Bull. Chem. Soc. Ethiop. **2024**, 38(6), 1815-1826.
DOI: https://dx.doi.org/10.4314/bcse.v38i6.24

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

SYNTHESIS AND *IN VITRO* SCREENING OF BENZO[*h*]COUMARINYL HETEROCYCLES AS PROMISING ANTIBACTERIAL AGENTS

Abdallah. F. Al burgus, Omar T. Ali and Omar Y. Mohammad

Department of Chemistry, College of Education for Pure Science, University of Mosul, Nineveh-Iraq

(Received March 4, 2024; Revised June 13, 2024; Accepted June 18, 2024)

ABSTRACT. In this study, benzo[*h*]coumarin and the corresponding substituted chalcones were designed and synthesized. These compounds have been used as a precursor to prepare various heterocyclic compounds like pyrimidines, pyrazole, pyrazole-1-carbothioamide, diazepines, oxazepines, isoxazoles and epoxides. The structures of the synthesized compounds were confirmed by FT-IR, ^{1}H and ^{13}C-NMR spectroscopy. These target heterocyclic derivatives were biologically screened against *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) pathogenic bacteria. The best obtained result was for compound (**6b**) against *S. aureus*, Gram-positive bacteria.

KEY WORDS: Benzo[*h*]coumarin, heterocyclic compounds, antibacterial activity

INTRODUCTION

A primary cause of high morbidity and death globally is the continuing increase in bacterial infections, which is explained by the development of antibacterial and antifungal drug resistance [1]. The rise of new microbial diseases and the development of antibiotic resistance make the development of new antimicrobial drugs for the treatment of microbial infections critically necessary [2]. An antimicrobial is a substance that either inhibits the growth of bacteria or eliminates them [3]. Among significant types of biological molecules are the heterocyclic compounds [4]. They are thought to belong to a class of substances that significantly affect how different diseases are treated. Also, these heterocyclic motif-containing chemicals are often used as food additives, cosmetics, pharmaceuticals, and well-known antimicrobials [5]. Compounds containing N and O are highly potent and crucial for drug manufacturing. In the field of medical chemistry, oxygen-containing heterocyclic molecules are essential [6]. Among heterocycles, the lactone-ring system is one of the most prevalent [7]. Coumarin scaffolds and their derivatives exhibit many therapeutic and biological properties [8-10]. They have been described as, anticoagulant, antioxidan [11], potassium channel opener [12], antiviral [13], anti-Alzheimer [14], antifungal and anticancer [15] agents (Figure 1).

Furthermore, it has been found that coumarin derivatives function as acetyl cholinesterase inhibitors [16-18]. A few coumarin compounds have been found to be used as diagnostic tools. Drug resistance must become a growing concern in the treatment of incurable diseases [19]. The medical concern of bacterial resistance to the traditional antibiotics has been exacerbated [20]. As well as leading to challenges in the development of potent antimicrobial medications with optimum activity [21]. Usually, the benzopyran ring is chemically modified to produce coumarin derivatives. The von Pechmann, Perkin, Knoevenagel, Reformatski, Kostanecki-Robinson, Wittig and Baylis-Hillman reactions, in addition to the intramolecular Claisen condensation and Baker-Venkataraman rearrangement, are all used in the classical method of coumarin production [22]. Many application of benzocoumarin derivatives are in the field of medicinal chemistry [23]. The coumarin skeleton is still an important source of number of important antibiotics and antifungal components, including novobiocin, coumermycin A1, and chlorobiocin [24]. Therefore, what is presented herein is the synthesis of novel hybrid molecules by the reaction of 3-nitrobenzaldehyde

*Corresponding authors. E-mail: abdallah.21esp11@student.uomosul.edu.iq

or 4-methoxy benzaldehyde with 3-acetyl-2H-benzo [*h*] chromen-2-one for making substituted chalcones. These chalcones were used as a starting material for perparing important benzo[*h*]coumarin heterocycles such as pyrimidines, phenyl pyrazole, pyrazole-1-carbothioamide, oxazepine, isoxazole and epoxides. In addition, the initial in *vitro* assessment of some synthesized compounds as antimicrobial agents against two bacterial species, *S. aureus* and *E. coli* has been screened.

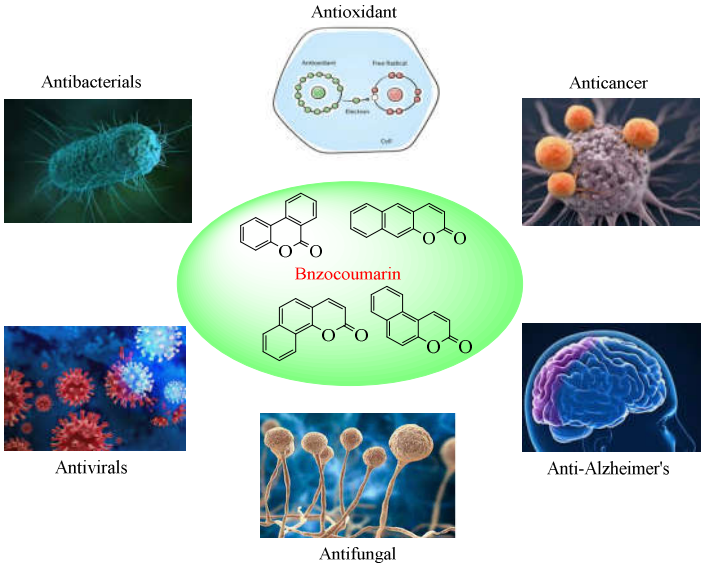
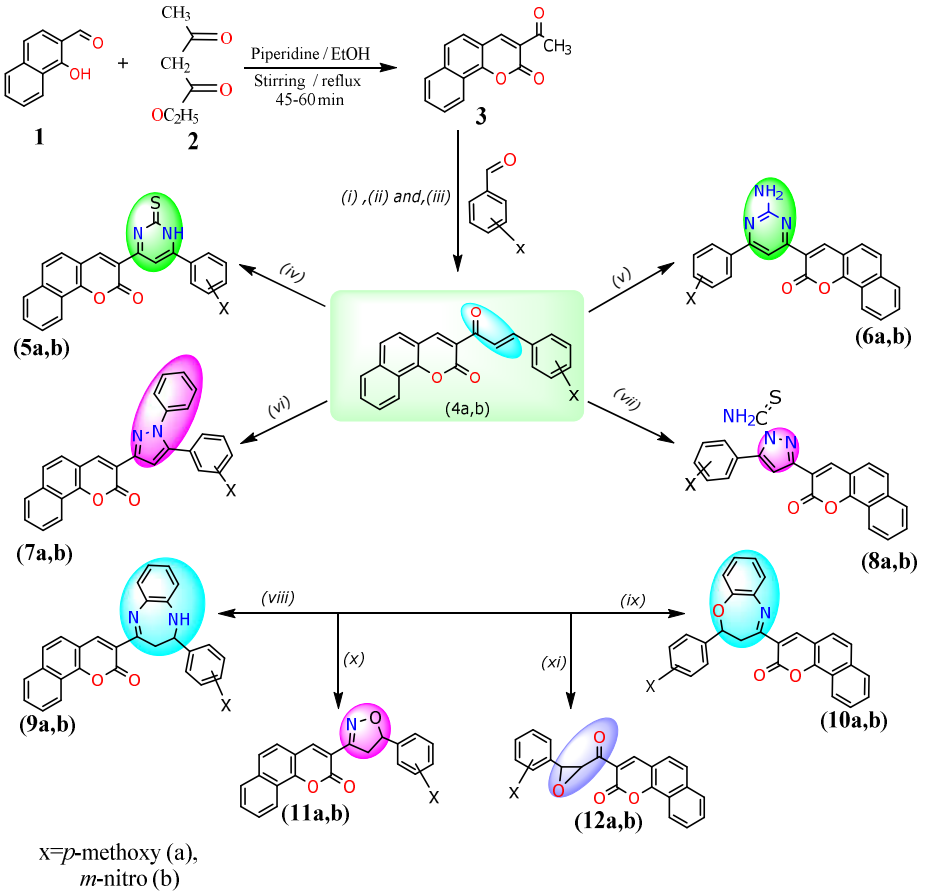


Figure 1. Some applications of benzocoumarin nucleus.

RESULTS AND DISCUSSION

Various nucleophilic reagents including thiourea, guanidine, phenyl hydrazine, thiosemicarbazide, benzene-1,2-diamine, 2-amino phenol, hydroxyl amine hydrochloride and hydrogen peroxide were used and reacted with chalcones **(4a,b)** to form the heterocyclic compounds such as pyrimidines, phenyl pyrazoles, pyrazole-1-carbothioamide, diazepines, oxazepines, isoxazoles and epoxides **(5a,b-12a,b)** respectively (Scheme 1). All the synthesized compounds were established by FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy.

The chemical structure of synthesized compounds was confirmed by spectral data. The FT-IR spectra of compounds **4a**–**12b** exhibited absorption bands in the range of 1708–1735 cm^{-1} due to the lactone carbonyl stretching. Compounds **4a** and **4b** showed two bands assignable to the (C=O) carbonyl group stretching of chalcone at 1672 and 1673 cm^{-1} respectively [25, 26]. Compounds **5a**–**11b** showed stretching bands of (C=N) group in the range of 1602–1680 cm^{-1}. Compounds **5a**, **b**, **9a** and **9b** presented stretching bands for (N-H) group in the range of 3324–3341 cm^{-1} [25-30]. In addition, compounds **6a**, **6b**, **8a** and **8b** showed two bands in the range of 3140–3293 cm^{-1} due to the primary amine (NH_2) stretching of pyrimidin-2-amine and pyrazole-1-carbothioamide [27-29]. Other absorption bands corresponding to substituents were comprehensively analyzed.



Scheme 1. Synthesis of benzo[h]coumarin-chalcone derivatives (**4a**,**b** - **12a**,**b**). Reagents and conditions: (i) EtOH. (ii) Piperidine. (iii) Stirring and reflux 6-10 h, 65-75 °C. (iv) NH_2CSNH_2, 10% KOH. (v) NH_2CNHNH_2, 10% KOH. (vi) $PhNHNH_2$, Gla, CH_3COOH. (vii) $NH_2NHCSNH_2$, Gla, CH_3COOH. (viii) benzene-1,2-diamine, Gla, CH_3COOH. (ix) 2-aminophenol, Gla, CH_3COOH. (x) $NH_2OH.HCl$, 10% KOH. (xi) 30% H_2O_2, (5N. NaOH).

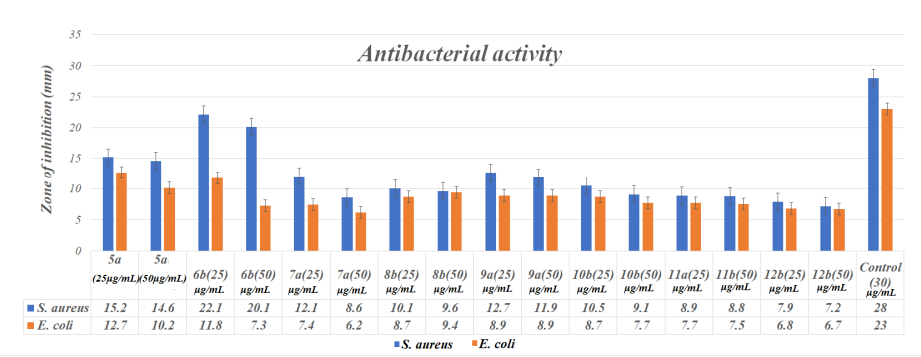
The ^{1}H-NMR spectral data of compounds **4a–12b** showed signals of the benzocoumarin moiety (C4-H), and were resonated as singlets in the range of δ = 8.12–8.90 ppm [25]. Compounds **4a** and **4b**, exhibited two doublets for each one related to protons of the α,β-unsaturated chalcone at δ = 6.98, 7.46 and 7.15, 7.30 ppm respectively [25, 26]. Compounds **5a**, **5b**, and **9a**, **9b** showed broad singlets in the range of δ = 11.53–11.93 ppm due to the N-H group [25-30]. Compounds **5a–6b** presented singlets in the range of δ = 6.78–7.20 ppm indicating to the (CH=C) group of the pyrimidine ring, whereas singlets of the (CH=C) group for pyrazoline ring **7a–8b** were appeared in the range of δ = 6.85–7.20 ppm [25, 28]. Compounds **9a-11b** demonstrated doublet of doublet in the range δ = 4.42–5.69 ppm, indicating that the (Ar-CH-) proton of diazpine, oxazpine, and isoxazole is present. Also, protons of the five and seven membered rings resonated as doublet of doublet in the range of δ = 2.38–3.47 ppm due to the (-CH_2-) [29-31]. Compounds **12a** and **12b**

exhibited two doublets for each corresponding to the oxirane (epoxide) ring at 3.75, 3.87 ppm, and 3.73, 3.86 ppm, respectively [32].

The ^{13}C-NMR spectra of compounds **4a–12b** showed that the C4 of the benzocoumarin moiety was resonated in the range of δ = 153.3–169.8 ppm [25-29]. Compounds **4a** and **4b** exhibited signals due to the carbonyl group (C=O) of the chalcone at δ = 195.0 and 196.0 ppm respectively [25, 26]. Compounds **5a–11b** presented peaks in the range of δ = 152.7–162.2 ppm due to the carbon of C=N group [27-32]. Compounds **5a–6b** revealed peaks in the range of δ = 91.7–110.6 ppm and δ = 156.4–185.4 ppm [27–29], referring to the (-CH=C-Ar) carbons of the pyrimidine ring, whereas **7a–8b** in the pyrazoline ring which have the same group appeared in the range of δ = 111.2–109.5 ppm and δ = 148.9–142.9 ppm, respectively [25, 28]. Compounds **9a–11b** presented two peaks in the range of δ = 67.7–39.8 ppm, and δ = 66.1–24.3 ppm, pointing to the (-CH_2-CH-) of the diazpine, oxazpine, and isoxazole ring [30-31]. Compounds **12a** and 12**b** showed peaks of the carbonyl group in the regions δ = 195.3 ppm and δ = 191.9 ppm, respectively. Also, same compounds showed peaks related to carbons of the oxirane (epoxide) ring at δ = 93.2, 66.1 ppm, and δ = 66.9, 56.12 ppm, respectively [32].

Antibacterial activity

As shown in Figure 2, the results exhibited that some of the synthetic compounds possessed antibacterial activity compared with ceftriaxone as control. It was noted that the best inhibition zone was for compound (**6b**) against *S. aureus*, while the least effect on the same bacteria was with compound (**12b**). The *E. coli* inhibition zone was effected significantly by using compound (**5a**), but slight effect was noted with compound (**8b**).



	5a (25µg/mL)	5a (50µg/mL)	6b(25) µg/mL	6b(50) µg/mL	7a(25) µg/mL	7a(50) µg/mL	8b(25) µg/mL	8b(50) µg/mL	9a(25) µg/mL	9a(50) µg/mL	10b(25) µg/mL	10b(50) µg/mL	11a(25) µg/mL	11b(50) µg/mL	12b(25) µg/mL	12b(50) µg/mL	Control (30) µg/mL
S. aureus	15.2	14.6	22.1	20.1	12.1	8.6	10.1	9.6	12.7	11.9	10.5	9.1	8.9	8.8	7.9	7.2	28
E. coli	12.7	10.2	11.8	7.3	7.4	6.2	8.7	9.4	8.9	8.9	8.7	7.7	7.7	7.5	6.8	6.7	23

Figure 2. Antibacterial activity of benzocoumarin derivatives.

EXPRIMENTAL

Materials and methods

All the chemicals ordered from BDH and Sigma-Aldrich were used without further purification. The following methods were employed in this research: ^{1}H NMR spectra were determined on Bruker 400 MHz, with TMS (Tetramethylsilane) used as an internal reference. ^{13}C NMR (100 MHz, Bruker) DMSO-d_6 was used as the solvent. FT-IR (Bruker Alpha Platinum- ATR) was conducted. 0.2 mm silica gel 60F_{254} plates from (Merck, Darmstadt, Germany) using UV light for detection, column chromatography and other equipment.

Synthesis methods

*Synthesis of 3-acetyl-2H-benzo[h]chromen-2-one **(3)***

A mixture of 1-hydroxy-2-naphthaldehyde (**1**) (0.05 mol) and ethyl acetoacetate (**2**) (0.01 mol) was dissolved in absolute ethanol (30) mL, and (0.5) mL of piperidine was added. The reaction mixture was refluxed with stirring on a water bath for 4 h. After the completion of reaction, the reaction mixture was poured into (100 g) of crushed ice with stirring [25]. The precipitate obtained was filtered off and purified by column chromatography to give the target compound.

*Synthesis of 3-acetyl-2H-benzo[h]chromen-2-one (**3**)*. $C_{15}H_{10}O_3$, color: yellowish crystals, yield: 70%, m.p.: 185-187 °C, R_f = 0.89, DCM: Hex : EtOAc (1:7:2); FT-IR(ATR) (ν, cm^{-1}): 3030 (ArC-H), 2929 (C–H, CH_3), 1739 (C=$O_{lactone}$), 1674 (C=O_{ketone}), 1209 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.56 (d, 1H, *J* = 8.5 Hz, H $_{Ar}$), 8.34 (s, 1H, $H_{4coumarin}$), 7.99–7.90 (m, 1H, H $_{Ar}$), 7.64–7.55 (m, 2H, H_{Ar}), 7.29–7.20 (m, 1H, H $_{Ar}$), 7.14–7.06 (m, 1H, H_{Ar}), 2.24 (s, 3H, -CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.6, 153.3, 150.3, 143.0, 135.8, 132.6, 131.1, 129.1, 125.1, 124.2, 119.1, 117.4, 116.0, 112.9, 30.0.

Synthesis of benzo[h]coumarin-chalcone

*A general procedure for the synthesis of 3-(3-aryl) acryloyl benzo[h]chromen-2-one (**4a**,**b**)*

4-Methoxybenzaldehyde and/or 3-nitrobenzaldehyde (0.02 mol) was dissolved in 25 mL of absolute ethanol, and 0.1 mL piperidine was added, the mixture was refluxed with stirring for 10-12 h [26]. Then the mixture was cooled, filtered off. The crude product was further purified by column chromatography to give the target compounds (**4a**,**b**).

*3-(3-(4-Methoxyphenyl) acryloyl)-2H-benzo[h]chromen-2-one (**4a**)*. $C_{23}H_{16}O_4$, color: yellow crystals, yield: 60%, m.p.: 190-192 °C, R_f = 0.85, DCM: Hex:EtOAc (1:7:2); FT-IR(ATR) (ν, cm^{-1}): 3044 (ArC-H), 2930 (Ar-OCH_3), 1731 (C=$O_{lactone}$), 1672 (C=$O_{chalcone}$), 1621, 1596 (C=C), 1207 (C-O), ^{1}H NMR (400 MHz, DMSO-d_6 , ppm) : δ 8.61 (s, 1H, $H_{4coumarin}$), 7.88–7.75 (m, 3H, H_{Ar}), 7.60 (d, *J* = 7.4 Hz, 2H, H_{Ar}), 7.46 (d, *J* = 8.7 Hz, 1H, Hβ$_{vinylic}$), 7.35–7.24 (m, 2H, H_{Ar}), 7.23–7.14 (m, 1H, H_{Ar}), 6.98 (d, *J* = 7.5 Hz, 1H, Hα$_{vinylic}$), 3.85 (s, 3H, -OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ195.0, 162.4, 158.3, 155.2, 142.3, 136.1, 133.5, 129.8, 129.3, 129.0, 128.9, 126.5, 126.4, 122.9, 122.3, 122.1, 116.5, 116.2, 114.4, 113.3, 57.4.

*3-(3-(3-Nitrophenyl) acryloyl)-2H-benzo[h]chromen-2-one(**4b**)*. $C_{22}H_{13}NO_5$, color: greenish yellow crystals, yield: 63%, m.p.: 203-205 °C, R_f = 0.81, DCM:Hex:EtOAc (2:6:2); FT-IR(ATR) (ν, cm^{-1}): 3018 (ArC-H), 1733(C=$O_{lactone}$), 1673 (C=$O_{chalcone}$), 1591, 1581 (C=C), 1207 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.70(s, 1H, $H_{4coumarin}$), 8.62-8.53 (m, 2H, H_{Ar}), 8.01-7.92 (m, 2H, H_{Ar}), 7.61(m, 6H, H_{Ar}), 7.30 (d, 1H, *J* = 8.4 Hz,Hβ$_{vinylic}$), 7.15 (d, 1H, *J* = 7.2 Hz,Hα$_{vinylic}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.0, 169.8, 163.8, 163.5, 159.4, 156.3, 143.4, 137.1, 134.5, 130.8, 130.3, 130.1, 130.0, 127.5, 127.4, 124.0, 123.3, 123.2, 117.4, 117.3, 115.5, 114.3.

Synthesis of different pyrimidines

A mixture of the selected chalcone (**4a**,**b**) (0.004 mol), thiourea and/or guanidine HCl (0.004 mol) in ethanol 25 mL, and a solution of potassium hydroxide (0.2 g) in water 2 mL was added, the reaction mixture was refluxed with stirring for 5–7 h. Then, dried under vacuo using a rotary evaporator until dryness and the residue was acidified with dil. HCl and washed, filtered off [27]. The crude product was further purified by column chromatography to give the target compounds (**5a**,**b**) and (**6a**,**b**).

3-(6-(4-Methoxyphenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)-2H-benzo[h]chromen-2-one ***(5a)***. $C_{24}H_{16}N_2O_2S$, color: brown crystals, yield: 65%, m.p.: 214–216 °C, R_f = 0.73, DCM : Hex : EtOAc (2:7:1); FT-IR (ATR) (ν, cm^{-1}): 3064 (ArC-H), 2931(Ar-OCH_3), 1710 (C=$O_{lactone}$), 1682 (C=N), 1213 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 11.93 (s, 1H, NH-C=S), 8.34 (s, 1H, $H_{4coumarin}$), 8.18–8.06 (m, 1H, H_{Ar}), 7.69–7.61 (m, 1H, H_{Ar}), 7.45–7.36 (m, 1H, H_{Ar}), 7.18–7.10 (m, 1H, H_{Ar}), 7.01–6.92 (m, 2H, H_{Ar}), 6.89–6.80 (m, 2H, H_{Ar}), 6.78 (s, 1$H_{pyrmidine}$), 6.54 (m, 1H), 3.63 (s, 3H, -OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6): 181.1, 170.1, 160.2, 158.3, 154.7, 150.2, 149.8, 143.0, 136.2, 130.4, 129.5, 129.3, 128.2, 127.0, 125.7, 124.1, 122.9, 122.7, 119.4, 118.5, 91.7, 55.9.

3-(6-(3-Nitrophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)-2H-benzo[h]chromen-2-one ***(5b)***. $C_{23}H_{13}N_3O_4S$, color: light yellow crystals, yield: 69%, m.p.: 224-226 °C, R_f = 0.70, DCM : Hex : EtOAc (2:7:1); FT-IR (ATR) (ν, cm^{-1}): 3018 (ArC-H), 1735 (C=$O_{lactone}$), 1672 (C=N), 1207 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6,ppm): δ 11.58 (s, 1H, NH-C=S), 8.12 (s, 1H, $H_{4coumarin}$), 7.69–7.61 (m, 2H, H_{Ar}), 7.44–7.35 (m, 1H, H_{Ar}), 7.30–7.22 (m, 2H, H_{Ar}), 7.15–7.08 (m, 1H, H_{Ar}), 7.01–6.92 (m, 2H, H_{Ar}), 6.83 (s, 1$H_{pyrmidine}$), 6.80 (m, 2H, H_{Ar}), 6.74 (m, 1H, H_{Ar}). ^{13}C NMR (100 MHz, DMSO-d_6): δ 187.3, 185.4, 161.9, 160.7, 158.8, 155.1, 150.6, 150.2, 143.4, 136.6, 135.5, 130.8, 129.9, 129.7, 128.6, 127.4, 126.1, 124.5, 123.3, 123.1, 119.8, 119.0, 92.1.

3-(2-Amino-6-(4-methoxyphenyl)pyrimidin-4-yl)-2H-benzo[h]chromen-2-one ***(6a)***. $C_{24}H_{17}N_3O_3$, color: yellowish crystals, yield: 66%, m.p.: 231–233 °C, R_f = 0.77, DCM : Hex : EtOAc (2:7:1) ; FT-IR (ATR) (ν, cm^{-1}): 3214, 3293 (NH_2), 3023 (ArC-H), 2933 (Ar-OCH_3), 1735(C=$O_{lactone}$), 1602 (C=N), 1211 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.12 (s,1H, $H_{4coumarin}$), 7.72–7.59 (m, 2H, H_{Ar}), 7.44 (d, 1H, J = 8.6 Hz, H_{Ar}), 7.30–7.22 (m, 2H, H_{Ar}), 7.12 (s, 1$H_{pyrmidine}$), 6.85 (s, 2H, H $_{Ar}$), 6.81–6.74 (m, 1H, H $_{Ar}$), 5.34 (s, 2H, $NH_{2pyrmidine}$), 3.81 (s, 3H, -OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.3, 156.4, 152.7, 148.3, 147.9, 146.5, 141.1, 134.3, 128.4, 127.5, 127.3, 125.1, 123.7, 121.0, 120.8, 117.5, 116.6, 114.8, 113.9, 111.1, 107.8, 54.0.

3-(2-Amino-6-(3-nitrophenyl) pyrimidin-4-yl)-2H-benzo[h]chromen-2-one ***(6b)***. $C_{23}H_{14}N_4O_4$, color: yellowish crystals, yield: 69%, m.p.: 241-243 °C, R_f = 0.71, DCM : Hex : EtOAc (2:7:1); FT-IR (ATR) (ν, cm^{-1}): 3243, 3293 (NH_2), 3060 (ArC-H), 1720 (C=$O_{lactone}$), 1602 (C=N), 1207 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.51 (s, 1H, $H_{4coumarin}$), 8.44–8.31 (m, 1H, H_{Ar}), 7.98–7.90 (m, 2H, H_{Ar}), 7.89–7.75 (m, 1H, H_{Ar}), 7.68–7.58 (m, 1H. H $_{Ar}$), 7.56–7.47 (m, 1H, H_{Ar}), 7.45–7.31 (m, 2H, H_{Ar}), 7.20(s, 1H, H_{Ar}), 7.08–6.94 (m, 2H, H_{Ar}), 6.34 (s, 2H, $NH_{2pyrmidine}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.2, 161.0, 159.1, 155.5, 151.0, 150.6, 149.2, 143.8, 137.0, 135.8, 133.5, 131.1, 130.2, 127.8, 126.5, 123.7, 123.5, 120.2, 119.3, 117.6, 116.7, 113.9, 110.6.

Synthesis of phenyl pyrazoline

A mixture of the selected chalcone (**4a,b**) (0.004 mol) was refluxed with phenyl hydrazine (0.004 mol) in absolute ethanol (20) mL and (5 drops) of glacial acetic acid was added, at (80 °C) for 8 h. After completion of the reaction, the solvent was removed under vacuo [28]. The crude product was purified by column chromatography to give the target compounds **(7a,b)**.

3-(5-(4-Methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)-2H-benzo[h]chromen-2-one ***(7a)***. $C_{29}H_{20}N_2O_3$, color: orange crystals, yield: 70%, m.p.: 227-229 ℃, R_f = 0.64, Hex : EtOAc : MeOH (8:1:1); FT-IR(ATR) (ν, cm^{-1}): 3020 (ArC-H), 2931 (Ar-OCH_3), 1733 (C=$O_{lactone}$), 1672 (C=N), 1207 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.52 (s, 1H, $H_{4coumarin}$), 8.24 (d, 1H, J = 8.4 Hz, H_{Ar}), 7.91–7.84 (m, 2H, H_{Ar}), 7.72–7.67 (m, 3H, H_{Ar}), 7.64–7.58 (m, 2H, H_{Ar}), 7.55–7.46 (m, 1H, H_{Ar}), 7.33–7.24 (m, 3H, H_{Ar}), 7.18–7.13 (m, 1H, H_{Ar}), 6.99 (s, 1$H_{pyrazol}$), 3.79 (s, 3H, -OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6):δ 160.1, 158.2, 154.6, 150.1, 149.7, 148.3, 142.9, 136.1, 134.9, 132.6, 130.2, 129.3, 129.2, 126.9, 125.6, 124.0, 122.8, 122.6, 122.1, 119.3, 118.4, 116.7, 115.8, 109.7, 55.8.

*3-(3-(3-Nitrophenyl)-1-phenyl-1H-pyrazol-5-yl)-2H-chromen-2-one (**7b**).* $C_{24}H_{15}N_3O_4$, color: orange yellow needles, yield: 75%, m.p.: 240-242 °C, R_f = 0.65, Hex : EtOAc : MeOH (8:1:1); FT-IR (ATR) (ν, cm^{-1}): 3053 (ArC-H), 1722 ($C{=}O_{lactone}$), 1672 (C=N), 1204 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 8.57 (s,1H, $H_{4coumarin}$), 8.34–8.23 (m, 2H, H_{Ar}), 7.98–7.89 (m, 1H, H_{Ar}), 7.76 (dd, 1H, *J* = 7.3, 3.5 Hz, H_{Ar}), 7.70–7.62 (m, 2H, H_{Ar}), 7.61–7.51 (m, 1H, H_{Ar}), 7.48–7.39 (m, 1H, H_{Ar}), 7.38–7.25 (m, 2H, H_{Ar}), 7.24–7.18 (m, 2H, H_{Ar}), 7.17–7.08 (m, 3H, H_{Ar}), 6.85 (s, 1H,$_{pyrazol}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 162.6, 160.7, 157.0, 152.6, 152.1, 150.8, 145.4, 138.5, 137.4, 135.1, 132.7, 131.8, 131.6, 129.3, 128.0, 126.5, 125.3, 125.1, 124.5, 121.8, 120.9, 119.1, 118.2, 112.1, 111.2.

Synthesis of pyrazole-1-carbothioamide

A mixture of the selected chalcone (**4a**,**b**) (0.004 mol) in absolute ethyl alcohol 20 mL, thiosemicarbazide (0.004 mol) and (3-5 drops) of glacial acetic acid was added. The reaction mixture was refluxed with stirring for 10-12 h. After reaction completion, a mixture was poured into (100 g) of crushed ice with stirring to give a precipitated solid that was filtered and washed [29]. The crude product was purified by column chromatography to give the target compounds (**8a**,**b**).

*5-(4-Methoxyphenyl)-3-(2-oxo-2H-benzo[h]chromen-3-yl)-1H-pyrazole-1-carbothio amide (**8a**).* $C_{24}H_{17}N_3O_3S$, color: pale yellow crystals, yield: 65%, m.p.: 228-230 °C, R_f = 0.69, Hex : EtOAc : MeOH (8:1:1); FT-IR (ATR) (ν, cm^{-1}): 3243, 3241 (NH_2), 3057 (ArC-H), 2980 (Ar-OCH_3), 1731 ($C{=}O_{lactone}$), 1602 (C=N), 1211 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.22 (s, 1H, $H_{4coumarin}$), 8.10 (s, 1H, H_{Ar}), 7.99 (m, 1H, *J* = 7.8, 1.5 Hz, H_{Ar}), 7.68–7.60 (m, 3H, H_{Ar}), 7.56–7.46 (m, 2H, H_{Ar}), 7.33–7.27 (m, 1H, H_{Ar}), 7.20 (s, 1H,$_{pyrazol}$), 6.4 (s, 2H, S=C-NH_2), 3.83 (-OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.9, 160.7, 158.8, 155.1, 150.7, 150.2, 148.9, 136.6, 130.8, 129.9, 129.7, 127.4, 126.1, 123.4, 123.2, 122.6, 119.9, 119.0, 117.2, 116.3, 110.2, 56.4.

*5-(3-Nitrophenyl)-3-(2-oxo-2H-benzo[h]chromen-3-yl)-1H-pyrazole-1-carbothioamide (**8b**).* $C_{23}H_{14}N_4O_4S$, color: pale yellow crystals, yield: 69%, m.p.: 235-237 °C, R_f = 0.67, Hex : EtOAc : MeOH (8:1:1); FT-IR (ATR) (ν, cm^{-1}): 3241, 3214 (NH_2), 3053 (ArC-H), 1732 ($C{=}O_{lactone}$), 1676 (C=N), 1211 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.30 (s, 1H, $H_{4coumarin}$), 8.00–7.89 (m, 2H, H_{Ar}), 7.83–7.74 (m, 1H, H_{Ar}), 7.61 (d, 2H, *J* = 7.3 Hz, H_{Ar}), 7.63–7.53 (m, 1H, H_{Ar}), 7.53–7.41 (m, 2H, H_{Ar}), 7.36–7.22 (m, 2H, H_{Ar}), 7.16 (s, 1H,$_{pyrazol}$), 6.74 (s, 2H, S=C-NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.7, 160.0, 158.1, 154.4, 149.9, 149.5, 148.1, 135.9, 134.4, 133.1, 130.1, 129.2, 129.0, 126.7, 125.4, 122.6, 122.4, 121.9, 119.2, 118.3, 116.5, 115.6, 109.5.

Synthesis of benzo[b] [1,4] diazepine and benzo[b] [1,4] oxazepane

A mixture of the selected chalcone **(4a,b)** (0.004 mol) in absolute ethanol 20 mL was added to 1,2-diaminobenzene and/or 2-aminophenol (0.004 mol) and (3-5 drops) of glacial acetic acid was added. The reaction mixture was refluxed with stirring for 10-12 h [30]. The mixture was then cooled, after evaporating the solvent, the crude product was purified by column chromatography to give the target compounds **(9a,b)** and **(10a,b)**.

*3-(2-(4-Methoxyphenyl)-2,3-dihydro-1H-benzo[b] [1,4] diazepin-4-yl)-2H-benzo [h] chromen-2-one (**9a**).* $C_{29}H_{22}N_2O_3$, color: pale yellow crystals, yield: 57%, m.p.: 242-244 °C, R_f = 0.66, Hex : EtOAc (8:2); FT-IR(ATR) (ν, cm^{-1}): 3324 (NH), 3060 (ArC-H), 2980 (Ar-OCH_3), 1711 ($C{=}O_{lactone}$), 1672 (C=N), 1211 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.57 (s, 1H, $H_{4coumarin}$), 8.42 (d, 2H, *J* = 7.2 Hz, H_{Ar}), 8.20 (d, 2H, *J* = 8.4 Hz, H_{Ar}), 7.92–7.88 (m, 1H, H_{Ar}), 7.85 (d, 1H, *J* = 7.8 Hz, H_{Ar}), 7.72 (dd, 1H, *J* = 7.5, 1.4 Hz, H $_{Ar}$), 7.68–7.60 (m, 3H, H_{Ar}), 7.50–7.41 (m, 2H, H_{Ar}), 5.61 (s,1H, NH), 3.60 (m, 1H$_{diazepin}$), 3.41 (s, 3H, -OCH_3), 2.67(dd, 1H, *J* = 7.7, 3.2 Hz, $CH_{2diazepin}$),

2.38 (dd, 1H, J = 7.5, 3.7 Hz, $CH_{2diazepin}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.2, 160.0, 158.1, 154.4, 149.9, 149.5, 148.1, 135.9, 132.5, 130.1, 129.2, 129.0, 127.9, 126.7, 125.4, 122.6, 122.4, 121.9, 119.2, 118.3, 116.5, 115.6, 112.8, 109.5, 67.0, 55.7, 38.8.

*3-(2-(3-Nitrophenyl)-2,3-dihydro-1H-benzo[b] [1,4] diazepin-4-yl)-2H-benzo [h] chromen-2-one (**9b**).* $C_{28}H_{19}N_3O_4$, color: brown crystals, yield: 68%, m.p.: 255-257 °C, R_f = 0.63, Hex : EtOAc (8:2); FT-IR (ATR) (ν, cm^{-1}): 3336 (NH), 3073 (ArC-H), 1720 (C=$O_{lactone}$), 1677 (C=N), 1205 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.62 (s, 1H, $H_{4coumarin}$), 8.49-8.35(m, 2H, H $_{Ar}$), 8.25(d, 1H, J = 8.4 Hz, H_{Ar}), 7.86 (dd, 1H, J = 7.6, 1.5 Hz, H_{Ar}), 7.72 (ddd, 1H, J = 8.9, 7.3, 1.6 Hz, H_{Ar}), 7.68-7.60 (m, 2H, H_{Ar}), 7.56-7.50 (m, 5H, H_{Ar}), 7.50-7.45 (m, 1H, H_{Ar}), 7.45 (d, J = 7.8 Hz, 1H, H_{Ar}), 5.69 (s, 1H, -NH), 3.52 (m, 1H, $CH_{diazepin}$), 2.67 (dd, J = 7.7, 4.4 Hz, 1H, $CH_{2diazepin}$), 2.36-2.29 (dd, J = 7.5, 1.4 Hz, 1H, $CH_{2diazepin}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.9, 160.7, 158.8, 155.1, 150.6, 150.2, 148.8, 136.6, 135.5, 133.2, 130.8, 129.9, 129.7, 128.6, 127.4, 126.1, 124.5, 123.3, 123.1, 122.6, 119.8, 119.0, 117.2, 116.3, 113.5, 110.2, 67.7, 39.5.

*3-(2-(4-Methoxyphenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4-yl)-2H-benzo[h] chromen -2-one (**10a**).* $C_{29}H_{21}NO_4$, color: golden yellow needles, yield: 69%, m.p.: 246-248 °C, R_f = 0.68, Hex : EtOAc (8:2); FT-IR (ATR) (ν, cm^{-1}): 3043 (ArC-H), 2984 (Ar-OCH_3), 1720 (C=$O_{lactone}$), 1677 (C=N), 1207 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.80 (s,1H, $H_{4coumarin}$), 8.34-8.15 (m, 3H, H_{Ar}), 8.16 (d, 2H, J = 8.4 Hz, H_{Ar}), 7.92 (d, 2H, J = 8.1 Hz, H_{Ar}), 7.65 (dd, 2H, J = 7.3, 1.5 Hz, H_{Ar}), 7.50-7.40 (m, 3H, H $_{Ar}$), 4.50(m, 1H, $CH_{oxazepin}$), 3.46 (dd, 1H, J = 7.9, 1.4 Hz, $CH_{2oxazepin}$), 3.01 (dd, 1H, J = 7.1, 3.1Hz, $CH_{oxazepin}$), 3.80 (s, 3H, -OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.2, 161.0, 159.1, 155.5, 151.0, 150.6, 149.2, 137.0, 131.1 , 130.2, 130.1, 128.9, 127.8, 126.5, 124.9, 123.7, 123.5, 123.0, 120.2, 119.3, 117.6, 116.7, 113.9, 110.6, 67.5, 56.7, 39.8.

*3-(2-(3-Nitrophenyl)-2,3-dihydrobenzo[b] [1,4] oxazepin-4-yl)-2H-benzo [h] chromen-2-one (**10b**).* $C_{28}H_{18}N_2O_5$, color: light yellow needles, yield: 70%, m.p.: 248-250 °C, R_f = 0.65, Hex : EtOAc (8:2); FT-IR (ATR) (ν, cm^{-1}): 3043 (ArC-H), 2984 (Ar-OCH_3), 1708 (C=$O_{lactone}$), 1672 (C=N), 1205 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.90 (s, 1H, $H_{4coumarin}$), 8.58–8.39 (m, 3H, H_{Ar}), 8.23–8.09 (m, 3H, H_{Ar}), 7.98–7.86 (m, 3H, H_{Ar}), 7.70–7.58(m, 3H, H_{Ar}), 7.56–7.44(m, 2H, H_{Ar}), 4.59 (t, 1H, J = 6.8 Hz $CH_{oxazepin}$), 3.47 (dd, 1H, J = 7.2, 2.4,Hz, $CH_{2oxazepin}$), 3.04 (dd, 1H, J = 7.3, 2.3 Hz, $CH_{2oxazepin}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.8, 159.5, 157.6, 154.0, 149.5, 149.1, 147.7, 135.5, 134.4, 132.1, 129.7, 128.8, 128.6, 127.5, 126.3, 125.0, 123.4, 122.2, 122.0, 121.5, 118.7, 117.8, 116.1, 115.2, 112.4, 109.1, 66.1, 38.4.

Synthesis of isoxazole

A mixture of the selected chalcone (**4a**,**b**) (0.004 mol) and hydroxyl amine. HCl (0.004 mol) in 25 mL ethanol, a solution of potassium hydroxide 0.2 g in 2 mL water was added, the reaction mixture was refluxed with stirring for 8–10 h. The alcohol was evaporated under vacuum until dryness, and the residue was acidified with dil. HCl to give a precipitated solid that was filtered and washed [31]. The crude product was purified by column chromatography to give the target compounds (**11a**,**b**).

*3-(5-(4-Methoxyphenyl)-4,5-dihydroisoxazol-3-yl)-2H-benzo[h]chromen-2-one (**11a**).* $C_{23}H_{17}NO_4$, color: pale yellow crystals, yield: 52%, m.p.: 215-2217 °C, R_f = 0.76, DCM : Hex : EtOAc (2:7:1); FT-IR (ATR) (ν, cm^{-1}): 3063 (ArC-H), 2980 (C-H,OCH_3), 1710 (C=$O_{lactone}$), 1681 (C=N), 1209 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.68 (s, 1H, $H_{4coumarin}$), 8.23 (m, 1H, H $_{Ar}$), 8.59–8.46 (m, 1H, H_{Ar}), 8.40 (d, 1H, J = 8.4 Hz, H_{Ar}), 8.13–7.99 (m, 1H, H_{Ar}), 7.72 (d, 1H, J = 8.1 Hz, H_{Ar}), 7.43–7.35 (m, 1H, H_{Ar}), 7.33–7.24 (m, 1H, H_{Ar}), 7.24–7.18 (m, 1H, H_{Ar}), 5.49 (m, 1H, $CH_{isoxazole}$), 3.48 (s, 3H, -OCH_3), 2.76 (dd, 1H, J = 7.1, 2.1 Hz, $CH_{isoxazole}$), 2.28 (dd, J = 7.4,

2.6 Hz, 1H, $CH_{isoxazole}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.6, 155.0, 150.5, 150.1, 148.7, 136.5, 133.0, 130.6, 129.7, 129.6, 128.4, 127.3, 126.0, 124.4, 123.2, 123.0, 118.8, 117.1, 67.0, 56.2, 27.1.

*3-(5-(3-Nitrophenyl)-4,5-dihydroisoxazol-3-yl)-2H-benzo[h]chromen-2-one (**11b**).* $C_{22}H_{14}N_2O_5$, color: yellow crystals, yield: 68%, m.p.: 226-228 °C, R_f = 0.72, DCM : Hex : EtOAc (2:7:1); FT-IR(ATR) (ν, cm^{-1}): 3053 (ArC-H), 1711 ($C{=}O_{lactone}$), 1622 (C=N), 1209 (C-O). ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 8.62 (s, 1H, $H_{4coumarin}$), 8.17 (d, 1H, J = 8.2 Hz, H_{Ar}), 8.53–8.40 (m, 1H, H_{Ar}), 8.34 (d, 1H, J = 8.4 Hz, H_{Ar}), 7.99 (d, 1H, J = 9.0 Hz, H_{Ar}), 7.88–7.78 (m, 1H, H_{Ar}), 7.58–7.47 (m, 1H, H_{Ar}), 7.72–7.63 (m, 1H, H_{Ar}), 7.38–7.30 (m, 1H, H_{Ar}), 7.27–7.19 (m, 1H, H_{Ar}), 7.19–7.12 (m, 1H, H_{Ar}), 3.01 (dd, 1H, J = 8.8, 2.9 Hz, $CH_{2isoxazole}$), 4.42 (m, 1H, $CH_{isoxazole}$), 2.27 (dd, 1H, J = 8.1, 2.7 Hz, $CH_{2isoxazole}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.1, 158.2, 154.5, 150.1, 149.7, 148.3, 136.1, 134.9, 132.6, 130.2, 129.3, 129.1, 128.0, 126.9, 125.5, 124.0, 122.8, 122.6, 118.4, 116.6, 66.6, 24.3.

Synthesis of epoxides

A mixture of the selected chalcone (**4a**,**b**) (0.004 mol) in 40 mL methanol was treated with 3 mL of 30% hydrogen peroxide and 1.5 mL of 5 N NaOH) with stirring and cooling to keep the temperature below 5 °C. After completion reaction the solution poured into crushed ice (100 g). The yellow turbid solution was extracted with chloroform (3×40 mL) and the combined organic layers were dried over $MgSO_4$ [32]. Evaporation of the solvent left and the crude product which was purified by column chromatography to give the target compounds (**12a**,**b**).

*3-(3-(4-Methoxyphenyl) oxirane-2-carbonyl)-2H-benzo[h]chromen-2-one (**12a**).* $C_{23}H_{16}O_5$, color: pale yellow crystals, yield: 53%, m.p.:197-199 °C, R_f = 0.77, DCM : Hex : EtOAc (3:5:2); FT-IR(ATR) (ν, cm^{-1}): 3061 (ArC-H), 2980 (Ar-OCH_3), 2880 (C-H_{oxirn}), 1708 ($C{=}O_{lactone}$), 1201 (C-O). ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 8.62 (s, 1H, $H_{4,coumarin}$), 8.42 (dd, 2H, J = 7.7, 1.3 Hz, H_{Ar}), 8.25 (dd, 1H, J = 7.3, 1.5 Hz, H_{Ar}), 7.89–7.84 (m, 1H, H_{Ar}), 7.74–7.68 (m, 1H, H_{Ar}), 7.65–7.61 (m, 1H, H_{Ar}), 7.53–7.46 (m, 1H, H_{Ar}), 7.47–7.41 (m, 1H, H_{Ar}), 3.87 (d, 1H, J = 2.4 Hz, $CH_{oxirane}$), 3.75 (d, 1H, J = 3.5 Hz, $CH_{oxirane}$), 3.47 (s, 3H, -OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 191.9, 159.6, 157.7, 154.0, 149.5, 135.5, 134.4, 132.1, 129.7, 128.8, 128.6, 126.3, 125.0, 123.4, 122.2, 122.0, 117.9, 116.1, 93.2, 66.1, 55.2.

*3-(3-(3-Nitrophenyl) oxirane-2-carbonyl)-2H-benzo[h]chromen-2-one (**12b**).* $C_{22}H_{13}NO_6$, color: pale yellow crystals, yield: 52%, m.p.: 210-212 °C, R_f = 0.75, DCM : Hex : EtOAc (3:5:2); FT-IR (ATR) (ν, cm^{-1}): 3063 (ArC-H), 2817 (C-$H_{oxirane}$), 1706 ($C{=}O_{lactone}$), 1207 (C-O). ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 8.61 (s,1H $H_{4,coumarin}$), 8.43–8.39 (m, 2H, H_{Ar}), 7.89–7.81 (m, 2H, H_{Ar}), 7.73–7.67 (m, 1H, H_{Ar}), 7.68–7.57 (m, 2H, H_{Ar}), 7.56–7.45 (m, 2H, H_{Ar}), 7.48–7.39 (m, 1H, H_{Ar}), 3.86 (d, 1H, J = 2.4 Hz, $CH_{oxirane}$), 3.73 (d, 1H, J = 3.1 Hz, $CH_{oxirane}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.3, 160.4, 158.5, 154.8, 150.4, 143.2, 136.3, 135.2, 132.9, 130.5, 129.6, 129.4, 127.1, 125.8, 124.3, 123.1, 122.9, 119.6, 118.7, 116.9, 66.9, 56.12.

Anti-bacterial activity studies

The antibacterial activity of the prepared compounds was assessed against two types of bacteria: *E. coli* and *S. aureus*. Sensitivity testing was conducted using the disk diffusion method, with ceftriaxone (30 µg/disc) as a standard drug. The antibacterial activity solution was prepared (50 µg/mL and 25 µg/mL) of each compound were dissolved in 30 µg/mL dimethyl sulfoxide and mixed to generate a homogenous solution. Using a sterile micropipette, a predefined volume of 50 µg/mL and 25 µg/mL of solution was added to Whatman filter paper discs that had already

undergone sterilization. For quality control, aseptic injection of strains on sterile nutrient agar plate was performed. The plate was then incubated at 37 °C for 24 h. For the preparation of 5 mL nutrient broth bacterial cultures, three to five colonies were selected to provide a 0.5 Mc Farland standard, next a sterile cotton swab was used to inoculate the culture fluid in three different orientations on a sterile Muller-Hinton agar plate. Each disk was labeled with its unique ID number on the back of the Petri dish. The anti-bacterial activity was evaluated by measuring the zone of inhibition around the disk.

CONCLUSION

The aim of this work was the synthesis of heterocyclic compounds derived from chalcobenzo[*h*]coumarin. The target molecules were synthesized and characterized using spectroscopic techniques such as FT-IR, ^{1}H, and ^{13}C-NMR. The final compounds were evaluated for their antibacterial activity against two types of bacteria; Gram-negative *E. coli* (ATCC 25922) and Gram-positive *S. aureus* (ATCC 5923) clinical antibiotic-resistant isolates, using the disk diffusion method. Ceftriaxone was used as standard control. Compound (**6b**) showed better activities with 22.1 mm zone of inhibition at concentration of 25 µg/mL against *S. aureus* and (**5a**), showed the least activity against *S. aureus* at a concentration of 25 µg/mL, while the other compounds showed moderate to weak activity.

ACKNOWLEDGMENT

The authors are thankful to the University of Mosul, Department of Chemistry, College of Education for Pure Science, for their support and providing the research facilities to complete this work.

REFERENCES

1. Al-Wabli, R.I.; Alsulami, M.A.; Bukhari, S.I.; Moubayed, N.M.; Al-Mutairi, M.S.; Attia, M.I. Design, synthesis, and antimicrobial activity of certain new indole-1,2,4-triazole conjugates. *Molecules* **2021**, 26, 2292.
2. Xue, Y.J.; Li, M.Y.; Jin, X.J.; Zheng, C.J.; Piao, H.R. Design, synthesis and evaluation of carbazole derivatives as potential antimicrobial agents. *J. Enzyme Inhib. Med. Chem*. **2021**, 36, 296-3073.
3. Di Martino, P. Antimicrobial agents and microbial ecology. *AIMS Microbiol*. **2022**, 8, 1.
4. Carullo, G.; Mazzotta, S.; Giordano, F.; Aiello, F. Green synthesis of new pyrrolo [1,2-a] quinoxalines as antiproliferative agents in GPER-expressing breast cancer cells. *J. Chem.* **2021**, 2021, 5596816.
5. Al-Abbasy, O.Y.; Younus, S.A.; Rashan, A.I.; Ahmad, O.A. Maillard reaction: Formation, advantage, disadvantage and control. A review. *Food Sci. Appl. Biotechnol.* **2024**, 7, 145-161.
6. Kaur, J.; Utreja, D.; Jain, N.; Sharma, S. Recent developments in the synthesis and antimicrobial activity of indole and its derivatives. *Curr. Org. Synth*. **2019**, 16, 17-37.
7. El-Bana, G.G.; Salem, M.A.; Helal, M.H.; Alharbi, O.; Gouda, M.A. A review on the recent multicomponent synthesis of 4H-pyran derivatives. *Mini Rev .Org. Chem*. **2024**, 21, 73-91.
8. Hamama, W.S.; Berghot, M.A.; El Baz, E.; Hanashalshahaby, E.H.; Gouda, M.A. 3-Acyl (aroyl) coumarins as synthon in heterocyclic synthesis. *Org. Commun.* **2019**, 12, 100.
9. Gouda, M.A.; Abu-Hashem, A.A.; Salem, M.A.; Helal, M.H.; Al-Ghorbani, M.; Hamama, W.S. Recent progress on coumarin scaffold-based anti-microbial agents (Part III). *J. Heterocycl. Chem*. **2020**, 57, 3784-3817.
10. Hamama, W.S.; Berghot, M.A.; Baz, E.A.; Gouda, M.A. Synthesis and antioxidant evaluation of some new 3-substituted coumarins. *Archiv. der Pharmazie* **2011**, 344, 710-718.

11. Heravi, M.M.; Ansari, P.; Saeedi, M.; Tavakoli-Hosseini, N.; Karimi, N. Green and practical synthesis of benzopyran and 3-substituted coumarin derivatives by Bronsted acid ionic liquid [$(CH_2)_4SO_3HMIM][HSO_4$]. *Bull. Chem. Soc. Ethiop.* **2011**, 25, 315-320.
12. Gad wood, R.C.; Kamdar, B.V.; Dubray, L.A.C.; Wolfe, M.L.; Smith, M.P.; Watt, W. Groppi, V.E. Synthesis and biological activity of spirocyclic benzopyran imidazolone potassium channel openers. *J. Med. Chem*. **1993**, 36, 1480-1487.
13. Badavath, V.; Jadav, S.; Pastorino, B.; de Lamballerie, X.; Sinha, B.; Jayaprakash, V. Synthesis and antiviral activity of 2-aryl-4H-chromen-4-one derivatives against chikungunya virus. *Lett. Drug. Des. Discov*. **2016**, 13, 1019-1024.
14. Hamulakova, S.; Kozurkova, M.; Kuca, K. Coumarin derivatives in pharmacotherapy of Alzheimer´s disease. *Curr. Org. Chem*. **2017**, 21, 602-612.
15. Gouda, M.A.; Hussein, B.H.; El-Demerdash, A.; Ibrahim, M.E.; Salem, M.A.; Helal, M.H.; Hamama, W.S. A review: Synthesis and medicinal importance of coumarins and their analogues (Part II). *Curr. Bioact. Compd*. **2020**, 16, 993-1008.
16. Li, K.; Liang, Y.; Cheng, A.; Wang, Q.; Li, Y.; Wei, H.; Wan, X. Antiviral properties of baicalin. *Rev. Bras. Farmacogn*. **2021**, 31, 408-419.
17. Ali, O.T.; Mohammed, M.O.; Al Dulayymi, J.R.; Baird, M.S. Synthesis of a di-mycoloyl tri-arabinofuranosyl glycerol fragment of the mycobacterial cell wall, based on synthetic mycolic acids. *Molecules* **2019**, 24, 3596.
18. Vazquez-Rodriguez, S.; Matos, M.J.; Santana, L.; Uriarte, E.; Borges, F.; Kachler, S.; Klotz, K.N. Chalcone-based derivatives as new scaffolds for h A3 adenosine receptor antagonists. *J. Pharm. Pharmacol. Res*. **2013**, 65, 697-703.
19. Khursheed, A.; Jain, V. Medicinal research progress of natural coumarin and its derivatives. *Nat. Prod. J*. **2021**, 11, 648-662.
20. Jasim, S.F.; Waheed, S.A.; Jebir, R.M.; Ismael, R.N.; Mustafa, Y.F. Benzocoumarin as a potential scaffold: A review of its biomedical activities. *AVFT* **2022**, 41, 139-148.
21. Goecke, F.; Labes, A.; Wiese, J.; Imhoff, J.F. Chemical interactions between marine macroalgae and bacteria. *Mar. Ecol. Prog. Ser*. **2010**, 409, 267-299.
22. Onar, H.Ç.; Vardar, B.A. Synthesis and antioxidant activity of novel 8-formyl-4-substitued coumarins. *Bull. Chem. Soc. Ethiop*. **2018**, 32, 175-178.
23. Al-Masoudi, N.A.; Al-Salihi, N.J.; Marich, Y.A.; Markus, T. Synthesis, and fluorescence properties of coumarin and benzocoumarin derivatives conjugated pyrimidine scaffolds for biological imaging applications. *J. Fluoresc*. **2015**, 25, 1847-1854.
24. Ambre, P.K.; Pissurlenkar, R.R.; Wavhale, R.D.; Shaikh, M.S.; Khedkar, V.M.; Wan, B.; Coutinho, E.C. Design synthesis, and evaluation of 4-(substituted) phenyl-2-thioxo-3,4-dihydro-1H-chromino [4,3-d] pyrimidin-5-one and 4-(substituted) phenyl-3,4-dihydro-1H-chromino [4,3-d] pyrimidine-2,5-dione analogs as antitubercular agents. *J. Med. Chem.* **2014**, 23, 2564-2575.
25. Nabeel, Z.; Jaber, Q.A.H.; Abdul-Rida, N.A. Novel benzo [f] coumarin derivatives as probable acetylcholinesterase inhibitors: synthesis, in vitro, and in silico studies for evaluation of their anti-AChE activity. *Indones. Chem*. **2021**, 22, 35-46.
26. Ghouili, A.; Rohlicek, J.; Ayed, T.B.; Hassen, R.B. Crystal structure determination from powder diffraction data of the coumarin vanillin chalcone. *Powder Diffr*. **2014**, 29, 361-365.
27. Ahmed, E.Y.; Abdelhafez, O.M.; Zaafar, D.; Serry, A.M.; Ahmed, Y.H.; El-Telbany, R F.; Abd Elmageed, Z.Y.; Ali, H.I. Antitumor and multikinase inhibition activities of some synthesized coumarin and benzofuran derivatives. *Annalen der Pharmacie* **2022**, 355, 2100327.
28. Herfindo, N.; Prasetiawati, R.; Sialagan, D.; Frimayanti, N.; Zamri, A. Synthesis, antiproliferative activity and molecular docking studies of 1,3,5-triaryl pyrazole compound as estrogen α receptor inhibitor targeting MCF-7 cells line. *Molekul*. **2020**, 15, 18-25.

29. Neha, S.; Nitin, K.; Devender, Y.M.P. Synthesis of pyrazole derivatives: a new therapeutic approach for antitubercular and anticancer activity. *J. Pharm. Res*. **2013**, 12, 5-14.
30. Poursan, S.; Ahadi, S. Balalaie, S.; Rominger, F.; Bijanzadeh, H.R. Design and synthesis of novel functionalized fused oxazepine and diazepine analogues containing coumarin backbone through domino reaction. *Chemistry Select* **2019**, 4, 6403-6407.
31. Sandhu, S.; Bansal, Y.; Silakari, O.; Bansal, G. Coumarin hybrids as novel therapeutic agents, *Bioorg. Med. Chem.* **2014** , 22, 3806-3814.
32. Ali, K. Synthesis, identification and study of the anti-microbial activity of novel chalcone and epoxy chalcone compounds. *Egypt. J. Chem.* **2021**, 64, 2297-2304.