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Evaluation of 6, 8-Dichloro-2-methyl-4H-Chromen-4-one Derivatives as Antileishmanial Agents

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Abstract - The present work aims at study of antileishmanial activity of some 6, 8-dichloro-2-methyl-4H-chromen-4-one derivatives. The synthesized chromenes have been screened for antileishmanial activity on *L. major* parasite. The results were promising and showed that all compounds under investigation have some degree of activity against leishmania *L. major* parasite and compound 5 showed potential activity with IC₅₀ value 0.58 ± 0.09 µg/ml, comparatively with the standard drug Amphotericin B.

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I. INTRODUCTION

The chromone system (benzo- γ -pyrone) is present in many compounds widely found in plants and particularly in flavones and isoflavones. It also forms the important components of pharmacophores of large number of molecules of medicinal significance [1]. Moreover, chromone-fused heterocyclic derivatives have attracted a great deal of interest due to their wide applications in the field of pharmaceuticals [2]. Some flavonoids have been reported to possess anticancer, anti HIV, anti-inflammatory and several other activities [3-5]. It was also reported that chromones have different biological activities and could be utilized as cytotoxic (anticancer) [6-12], antihypertensive, estrogenic [13], antimicrobial [14-16], antifungal [17], antibacterial [18-20]. Due to their abundance in plants and their low mammalian toxicity, chromone derivatives are present in large amounts in the diets of human [21, 22].

Leishmaniasis is arising as a severe public health problem. It is epidemic in 88 countries and 350 million are at risk to be infected world wide. Balochistan and Sindh provinces of Pakistan are vulnerable to cutaneous leishmaniasis. The appearance of new cases of leishmaniasis is around 2 million annually. Currently, there are no effective drugs available for leishmaniasis. The available drugs to treat the disease are frequently ineffective. Thus, there is a growing interest to investigate inexpensive, low side effect and more potent compounds against leishmaniasis.

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Herein, and in continuation of our previous work [23-31], the authors aimed at utilization of the reactivity of 6, 8-dichloro-2-methyl-4H-chromen-4-one (1) towards carbon electrophiles and nucleophiles to get chromene derivatives and evaluated them as antileishmanial agents.

II. EXPERIMENTAL

a) 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. ¹H NMR and ¹³C 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.

b) Synthesis

6,8-Dichloro-2-styryl-4H-chromen-4-one(2a), 2-(4-fluoro styryl)-6,8-dichloro-4H-chromen-4-one (2b) and 2-(4-methoxystyryl)-6,8-dichloro-4H-chromen-4-one (2c)

To a solution of 2-methylchromone derivative (1) (10 mmol, 2.29 g) in dry ethanol (20 mL), the appropriate aldehyde such as benzaldehyde, 4-fluorobenzaldehyde 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 (2a)**: Pale brown crystals. Yield: 96%. M.p.: 163-166 oC. FT-IR (KBr, cm⁻¹): 1658 - (C=O)(chromone), 1631 -(C=C). ¹H NMR (300 MHz, CDCl₃, δ , ppm): 8.08-7.40 (m, 7H, Ar-H), 6.83 (d, 1H, -CH=CH-), 6.78 (d, 1H, -CH=CH-), 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 (2b): Pale brown crystals. Yield: 63%. M.p.: 186-188 °C. FT-IR (KBr, cm⁻¹): 1649 -(C=O) (chromone).

¹H NMR (300 MHz, DMSO-*d*₆, δ, ppm): 8.16-7.60 (m, 6H, Ar-*H*), 7.33 (d, 1H, -CH=CH-), 7.24 (d, 1H, -CH=CH-), 6.54 (s, 1H, pyran ring). ¹³C 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 1). MS (EI, *m/z*, %): 334 (M+, 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 (2c): Green crystals. Yield: 38%. M.p.: 195-198 oC. FT-IR (KBr, cm⁻¹): 1652 -(C=O) (chromone), 1643 -(C=C). ¹H NMR (300 MHz, DMSO-*d*₆, δ, ppm): 8.07-7.35 (m, 6H, Ar-*H*), 7.05 (d, 1H, -CH=CH-), 6.98 (d, 1H, -CH=CH-), 6.44 (s, 1H, pyran ring), 3.79 (s, 3H, -OCH₃). MS (EI, *m/z*, %): 348 (M+2, 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%.

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

A mixture of 2-styryl derivative **2a** (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 **3a** as brown crystals (Scheme 1). Yield: 58%. M.p.: >300 oC. FT-IR (KBr, cm⁻¹): br. centered at 1722 -(C=O) anhydride, 1631 -(C=O) (chromone). ¹H 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 (MC4O₃+ 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%.

Reaction of 2-styrylchromone derivatives (2b) with *N*-Phenylmaleimide; formation of adducts (3b)

2 mmol of 2-Styryl derivatives (**2b**) was fused with *N*-phenylmaleimide (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 (**3b**) (Scheme 1).

7,9-Dichloro-4-(4-fluorophenyl)-2-phenylchromeno[3,2-*e*] isoindole-1,3,11(2H)-trione (3b): Re crystallized from acetic acid to afford the adduct as brown crystals. Yield: 80%. M.p.: 197- 200 oC. FT-IR (KBr, cm⁻¹): 1776, 1707 -(C=O) imide. ¹H NMR (300 MHz, CDCl₃, δ, ppm): 8.10-7.10 (m, 11H, Ar-*H*), 6.36 (s, 1H, C5-*H*). MS (EI, *m/z*, %): 503 (M+, 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%.

Ethyl 3-(6,8-dichloro-4-oxo-4H-chromen-2-yl)-2-oxo-propanoate (4)

To a mixture of chromone derivative **1** (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 **4** as orange crystals (Scheme 1). Yield: 65%. M.p.: 218-220 oC. FT-IR (KBr, cm⁻¹): 1730 -(C=O) ketoester, 1653 -(C=O) chromone. ¹H NMR (300 MHz, DMSO-*d*₆, δ, ppm): 8.12-7.84 (2s, 2H, Ar-*H*), 6.96 (s, 1H, -CH=C-OH), 6.08 (s, 1H, pyran ring), 4.30 (q, 2H, -CH₂CH₃, *J* = 7.2 Hz), 3.75 (s, 1H, OH, exchangeable), 1.31 (t, 3H, -CH₂CH₃, *J* = 7.2 Hz). ¹³C 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+, 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-(6,8-Dichloro-2-methyl-4H-chromene-4-ylidene)malonitrile (5)

A mixture of chromone derivative **1** (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 (**5**) as brown crystals (Scheme 2). Yield: 59%. M.p.: 121-123 oC. FT-IR (KBr, cm⁻¹): 2212 -(C≡N), 1652 -(C≡C). ¹H 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, CH₃). 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-Amino-3-(6,8-dichloro-2-methyl-4H-chromen-4-ylidene)prop-1-ene-1,1,3-tricarbonitrile (6)

A mixture of chromone derivative **1** (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 **6** as yellow crystals (Scheme 2). Yield: 59%. M.p.: 198-200 °C. FT-IR (KBr, cm⁻¹): 3411, 3322 -(NH₂), 2212 -(C≡N). ¹H NMR (300 MHz, DMSO, δ, ppm): 8.25 (s, 2H, NH₂, exchangeable), 7.65 (s, 1H, Ar-*H*), 7.28 (s, 1H, Ar-*H*), 6.79 (s, 1H, C3-*H*), 2.32 (s, 3H, CH₃). 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%.

c) Antileishmanial Assay

Each compound (1 mg) was dissolved in DMSO (1 mL) and Amphotericin B (1 mg) was also dissolved in DMSO (1 mL) as positive control. Parasites at log phase were centrifuged at 3,000 rpm for 3 minutes. Parasites were diluted in fresh culture medium to a final density of 2×10^6 cells/mL. In 96-well plates, 180 μ L of medium was added in different wells. Twenty μ L of the compound was added in medium and serially diluted. Parasite culture (100 μ L) was added in all wells. Three rows were left for negative and positive controls. In the negative controls, DMSO was serially diluted in medium while the positive control contained varying concentrations of the standard antileishmanial compound Amphotericin B. The plates were incubated for 72 hours at 24 °C. The culture was examined microscopically on an improved Neubauer counting chamber and IC₅₀ values of compounds possessing antileishmanial activity were calculated. All assays were run in duplicate. IC₅₀ of samples was determined by using the Prism software [27].

III. RESULTS AND DISCUSSIONS

a) Synthesis

6, 8-Dichloro-2-methyl-4H-chromen-4-one (1) was prepared *via* acid-catalyzed cyclodehydration of the β -diketone; 1-(3,5-dichloro-2-hydroxyphenyl)butane-1,3-dione [32]. 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-4H-chromen-4-one (1) condensed under Knoevenagel reaction conditions, with different aromatic aldehydes namely, benzaldehyde, 4-fluorobenzaldehyde and 4-methoxybenzaldehyde to afford the corresponding 2-styrylchromones (2a-c) [7, 24, 25, 32-35].

2-Styryl chromones (2a-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 (3a-b).

Condensation of 2-methylchromone 1 with diethyl oxalate in the presence of sodium metal gave the corresponding pyruvate esters (4) [36], which exists as keto-enol tautomers.

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 1 was allowed to react with malononitrile (1:1) in boiling acetic anhydride, the

corresponding condensation product 5 was obtained [25]. The product 5 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, 1 was allowed to react with excess malononitrile in refluxing ethanol containing few drops of piperidine, the product was identified to be the tricarbonitrile (6) which is formed from the attack of a second malononitrile molecule on the initially formed condensation intermediate of type (5). The attack occurs at one cyano group but not on both probably due to steric hindrance.

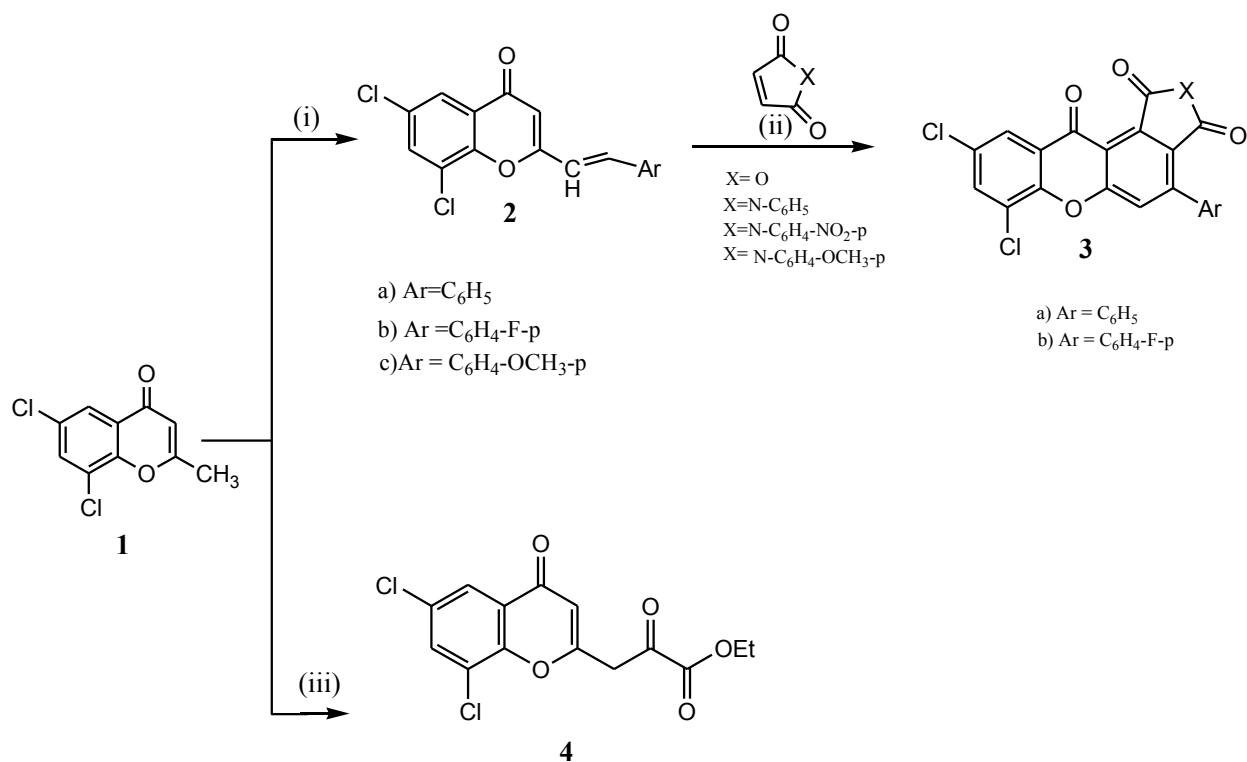
b) Antileishmanial activity

Antileishmanial activity of nine 4H-chromen-4-one derivatives was evaluated in order to utilize as antileishmanial agents. Compounds (5 and 6) showed significant activity with IC₅₀ values 0.58 ± 0.09 and 0.59 ± 0.05 μ g/ml respectively. These IC₅₀ values are comparable with IC₅₀ of the standard drug Amphotericin B. Compounds 2a, 2b, 2c 3b and 4 showed good activity with IC₅₀ values between 0.61 ± 0.02 μ g/ml to 0.69 ± 0.07 μ g/ml. On other hand compounds 1 and 3a showed moderate activity with IC₅₀ values 0.72 ± 0.04 μ g/ml, 0.78 ± 0.02 μ g/ml.

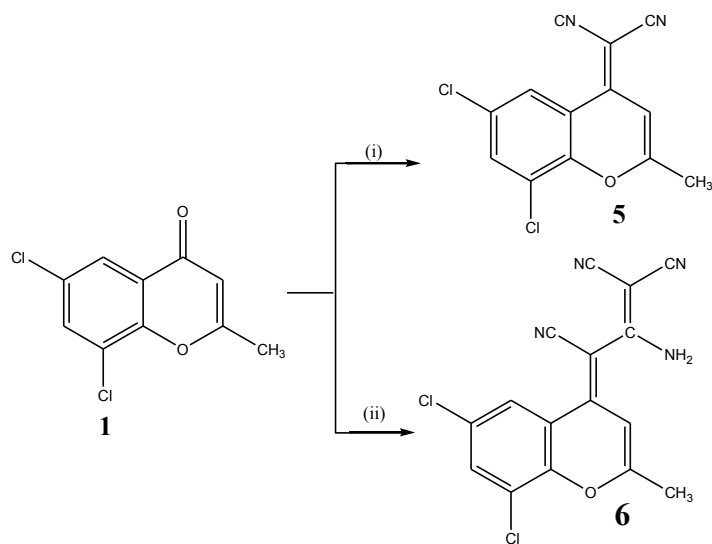
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Scheme 1



Scheme 2

Table 1 : %Inhibition of compounds **1-6** against *L. major*

Compound	<i>L. major</i> IC ₅₀ value
1	0.78±0.02
2a	0.68±0.08
2b	0.69±0.07
2c	0.61±0.02
3a	0.72±0.04
3b	0.66±0.07
4	0.62±0.01
5	0.58±0.09
6	0.59±0.05
DMSO	0.99±0.00
Standard IC ₅₀	0.56±0.01

^a percentage inhibition activity: 100 = (non-significant; 0.95–0.80 = low; 0.79–0.70 = Moderate; 0.69–0.60 = Good; below 0.59–0.56 = Significant activity).