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SYNTHESIS OF BIOACTIVE HETEROCYCLIC COMPOUNDS USING CAMPHOR

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ABSTRACT. The aim of the work was to synthesize novel heterocyclic compounds derived from camphor with antibacterial activity. The pyridazine, xanthene, pyranothiazole, pyridinothiazole, thiophene and pyrazole derivatives were produced from 4,11,11-trimethyl-9-phenyl-7-(2-phenylhydrazono)-3,4,5,6,7,9-hexahydro-1*H*-1,4-methanoxanthen-8(2*H*)-one (**1**). Thiophene derivatives **6a,b** were produced according to the Gewald's reaction for thiophene synthesis. On the other hand, pyranothiazol derivatives **8a,b** were synthesized by the multicomponent reactions between xanthene derivative **5**, benzaldehyde and ethylcyanoacetate or malononitrile in ethanol/triethylamine. Whereas, pyridinothiazole derivative **9** was produced in ethanol/ammonium acetate by the multicomponent reaction between xanthene derivative **5**, benzaldehyde and malononitrile. The antibacterial activity of the synthesized compounds was evaluated against *E. coli* bacteria. All synthesized compounds showed moderate activity against *E. coli* bacteria.

KEY WORDS: Anti-microbial, Camphor, Heterocyclic, Pyrazol-3(2*H*)-one, Thiazol-4(5*H*)-one, Thieno[3,2-*d*]thiazole, Xanthenes

INTRODUCTION

Heterocyclic chemistry is one of the most important classes in pharmaceutical chemistry and organic synthesis [1]. Lots of these compounds were used as active ingredients in various pharmaceutical drugs due to their anti-tumor [2], anti-inflammatory [3], anti-hypertensive [4], anti-hyperlipidemic [5], anti-HIV infections [6], and other biological activities [7]. Many natural bioactive molecules contain thiazole ring in their structures as vitamin thiamine which has a role in the metabolic process [8]. Determined cephalosporins, penicillins and other antibiotics have a ring of thiazole as a part of their structures [9, 10]. Tubulin modulator and epothilone metabolite used as an antineoplastic agent [11], a cyclic peptide bacitracin which is formed by organisms of the licheniformis group of *Bacillus subtilis* [12], bleomycin antitumor antibiotic [13], and many other bioactive compounds have a thiazole ring [14, 15]. Through toxophoric unit transport (S-C=N), the therapeutic activities occurred [16], by way of many mechanisms, among these, the prevention of the biosynthesis of bacterial lipids [17]. Numerous studies were carried out for the synthesis of 2-aminothiazole scaffold and its activity was proven [18]. Since 30 years ago, thiazole-containing drugs have been recorded in clinical use. Such as, cefdinir is a third-generation cephalosporin and a well-known FDA-approved antibiotic [19]. Abafungin is an antifungal drug that treats dermatomycoses [20], dabrafenib (B-RAF enzyme inhibitor) [21], dasatinib (Bcr-Abl tyrosine kinase inhibitor) [22] and tiazofurin (IMP dehydrogenase inhibitor) [23]. At present, researchers are interested in molecular hybridization, which is considered one of the important branches of pharmaceutical chemistry. For example, thiazole-thiophene hybrids, often have improved pharmacodynamic and pharmacokinetic behavior compared to if each unit was used separately [21, 24]. Furthermore, Ensaf and Mohareb demonstrated the synthesis of thiazoles, pyrans and pyridines from 1,3-diketones [25-27]. Herein, our goal was a synthesis of pyridazine, xanthene, pyranothiazole, pyridinothiazole, thiophene and pyrazole derivatives from camphor.

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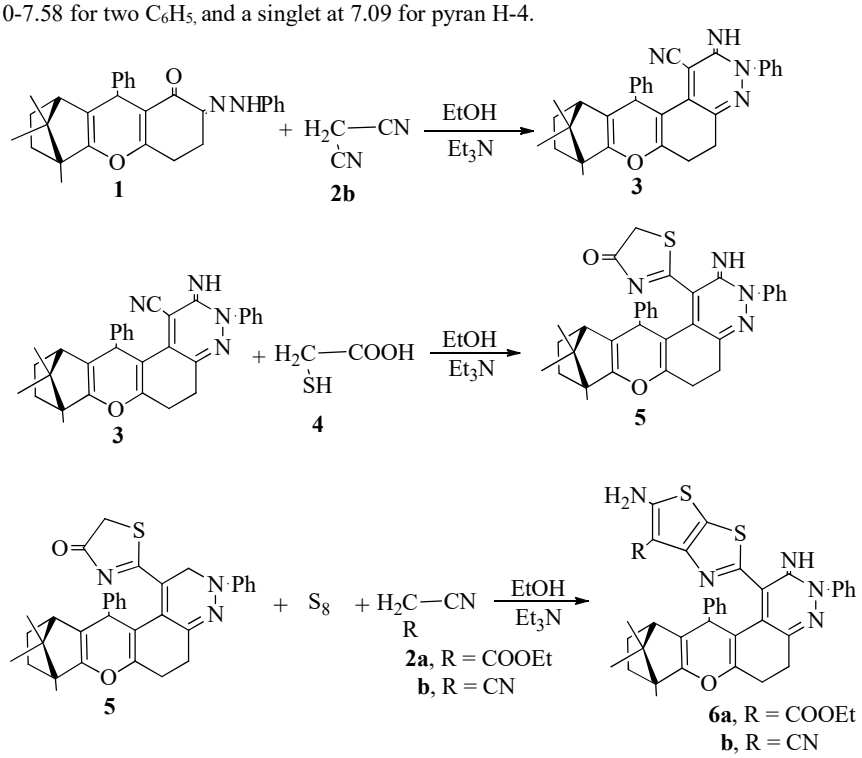
These compounds were examined against *E. coli* bacteria and the produced compounds showed moderate activity.

RESULT AND DISCUSSION

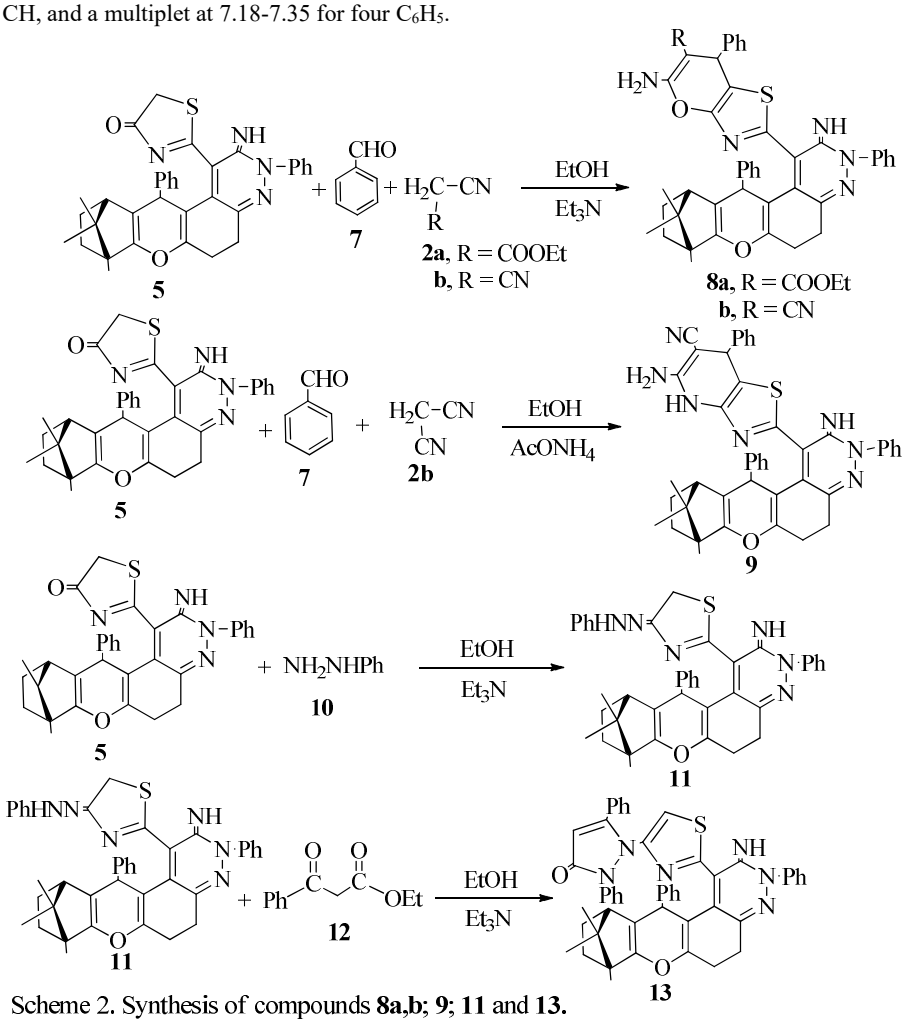
We started working on compound **1**, which was prepared from camphor in our previous work [26] to synthesize bioactive pyridazine, xanthene, pyranothiazole, pyridinothiazole, thiophene and pyrazole derivatives. Thus, the reaction of compound **1** with malononitrile (**2b**) gave the methanochromeno[3,2-*f*]cinnoline-1-carbonitrile **3** which reacted with thioglycolic acid (**4**) to produce thiazol-4(5*H*)-one derivative **5**. Compound **5** reacted with ethyl cyanoacetate (**2a**) or malononitrile (**2b**) and sulfur to produce thieno[3,2-*d*]thiazole derivatives **6a,b** (Scheme 1). The compounds structure was proven by spectral analyses. For example, the proton spectrum of compound **6b** showed a multiplet at δ 1.81-1.95 for four CH_2, three singlet at δ 2.21-2.50 for three CH_3, a singlet at 4.56 for NH, a triplet at 3.06 for CH, a singlet at 3.34 for NH_2, a multiplet at 7.10-7.58 for two C_6H_5, and a singlet at 7.09 for pyran H-4.



Scheme 1. Synthesis of compounds **3**, **5** and **6a**,**b**.

Compound **5** reacted with benzaldehyde (**7**) and ethyl cyanoacetate (**2a**) or malononitrile (**2b**) in EtOH/Et_3N to give pyrano-thiazole derivatives **8a,b**. Furthermore, compound **5** reacted with benzaldehyde **7** and malononitrile (**2b**) in EtOH/NH_4OAc to give dihydrothiazolo-pyridine-6-carbonitrile **9**. The reaction between compound **5** and phenylhydrazine (**10**) gave phenyl hydrazone derivative **11**. The latter compound reacted with ethylbenzoylacetate (**12**) to afford pyrazol-3(2*H*)-one derivative **13** (Scheme 2). The compounds structure was proven by spectral analyses. For example, the proton spectrum of compound **13** showed a multiplet at δ 1.84-2.26 for four CH_2, three singlet at δ 2.34-3.36, a triplet at 2.71 for camphor CH, a singlet at 4.58 for

NH, a singlet at 5.42 for thiazole CH, a singlet at 7.09 for pyran H-4, a singlet at 3.42 for pyrazole CH, and a multiplet at 7.18-7.35 for four C_6H_5.



Scheme 2. Synthesis of compounds **8a,b**; **9**; **11** and **13.**

Antibacterial assay

Susceptibility test

The susceptibility tests were performed according to NCCLS recommendations (National Committee for Clinical Laboratory Standards, 1993). Screening tests regarding the inhibition zone were carried out by the well diffusion method [28]. The inoculum suspension was prepared from colonies grown overnight on an agar plate, and inoculated into Mueller-Hinton broth (fungi using malt broth). A sterile swab was immersed in the suspension and used to inoculate Mueller-Hinton agar plates (fungi using malt agar plates and bacteria using nutrient agar plates). The compounds were dissolved in dimethyl sulfoxide (DMSO) with different concentrations (10, 5, 2.5, …… mg/mL) to determine MIC value. The inhibition zone was measured around each well after 48h at 28 °C for fungi and 24 h at 37 °C for bacteria.

The novel synthesized compounds were screened against *Escherichia coli* ATCC25922 as gram-negative bacteria using Gentamycin as a positive control for bacteria (4 μg/mL). The mean zone of inhibition in mm produced on a range of pathogenic microorganisms. Results are depicted in Table 1.

Table 1. The mean zone of inhibition in mm produced on a range of pathogenic microorganisms.

Comp. No.	**3**	**5**	**6a**	**6b**	**8a**	**8b**	**9**	**11**	**13**	**Gentamycin**
E. coli	10	9	9	10	9	11	10	10	11	30

The test was done using the diffusion agar technique, well diameter: 6.0 mm (100 μL was tested). From the table, we note all synthesized compounds showed moderate activity against *Escherichia coli* bacteria.

EXPERIMENTAL

Chemistry

The melting points of the produced compounds were measured at Cairo University. The prepared compounds were analysed at Cairo University using spectrophotometers, they were FTIR plus 460 to measure IR spectra, Hewlett Packard 5988 A GC/MS system to measure MS, Varian Gemini-300 to measure ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) using DMSO-d_6 as a solvent. The antimicrobial activity data was obtained from the antimicrobial activity data unit at the Regional Center for Mycology and Biotechnology (RCMB) in AL-Azhar University.

*2-imino-8,13,13-trimethyl-3,12-diphenyl-3,5,6,8,9,10,11,12-octahydro-2H-8,11-methanochromeno[3,2-f]cinnoline-1-carbonitrile (**3**).* Refluxing malononitrile (0.66 g, 0.01 mol) with compound **1** (4.38 g, 0.01 mol) in EtOH/Et_3N for 4 h. Then the mixture was poured onto ice with stirring, followed by filtration. Beige powder from EtOH, yield (4.00 g, 82.3%), mp 110-112 °C. IR υ_{max} cm^{-1}: 2320 (CN), 2992 (aliphatic CH), 3053 (aromatic CH), NH (3484), C=C (1668). ^{1}H NMR: δ 2.36-2.54 (3s, 9H, $3CH_3$), 1.81-1.91 (2m, 8H, $4CH_2$), 3.30 (t, 1H, camphor CH), 4.57 (s, 1H, NH), 7.07 (s, pyran H-4, 1H), 7.08-7.32 (m, $2C_6H_5$, 10H). ^{13}C NMR: δ 34.4, 36.5, 36.6, 38.89 ($4CH_2$), 14.1, 19.7, 26.8 ($3CH_3$), 125.8, 126.5, 127.8, 128.3, 128.6, 128.8, 129.3, 129.9 ($2C_6H_5$), 56.2, 65.4, 66.8 (camphor CH, camphor 2C), 76.9 (pyran C-4), 128.4, 130.7, 131.9, 132.5 (pyran 2C=C), 115.8 (CN), 155.8, 155.4, 130.2 (pyridazine 2C=N, C=C). Anal. calcd. for $C_{32}H_{30}N_4O$: C, 78.98; H, 6.21; N, 11.51%. Found: C, 78.68; H, 6.11; N, 11.45%. MS: m/z 486.

*2-Imino-8,13,13-trimethyl-3,12-diphenyl-3,5,6,8,9,10,11,12-octahydro-2H-8,11-methanochromeno[3,2-f]cinnolin-1-yl)thiazol-4(5H)-one (**5**).* Refluxing of thioglycolic acid (0. 92 g, 0.01 mol) with compound **3** (4. 86 g, 0.01 mol) in EtOH/Et_3N for 3 h. Then the mixture was poured onto ice with stirring, followed by filtration. Greenish brown powder from EtOH, yield (4.80 g, 85.71%), mp 120-122 °C. IR υ_{max} cm^{-1}: 2992 (aliphatic CH), 3053 (aromatic CH), NH (3485), C=O (1760). ^{1}H NMR: δ 2.26-2.38 (3s, 9H, $3CH_3$), 1.78-1.98 (2m, 8H, $4CH_2$), 3.09 (t, 1H, camphor CH), 4.85 (s, 1H, NH), 6.79 (s, pyran H-4, 1H), 7.07-7.47 (m, $2C_6H_5$, 10H), 3.65 (s, 2H, thiazole). ^{13}C NMR: δ 33.9, 35.4, 37.6, 39.8 ($4CH_2$), 38.8 (thiazole CH_2), 14.6, 19.8, 26.6 ($3CH_3$), 124.8, 125.5, 126.8, 127.3, 129.6, 129.8, 130.2, 130.3 ($2C_6H_5$), 56.1, 65.3, 66.9 (camphor CH, camphor 2C), 77.2 (pyran C-4), 127.3, 128.6, 128.8, 130.4 (pyran 2C=C), 155.2, 155.3, 132.6 (pyridazine 2C=N, C=C), 160.4 (thiazole C=N), 166.4 (thiazole C=O). Anal. calcd. for $C_{34}H_{32}N_4O_2S$: C, 72.83; H, 5.75; N, 9.99; S, 5.72%. Found: C, 72.43; H, 5.49; N, 9.68; S, 5.35%. MS: m/z 560.

*Synthesis of the methanochromeno[3,2-f]cinnolin-1-yl)thieno[3,2-d]thiazole derivatives **6a,b**.* Refluxing of ethyl cyanoacetate (1.13 g, 0.01 mol) or malononitrile (0.66 g, 0.01 mol) and sulfur

(0.32 g, 0.01 mol) with compound **5** (5.60 g, 0.01 mol) in EtOH/Et_3N for 4 h. Then the mixture was poured onto ice with stirring, followed by filtration.

Ethyl 5-amino-2-imino-8,13,13-trimethyl-3,12-diphenyl-3,5,6,8,9,10,11,12-octahydro-2H-8,11-methanochromeno[3,2-f]cinnolin-1-yl)thieno[3,2-d]thiazole-6-carboxylate ***6a***. Yellowish green powder from EtOH, yield (5.80 g, 84.43%), mp 171-173 °C. IR υ_{max} cm^{-1}: 2997 (aliphatic CH), 3055 (aromatic CH), NH (3480), C=C (1668). ^{1}H NMR: δ 2.20-2.66 (3s, 9H, $3CH_3$), 1.84-1.92 (2m, 8H, $4CH_2$), 3.10 (t, 1H, camphor CH), 4.56 (s, 1H, NH), 7.10 (s, pyran H-4, 1H), 7.11-7.59 (m, $2C_6H_5$, 10H), 4.2 (q, 2H, CH_2), 1.15 (t, 3H, CH_3), 4.7 (s, 2H, NH_2). ^{13}C NMR: δ 32.2, 32.4, 34.2, 34.8 ($4CH_2$), 14.2, 18.6, 28.2 ($3CH_3$), 122.8, 123.4, 123.5, 123.6, 123.8, 124.4, 125.3, 125.8 ($2C_6H_5$), 55.2, 64.4, 67.8 (camphor CH, camphor 2C), 75.6 (pyran C-4), 126.3, 126.6, 128.4, 128.6 (pyran 2C=C), 155.4, 155.8, 130.4 (pyridazine 2C=N, C=C), 164.6 (thiazole C=N), 126.5, 126.7, 128.4, 129.4 (thiophene 2C=C), 159.2 (C=O), 38.9 (ester CH_2), 28.4 (ester CH_3). Anal. calcd. for $C_{39}H_{37}N_5O_3S_2$: C, 68.10; H, 5.42; N, 10.18; S, 9.32%. Found: C, 67.94; H, 5.35; N, 9.87; S, 8.98%. MS: m/z 687.

5-Amino-2-imino-8,13,13-trimethyl-3,12-diphenyl-3,5,6,8,9,10,11,12-octahydro-2H-8,11-methanochromeno[3,2-f]cinnolin-1-yl)thieno[3,2-d]thiazole-6-carbonitrile compound with methane (1:1) ***6b***. Brown powder from ethanol, yield (5.80 g, 90.63%), mp 160-162 °C. IR υ_{max} cm^{-1}: 2335 (CN), 2985 (aliphatic CH), 3056 (aromatic CH), NH (3485), C=C (1660). ^{1}H NMR: δ 2.21-2.50 (3s, 9H, $3CH_3$), 1.81-1.95 (2m, 8H, $4CH_2$), 3.06 (t, 1H, camphor CH), 4.56 (s, 1H, NH), 7.09 (s, pyran H-4, 1H), 7.10-7.58 (m, $2C_6H_5$, 10H), 3.34 (s, 2H, NH_2). ^{13}C NMR: δ 36.3, 37.4, 37.6, 38.8 ($4CH_2$), 14.2, 18.6, 20.7 ($3CH_3$), 126.8, 128.5, 128.8, 129.3, 129.8, 130.3, 130.6, 130.8 ($2C_6H_5$), 55.2, 66.5, 66.9 (camphor CH, camphor 2C), 75.2 (pyran C-4), 128.5, 128.6, 130.8, 130.4 (pyran 2C=C), 151.8, 152.4, 128.2 (pyridazine 2C=N, C=C), 163.2 (thiazole C=N), 128.4, 128.7, 130.2, 132,6 (thiophene 2C=C), 115.4 (CN). Anal. calcd. for $C_{37}H_{32}N_6OS_2$: C, 69.35; H, 5.03; N, 13.11; S, 10.01%. Found: C, 69.10; H, 4.93; N, 12.88; S, 9.82%. MS: m/z 640.

Synthesis of the methanochromeno[3,2-f]cinnolin-1-yl)-7-phenyl-7H-pyrano[2,3-d]thiazole derivatives ***8a,b***. Refluxing of ethyl cyanoacetate (1.13 g, 0.01 mol) or malononitrile (0.66 g, 0.01 mol) and benzaldehyde (1.06 g, 0.01 mol) with compound **5** (5.60 g, 0.01 mol) in EtOH/Et_3N for 4 h. Then the mixture was poured onto ice with stirring, followed by filtration.

*Ethyl 5-amino-2-imino-8,13,13-trimethyl-3,12-diphenyl-3,5,6,8,9,10,11,12-octahydro-2H-8,11-methanochromeno[3,2-f]cinnolin-1-yl)-7-phenyl-7H-pyrano[2,3-d]thiazole-6-carboxylate (****8a****)*. Beige powder from EtOH, yield (6.95 g, 91.33%), mp 227-229 °C. IR υ_{max} cm^{-1}: 2997 (aliphatic CH), 3058 (aromatic CH), NH_2 (3480), C=O (1730). ^{1}H NMR: δ 2.51-3.26 (3s, 9H, $3CH_3$), 1.92-2.25 (2m, 8H, $4CH_2$), 2.61 (t, 1H, camphor CH), 4.57 (s, 1H, NH), 7.17, 7.20 (s, 2pyran H-4, 2H), 7.57-7.66 (m, $3C_6H_5$, 15H), 8.04 (s, 2H, NH_2), 4.29 (q, 2H, CH_2), 1.29 (t, 3H, CH_3). ^{13}C NMR: δ 34.3, 36.4, 36.6, 38.8 ($4CH_2$), 14.4, 19.6, 26.7 ($3CH_3$), 120.2, 120.4, 120.6, 122.2, 122.6, 122.8, 123.2, 123.4, 124.6, 124.8, 125.2, 125.4 ($3C_6H_5$), 56.2, 64.6, 66.7 (camphor CH, camphor 2C), 78.2, 79.8 (2pyran C-4), 128.2, 128.4, 129.2, 130.2, 130.6, 131.8, 132.5, 132.8 (2pyran 4C=C), 154.4, 154.8, 134.2 (pyridazine 2C=N, C=C), 163.8 (thiazole C=N), 167.1 (CO), 44.6 (ester CH_2), 28.8 (ester CH_3). Anal. calcd. for $C_{46}H_{43}N_5O_4S$: C, 72.51; H, 5.69; N, 9.19; S, 4.21%. Found: C, 72.24; H, 5.43; N, 8.85; S, 3.94%. MS: m/z 761.

*5-Amino-2-imino-8,13,13-trimethyl-3,12-diphenyl-3,5,6,8,9,10,11,12-octahydro-2H-8,11-methanochromeno[3,2-f]cinnolin-1-yl)-7-phenyl-7H-pyrano[2,3-d]thiazole-6-carbonitrile (****8b****)*. Reddish brown powder from EtOH, yield (6.80 g, 95.24%), mp 149-150 °C. IR υ_{max} cm^{-1}: 2300 (CN), 2990 (aliphatic CH), 3050 (aromatic CH), NH_2 (3480), C=C (1665). ^{1}H NMR: δ 2.20-2.50 (3s, 9H, $3CH_3$), 1.84-1.97 (2m, 8H, $4CH_2$), 3.08 (t, 1H, camphor CH), 4.50 (s, 1H, NH), 6.75 (s, 2pyran

H-4, 2H), 7.09-7.60 (m, $3C_6H_5$, 15H), 8.14 (s, 2H, NH_2). ^{13}C NMR: δ 33.9, 35.4, 36.2, 38.4 ($4CH_2$), 14.6, 18.6, 27.8 ($3CH_3$), 121.3, 121.5, 122.2, 122.4, 123.2, 123.4, 124.3, 124.6, 124.8, 125.2, 125.4, 125.6 ($3C_6H_5$), 55.2, 64.3, 67.8 (camphor CH, camphor 2C), 76.2, 78.8 (2pyran C-4), 125.6, 125.8, 127.4, 127.6, 127.8, 129.2, 129.4, 130.4 (2pyran 4C=C), 155.4, 155.8, 130.7 (pyridazine 2C=N, C=C), 164.2 (thiazole C=N), 115.1 (CN). Anal. calcd. for $C_{44}H_{38}N_6O_2S$: C, 73.92; H, 5.36; N, 4.48; S, 4.49%. Found: C, 73.65; H, 5.09; N, 4.19; S, 4.52%. MS: m/z 714.

*5-Amino 2-imino-8,13,13-trimethyl-3,12-diphenyl-3,5,6,8,9,10,11,12-octahydro-2H-8,11-methanochromeno[3,2-f]cinnolin-1-yl)-7-phenyl-4,7-dihydrothiazolo[4,5-b]pyridine-6-carbonitrile **9**.* Refluxing of benzaldehyde (1.06 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) with compound **5** (5.60 g, 0.01 mol) in EtOH/$AcONH_4$ for 3 h. Then the mixture was poured onto ice with stirring, followed by filtration. Light brown powder from EtOH, yield (5.99 g, 84.01%), mp 144-146 °C. IR υ_{max} cm^{-1}: 2389 (CN), 2988 (aliphatic CH), 3059 (aromatic CH), NH_2 (3487), C=C (1668). ^1H NMR: δ 2.37-3.48 (3s, 9H, $3CH_3$), 1.85-2.26 (2m, 8H, $4CH_2$), 2.57 (t, 1H, camphor CH), 4.11, 4.58 (s, 2H, 2NH), 8.52 (s, 2H, NH_2), 7.96 (s, 1H, pyridine H-4), 6.74 (s, pyran H-4, 1H), 7.12-7.59 (m, $3C_6H_5$, 15H). ^{13}C NMR: 34.6, 36.6, 36.8, 39.2 ($4CH_2$), δ 14.8, 18.8, 28.7 ($3CH_3$), 122.2, 122.6, 122.8, 123.2, 123.4, 123.6, 123.8, 124.6, 124.8, 125.2, 125.4, 125.8 ($3C_6H_5$), 56.4, 65.6, 66.7 (camphor CH, camphor 2C), 78.4 (pyran C-4), 126.2, 126.4, 126.8, 127.2 (pyran 2C=C), 155.2, 155.4, 130.2 (pyridazine 2C=N, C=C), 166.2 (thiazole C=N), 115.4 (CN), 132.4, 133.2, 133.4, 133.6 (pyridine 2C=C), 78.6 (pyridine C-4). Anal. calcd. for $C_{44}H_{39}N_7OS$: C, 74.03; H, 5.51; N, 13.73; S, 4.49%. Found: C, 73.93; H, 5.24; N, 13.46; S, 4.52%. MS: m/z 713.

*(8S,11R)-8,13,13-Trimethyl-3,12-diphenyl-1-(4-(2-phenylhydrazono)-4,5-dihydrothiazol-2-yl)-3,5,6,8,9,10,11,12-octahydro-2H-8,11-methanochromeno[3,2-f]cinnolin-2-imine (**11**).* Refluxing of phenylhydrazine (1.08 g, 0.01 mol) with compound **5** (5.60 g, 0.01 mol) in EtOH/Et_3N for 3 h. Then the mixture was poured onto ice with stirring, followed by filtration. Brown powder from EtOH, yield (5.75 g, 88.46%), mp 149-150 °C. IR υ_{max} cm^{-1}: 2992 (aliphatic CH), 3057 (aromatic CH), NH (3483), C=C (1660). ^1H NMR: δ 2.50-3.34 (3s, 9H, $3CH_3$), 1.84-2.21 (2m, 8H, $4CH_2$), 2.70 (t, 1H, camphor CH), 3.87, 4.58 (s, 2H, 2NH), 1.23 (s, 2H, CH_2 of thiazole), 6.73 (s, pyran H-4, 1H), 7.10-7.62 (m, $3C_6H_5$, 15H). ^{13}C NMR: δ 32.4, 34.6, 34.8, 36.2 ($4CH_2$), 36.4 (thiazole CH_2), 14.2, 18.4, 22.8 ($3CH_3$), 122.2, 122.4, 123.6, 123.8, 124.6, 124.8, 126.4, 126.8, 127.2, 127.4, 127.6, 127.8 ($3C_6H_5$), 56.3, 65.5, 67.3 (camphor CH, camphor 2C), 76.8 (pyran C-4), 128.3, 130.6, 131.8, 132.4 (pyran 2C=C), 155.5, 155.8, 132.6 (pyridazine 2C=N, C=C), 163.20, 172.4 (thiazole 2C=N). Anal. calcd. for $C_{40}H_{38}N_6OS$: C, 73.82; H, 5.89; N, 12.91; S, 4.93%. Found: C, 73.55; H, 5.60; N, 12.64; S, 4.67%. MS: m/z 650.

*2-Imino-8,13,13-trimethyl-3,12-diphenyl-3,5,6,8,9,10,11,12-octahydro-2H-8,11-methanochromeno[3,2-f]cinnolin-1-yl)thiazol-4-yl)-2,5-diphenyl-1H-pyrazol-3(2H)-one (**13**).* Refluxing of ethyl benzoylacetate (1.92 g, 0.01 mol) with compound **11** (6.50 g, 0.01 mol) in EtOH/Et_3N for 3 h. Then the mixture was poured onto ice with stirring, followed by filtration. White powder from EtOH, yield (6.70 g, 86.12%), mp 236-238 °C. IR υ_{max} cm^{-1}: 2982 (aliphatic CH), 3046 (aromatic CH), NH (3460), C=O (1765). ^1H NMR: δ 2.34-3.36 (3s, 9H, $3CH_3$), 1.84-2.26 (2m, 8H, $4CH_2$), 2.71 (t, 1H, camphor CH), 3.42 (s, 1H, pyrazole CH), 5.42 (s, 1H, thiazole CH), 4.58 (s, 1H, NH), 7.09 (s, pyran H-4, 1H), 7.18-7.35 (m, $4C_6H_5$, 20H). ^{13}C NMR: δ 34.6, 36.8, 37.2, 38.6 ($4CH_2$), 14.6, 20.2, 26.8 ($3CH_3$), 120.2, 120.4, 121.6, 121.8, 124.8, 125.2, 125.4, 125.6, 125.8, 126.0, 126.2, 126.4, 126.8, 127.4, 127.6, 127.8 ($4C_6H_5$), 55.4, 65.6, 66.8 (camphor CH, camphor 2C), 77.6 (pyran C-4), 128.3, 130.6, 131.8, 132.4 (pyran 2C=C), 154.8, 155.6, 132.6 (pyridazine 2C=N, C=C), 163.5 (thiazole C=N), 125.2, 130.8 (thiazole C=C), 132.8, 133.4 (pyrazole C=C), 168 (C=O). Anal. calcd. for $C_{49}H_{42}N_6O_2S$: C, 75.55; H, 5.43; N, 10.79; S, 4.12%. Found: C, 75.37; H, 5.15; N, 10.55; S, 3.87%. MS: m/z 778.

CONCLUSION

In this work we focused on the synthesis of fused heterocyclic compounds derived from camphor with antibacterial activity. Pyridazine, xanthene, pyranothiazole, pyridinothiazole, thiophene and pyrazole derivatives were produced from 1,4-methanoxanthen-8(2*H*)-one derivative **1**. These fused heterocyclic compounds formed by the multicomponent reactions between reactants. The antibacterial activity of the synthesized compounds was examined against *E. coli* bacteria. The result showed that all synthesized compounds **3**, **5**, **6a**,**b**, **8a**,**b**, **9**, **11** and **13** have moderate activity against *E. coli* bacteria. The work can be extended for the synthesis of different heterocyclic compounds using camphor and applying our procedures for the multicomponent reactions.

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