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Synthesis, structure characterization and biological evaluation of new 6,8-dichloro-2-methyl-4*H*-chromen-4-one derivatives

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ABSTRACT

The typical active methyl functionality of 6,8-dichloro-2-methyl-4*H*-chromen-4-one is utilized to obtain 2-styrylchromones, pyruvate ester and phthalide *via* reactions with aromatic carboxaldehydes, diethyl oxalate and phthalic anhydride respectively. The phthalide provides illustrative example to convert a heterocyclic compound to an aliphatic one *via* the effect of alcoholic sodium methoxide. Bromination and cycloaddition reactions of 2-styrylchromones afford vicinal dibromide and adducts respectively. This work presents to the art a typical example of heterocyclic systems transformations through the conversion of the starting chromone to coumarin under the influence of thionyl chloride followed by aqueous potassium hydroxide. Some heterocyclic systems like pyrazole, isoxazol and quinolinone are obtained from the target chromone by treatment with hydrazines, hydroxylamine hydrochloride and ammonium acetate respectively. Thiation of starting chromone interestingly affords a dithiated product instead of the expected monothiated one. Antibacterial and antifungal activities of some synthesized compounds have been screened.

1. Introduction

2-Methylchromones and their derivatives are well known naturally occurring oxygen-containing heterocyclic compounds, which perform important biological functions in nature. It is known that certain natural and synthetic chromone derivatives possess important biological activities, such as cytotoxic (anticancer) [1-7], antihepatotoxic, antioxidant [8,9], anti-inflammatory [10], antispasmodic, estrogenic [11], antimicrobial [12-14], antifungal [15], antibacterial [16-18], and HIV-inhibition [19]. Due to their abundance in plants and their low mammalian toxicity, chromone derivatives are present in large amounts in the diets of human [20,21].

In continuation of our previous works [22-24], the present report aimed at utilization of the reactivity of 6,8-dichloro-2-methyl-4H-chromen-4-one (**2**) towards nitrogen and carbon nucleophiles to get new derivatives and evaluated them for antifungal and antibacterial activities.

2. Experimental

2.1. Instrumentation

All melting points were measured on a Gallenkamp electric melting point apparatus and are uncorrected. The infrared spectra were recorded using potassium bromide disks on a Pye Unicam SP-3-300 infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR experiments were run at 300 MHz on a Varian Mercury VX-300 NMR spectrometer using tetramethylsilane (TMS) as internal standard in deuterated chloroform or dimethyl sulphoxide. Chemical shifts are quoted as δ. The mass spectra were recorded on Shimadzu GCMS-QP-1000EX mass spectrometers at 70 eV. All the spectral measurements as well as the elemental analyses were carried out at the Micro analytical Center of Cairo University. All the newly synthesized compounds gave satisfactory elemental analyses.

2.2. Synthesis

2.2.1. 6,8-Dichloro-2-styryl-4H-chromen-4-one (3a), 2-(4-fluorostyryl)-6,8-dichloro-4H-chromen -4-one (3b) and 2-(4-methoxystyryl)-6,8-dichloro-4H-chromen-4-one (3c)

To a solution of 2-methylchromone derivative (**2**) (10 mmol, 2.29 g) in dry ethanol (20 mL), the appropriate aldehyde such as benzaldehyde, 4-flourobenzaldehyde and 4-methoxybenzaldehyde (10 mmol) was added. The reaction mixture was stirred at room temperature for 2h in the presence of sodium ethoxide (prepared by reaction 0.33 g sodium metal with 10 mL dry ethanol). The solid product that formed was collected by suction, dried and then recrystallised from benzene (Scheme 1).

6,8-Dichloro-2-styryl-4H-chromen-4-one (**3a**): Pale brown crystals. Yield: 96%. M.p.: 163-166 °C. FT-IR (KBr, cm^{-1}): 1658 ν(C=O)(chromone), 1631 ν(C=C). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.08-7.40 (m, 7H, Ar-H), 6.83 (d, 1H, -C*H*=CH-), 6.78 (d, 1H, -CH=C*H*-), 6.35 (s, 1H, pyran ring). MS (EI, *m/z*, %): 316 (M^+, 25.1). Anal. calcd. for $C_{17}H_{10}Cl_2O_2$: C, 64.38; H, 3.18; Cl, 22.36; Found: C, 64.24; H, 2.98, Cl, 22.24%.

2-(4-fluorostyryl)-6,8-dichloro-4H-chromen-4-one (**3b**): Pale brown crystals. Yield: 63%. M.p.: 186-188 °C. FT-IR (KBr, cm^{-1}): 1649 ν(C=O) (chromone).

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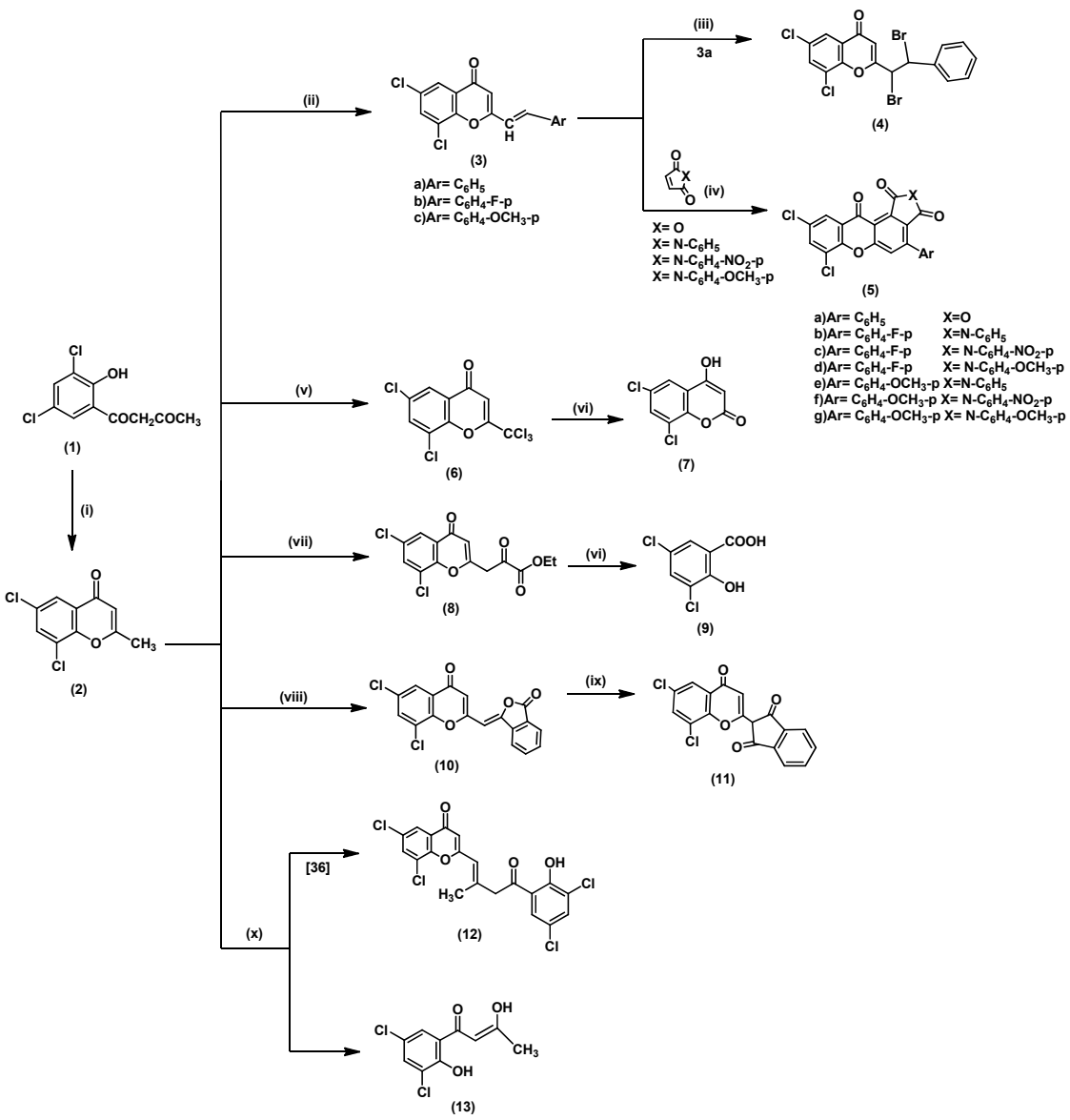


(i) Conc H_2SO_4, stirring, rt; (ii) Ar-CHO, EtONa, EtOH, stirring; (iii) Br_2 / AcOH, stirring; (iv) fusion; (v) $SOCl_2$,benzene, reflux; (vi) 10% alc.KOH, reflux;(vii) Diethyloxalate, dry diethyl ether , sodium metal, stirring, rt; (viii) phthalic anhydride, sodium acetate, fusion; (ix) MeONa, MeOH, reflux; (x) EtONa, diethyl ether, rt.

Scheme 1

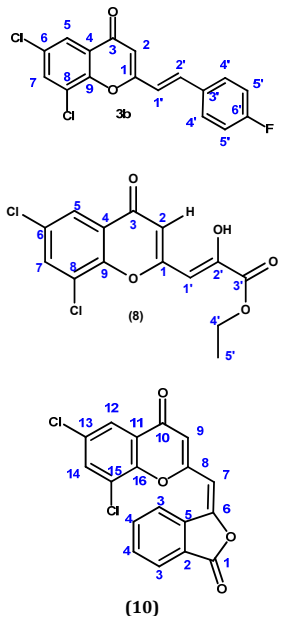
^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.16-7.60 (m, 6H, Ar-*H*), 7.33 (d, 1H, -C*H*=CH-), 7.24 (d, 1H, -CH=C*H*-), 6.54 (s, 1H, pyran ring). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 175.0 (C-3), 161.6 (C-1 & C-6'), 149.8 (C-9), 135.9 (C-7), 133.4 (C-2'), 131.2 (C-6), 130.1 (C-3'), 130.0 (C-5), 129.4 (C-4'), 125.4 (C-8), 123.0 (C-4), 119.9 (C-1'), 116.0 (C-5'), 110.0 (C-2) (Scheme 2). MS (EI, *m/z*, %): 334 ($M^{+\cdot}$, 27.4). Anal. calcd. for $C_{17}H_9Cl_2FO_2$: C, 60.92; H, 2.71; Cl, 21.16. Found: C, 60.84; H, 2.59; Cl, 21.00%.

2-(4-methoxystyryl)-6,8-dichloro-4H-chromen-4-one (**3c**): Green crystals. Yield: 38%. M.p.: 195-198 °C. FT-IR (KBr, cm^{-1}): 1652 ν(C=O) (chromone), 1643 ν(C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.07-7.35 (m, 6H, Ar-*H*), 7.05 (d, 1H, -C*H*=CH-), 6.98 (d, 1H, -CH=C*H*-), 6.44 (s, 1H, pyran ring), 3.79 (S, 3H, -OC*H*$_3$). MS (EI, *m/z*, %): 348 ($M+2^{+\cdot}$, 27.8). Anal. calcd. for $C_{18}H_{12}Cl_2O_3$: C, 62.27; H, 3.48; Cl, 20.42. Found: C, 62.14; H, 3.38; Cl, 20.20%.

2.2.2. 6,8-Dichloro-2-(1,2-dibromo-2-phenylethyl)-4H-chromen-4-one (4)

To a solution of compound **3a** (4 mmol, 1.28 g) in glacial acetic acid (30 mL), bromine (3 mmol, 0.5 g) in acetic acid (3 mL) was added. The reaction mixture was stirred for 0.5 h, and left to overnight at room temperature. The crude solid product that deposited was collected by suction, washed with water, dried and then recrystallised from light petroleum ether (80-100 °C) and benzene to give vicinal dibromochromone derivative **4** as orange crystals (Scheme 1). Yield: 58%. M.p.: 179-182 °C. FT-IR (KBr, cm^{-1}): 1660 ν(C=O) chromone. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.16-7.40 (m, 7H, Ar-*H*), 7.23 (s, 1H, pyran ring), 6.07 (d, 1H, Br-CH-C*H*-Br, *J* = 11.7 Hz), 5.65 (d, 1H, Br-C*H*-CH-Br, *J* = 11.7 Hz). MS (EI, *m/z*, %): 474 ($M^{+\cdot}$, 33.7).

Anal. calcd. for $C_{17}H_{10}Br_2Cl_2O_2$: C, 42.81; H, 2.11; Cl, 14.87. Found: C, 42.69; H, 1.98; Cl, 14.69%.



Scheme 2

2.2.3. 7,9-Dichloro-4-phenyl-1H-furo[3,4-a]xanthene-1,3,11-trione (5a)

A mixture of 2-styryl derivative **3a** (2 mmol) and maleic anhydride (20 mmol) in molar ratio 1:10 was fused on sand bath at fused temperature for 3 h and left to cool. The solid that formed was triturated with warm ethanol, filtered and recrystallized from ethanol to afford xanthone derivative **5a** as brown crystals (Scheme 1). Yield: 58%. M.p.: >300 °C. FT-IR (KBr, cm^{-1}): br. centered at 1722 ν(C=O) anhydride, 1631 ν(C=O) (chromone). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.18-7.26 (m, 7H, Ar-*H*), 6.58 (s, 1H, C5-*H*). MS (EI, *m/z*, %): 315 (M-C_4O_3,+H┐‡, 17.8). Anal. calcd. for $C_{21}H_8Cl_2O_5$: C, 61.34; H, 1.96; Cl, 17.24. Found: C, 61.22; H, 1.78; Cl, 17.17%.

2.2.4. Reaction of 2-styrylchromone derivatives (3b,c) with N-Arylmaliemides; formation of adducts (5b-g)

2 mmol of 2-Styryl derivatives (**3b**, **c**) was fused with the appropriate *N*-arylmaliemide (4 mmol) in molar ratio 1:2 on sand bath at fused temperature for 3 h; left to cool. The solid that formed was triturated with warm ethanol; filtered and recrystallised from the proper solvent to afford the expected adducts (**5b-g**) (Scheme 1).

7,9-Dichloro-4-(4-fluorophenyl)-2-phenylchromeno[3,2-e] isoindole-1,3,11(2H)-trione (**5b**): Recrystallized from acetic acid to afford the adduct as brown crystals. Yield: 80%. M.p.: 197-200 °C. FT-IR (KBr, cm^{-1}): 1776, 1707 ν(C=O) imide.. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.10-7.10 (m, 11H, Ar-*H*), 6.36 (s, 1H, C5-*H*). MS (EI, *m/z*, %): 503 ($M^{+\cdot}$, 50). Anal. calcd. for $C_{27}H_{12}Cl_2FNO_4$: C, 64.31; H, 2.40; Cl, 14.06; N, 2.78. Found: C, 64.22; H, 2.35; Cl, 13.97; N, 2.67%.

7,9-Dichloro-4-(4-fluorophenyl)-2-(4-nitrophenyl)chromeno [3,2-e]isoindole-1,3,11(2H)-trione (**5c**): Recrystallised from ethanol to afford the adduct as brown crystals. Yield: 51%. M.p.: 200-202 °C. FT-IR (KBr, cm^{-1}): 1670,1656 ν(C=O) imide, 1633 ν(C=O) (chromone). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.23-6.34 (m, 10H, Ar-*H*), 6.31(s, 1H, C5-*H*). MS (EI, *m/z*, %): (M-$C_{10}H_4O_4N_2$,-2H┐‡, 19.1). Anal. calcd. for $C_{27}H_{11}Cl_2FN_2O_6$: C, 59.04; H, 2.02; Cl, 12.91; N, 5.10.Found: C, 58.96; H, 1.98; Cl, 12.79; N, 4.97%.

7,9-Dichloro-4-(4-fluorophenyl)-2-(4-methoxyphenyl) chromeno[3,2-e]isoindole-1,3,11(2H)-trione (**5d**): Recrystallised from ethanol to afford the adduct as brown crystals. Yield: 75%. M.p.: 202-205 °C. FT-IR (KBr, cm^{-1}): 1708, 1656 ν(C=O) imide, 1634 ν(C=O) chromone. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.13-7.17 (m, 10H, Ar-*H*), 6.52 (s, 1H, C5-*H*), 3.39 (s, 3H, -OC*H*$_3$). MS (EI, m/z, %): 538 (M+5┐‡, 80.0). Anal. calcd. for $C_{28}H_{14}Cl_2FNO_5$: C, 62.94; H, 2.64; Cl, 13.27; N, 2.62. Found C, 62.78; H, 2.49; Cl, 13.15; N, 2.56%.

7,9-Dichloro-4-(4-methoxyphenyl)-2-phenylchromeno[3,2-e] isoindole-1,3,11(2H)-trione (**5e**): Recrystallised from acetic acid to afford the adduct as brown crystals. Yield: 79%. M.p.: >300 °C. FT-IR (KBr, cm^{-1}): 1771, 1721 ν(C=O) imide,. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.47-7.28 (m, 11H, Ar-*H*), 6.50 (s, 1H, C5-*H*), 3.83 (s, 3H, -OC*H*$_3$). MS (EI, *m/z*, %): 519 (M+4┐‡, 2.0). Anal. calcd. for $C_{28}H_{15}Cl_2NO_5$: C, 65.13; H, 2.93; Cl, 13.73; N, 2.71. Found: C, 64.98; H, 2.79; Cl, 13.69; N, 2.64%.

7,9-Dichloro-4-(4-methoxyphenyl)-2-(4-nitrophenyl) chromeno[3,2-e]isoindole-1,3,11(2H)-trione (**5f**): Recrystallised from acetic acid to afford the adduct as brown crystals. Yield: 63%. M.p.: >300 °C. FT-IR (KBr, cm^{-1}): 1729, 1643 ν(C=O) imide.. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.96-7.92, 6.68-6.57 (2 m, 11H, Ar-*H*), 3.30 (s, 3H, -OC*H*$_3$). Anal. calcd. for $C_{28}H_{14}Cl_2N_2O_7$: C, 59.91; H, 2.51; Cl, 12.63; N, 4.99. Found: C, 59.78; H, 2.45; Cl, 12.57; N, 4.79%.

7,9-Dichloro-2,4-bis(4-methoxyphenyl)chromeno[3,2-e] isoindole-1,3,11(2H)-trione (**5g**): Recrystallized from acetic acid to afford the adduct as brown crystals. Yield: 64%. M.p.: >300 °C. FT-IR (KBr, cm^{-1}): 1768, 1716 ν(C=O) imide, 1642 ν(C=O) chromone. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.43-7.05 (m, 11H, Ar-*H*), 3.87 (s, 3H, -OC*H*$_3$), 3.82 (s, 3H, -OC*H*$_3$). MS (EI, *m/z*, %): 547 (M+2┐‡, 43.8). Anal. calcd. for $C_{29}H_{17}Cl_2NO_6$: C, 63.75; H, 3.14; Cl, 12.98; N, 2.56. Found: C, 63.68; H, 3.08; Cl, 12.82; N, 2.47%.

2.2.5. 6,8-Dichloro-2-(trichloromethyl)-4H-chromen-4-one (6)

A mixture of chromone derivative **2** (5 mmol, 1.14 g) in benzene (15 mL) and thionyl chloride (20 mmol, 2.37 g) was heated at reflux temperature for 3 h and left to cool .the solid product that formed was filtered, dried and recrystallized from benzene to afford compound **6** as dark brown crystals (Scheme 1). Yield: 31%. M.p.: 178-180 °C. FT-IR (KBr, cm^{-1}): 1657 ν(C=O) chromone. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.24-7.78 (m, 2H, Ar-*H*), 6.98 (s, 1H, pyran ring). MS (EI, *m/z*, %): 331 (M+1┐‡, 27.5). Anal. calcd. for $C_{10}H_3Cl_5O_2$: C, 36.13; H, 0.91; Cl, 53.33. Found: C, 36.04; H, 0.72; Cl, 53.13%.

2.2.6. 6,8-Dichloro-4-hydroxy-2H-chromen-2-one (7)

A mixture of chromone derivative **6** (4 mmol, 1.00 g) aqueous ethanolic potassium hydroxide solution (10%, w/v) was added. The reaction mixture was heated at reflux for 11 h. The reaction mixture solution was left to cool and then acidified by 10% cold sulfuric acid to give the crude solid product which was collected by suction, washed by cold water dried and then recrystallised from toluene to give compound **7** as brown crystals (Scheme 1). Yield: 81%. M.p.: >300 °C. FT-IR (KBr, cm^{-1}): 3438 ν(OH), 1710 ν(C=O) coumarin. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 12.54 (s, 1H, OH, exchangeable), 7.98-7.71 (s, 2H, Ar-*H*), 6.94 (s, 1H, pyran ring). MS (EI, *m/z*, %): 216 (M-OH+2H┐‡, 3.9). Anal. calcd. for $C_9H_4Cl_2O_3$: C, 46.79; H, 1.75; Cl, 30.69. Found: C, 46.57; H, 1.58; Cl, 30.48%.

2.2.7. Ethyl 3-(6,8-dichloro-4-oxo-4H-chromen-2-yl)-2-oxopropanoate (8)

To a mixture of chromone derivative **2** (5 mmol, 1.14 g) and diethyl oxalate (25 mmol, 3.6 g) in dry diethyl ether (50 mL), sodium metal (0.5 g) was added at once. The reaction mixture was stirred for 0.5 h and left overnight at room temperature. Acidification with cold dilute acetic acid, the crude solid product that deposited was collected by suction, dried and then recrystallized from toluene to give pyruvic ester derivative **8** as orange crystals (Scheme 1 and 2). Yield: 65%. M.p.: 218-220 °C. FT-IR (KBr, cm^{-1}): 1730 ν(C=O) ketoester, 1653 ν(C=O) chromone. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.12-7.84 (2s, 2H, Ar-*H*), 6.96 (s, 1H, -C*H*=C-OH), 6.08 (s, 1H, pyran ring), 4.30 (q, 2H, -C*H*$_2$CH$_3$, *J* = 7.2 Hz), 3.75 (s, 1H, OH, exchangeable), 1.31 (t, 3H, -CH$_2$C*H*$_3$, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 184.0 (C-3), 177.6 (C-2'), 162.6 (C-1), 161.1 (C-3'), 149.9 (C-9), 133.4 (C-7), 129.4 (C-6), 125.1 (C-5), 123.5 (C-8), 122.8 (C-4), 110.3 (C-1'), 109.3 (C-2), 62.4 (C-4'), 14.0 (C-5'). MS (EI, *m/z*, %): 328 (M$^{+\cdot}$, 47.9). Anal. calcd. for $C_{14}H_{10}Cl_2O_5$: C, 51.09; H, 3.06; Cl, 21.54. Found: C, 51.00; H, 2.98; Cl, 21.32%.

2.2.8. 3,5-Dichloro-2-hydroxybenzoic acid (9)

Pyruvic ester derivative **8** (5 mmol, 1.6 g) was heated under reflux for 4 h in 30 mL of 10% aq. potassium hydroxide. Left to cool and acidified with cold dilute hydrochloric acid, the crude solid product that deposited was collected by suction, dried and then recrystallised from toluene to give salicylic acid derivative **9** as crystals which gave positive acidity test and deep violet coloration with aqueous $FeCl_3$ solution (Scheme 1). Yield: 50%. M.p.: 220-222 °C (the same M.p. in literature [25]). FT-IR (KBr, cm^{-1}): 3334 ν(OH), 1679 ν(C=O) acid. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 11.07 (s, 1H, OH carboxylic acid, exchangeable), 7.82 (s, 1H, Ar-*H*), 7.61 (s, 1H, Ar-*H*), 2.67 (s, 1H, aromatic C-O*H*, exchangeable). MS (EI, *m/z*, %): 208 (M+2$^{+\cdot}$, 2.6). Anal. calcd. for $C_7H_4Cl_2O_3$: C, 40.61; H, 1.95; Cl, 34.25. Found: C, 40.44; H, 1.49; Cl, 34.15%.

2.2.9. 6,8-Dichloro-2-((3-oxoisobenzofuran-1(3H)-ylidene) methyl)-4H-chromen-4-one (10)

A mixture of 2-methylchromone derivative **2** (9 mmol, 2 g) and phthalic anhydride (41 mmol, 6 g) in the presence of fused sodium acetate (36 mmol, 3 g) was fused at 125 °C for 8 h. The reaction mixture was left to cool at room temperature and then triturated by aqueous sodium carbonate solution. The solid obtained was filtered off, washed with cold water, dried and recrystallised from aqueous ethanol to give compound **10** as green crystals (Scheme 1 and 2). Yield: 54%. M.p.: >300 °C. FT-IR (KBr, cm^{-1}): 1798 ν(C=O) lactone, 1669 ν(C=O) chromone. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.90-7.40 (m, 6H, Ar-*H*), 7.13 (s, 2H, C7-H & C9-*H*). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 187.9 (C-10), 164.7 (C-1), 164.3 (C-8), 139.7 (C-16), 131.4 (C-6), 131.2 (C-5), 127.8 (C-14), 123.0 (C-13), 122.2 (C-4), 120.7 (C-12), 120.6 (C-15), 120.5 (C-11), 120.4 (C-3), 119.0 (C-2), 106.0 (C-9), 99.0 (C-7). MS (EI, m/z, %): 358 (M$^{+\cdot}$, 42.9). Anal. calcd. for $C_{18}H_8Cl_2O_4$: C, 60.19; H, 2.25; Cl, 19.74. Found: C, 60.04; H, 2.12; Cl, 19.53%.

2.2.10. 2-(6,8-Dichloro-4-oxo-4H-chromen-2-yl)-2H-indene-1,3-dione (11)

To a suspension of compound **10** (1.4 mmol, 0.5 g) in absolute methanol (10 mL) and solution of methoxide (prepared by reaction 0.5 g sodium metal with 10 mL of absolute methanol) was added. The solution was heated at reflux for 5 h, left to cool, diluted with water and acidified with cold dilute H_2SO_4, the solid formed was collected, dried and recrystallized from ethanol and toluene to afford 6,8-dichloro-2-(4-oxochroman-3-yl)-4H-chromen-4-one (11) as brown crystals (Scheme 1). Yield: 89%. M.p.: >300 °C. FT-IR (KBr, cm^{-1}): 1707 ν(C=O) indandione, 1642 ν(C=O) chromone. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.99-7.51 (m, 6H, Ar-*H*), 6.27 (s, 1H, C-3), 5.15 (s, 1H, C-9). Anal. calcd. for $C_{18}H_8Cl_2O_4$: C, 60.19; H, 2.25; Cl, 19.74. Found: C, 60.01; H, 2.16; Cl, 19.64%.

2.2.11. 1-(3,5-Dichloro-2-hydroxyphenyl)-3-hydroxybut-2-en-1-one (13)

To a solution of 2-methylchromone derivative **2** (9 mmol, 2 g) in diethyl ether (50 mL), sodium ethoxid solution (prepared by reaction 1 g of sodium metal in 30 mL of absolute) was added. The reaction mixture was shaken in tightly closed vessel for 2 h, kept at room temperature for 72 h. The solid product was collected, washed with dry diethyl ether and acidified with cold 10% acetic acid .The solid crude product was collected by suction, dried and then recrystallized from light petroleum ether (B.p.: 40-60 °C) to give compound **13** as orange crystals (Scheme 1). Yield: 14%. M.p.: 107-108 °C. FT-IR (KBr, cm^{-1}): 3435ν(OH), 1642 ν(C=O) (α,β-unsaturated ketone). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 14.73 (s, 1H, O*H* enol, exchangeable), 12.59 (s, 1H, O*H* phenolic, exchangeable), 7.55-7.53 (m, 2H, Ar-*H*), 6.11 (s, 1H, C*H*=C-OH), 2.35 (s, 3H, C*H*$_3$). MS (EI, *m/z*, %): 247 (M+1$^{+\cdot}$, 30.0). Anal. calcd. for $C_{10}H_8Cl_2O_3$: C, 48.61; H, 3.26; Cl, 28.70. Found: C, 48.49; H, 3.14; Cl, 28.65%.

2.2.12. 6,8-Dichloro-2-methyl-4H-thiochromene-4-thione (15)

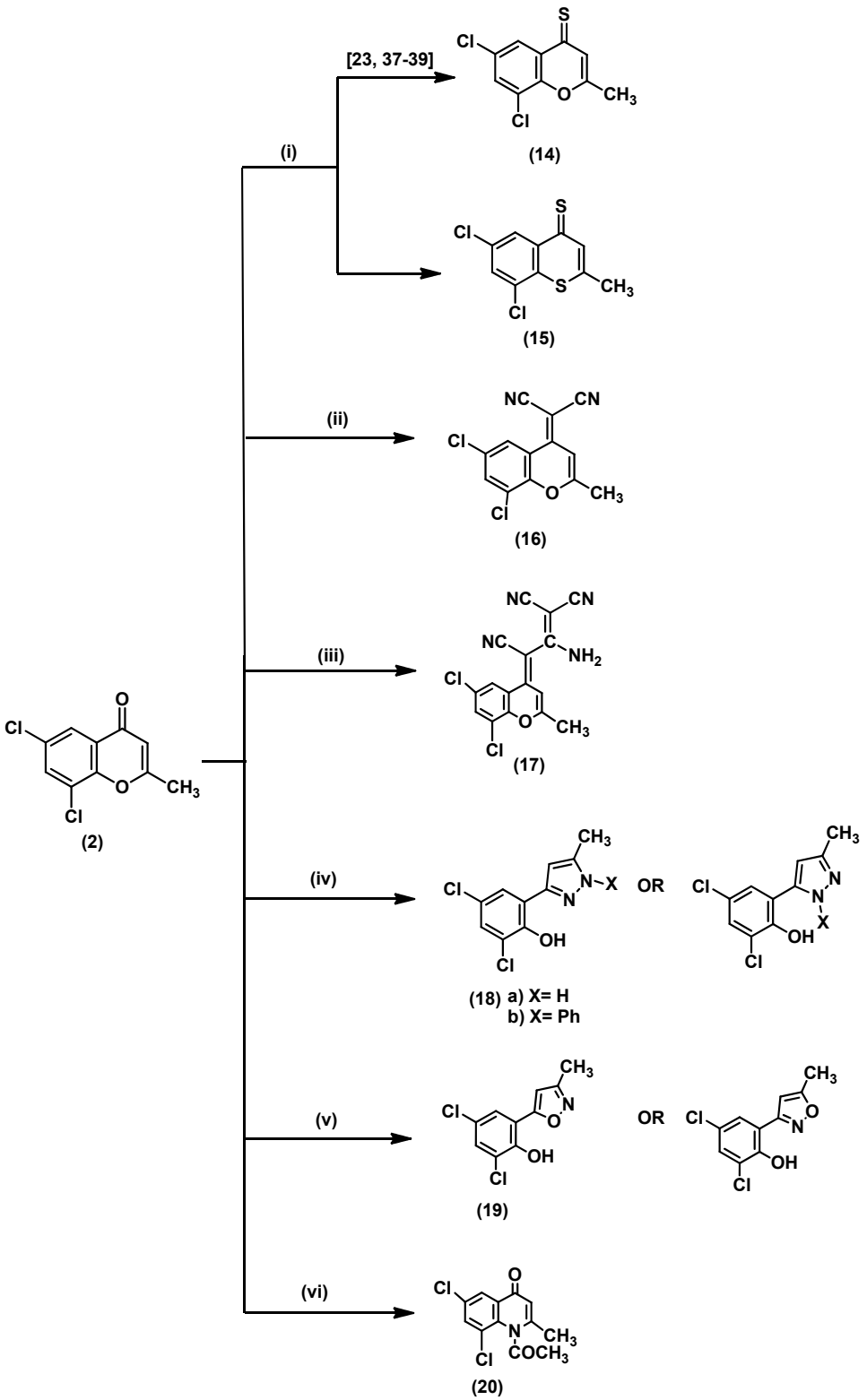
A mixture of 2-methylchromone **2** (5 mmol, 1.14 g) and phosphorous pentasulfied (25 mmol, 0.55 g) in dry toluene (30 mL) was heated at reflux for 2 h. The reaction solution was filtered off while hot and the filtrate was left to cool. The solid that separated out was collected, dried and recrystallized from light petroleum ether (B.p.: 80-100 °C) and benzene to give compound **15** as red crystals (Scheme 3). Yield: 89%. M.p.: 177-178 °C. FT-IR (KBr, cm^{-1}): 1613 ν(C=C), 1377 ν(C=S). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.44 (s, 1H, Ar-*H*), 7.72 (s, 1H, Ar-*H*), 7.15 (s, 1H, thiopyran ring), 2.39 (s, 3H, C*H*$_3$). MS (EI, *m/z*, %): 260 (M+1$^{+\cdot}$, 4.2). Anal. calcd. for $C_{10}H_6Cl_2S_2$: C, 45.98; H, 2.32; Cl, 27.15; S, 24.55. Found: C, 45.87; H, 2.16; Cl, 27.07; S, 24.43%.

2.2.13. 2-(6,8-Dichloro-2-methyl-4H-chromene-4-ylidene) malononitrile (16)

A mixture of chromone derivative **2** (5 mmol, 1.14 g) and malononitrile (5 mmol, 0.33 g) in freshly distilled acetic anhydride (12.5 mL) was heated under reflux for 3 h., left to cool. Excess acetic anhydride was distilled off and the crude product was filtered and washed with water, dried and then recrystallized from ethanol to give malononitrile derivative (**16**) as brown crystals (Scheme 3). Yield: 59%. M.p.: 121-123 °C. FT-IR (KBr, cm^{-1}): 2212 ν(C≡N), 1652 ν(C≡C). ^{1}H NMR (300 MHz, DMSO, δ, ppm): 8.14 (s, 1H, Ar-*H*), 7.89 (s, 1H, Ar-*H*), 6.37 (s, 1H, C3-*H*), 2.32 (s, 3H, C*H*$_3$). Anal. calcd. for $C_{13}H_6Cl_2N_2O$: C, 56.35; H, 2.18; Cl, 25.59; N, 10.11. Found: C, 56.19; H, 2.10; Cl, 25.45; N, 10.03%.

2.2.14. 2-Amino-3-(6,8-dichloro-2-methyl-4H-chromen-4-ylidene)prop-1-ene-1,1,3-tricarbonitrile (17)

A mixture of chromone derivative **2** (5 mmol, 1.14 g) and malononitrile (10 mmol, 0.66 g) in ethanol (20 mL) in presence of few drops of piperidine was heated under reflux for 4 h. The crude solid product that deposited was collected by suction, dried and then recrystallized from ethanol to give compound **17** as yellow crystals (Scheme 3). Yield: 59%. M.p.: 198-200 °C. FT-IR (KBr, cm^{-1}): 3411, 3322 ν(NH$_2$), 2212 ν(C≡N).



(i) P_2S_5, dry toluene, reflux; (ii) malononitrile, Ac_2O, reflux; (iii) malononitrile, piperidine, EtOH, reflux; (iv) NH_2NHX, X = H, Ph, EtOH, reflux; (v) $NH_2OH.HCl$, pyridine, reflux; (vi)CH_3COONH_4, fusion.

Scheme 3

^{1}H NMR (300 MHz, DMSO, δ, ppm): 8.25 (s, 2H, N*H*$_2$, exchangeable), 7.65 (s, 1H, Ar-*H*), 7.28 (s, 1H, Ar-*H*), 6.79 (s, 1H, C3-*H*), 2.32 (s, 3H, C*H*$_3$). MS (EI, *m/z*, %): 317 (M-CN+H┐‡, 17.7). Anal. calcd. for $C_{16}H_8Cl_2N_4O$: C, 56.00; H, 2.35; Cl, 20.66; N, 16.33. Found: C, 55.92; H, 2.17; Cl, 20.49; N, 16.29%.

2.2.15. 2,4-Dichloro-6-(5-methyl-1H-pyrazol-3-yl)phenol (18a)

A mixture of chromone derivative **2** (5 mmol, 1.14 g) in ethanol (20 mL), hydrazine hydrate (10 mmol, 5 g), ethanol (10 mL) was added. The reaction mixture was heated at reflux for 8 h, left to cool .The solid product that formed was collected, dried and recrystallized from toluene to give compound **18a** as grey crystals (Scheme 3). Yield: 26%. M.p.: 207-208 ^{o}C. FT-IR (KBr, cm^{-1}): 3457 ν(OH), 3381 ν(NH). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.42 (s, 1H, N*H*, exchangeable), 7.38-7.22 (m, 2H, Ar-*H* and 1H, O*H* phenolic, exchangeable), 6.43 (s, 1H, *H*-Pyrazole), 2.43 (s, 3H,C*H*$_3$). MS (EI, *m/z*, %): 246 (M+4┐‡, 40.0). Anal. calcd. for $C_{10}H_8Cl_2N_2O$: C, 49.41; H, 3.32; Cl, 29.17; N, 11.52. Found: C, 46.34; H, Cl, 28.97; 3.97; N, 6.64%.

2.2.16. 2,4-Dichloro-6-(5-methyl-1-phenyl-1H-pyrazol-3-yl) phenol (18b)

To a solution of chromone derivative **2** (5 mmol, 1.14 g) in ethanol (20 mL), phenyl hydrazine(47 mmol, 5 g) in ethanol (10 mL) was added, and few drops from acetic acid was heated at reflux for 12 h . The cooled reaction mixture was diluted with water, and the precipitated solid was recrystallized from benzene to give compound **18b** as brown crystals (Scheme 3). Yield: 91%. M.p.: 172-174 ^{o}C. FT-IR (KBr, cm^{-1}): 3487 ν(OH), 1595 ν(C=C). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.34-7.28 (m, 7H, Ar-*H*, 1H, O*H* phenolic, exchangeable), 6.37 (s, 1H, *H*-pyrazole), 2.39 (s, 3H, C*H*$_3$). MS (EI, *m/z*, %): 318 (M$^{+\cdot}$, 88.9). Anal. calcd. for $C_{16}H_{12}Cl_2N_2O$: C, 60.21; H, 3.79; Cl, 22.21; N, 8.78. Found: C, 60.10; H, 3.59; Cl, 22.09; N, 8.63%.

2.2.17. 2,4-dichloro-6-(5-methylisoxazol-3-yl)phenol (19)

A solution of chromone derivative **2** (prepared by dissolving 2.2 mmol, 0.5 g in 3 mL pyridine), hydroxylamine hydrochloride (2.2 mmol, 0.15 g in 1mL water) was added. The solution was heated at reflux for 6 h, allowed to cool and acidified with cold diluted acetic acid. The solid product that formed was collected, dried and recrystallized from toluene to give isoxazol **19** as grey crystals (Scheme 3). Yield: 64%. M.p.: 196-198 ^{o}C. FT-IR (KBr, cm^{-1}): 3312 ν(OH), 3080 ν(CH) (aromatic), 2960 ν (CH) (aliphatic), 1610 ν(C=N). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.82 (s, 1H, Ar-*H*), 7.42 (s, 1H, Ar-*H*), 6.71 (s, 1H, isoxazole ring), 6.35 (s, 1H, O*H* phenolic, exchangeable), 2.39 (s, 3H, C*H*$_3$). MS (EI, *m/z*, %): 243 (M$^{+\cdot}$, 9.5). Anal. calcd. for $C_{10}H_7Cl_2NO_2$: C, 49.21; H, 2.89; Cl, 29.05; N, 5.74. Found: C, 49.11; H, 2.78; Cl, 28.95; N, 5.58%.

2.2.18. 1-Acetyl-6,8-dichloro-2-methylquinolin-4(1H)-one (20)

A mixture of chromone derivative **2** (5 mmol, 1.14 g) and ammonium acetate (25 mmol, 1.5 g) was fused for 3 h, left the mixture to cool and then poured into ice/water. The solid formed was collected by suction, dried and then recrystallized from benzene to give compound **20** as yellow crystals (Scheme 3). Yield: 57%. M.p.: 118-120 ^{o}C. FT-IR (KBr, cm^{-1}): 1670 ν(CO) amide, 1651 ν(CO) chromone. MS (EI, *m/z*, %): 269 (M$^{+\cdot}$, 20.0). Anal. calcd. for $C_{12}H_9Cl_2NO_2$: C, 53.36; H, 3.36; Cl, 26.25; N, 5.19. Found: C, 53.21; H, 3.23; Cl, 26.14; N, 5.05%.

2.3. Measurement of antimicrobial activity using the disc diffusion method

A filter paper sterilized disc (diameter 80 mm) saturated with measured quantity of the sample is placed on plate containing solid bacterial medium (nutrient agar broth) or fungal medium (Dox's medium) which has been heavily seeded with the spore suspension of the tested organism. After inoculation, the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism [26-29].

3. Results and discussion

3.1. Synthesis

6,8-Dichloro-2-methyl-4*H*-chromen-4-one (**2**) was prepared *via* acid-catalyzed cyclodehydration of the β-diketone; 1-(3,5-dichloro-2-hydroxyphenyl)butane-1,3-dione (**1**) [30]. 2-Methylchromones are typical substances containing an active methyl group due to the considerable stabilization of the produced carbanion by abstracting a proton from the methyl group as a result of conjugation with the double bond and carbonyl functionality. Thus 6,8-dichloro-2-methyl-4*H*-chromen-4-one (**2**) condensed under Knovenagel reaction conditions, with different aromatic aldehydes namely, benzaldehyde, 4-flurorobenzaldehyde and 4-methoxy benzaldehyde to afford the corresponding 2-styrylchromones (**3a-c**) [2,23,24,30-33].

Bromination of 2-styryl chromone (**3a**) in glacial acetic acid gave the corresponding vicinal dibromide (**4**). 2-Styryl chromones (**3a-c**) are typical dienes which underwent cycloaddition reactions under Diels Alder reaction conditions with maleic anhydride and/or *N*-arylmaleimides as dienophiles, to yield the initial adducts which subsequently underwent dehydrogenation to afford the desired adducts (**5a-g**).

Treatment of starting chromone **2** with thionyl chloride in boiling benzene yielded 6,8-dichloro-2-(trichloromethyl)-4*H*-chromen-4-one (**6**), which underwent heterocyclic systems transformation under the effect of aqueous alcoholic KOH to yield coumarin derivative (**7**).

Condensation of 2-methylchromone **2** with diethyl oxalate in the presence of sodium metal gave the corresponding pyruvate esters (**8**) [34], which exists as keto-enol tautomers. The alkaline hydrolysis of compound **8** afforded salicylic acid derivative (**9**) [22,24].

When chromone **2** was allowed to react with phthalic anhydride at elevated temperature in absence of solvents in the presence of fused anhydrous sodium acetate, a phthalide (**10**) was formed and readily rearranged under the influence of alcoholic sodium methoxide solution to afford the corresponding 1,3-indandione derivative (**11**) [22,35].

It was claimed that [36] treatment of 2-methylchromones with an ethereal sodium ethoxide solution, afforded dimeric product (**12**). In our laboratory, treatment of chromone **2** with the same reagent gave 1-(3,5-dichloro-2-hydroxyphenyl)-3-hydroxybut-2-en-1-one (**13**) was isolated as a sole product. According to our speculation, ethoxide acts as an oxygen nucleophile not as a base and attacks at C-2 with ring opening followed by hydrolysis. The structure of compound **13** was ascertained from elemental analysis as well as spectral data (IR, ^{1}H NMR and MS) (Scheme 1).

Thiation of chromone **2** is an interesting point as we obtain results which are contradictory with the previously reported ones [23,37-39]. All these publications have been previously reported to provide the monothio compound; whether the thiation was carried out by P_2S_5/dry toluene or xylene or by Lawesson's reagent. 6,8-Dichloro-2-methyl-4*H*-chromene-4-thione (**14**) was believed to be obtained *via* thiation of 6,8-

dichloro-2-methyl-4*H*-chromen-4-one (**2**) with phosphorus pentasulfide in dry toluene. However, the 6,8-dichloro-2-methyl-4*H*-thiochromene-4-thione (**15**) was the sole product.

The reaction of 2-methylchromones with malononitrile as an example of compounds containing active methylene groups yields a product, which depends upon the reaction conditions. Thus, when 2-methylchromone **2** was allowed to react with malononitrile (1:1) in boiling acetic anhydride, the corresponding condensation product **16** was obtained [24]. The product **16** is formed *via* carbon nucleophile attack of the active methylene on the electronically deficient carbonyl carbon of chromone nucleus.

On the other hand, when 2-methylchromone, **2** was allowed to react with excess malononitrile in refluxing ethanol containing few drops of piperidine, the product was identified to be the tricarbonitrile (**17**) which is formed from the attack of a second malononitrile molecule on the initially formed condensation intermediate of type (**16**). The attack occurs at one cyano group but not on both probably due to steric hindrance. The present work extended to investigate the behaviour of 6,8-dichloro-2-methyl-4*H*-chromen-4-one (**2**) towards nitrogen nucleophiles namely, hydrazine hydrate, phenyl hydrazine, hydroxyl amine hydrochloride and ammonium acetate. Thus hydrazinolysis of the chromone derivative **2** with hydrazines namely hydrazine hydrate, phenyl hydrazine in boiling pyridine underwent cleavage of the pyran ring and afforded the corresponding pyrazoles (**18a**,**b**), respectively [22,24,40].

When 6,8-dichloro-2-methyl-4*H*-chromen-4-one, **2** was allowed to react with excess hydroxylamine hydrochloride, it gave the isoxazol derivative **19** *via* the attack of nitrogen atom by its lone pair on C-2 of chromone moiety leading to chromone ring cleavage. Both compounds **18** and **19** have two indistinguished probable structures obtained from the mode of the nitrogen nucleophile attack on two competitive electrophilic centers of the substrate (**2**). The latter are the C-2 and C-4 of chromone moiety. 1-Acetyl-6,8-dichloro-2-methylquinolin-4(1*H*)-one (**20**) was formed when a mixture of 2-methylchromone derivative (**2**) and ammonium acetate was fused for 3h in absence of solvents (Scheme 3).

3.2. Biological Activity

Antibacterial and antifungal activities of some selected synthesized compounds were screened using the disc diffusion method. The experiments were performed using test bacterial organisms belonging to the Gram-positive and Gram-negative groups namely *Staphylococcus aureus* and *Escherichia coil* respectively as well as *Candida albicans* and *Aspergillus flavus* as tested fungi. Compounds under investigation were dissolved in DMSO as an inactive solvent towards all microorganisms. The concentration of DMSO solutions was 0.2 mg/ mL

Table 1 and Figure 1 revealed the inhibitory activity of nine selected compounds, **3b**, **4**, **5g**, **9**, **10**, **13**, **15**, **18b** and **19** derived from the starting 2-methylchromone (**2**). The following points have been noticed:

(1) The compounds under investigation have more inhibitory action than the starting compound except compounds, **3b**, **5g** and **15**.

(2) Compound **13** showed inhibitory effect against Gram-positive as the same as standard compound.

(3) The tested compounds could be classified, according to their activities into four groups:

a) *Group 1*: Compound 3,5-dichloro-2-hydroxybenzoic acid (**9**) showed inhibitory effect against all the tested microorganisms.

b) *Group 2*: Compound **5g** did not have any inhibitory effect except against *Candida albicans*.

c) *Group 3*: Compounds **18b**, **13** inhibited the growth of only three of the tested microorganisms.

d) *Group 4*: The other six compounds (**2**, **3b**, **4**, **10**, **15** and **19**) inhibited only the growth of bacteria strands of the tested microorganisms.

Table 1. The inhibition zone diameters of some selected compounds against tested organisms.

Sample/Standard	Inhibition zone diameter (mm/mg sample)			
	Escherichia coli (G-)	*Staphylococcus aureus* (G+)	*Aspergillus flavus* (Fungus)	*Candida albicans* (Fungus)
2	13.0	14.0	0.0	0.0
3b	12.0	12.0	0.0	0.0
4	12.0	15.0	0.0	0.0
5g	0.0	0.0	0.0	13.0
9	20.0	21.0	11.0	12.0
10	13.0	15.0	0.0	0.0
13	22.0	30.0	14.0	0.0
15	12.0	13.0	0.0	0.0
18b	14.0	17.0	0.0	11.0
19	15.0	18.0	0.0	0.0
Tetracycline (X)	32.0	30.0	-	-
Amphotericin B (Y)	-	-	19.0	21.0
DMSO	0.0	0.0	0.0	0.0

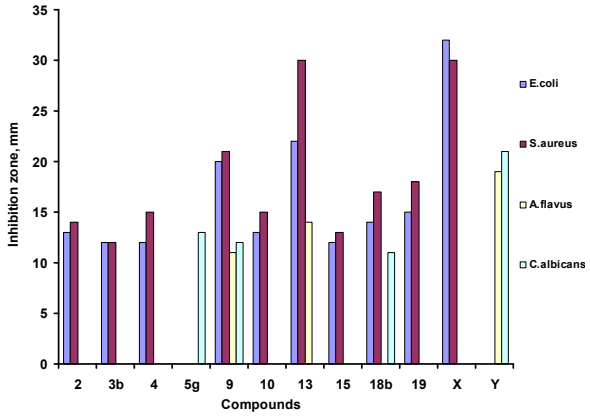


Figure 1. The effect of some selected compounds on inhibition zone diameters against tested organisms.

4. Conclusions

2-Methylchromones could be utilized to construct a variety of heterocyclic systems such as pyrazole, isoxazol and quinolinone. The phthalide and the 2-trichloromethyl derivative of the chromone exhibited two examples of heterocyclic-alicyclic and heterocyclic-heterocyclic trans-formations. Thiation of 2-methylchromone interestingly provides a dithiated product instead of the literature monothiated one.

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