.

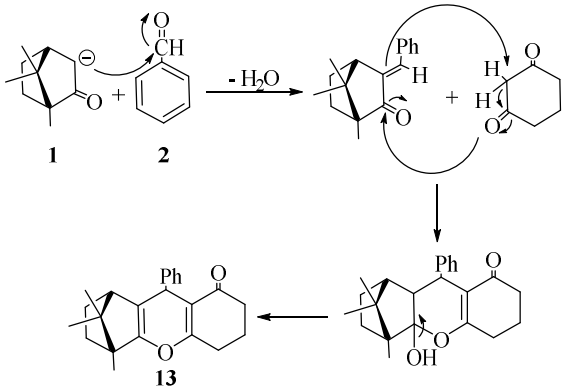



Scheme 3. Synthesis of compounds **19**, **20**, **22a,b**, **23** and **24**.

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.




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).

| Compound | $IC_{50}$ ± SEM (μM) | | | | | |
|---|---|---|---|---|---|---|
| | A549 | MKN-45 | HT29 | U87MG | H460 | SMMC-7721 |
| **3** | 2.22 ± 1.75 | 2.23 ±1.25 | 4.28 ± 1.12 | 2.38 ± 1.46 | 3.12 ± 1.48 | 3.74 ± 2.18 |
| **5** | 0.26± 0.16 | 0.50 ± 0.38 | 0.36 ± 0.26 | 0.21 ± 0.16 | 0.38 ±0.19 | 0.25 ± 0.12 |
| **7** | 8.28 ±2.26 | 6.24 ± 2.85 | 5.30 ± 1.18 | 7.38 ± 2.25 | 8.61 ±2.46 | 6.58 ±1.68 |
| **9** | 3.65±1.72 | 6.48 ±3.64 | 4.43±2.26 | 4.93 ±2.57 | 5.51±1.32 | 7.20±1.95 |
| **11** | 0.38 ± 0.20 | 0.48 ± 0.18 | 0.52 ± 0.23 | 0.58 ± 0.26 | 0.48 ± 0.17 | 0.33± 0.15 |
| **13** | 2.63± 1.11 | 0.59 ± 0.21 | 0.82 ± 0.37 | 0.93 ± 0.37 | 1.08± 0.69 | 0.62 ± 0.42 |
| **15a** | 2.41±0.96 | 3.18 ± 1.38 | 2.84 ± 1.72 | 4.24 ± 1.25 | 1.64 ± 1.88 | 4.45 ± 1.53 |
| **15b** | 0.28 ± 0.12 | 0.25 ± 0.16 | 0.44 ± 0.31 | 0.27 ±1.78 | 0.36 ±0.13 | 0.43 ± 0.26 |
| **16** | 0.32 ± 0.22 | 0.29 ± 0.09 | 0.31 ± 0.15 | 0.35 ± 0.18 | 0.18 ± 0.07 | 0.22 ± 0.24 |
| **17** | 4.94 ± 1.35 | 4.34± 1.38 | 6.58±1.26 | 5.61 ± 2.28 | 5.24 ± 2.39 | 4.28 ± 1.42 |
| **19** | 6.38 ± 2.43 | 6.25 ± 2.91 | 4.91 ± 2.18 | 4.52 ± 2.62 | 5.52 ± 2.22 | 5.31±2.61 |
| **20** | 6.83 ±2.18 | 4.42 ± 2.12 | 6.26 ± 1.07 | 6.36 ± 2.70 | 5.40 ± 3.15 | 4.43 ± 1.87 |
| **22a** | 1.53± 0.83 | 0.83± 0.43 | 1.09 ± 0.86 | 1.28± 0.59 | 0.96 ± 0.27 | 1.85 ± 0.61 |
| **22b** | 1.89 ± 0.33 | 2.27 ± 0.58 | 3.71 ± 0.55 | 1.58 ± 0.29 | 2.15± 0.63 | 1.62 ±0.41 |
| **23** | 4.25±1.82 | 6.53 ± 2.22 | 5.56 ± 2.12 | 5.23 ±2.62 | 4.21± 2.12 | 4.61 ± 2.32 |
| **24** | 5.80± 2.31 | 4.02 ± 1.55 | 3.59 ± 2.62 | 6.49 ± 3.27 | 3.40 ± 2.51 | 5.25± 2.47 |
| **25a** | 6.25 ± 3.52 | 6.38 ±2.36 | 5.47 ± 1.22 | 5.61 ± 2.46 | 5.41 ±2.37 | 5.33 ± 2.27 |
| **25b** | 0.51 ± 0.14 | 0.39 ± 0.20 | 0.45 ± 0.13 | 0.46 ± 0.13 | 0.63 ± 0.16 | 0.35 ±0.14 |
| **27a** | 2.40 ± 1.36 | 1.48 ±0 .81 | 2.49 ± 1.26 | 2.59 ± 1.43 | 3.19 ± 2.36 | 2.68 ± 1.52 |
| **27b** | 0.26 ± 0.08 | 0.28 ± 0.07 | 0.36 ± 0.18 | 0.32 ± 0.17 | 0.32 ± 0.19 | 0.41 ± 0.26 |
| **28** | 1.65± 1.05 | 3.90±1.59 | 5.49 ± 2.70 | 6.39 ± 2.07 | 1.35±1.02 | 8.38 ± 2.61 |
| **Foretinib** | 0.08 ± 0.01 | 0.03±0.0055 | 0.15 ± 0.023 | 0.90 ± 0.13 | 0.18 ± 0.03 | 0.44 ± 0.062 |

*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-methanobenzo[*d*]thiazole-2(3*H*)-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 $IC_{50's}$ 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 week 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 tetrahydropyrano[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-methanoxantheno[1,2-*d*]thiazole-2(11*H*)-thione derivative **28** exhibited moderate inhibitions toward H460 and A549 cell lines with $IC_{50}$'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 $^1$HNMR or (75 MHz) for $^{13}$CNMR using TMS as internal standard and DMSO-$d_6$ 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.

*4,5,11,11,12,12-hexamethyl-9-phenyl-2,3,4,5,6,7,8,9-octahydro-1H-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 $\nu_{max}$ cm$^{-1}$: 3050 (aromatic CH), 1640 (C=C), 2890, 2766 ($CH_3$, $CH_2$). $^1$H NMR: 7.22-7.31 (m, 5H, $C_6H_5$), 2.39-2.46 (3s, 18H, $6CH_3$), 1.73-1.87 (2m, 8H, camphor $4CH_2$), 6.10 (s, 1H, H-4 pyran), 3.38 (t, 2H, 2camphor CH). $^{13}$C NMR: 22.5, 22.6 ($4CH_3$), 23.3 ($2CH_3$), 27.7, 28.2 (camphor $4CH_2$), 39.6, 39.5, 40.3 (camphor CH, camphor 2C), 40.6 (pyran C-4), 125.1, 126.2, 127.3, 128.6 ($C_6H_5$), 135.3, 135.8, 136.2, 136.4 (pyran 2C=C). Anal. calcd. for $C_{27}H_{34}O$: 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-1H-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** (1.52 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. Yellow powder from alcohol, yield (2.90 g, 91%), mp 102-104 °C. IR $\nu_{max}$ cm$^{-1}$: 3054 (aromatic CH), 1643 (C=C), 2890, 2768 ($CH_3$, $CH_2$). $^1$H NMR: δ 2.39-2.40 (3s, 9H, $3CH_3$), 1.63-1.67 (2m, 4H, camphor $2CH_2$), 2.41-2.44 (2m, 8H, cyclohexane $4CH_2$), 3.38 (t, 1H, camphor CH), 7.33-7.64 (m, 5H, $C_6H_5$), 6.90 (s, 1H, H-4 pyran). $^{13}$C NMR: δ 22.5, 22.6 ($2CH_3$), 23.3 ($CH_3$), 27.9, 28.5 (camphor $2CH_2$), 38.9, 39.3 (cyclohexane $2CH_2$), 39.5, 39.8, 40.1 (camphor CH, camphor 2C), 40.4 (pyran C-4), 128.4, 128.5, 128.6, 128.8 ($C_6H_5$), 135.3, 135.8, 136.2, 136.4 (pyran 2C=C). Anal. calcd. for $C_{23}H_{28}O$: 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-[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 $\nu_{max}$ cm$^{-1}$: 3056 (aromatic CH), 1642 (C=C), 2893, 2769 ($CH_3$, $CH_2$). $^1$H NMR: δ 2.40-2.43 (3s, 9H, $3CH_3$), 1.65-1.69 (2m, 4H, camphor $2CH_2$), 2.44-2.46 (2m, 6H, cyclopentane $3CH_2$), 3.33 (t, 1H, camphor CH), 7.45-

7.70 (m, 5H, $C_6H_5$), 7.01 (s, 1H, H-4 pyran). $^{13}$C NMR: δ 22.5, 22.8 ($3CH_3$), 27.9, 28.8 (camphor $2CH_2$), 36.9, 43.6 (cyclopentane $3CH_2$), 39.2, 39.6, 40.6 (camphor CH, camphor 2C), 40.6 (pyran C-4), 128.6, 123.6, 125.2, 128.3 ($C_6H_5$), 133.6, 134.8, 136.0, 136.8 (pyran 2C=C). Anal. calcd. for $C_{22}H_{26}O$: C, 86.23; H, 8.55%. Found: C, 85.97; H, 8.25%. MS: m/z 306.

*Ethyl 8,9,9-trimethyl-2,4-diphenyl-5,6,7,8-tetrahydro-4H-5,8-methanochromene-3-carboxylate (**9**).* Each of ethyl benzoylacetate (1.92 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. Brown powder from alcohol, yield (3.80 g, 92%), mp 103-104 °C. IR $\nu_{max}$ $cm^{-1}$: 3053 (aromatic CH), 1688 (CO), 1640 (C=C), 2893, 2772 ($CH_3$, $CH_2$). $^1$H NMR: δ 2.36-2.41 (3s, 9H, $3CH_3$), 1.13-1.46 (2m, 4H, $2CH_2$), 3.35 (t, 1H, camphor CH), 1.07 (t, 3H, $CH_3$), 4.19 (q, 2H, $CH_2$), 7.32-7.95 (m, 10H, $2C_6H_5$), 7.22 (s, 1H, H-4 pyran). $^{13}$C NMR: δ 16.3 ($OCH_2\underline{CH_3}$), 22.2, 22.5 ($3CH_3$), 27.9, 28.6 (camphor $2CH_2$), 50.3 ($O\underline{CH_2}CH_3$), 39.0, 39.6, 40.8 (camphor CH, camphor 2C), 40.8 (pyran C-4), 120.8, 121.2, 121.4, 122.2, 122.6, 123.4, 125.0, 126.1 ($2C_6H_5$), 133.3, 134.8, 136.0, 137.2 (pyran 2C=C), 166.3 (CO). Anal. calcd. for $C_{28}H_{30}O_3$: 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-methanobenzo[d]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** (1.52 g, 0.01 mol) in ethanol\$Et_3N$. 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, yield (2.90 g, 96%), mp103-105 °C. IR $\nu_{max}$ $cm^{-1}$: 3056 (aromatic CH), 1210 (C=S), 1642 (C=C), 2893, 2772 ($CH_3$, $CH_2$). $^1$H NMR: δ 2.44-2.46 (3s, 9H, $3CH_3$), 1.06-1.36 (2m, 4H, $2CH_2$), 3.30 (t, 1H, camphor CH), 7.30-7.51 (m, 5H, $C_6H_5$). $^{13}$C NMR: δ 18.2, 18.8 ($3CH_3$), 26.8, 27.2 (camphor $2CH_2$), 56.1, 65.3, 66.9 (camphor CH, camphor 2C), 121.6, 123.0, 124.9, 125.9 ($C_6H_5$), 137.4, 138.2 (thiazole C=C), 179.6 (C=S). Anal. calcd. for $C_{17}H_{19}NS_2$: 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** (1.52 g, 0.01 mol) in ethanol/piperidine. The combination has been refluxed for 4 h, and it has been poured on ice/water, then the product has been filtrated. Beige powder from alcohol, yield (2.90 g, 87%), mp181-182 °C. IR $\nu_{max}$ $cm^{-1}$: 3053 (aromatic CH), 1640 (C=C), 1689 (CO), 2893, 2772 ($CH_3$, $CH_2$). $^1$H NMR: δ 2.41-2.47 (3s, 9H, $3CH_3$), 1.68-1.71 (2m, 4H, camphor $2CH_2$), 2.44-2.47 (2m, 6H, cyclohexane $3CH_2$), 3.40 (t, 1H, camphor CH), 7.35-7.73 (m, 5H, $C_6H_5$), 7.10 (s, 1H, H-4 pyran). $^{13}$C NMR: 18.0, 18.7 ($3CH_3$), 26.4, 26.8, 28.2, 28.4, 28.6 ($5CH_2$), 50.9 (pyran C-4), 56.2, 65.6, 66.9 (camphor CH, camphor 2C), 121.8, 122.6, 124.5, 125.3 ($C_6H_5$), 166.3 (CO), 134.2, 134.4, 135.4, 135.6 (pyran 2C=C). Anal. calcd. for $C_{23}H_{26}O_2$: C, 82.60; H, 7.84%. Found: C, 82.43; H, 7.44%. MS: m/z 334.

*Synthesis of methanothieno[3,2-a]xanthene 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/$Et_3N$. 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]xanthene-1-carboxylate (**15a**).* Yellowish white powder from alcohol, yield (4.00 g, 87%), mp 160-162 °C. IR $\nu_{max}$ $cm^{-1}$: 3055 (aromatic CH), 1643 (C=C), 1698 (CO), 3338 ($NH_2$), 2890, 2776 ($CH_3$, $CH_2$). $^1$H NMR: δ 2.29-2.43 (3s, 9H, $3CH_3$), 1.37-2.44 (2m, 8H, $4CH_2$), 3.25 (t, 1H, camphor CH), 1.10 (t, 3H, $CH_3$), 4.30 (q, 2H, $CH_2$), 4.57 (s, 2H, $NH_2$), 7.12 (s, 1H, H-4 pyran),

7.35-7.50 (m, 5H, $2C_6H_5$). $^{13}$C NMR: 16.6 ($OCH_2\underline{CH_3}$), 18.0, 18.9 ($3CH_3$), 50.3 ($O\underline{CH_2}CH_3$), 51.2 (pyran C-4), 26.6, 26.8, 27.8, 28.0 ($4CH_2$), 56.0, 65.6, 66.9 (camphor CH, camphor 2C), 121.3, 122.6, 124.5, 125.6 ($C_6H_5$), 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 $C_{28}H_{31}NO_3S$: 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 $\nu_{max}$ cm$^{-1}$: 3054 (aromatic CH), 1642 (C=C), 2224 (CN), 2893, 2772 ($CH_3$, $CH_2$), 3345 ($NH_2$). $^1$H NMR: δ 2.30-2.44 (3s, 9H, $3CH_3$), 1.39-2.47 (2m, 8H, $4CH_2$), 3.22 (t, 1H, camphor CH), 4.53 (s, 2H, $NH_2$), 7.10 (s, 1H, H-4 pyran), 7.35-7.50 (m, 5H, $2C_6H_5$). $^{13}$C NMR: 18.0, 18.9 ($3CH_3$), 26.6, 26.8, 28.2, 28.6 ($4CH_2$), 56.0, 65.6, 66.9 (camphor CH, camphor 2C), 50.9 (pyran C-4), 121.3, 122.6, 124.5, 125.6 ($C_6H_5$), 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 $C_{26}H_{26}N_2OS$: 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 414.

*Synthesis of methanoxantheno[1',2':4,5]thieno[2,3-d]pyrimidine derivatives **16** and **17**.* Phenylisothiocyanate (1.35 g, 0.01 mol) has been added to compound **15a** (4.14 g, 0.01 mol) or **15b** (4.61 g, 0.01 mol) in ethanol/$Et_3N$. The combination has been refluxed for 4 h, and it has been poured over small pieces of ice, then the product has been filtrated.

*9,14,14-Trimethyl-2,13-diphenyl-3-thioxo-2,3,4,6,7,9,10,11,12,13-decahydro-1H-9,12-methan-oxantheno[1',2':4,5]thieno[2,3-d]pyrimidin-1-one (**16**).* Beige powder from alcohol, yield (5.20 g, 94%), mp 62-63 °C. IR $\nu_{max}$ cm$^{-1}$: 3320-3480 (NH), 2890, 2776 ($CH_3$, $CH_2$), 1212 (C=S), 1643 (C=C), 1755 (C=O). $^1$H NMR: δ 2.29-2.38 (3s, 9H, $3CH_3$), 1.34-2.47 (2m, 8H, $4CH_2$), 3.17 (t, 1H, camphor CH), 7.13 (s, 1H, H-4 pyran), 10.88 (s, 1H, NH), 7.25-7.50 (m, 10H, $2C_6H_5$). $^{13}$C NMR: 18.1, 18.8 ($3CH_3$), 26.2, 26.8, 28.6, 28.8 ($4CH_2$), 56.4, 65.8, 66.9 (camphor CH, camphor 2C), 121.3, 121.5, 122.4, 122.6, 124.2, 124.5, 125.6, 125.8 ($2C_6H_5$), 51.2 (pyran C-4), 133.2, 136.4, 138.4, 140.6 (thiophene C), 132.7, 133.3, 133.5, 133.7 (pyran 2C=C), 167.8 (C=O), 180.6 (C=S). Anal. calcd. for $C_{33}H_{30}N_2O_2S_2$: C, 71.97; H, 5.49; N, 5.09; S, 11.64%. Found: C, 71.57; H, 5.45; N, 4.93; S, 11.29%. MS: m/z 550.

*1-Imino-9,14,14-trimethyl-2,13-diphenyl-4,6,7,9,10,11,12,13-octahydro-1H-9,12-methanoxant-heno[1',2':4,5]thieno[2,3-d]pyrimidine-3(2H)-thione (**17**).* Beige powder from alcohol, yield (5.10 g, 93%), mp 64-65 °C. IR $\nu_{max}$ cm$^{-1}$: 3320-3380 (2NH), 3055 (aromatic CH), 1215 (C=S), 1643 (C=C), 2890, 2776 ($CH_3$, $CH_2$). $^1$H NMR: δ 2.36-2.40 (3s, 9H, $3CH_3$), 1.31-2.43 (2m, 8H, $4CH_2$), 3.19 (t, 1H, camphor CH), 10.99, 11.0 (2s, 2H, 2NH), 7.33-7.49 (m, 10H, $2C_6H_5$), 7.13 (s, 1H, H-4 pyran). $^{13}$C NMR: 18.3, 18.8 ($3CH_3$), 26.1, 26.6, 26.8, 27.6 ($4CH_2$), 56.2, 65.6, 66.9 (camphor CH, camphor 2C), 121.3, 122.6, 124.5, 125.6, 125.8, 126.6, 127.4, 127.6 ($2C_6H_5$), 50.5 (pyran C-4), 133.2, 136.1, 138.4, 140.6 (thiophene C), 133.8, 134.0, 134.2, 135.4 (pyran 2C=C), 170.2 (C=N), 180.4 (C=S). Anal. calcd. For $C_{33}H_{31}N_3OS_2$: C, 72.10; H, 5.68; N, 7.64; S, 11.67%. Found: C, 71.86; H, 5.39; N, 7.35; S, 11.29%. MS: m/z 549.

*4,11,11-Trimethyl-9-phenyl-7-(2-phenylhydrazono)-3,4,5,6,7,9-hexahydro-1H-1,4-methanoxan-then-8(2H)-one (**19**).* Benzenediazonium chloride (**18**) (1.41, 0.01 mol) has been added to a cold solution of compound **13** (3.34 g, 0.01 mol), in ethanol/sodium acetate with stirring. The combination has been left at room temperature and the formed product has been filtrated. Beige powder from alcohol, yield (3.90 g, 89%), mp 79-80 °C. $\nu_{max}$ cm$^{-1}$: 3325 (NH), 3050 (aromatic CH), 2782, 2889 ($CH_3$, $CH_2$), 1647 (C=C), 1755 (C=O),1639 (C=N). $^1$H NMR: δ 2.36-2.39 (3s, 9H, $3CH_3$), 1.03-1.33 (2m, 8H, $4CH_2$), 3.28 (t, 1H, camphor CH), 5.80 (s, 1H, NH), 6.76 (s, 1H, H-4 pyran), 7.11-7.20 (m, 10H, $2C_6H_5$). $^{13}$C NMR:18.2, 18.9 ($3CH_3$), 26.2, 26.4, 28.6, 28.8

($4CH_2$), 56.6, 65.8, 67.0 (camphor CH, camphor 2C), 121.8, 122.6, 124.5, 125.3, 125.8, 126.6, 126.8, 127.0 ($2C_6H_5$), 134.6, 135.2, 136.5, 139.8 (pyran 2C=C), 166.3 (CO), 164 (C=N). Anal. calcd. for $C_{29}H_{30}N_2O_2$: C, 79.42; H, 6.89; N, 6.39%. Found: C, 79.12; H, 6.43; N, 5.99%. MS: m/z 438.

*8,13,13-Trimethyl-3,12-diphenyl-4-(phenylamino)-3,4,5,6,8,9,10,11-octahydro-8,11-methanoxantheno[2,1-e][1,3,4]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/$Et_3N$. The combination has been refluxed for 4 h, and it has been poured over small pieces of ice, then the product has been filtrated. Beige powder from alcohol, yield (5.15 g, 90%), mp 65-66 °C. IR $\nu_{max}$ $cm^{-1}$: 3335 (NH), 3053 (aromatic CH), 1215 (C=S), 1657 (C=C), 2784, 2899 ($CH_3$, $CH_2$). $^1H$ NMR: δ 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, $3C_6H_5$), 11.02 (s, 1H, NH). $^{13}C$ NMR: δ 18.52, 19.8 ($3CH_3$), 26.4, 26.8, 30.8, 36.3 ($4CH_2$), 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 ($3C_6H_5$), 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 $C_{36}H_{35}N_3O_2S$: 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/$Et_3N$, 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 filtrated.

*1-Phenyl-4,11,11-trimethyl-9-phenyl-3,4,6,7-tetrahydro-1H-1,4-methanoxanthen-8(2H,5H,9H)-ylidene)hydrazine **(22a)**.* Orange powder from alcohol, yield (4.00 g, 94%), mp 70-71 °C. IR $\nu_{max}$ $cm^{-1}$: 3327 (NH), 3056 (aromatic CH), 2785, 2920 ($CH_3$, $CH_2$). $^1H$ NMR: δ 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, $2C_6H_5$). $^{13}C$ NMR: δ 18.54, 20.2 ($3CH_3$), 28.4, 28.8, 32.8, 37.3, 39.5 ($5CH_2$), 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 ($2C_6H_5$), 134.1, 135.3, 136.5, 140.5 (pyran 2C=C), 163.2 (C=N). Anal. calcd. for $C_{29}H_{32}N_2O$: C, 82.04; H, 7.60; N, 6.60%. Found: C, 81.96; H, 7.44; N, 6.37%. MS: m/z 424.

*4,11,11-Trimethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1H-1,4-methanoxanthen-8(2H)-one oxime **(22b)**.* Yellow powder from alcohol, yield (3.10 g, 89%), mp 166-168 °C. IR $\nu_{max}$ $cm^{-1}$: 3537 (OH), 3057 (aromatic CH), 2787, 2923 ($CH_3$, $CH_2$). $^1H$ NMR: δ 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, $C_6H_5$). $^{13}C$ NMR: δ 18.54, 20.2 ($3CH_3$), 28.4, 28.8, 32.8, 37.3, 39.5 ($5CH_2$), 56.2, 65.4, 67.3 (camphor CH, camphor 2C), 50.3 (pyran C-4), 122.8, 123.5, 124.3, 125.7 ($C_6H_5$), 134.5, 135.3, 136.3, 140.9 (pyran 2C=C), 163.2 (C=N). Anal. calcd. for $C_{23}H_{27}NO_2$: 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/$Et_3N$. The combination has been refluxed for 4 h, and it has been poured over small pieces of ice, then the product has been filtrated.

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

79-80 °C. IR $\nu_{max}$ $cm^{-1}$: 3339 ($NH_2$), 3053 (aromatic CH), 2787, 2890 ($CH_3$, $CH_2$), 1648 (C=C), 1765 (C=O). $^1$H NMR: δ 2.30-2.38 (3s, 9H, $3CH_3$), 1.17-1.49 (2m, 8H, $4CH_2$), 3.29 (t, 1H, camphor CH), 4.57 (s, 2H, $NH_2$), 7.10 (s, 1H, H-4 pyran), 4.55, 5.22 (2t, 2H, 2CH=C), 7.18-7.30 (m, 10H, $2C_6H_5$). Anal. calcd. for $C_{32}H_{33}N_3O_2$: 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-methanoxanthen-8-yl)isoxazol-5(2H)-one (**24**).* Yellow crystals from alcohol, yield (3.80 g, 91%), mp 104-106 °C. IR $\nu_{max}$ $cm^{-1}$: 3340 ($NH_2$), 3053 (aromatic CH), 2789, 2891 ($CH_3$, $CH_2$), 1658 (C=C), 1766 (C=O). $^1$H NMR: δ 2.29-2.33 (3s, 9H, $3CH_3$), 1.11-1.45 (2m, 8H, $4CH_2$), 3.28 (t, 1H, camphor CH), 4.58 (s, 2H, $NH_2$), 7.09 (s, 1H, H-4 pyran), 4.00, 5.27 (2t, 2H, 2CH=C), 7.12-7.23 (m, 5H, $C_6H_5$). Anal. calcd. for $C_{26}H_{28}N_2O_3$: 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/$Et_3N$. 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-methanopyrano[2,3-a]xanthene-3-carboxylate (**25a**).* White powder from alcohol, yield (5.10 g, 95%), mp 156-158 °C. IR $\nu_{max}$ $cm^{-1}$: 3349 ($NH_2$), 3055 (CH aromatic), 2791, 2893 ($CH_3$, $CH_2$), 1657 (C=C), 1690 (CO). $^1$H NMR: δ 2.40-2.48 (3s, 9H, $3CH_3$), 1.06-1.36 (2m, 8H, $4CH_2$), 3.39 (t, 1H, camphor CH), 1.05 (t, 3H, $CH_3$), 3.93 (q, 2H, $CH_2$), 4.55 (s, 2H, $NH_2$), 7.04, 7.10 (2s, 2H, 2pyran H-4), 7.18-7.51 (m, 10H, $2C_6H_5$). $^{13}$C NMR: δ 14.2, 19.8, 26.3 ($3CH_3$), 14.8 (ester $CH_3$), 33.1, 36.1, 36.3, 38.6 ($4CH_2$), 38.2 (ester $CH_2$), 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 ($2C_6H_5$), 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 $C_{35}H_{37}NO_4$: 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-carbonitrile (**25b**).* Yellow powder from alcohol, yield (4.50 g, 92%), mp 222-224 °C. IR $\nu_{max}$ $cm^{-1}$: 3348 ($NH_2$), 3055 (aromatic CH), 2790, 2892 ($CH_3$, $CH_2$), 1654 (C=C), 2220 (CN). $^1$H NMR: δ 2.38-2.40 (3S, 9H, $3CH_3$), 1.07-1.35 (2m, 8H, $4CH_2$), 3.33 (t, 1H, camphor CH), 4.19 (s, 2H, $NH_2$), 7.04, 6.95 (2s, 2H, 2pyran), 7.14-7.30 (m, 10H, $2C_6H_5$). $^{13}$C NMR: δ 14.4, 19.6, 26.7 ($3CH_3$), 34.3, 36.4, 36.6, 38.8 ($4CH_2$), 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 ($2C_6H_5$), 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 $C_{33}H_{32}N_2O_2$: 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/$Et_3N$. 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 $\nu_{max}$ $cm^{-1}$: 3352 ($NH_2$), 3056 (aromatic CH), 2793, 2895 ($CH_3$, $CH_2$), 1658 (C=C), 1692 (CO). $^1$H NMR: δ 2.38-2.49 (3S, 9H, $3CH_3$), 1.11-1.38 (2m, 8H, $4CH_2$), 3.40 (t, 1H, camphor CH),1.20-128 (2t, 6H, $2CH_3$), 4.15-4.30 (2q, 4H, $2CH_2$), 4.47 (s, 2H, $NH_2$),

7.12, 7.19 (2s, 2H, 2pyran H-4), 7.20-7.49 (m, 5H, $C_6H_5$). Anal. calcd. for $C_{31}H_{37}NO_5$: C, 73.93; H, 7.41; N, 2.78%. Found: C, 73.64; H, 7.13; N, 2.39%. MS: m/z 503.

*2-Amino-4-ethoxy-8,13,13-trimethyl-12-phenyl-4,5,6,8,9,10,11,12-octahydro-8,11-methano-pyrano[2,3-a]xanthene-3-carbonitrile (**27b**).* Pale brown powder from alcohol, yield (3.00 g, 66%), mp 183-185 °C. IR $\nu_{max}$ $cm^{-1}$: 3368 ($NH_2$), 3050 (aromatic CH), 2793, 2895 ($CH_3$, $CH_2$), 1658 (C=C), 2223 (CN). $^1$H NMR: δ 2.38-2.49 (3S, 9H, $3CH_3$), 1.11-1.38 (2m, 8H, $4CH_2$), 3.40 (t, 1H, camphor CH), 1.15 (t, 3H, $CH_3$), 4.13 (q, 2H, $CH_2$), 4.45 (s, 2H, $NH_2$), 7.14, 7.13 (2s, 2H, 2pyran H-4), 7.25-7.55 (m, 5H, $C_6H_5$). Anal. calcd. for $C_{29}H_{32}N_2O_3$: C, 76.29; H, 7.06; N, 6.14%. Found: C, 75.89; H, 6.86; N, 5.94%. MS: m/z 456.

*7,12,12-Trimethyl-1,11-diphenyl-4,5,7,8,9,10-hexahydro-1H-7,10-methanoxantheno[1,2-d]thiazole-2(11H)-thione (**28**).* Phenylisothiocyanate (1.35 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/$Et_3N$. The combination has been refluxed for 4 h, and it has been poured over ice/water, then the formed product has been filtrated. Orange crystals from alcohol, yield (4.15 g, 86%), mp 61-62 °C. IR $\nu_{max}$ $cm^{-1}$: 3059 (aromatic CH), 2897, 2775 ($CH_3$, $CH_2$), 1646 (C=C), 1217 (C=S). $^1$H NMR: δ 2.39-2.43 (3s, 9H, $3CH_3$), 1.16-1.45 (2m, 8H, $4CH_2$), 3.37 (t, 1H, camphor CH), 6.59 (s, 1H, H-4 pyran), 7.30-7.61 (m, 10H, $2C_6H_5$). $^{13}$C NMR: δ 14.0, 18.5, 18.6 ($3CH_3$), 14.2, 20.4, 36.3 ($4CH_2$), 39.8, 40.0, 40.1 (camphor CH, camphor 2C), 56.0 (pyran C-4), 121.6, 122.9, 123.4, 124.6, 125.9, 126.1, 127.4, 128.9 ($2C_6H_5$), 196.2 (C=S), 134.1, 135.3, 135.8, 136.2 (pyran 2C=C), 137.0, 137.2 (thiazole C=C). Anal. calcd. for $C_{30}H_{29}NOS_2$: C, 74.49; H, 6.04; N, 2.90; S, 13.26%. Found: C, 74.20; H, 5.87; N, 2.52; S, 12.93%. MS: m/z 483.

## CONCLUSION

Xanthene, chromene, thiazole, thiophene, pyrazole, and isoxazole derivatives have been synthesized from camphor-D monoterpene. 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

1. Poupelin, J.P.; Saint-Ruf, G.; Foussard-Blanpin, O.; Marcisse, G.; Uchida-Ernouf, G.; Lacroix, R. Synthesis and antiinflammatory properties of bis (2-hydroxy-1-naphthyl) methane derivatives. I. Monosubstituted derivatives. *Eur. J. Med. Chem.* **1978**, 13, 67-71.
2. Omolo, J.J.; Johnson, M.M.; Van Vuuren, S.F.; de Koning, C.B. The synthesis of xanthones, xanthenediones, and spirobenzofurans: their antibacterial and antifungal activity. *Bioorg. Med. Chem. Lett.* **2011**, 21, 7085-7088.
3. Pirouzmand, M.; Gharehbaba, A.M.; Ghasemi, Z. Synthesis of xanthene derivatives using template-containing Zn/MCM-41 as a green and reusable catalyst; effect of the template. *J. Mex. Chem. Soc.* **2016**, 60, 183-187.
4. Djoufack, G.L.N.; Valant-Vetschera, K.M.; Schinnerl, J.; Brecker, L.; Lorbeer, E.; Robien, W. Xanthones, biflavanones and triterpenes from *Pentadesma grandifolia* (Clusiaceae): structural determination and bioactivity. *Nat. Prod. Commun.* **2010**, 5, 1055-1060.

5. Khurana, J.M.; Magoo, D.; Aggarwal, K.; Aggarwal, N.; Kumar, R.; Srivastava, C. Synthesis of novel 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-thiones and evaluation of their biocidal effects. *Eur. J. Med. Chem.* **2012**, 58, 470-477.
6. Hashim, N.; Rahmani, M.; Sukari, M.A. Two new xanthones from *Artocarpus obtusus*. *J. Asian Nat. Prod. Res.* **2010**, 12, 106-112.
7. Tao, S.-J.; Guan, S.-H.; Wang, W. Cytotoxic polyprenylated xanthones from the resin of *Garcinia hanburyi*. *J. Nat. Prod.* **2009**, 72, 117-124.
8. Azebaze, A.G.B.; Meyer, M.; Valentin, A.; Nguemfo, E.L.; Fomum, Z.T.; Nkengfack, A.E. Prenylated xanthone derivatives with antiplasmodial activity from *Allanblackia monticola* Staner L.C. *Chem. Pharm. Bull.* **2006**, 54, 111-113.
9. Zelefack, F.; Guilet, D.; Fabre, N. Cytotoxic and antiplasmodial xanthones from *Pentadesma butyracea*. *J. Nat. Prod.* **2009**, 72, 954-957.
10. Lee, K.-H.; Chai, H.-B.; Tamez, P.A. Biologically active alkylated coumarins from *Kayea assamica*. *Phytochemistry* **2003**, 64, 535-541.
11. Hay, A.-E.; Aumond, M.-C.; Mallet, S. Antioxidant xanthones from *Garcinia vieillardii*. *J. Nat. Prod.* **2004**, 67, 707-709.
12. Laphookhieo, S.; Syers, J.K.; Kiattansakul, R.; Chantrapromma, K. Cytotoxic and antimalarial prenylated xanthones from *Cratoxylum cochinchinense*. *Chem. Pharm. Bull.* **2006**, 4, 745-747.
13. Cao, S.; Brodie, P.J.; Miller, J.S. Antiproliferative xanthones of *Terminalia calcicola* from the Madagascar rain forest. *J. Nat. Prod.* **2007**, 70, 679-681.
14. Han, Q.-B.; Tian, H.-L.; Yang, N.-Y. Polyprenylated xanthones from *Garcinia lancilimba* showing apoptotic effects against HeLa-C3 cells. *Chem. Biodivers.* **2008**, 5, 2710-2717.
15. Moosophon, P.; Kanokmedhakul, S.; Kanokmedhakul, K.; Soytong, K. Prenylxanthones and a bicyclo[3.3.1]nona-2,6-diene derivative from the fungus *Emericella rugulosa*. *J. Nat. Prod.* **2009**, 72, 1442-1446.
16. Jamison, J.M.; Krabill, K.; Hatwalkar, A.; Jamison, E.; Tsai, C.C. Potentiation of the antiviral activity of polyr(A-U) by xanthene dyes. *Cell Biol. Int. Rep.* **1990**, 14, 1075-1084.
17. Britt, A.D.; Moniz, W.B. Reactivity of first-singlet excited xanthene laser dyes in solution. *J. Org. Chem.* **1973**, 38, 1057-1059.
18. Carreon, J.R.; Roberts, M.A.; Wittenhagen, L.M.; Kelley, S.O. Synthesis, characterization, and cellular uptake of DNA-binding Rose Bengal Peptidoconjugates. *Org Lett.* **2005**, 7, 99-102.
19. Nguyen, H.T.; Lallemand, M.C.; Boutefnouchet, S.; Michel, S.; Tillequin, F. Antitumor psoropermum xanthones and sarcomelicope acridones: Privileged structures implied in DNA alkylation. *J. Nat. Prod.* **2009**, 72, 527-539.
20. Knight, C.G.; Stephens, D. Xanthene-dye-labelled phosphatidylethanolamines as probes of interfacial pH studies in phospholipid vesicles. *Biochem. J.* **1989**, 258, 683-687.
21. Oskooie, H.A.; Tahershamsi, L.; Heravi, M.M.; Baghernejad, B. Cellulose sulfonic acid: An efficient heterogeneous catalyst for the synthesis of 1,8-dioxo-octahydroxanthenes. *Electron. J. Chem.* **2010**, 7, 717-720.
22. Seyyedhamzeh, M.; Mirzaei, P.; Bazgir, A. Solvent-free synthesis of aryl-14*H*-dibenzo[*a,*j]xanthenes and 1,8-dioxooctahydro-xanthenes using silica sulfuric acid as catalyst. *Dyes Pigm.* **2008**, 76, 836-839.
23. Su, W.; Yang, D.; Jin, C.; Zhang, B. $Yb(OTf)_3$ catalyzed condensation reaction of β-naphthol and aldehyde in ionic liquids: A green synthesis of aryl-14*H*-dibenzo[*a*,j]xanthenes. *Tetrahedron Lett.* **2008**, 49, 3391-3394.
24. Kumar, R.; Nandi, G.C.; Verma, R.K.; Singh, M.S. A facile approach for the synthesis of 14-aryl- or alkyl-14*H* dibenzo[*a*,j]xanthenes under solvent-free condition. *Tetrahedron Lett.* **2010**, 51, 442-445.

25. Shaterian, H.R.; Ghashang, M.; Mir, N. Aluminium hydrogensulfate as an efficient and heterogeneous catalyst for preparation of aryl 14*H*-dibenzo[*a*,j]xanthene derivatives under thermal and solvent-free conditions. *Arkivoc* **2007**, 2007, 1-10.
26. Mirjalili, B.F.; Bamoniri, A.; Akbari, A.; Taghavinia, N. Nano-$TiO_2$: An eco-friendly and reusable catalyst for the synthesis of 14-aryl or alkyl-14*H*-dibenzo[*a*,j]xanthenes. *J. Iran. Chem. Soc.* **2011,** 8, S129-S134.
27. Shaterian, H.R.; Doostmohammadi, R.; Ghashang, M. Sodium hydrogen sulfate as effective and reusable heterogeneous catalyst for the one-pot preparation of 14*H*-[(un)substituted phenyl] dibenzo[*a*,j]xanthene leuco-dye derivatives. *Chin. J. Chem.* **2008**, 26, 338-342.
28. Gong, K.; Fang, D.; Wang, H.-L.; Zhou, X.-L.; Liu, Z.-L. The one-pot synthesis of 14-alkyl- or aryl-14*H*-dibenzo[*a*,j]xanthenes catalyzed by task-specific ionic liquid. *Dyes Pigm.* **2009**, 80, 30-33.
29. Ko, S.; Yao, C.-F. Heterogeneous catalyst: Amberlyst-15 catalyzes the synthesis of 14-substituted-14*H*-dibenzo[*a*,j]xanthenes under solvent-free conditions. *Tetrahedron Lett.* **2006**, 47, 8827-8829.
30. Amini, M.M.; Seyyedhamzeh, M.; Bazgir, A. Heteropoly acid: an efficient and eco-friendly catalyst for the synthesis of 14-aryl-14*H*-dibenzo[*a*,j]xanthene. *Appl. Catal.* **2007**, 323, 242-245.
31. Shaterian, H.R.; Ghashang, M.; Hassankhani, A. One-pot synthesis of aryl 14*H*-dibenzo[*a*,j]xanthene leuco-dye derivatives. *Dyes Pigm.* **2008**, 76, 564-568.
32. Khoramabadi-Zad, A.; Akbari, S.-A.; Shiri, A.; Veisi, H. One-pot synthesis of 14*H*-dibenzo[*a*,j]xanthene and its 14-substituted derivatives. *J. Chem. Res.* **2005**, 5, 277-279.
33. Rajitha, B.; Kumar, B.S.; Reddy, Y.T.; Reddy, P.N.; Sreenivasulu, N. Sulfamic acid: A novel and efficient catalyst for the synthesis of aryl-14*H*-dibenzo[*a*.j]xanthenes under conventional heating and microwave irradiation. *Tetrahedron Lett.* **2005**, 46, 8691-8693**.**
34. Khosropour, A.R.; Khodaei, M.M.; Moghannian, H. A facile, simple and convenient method for the synthesis of 14-alkyl or aryl-14-*H*-dibenzo[*a*,j]xanthenes catalyzed by pTSA in solution and solvent-free conditions. *Synlett* **2005**, 6, 955-958.
35. Sarma, R.J.; Baruah, J.B. One step synthesis of dibenzoxanthenes. *Dyes Pigm.* **2005**, 64, 91-92.
36. Paliwal, P.; Jetti, S.R.; Bhatewara, A.; Kadre, T.; Jain, S. DABCO catalyzed synthesis of xanthene derivatives in aqueous media. *ISRN Org. Chem.* **2013,** 2013, 1-6.
37. Bhat, S.U.; Naikoo, R.A.; Mir, M.A.; Bhat, R.A.; Malla, M.A.; Tomar, R. Synthesis of 14-aryl-14*H*-dibenzo[*a*,j]xanthene derivatives using H-zeolite A as an efficient and reusable catalyst under solvent-free condition. *J. Mater.* **2016**, 1-10.
38. Mohareb, R.M.; Ibrahim, R.A.; Alwan, E.S. Multi-component reactions of cyclohexan-1,3-dione to synthesize heterocyclic derivatives with c-MET enzymatic activity, anti-prostate, anti-proliferative and tyrosine kinase activities. *Bull. Chem. Soc. Ethiop.* **2022**, 36, 119-136.
39. Mohareb, R.M.; Ibrahim, B.A.; Al Farouk, F.O. Anti-proliferative activities of 4*H*-pyran derivatives synthesized from benzoylacetone. *Bull. Chem. Soc. Ethiop.* **2023**, 37, 405-425.
40. Peach, M.L.; Tan, N.; Choyke, S.J.; Giubellino, A.; Athauda, G.; Burke, T.R.; Nicklaus, M.C.; Bottaro, D.P. Directed discovery of agents targeting the Met tyrosine kinase domain by virtual screening. *J. Med. Chem.* **2009**, 52, 943-951.