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Synthesis and Anti-Tuberculosis Activity of Substituted 3,4-(dicoumarin-3-yl)-2,5-diphenyl Furans and Pyrroles †

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Abstract: Increasing rates of multi-drug resistant (MDR) and extremely-drug resistant (XDR) cases of tuberculosis (TB) strains are alarming, and eventually hampered an effective control of the pathogenic disease. In the present study, nine derivatives of 2,3-bis(2-oxochromen-3-yl)-1,4-diphenyl-butane-1,4-dione (**11a–c**) and 3,4-(dicoumarin-3-yl)-2,5-diphenyl furans and pyrroles (**12a–f**) have been synthesized successfully. The experimental data for the anti-tuberculosis activity (using MABA assay) of 2,3-bis(2-oxochromen-3-yl)-1,4-diphenyl-butane-1,4-dione (**11a–c**) revealed that, in this series, compound 11a showed a better minimum inhibitory concentration of 1.6 µg/mL against *Mycobacterium tuberculosis* (H37 RV strain) ATCC No-27294, which was better than the MIC value of Pyrazinamide-3.125 µg/mL, Streptomycin-6.25 µg/mL and Ciprofloxacin-3.125 µg/mL. Our synthesis and in-vitro studies thus pointed out the moderate to good anti-TB profiles of substituted furans and pyrroles.

Keywords: tuberculosis; *Mycobacterium*; furans; pyrroles

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1. Introduction

Coumarins are naturally occurring compounds known for their low toxicity and varied biological activity. The biological spectrum of coumarin has intrigued medicinal researchers to investigate coumarin scaffolds for their relevance as anti-TB drugs [1]. Akiyama K et al. [1] evaluated the antifungal activities of the optically pure (>99%ee) (-)- and (+)-virgatusin, a tetra-substituted tetrahydrofuran lignan. Molvi KI et al. [2] synthesized various tetrasubstituted thiophene compounds and evaluated them for their anti-inflammatory activity. The same group has also developed a synthesis of tetrasubstituted thiophene esters and evaluated them for anti-inflammatory, analgesic and antioxidant activities [3]. Padron JM et al. [4] synthesized various tetrasubstituted pyrrole derivatives and evaluated them for their in vitro anti-proliferative activities using the human promyelocytic leukemia cell line HL60.

Pagadala LR et al. [5] developed the synthesis of 1,2,3,5-tetrasubstituted pyrrolyl-N-acetic acid derivatives and evaluated them for anti-mycobacterial activity. Jose M. Padron et al. [6] developed the synthesis of tetrasubstituted pyrrole derivatives and evaluated them for anti-breast cancer activity. W. M. Basyouni et al. [7] synthesized a series of 3,4,5-trisubstituted 2(5H)-furanone derivatives through a one-pot reaction of amines, aldehydes and diethyl acetylenedicarboxylate. The synthesized compounds were tested against HEPG-2, MCF-7 and CACO tumor cell lines. Babu S. P. et al. [8] synthesized 2,4-disubstituted furan derivatives and evaluate them for anti-diabetic activity. Molvi K. I.

et al. [9] synthesized various trisubstituted thiophene compounds and evaluated them for their anti-inflammatory activity. Weiqin Jiang et al. [10] synthesized various trisubstituted thiophene compounds and evaluated them for their progesterone receptor modulator activity. Gonul Velicelebi et al. [11] synthesized various trisubstituted thiophine analogs and evaluated them as compounds, which modulate the activity of store-operated calcium (SOC) channels. Raquel Pereiraet et al. [12] synthesized various trisubstituted heterocyclic scaffolds, mostly thiophenes of PPAR ligands, which displayed PPAR agonist activity as revealed by reporter assay in living cells.

Dhruv Panchal et al. [13] synthesized and evaluated the activity of a trisubstituted pyrrole in inhibiting sporozoite invasion and blocking malaria infection. Giuseppe Vecchi [14] synthesized various trisubstituted pyrrole and evaluated their activity against pathogenic microorganisms, and particularly against mycetes and Gram-positive and Gram-negative bacteria.

After successfully synthesizing hydrazone–hydrazides and evaluating their biological or anti-tuberculosis activity, we diverted our research interest towards the synthesis of tetra-substituted furans and pyrroles, which carried two units of such ortho substitution. The general structure shown below (Figure 1) shows two such units in a five-member heterocyclic ring with expected activity on the higher side. Here, R1 and R2, along with C=C linkage forms the first ortho-substituted unit, whereas R3 and R4, along with C=C linkage forms the second ortho-substituted unit, where in each of the pairs, one of the substituents is phenyl while the other substituent is coumarin. Based on the observation above, we concluded that it was worth attempting the synthesis of such substituted 3,4-(dicoumarin-3-yl)-2,5-diphenyl furans and pyrroles and evaluate them for anti-tuberculosis activity. In the present study, all the synthesized compounds were tested for their anti-tubercular activity using the microplate Alamar Blue assay method (MABA) [15–39]. Moreover, our research group is also currently focusing on biological activities of various natural, as well as synthetic molecules [40–50].

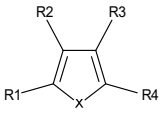


Figure 1. General chemical structures of the synthesized derivatives' furans and pyrroles.

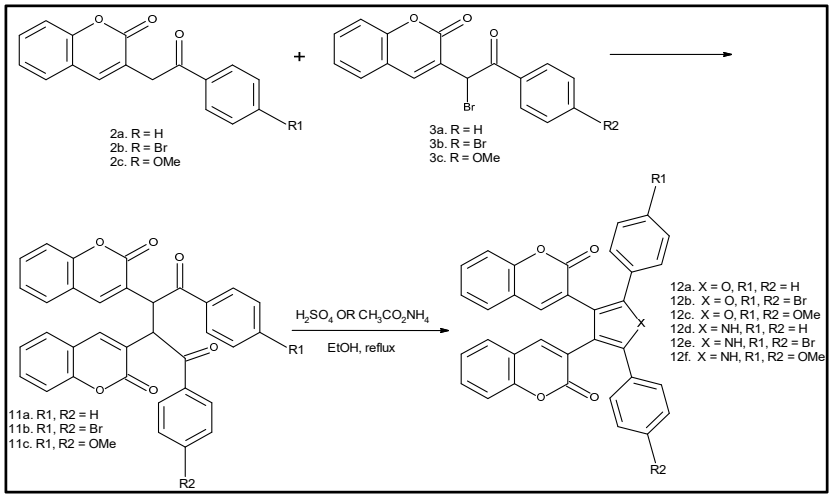
2. Materials and Methods

The structures of the synthesized compounds were confirmed using modern spectroscopic techniques like ^{1}H-NMR, ^{13}C-NMR, mass spectrum and FT-IR. The purity of the compounds was monitored by TLC on silica F_{254}-coated aluminum plates (Merck) as the adsorbent and U.V. light and an iodine chamber as visualizing agents. Column chromatography was performed on silica gel 100–200 mesh, using an ethyl acetate and hexanes mixture as eluent. The melting points were determined by using a super fit hot-stage melting point apparatus and are uncorrected.

*2.1. Synthesis of Substituted 3,4-(dicoumarin-3-yl)-2,5-diphenyl Furans and Pyrroles (***12a–f***)*

For the current study, Scheme 1 envisages the schematic representation for the synthesis of substituted 3,4-(dicoumarin-3-yl)-2,5-diphenyl furans and pyrroles (**12a–f**). For the synthesis of the desired molecules, 3-(2-oxo-2-phenylethyl)-2H-chromen-2-ones (**2a–c**) was reacted with 3-(1-bromo-2-oxo-2-phenylethyl)-2H-chromen-2-ones (**3a–c**) in the presence of a strong base to give 2,3-bis(2-oxochromen-3-yl)-1,4-diphenyl-butane-1,4-dione (**11a–c**).

These 1,4-diones were then cyclized by refluxing either with sulfuric acid or ammonium acetate using ethanol as a solvent to give hydrolyzed, substituted 3,4-(dicoumarin-3-yl)-2,5-diphenyl furans and pyrroles (**12a–f**). The final substituted 3,4-(dicoumarin-3-yl)-2,5-diphenyl furans and pyrroles (**12a–f**) isolated are shown in Scheme 1 (Please refer Supporting Information Figures S1–S9).



Scheme 1. Synthesis of (**11a–c**) and substituted 3,4-(dicoumarin-3-yl)-2,5-diphenyl furans and pyrroles (**12a–f**).

2.2. Experimental

2.2.1. Synthesis of 2,3-bis(2-oxo-2H-chromen-3-yl)-1,4-diphenylbutane-1,4-dione (**11a**)

A mixture of 3-(2-oxo-2-phenylethyl)-2H-chromen-2-one **2a** (1.5 g, 5.68 mmol), 3-(1-bromo-2-oxo-2-phenylethyl)-2H-chromen-2-one **3a** (1.948 g, 5.68 mmol) and potassium carbonate (1.569 g, 11.35 mmol) in acetone (56.8 mL) was heated to 60 °C for 16 hrs. The mixture was cooled to room temperature and then added to 150 mL water. The solid was separated out, filtered and washed with 15 mL water and dried. The crude compound was purified by column chromatography to obtain a pure compound in 81% yield (2.42 g), white solid; M.P = 160–162 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.14 (s, 2H), 7.24–7.15 (m, 4H), 7.58–7.33 (m, 10H), 7.97 (s, 2H), 8.16–8.14 (d, J = 8.0 Hz, 4H); **FT-IR** (cm^{-1}): 3020 (Aromatic C-H Stretch), 1714 (Pyrano C=O group), 1666 (Aryl ketone C=O Stretch), 1608 (Aromatic C=C stretching) (Please refer Supporting Information Figures S1–S9).

2.2.2. Synthesis of
1,4-bis(4-bromophenyl)-2,3-bis(2-oxo-2H-chromen-3-yl)butane-1,4-dione (**11b**)

A mixture of 3-(2-oxo-2-(4-bromophenyl)ethyl)-2H-chromen-2-one **2b** (1.94 g, 5.68 mmol), 3-(1-bromo-2-oxo-2-(4-bromophenyl)ethyl)-2H-chromen-2-one **3b** (2.38 g, 5.68 mmol) and potassium carbonate (1.569 g, 11.35 mmol) in acetone (56.8 mL) was heated to 60 °C for 16 h. The mixture was cooled to room temperature and then added to 150 mL water. The solid was separated out, filtered and washed with 15 mL water and dried. The crude compound was purified by column chromatography to obtain a pure compound in 74% yield (2.21 g) white solid; M.P = 156–58 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.05 (s, 2H), 7.19–7.17 (d, 2H), 7.26 (d, 1H), 7.28 (d, 1H), 7.52–7.45 (m, 4H), 7.61–7.59 (d, J = 8.0 Hz, 4H), 7.94 (s, 2H), 8.02–7.99 (d, J = 8.0 Hz, 4H); **FT-IR** (cm^{-1}): 3015 (Aromatic C-H Stretch), 1716.6 (Pyrano C=O group), 1664.5 (Aryl ketone C=O Stretch), 1608.6 (Aromatic C=C stretching).

2.2.3. Synthesis of
1,4-bis(4-methoxyphenyl)-2,3-bis(2-oxo-2H-chromen-3-yl)butane-1,4-dione (**11c**)

A mixture of 3-(2-oxo-2-(4-methoxyphenyl)ethyl)-2H-chromen-2-one **2c** (1.67 g, 5.68 mmol), 3-(1-bromo-2-oxo-2-(4-methoxyphenyl)ethyl)-2H-chromen-2-one **3c** (2.11 g, 5.68 mmol) and potassium carbonate (1.569 g, 11.35 mmol) in acetone (56.8 mL) was heated to 60 °C for 16 h. The mixture was cooled to room temperature and then added to 150 mL of water. The solid was separated out, filtered and washed with 15 mL water and dried. The crude compound was purified by column chromatography to obtain a pure compound in 78% yield (2.33 g), white solid; M.P = 145–149 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 3.83 (s, 6H), 6.08 (s, 2 H), 6.93–6.91 (d, J = 8.0 Hz, 4 H), 7.17–7.15 (d, 2H), 7.24–7.22 (m, 2H), 7.46–7.42

(m, 2H), 7.50–7.48 (dd, 2H), 8.00 (s, 2H), 8.15–8.13 (d, J = 8.0 Hz, 4 H); **FT-IR** (cm^{-1}): 3025 (Aromatic C-H Stretch), 1714.7 (Pyrano C=O group), 1662.6 (Aryl ketone C=O Stretch), 1595.1 (Aromatic C=C stretching).

2.2.4. Synthesis of 3-[4-(2-oxochromen-3-yl)-2,5-diphenyl-3-furyl]chromen-2-one (**12a**)

A total of 0.5 g, 0.950 mmol of 2,3-bis(2-oxo-2H-chromen-3-yl)-1,4-diphenylbutane-1,4-dione was combined with ethanol (18.99 mL) and 17 mL of conc. H_2SO_4 was added dropwise, whereupon the solid dissolved completely. The reaction mixture was cooled to room temperature and diluted with 100 mL of ice-cold water. The solid precipitates were filtered off and recrystallized from ethanol and dried with 79% yield (0.38 g) white solid; M.P = 149–151 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$):: δ 7.37–7.24 (m, 10H), 7.46–7.44 (dd, 2H), 7.55–7.50 (td, 2H), 7.64–7.62 (m, 4H), 7.87 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 116.3, 117.8, 118.7, 120.8, 124.2, 125.7, 127.8, 128.0, 128.4, 129.5, 131.5, 144.2, 149.8, 153.5, 160.2; **FT-IR** (cm^{-1}): 3018 (Aromatic C-H Stretch), 1718.5 (Pyrano C=O group), 1595.1 (Aromatic C=C stretching).

2.2.5. Synthesis of
3-[2,5-bis(4-bromophenyl)-4-(2-oxochromen-3-yl)-3-furyl]chromen-2-one (**12b**)

A total of 0.65 g, 0.950 mmol of 1,4-bis(4-bromophenyl)-2,3-bis(2-oxo-2H-chromen-3-yl)butane-1,4-dione **11b** was combined with ethanol (18.99 mL) and 17 mL of conc. H_2SO_4 was added dropwise, whereupon the solid dissolved completely. The reaction mixture was cooled to room temperature and diluted with 100 mL of ice-cold water. The solid precipitates were filtered off and recrystallized from ethanol and dried with 71% yield (0.447 gm) off white solid; M.P = 164–166 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.34–7.28 (m, 4H), 7.48–7.45 (m, 9H), 7.57–7.51 (m, 3H), 7.84 (s, 2H); **FT-IR** (cm^{-1}): 3018 (Aromatic C-H Stretch), 1718.5 (Pyrano C=O group), 1595.1 (Aromatic C=C stretching)

2.2.6. Synthesis of
3-[2,5-bis(4-methoxyphenyl)-4-(2-oxochromen-3-yl)-3-furyl]chromen-2-one (**12c**)

A total of 0.557 g, 0.950 mmol of 1,4-bis(4-methoxyphenyl)-2,3-bis(2-oxo-2H-chromen-3-yl)butane-1,4-dione **11c** was combined with ethanol (18.99 mL) and 17 mL of conc. H_2SO_4 was added dropwise, whereupon the solid dissolved completely. The reaction mixture was cooled to room temperature and diluted with 100 mL of ice-cold water. The solid precipitates were filtered off and recrystallized from ethanol and dried with 80% yield (0.43 g) off white solid; M.P = 136–137 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 6H), 6.88–6.86 (d, 4H), 7.27–7.23 (t, 2H), 7.32–7.30 (d, 2H), 7.44–7.42 (d, 2H), 7.51–7.49 (m, 2H), 7.55–7.53 (d, 4H), 7.84 (s, 2H); FT-IR (cm^{-1}): 3018 (Aromatic C-H Stretch), 1716.6 (Pyrano C=O group), 1606.7 (Aromatic C=C stretching); MS (ESI) (m/z): calcd for $C_{36}H_{24}O_7$, [M+1]+, 569.57; found, 569.1.

2.2.7. Synthesis of
3-[4-(2-oxochromen-3-yl)-2,5-diphenyl-1H-pyrrol-3-yl]chromen-2-one (**12d**)

A mixture of 2,3-bis(2-oxo-2H-chromen-3-yl)-1,4-diphenylbutane-1,4-dione (**11a**) (0.5 g, 0.950 mmol) and ammonium acetate (0.732 g, 9.50 mmol) in ethanol (47.5 mL) were heated to reflux for 15 hrs. The ethanol was evaporated under reduced pressure. A total of 100 mL of water was added to the reaction mixture. The solid precipitates were filtered off and recrystallized from ethanol and dried with 77% yield (0.37 g) yellow solid; M.P = 156–159 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.24–7.18 (m, 2H), 7.28–7.26 (m, 4H), 7.37–7.32 (m, 6H), 7.48–7.41 (m,6 H), 7.70 (s, 2H), 8.59 (broad s, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$): δ 116.1, 116.3, 119.1, 123.1, 123.9, 126.6, 127.1, 127.6, 128.6, 130.8, 131.0, 131.5, 143.1, 153.2, 161.1; **FT-IR** (cm^{-1}): 3015 (Aromatic C-H Stretch), 1712.6 (Pyrano C=O group), 1602.8 (Aromatic C=C stretching); MS (ESI) (*m*/*z*): calcd for $C_{34}H_{21}NO_4$, $[M^{+1}]^+$, 508.53; found, 508.

2.2.8. Synthesis of
3-[2,5-bis(4-bromophenyl)-4-(2-oxochromen-3-yl)-1H-pyrrol-3-yl]chromen-2-one (**12e**)

A mixture of 1,4-bis(4-bromophenyl)-2,3-bis(2-oxo-2H-chromen-3-yl)butane-1,4-dione **11b** (0.65 g, 0.950 mmol) and ammonium acetate (0.732 g, 9.50 mmol) in ethanol (47.5 mL) were heated to reflux for 15 h. The ethanol was evaporated under reduced pressure. A total of 100 mL of water was added to the reaction mixture. The solid precipitates were filtered off and recrystallized from ethanol and dried with 72% yield (0.35 g) yellow solid; M.P = 142–144 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.24–7.20 (m, 2H), 7.29–7.25 (m, 6H), 7.38–7.36 (dd, 2H), 7.50–7.43 (m,6 H), 7.66 (s, 2H), 8.68 (broad s, 1H); **FT-IR** (cm^{-1}): 1712.8 (Pyrano C=O group), 1608.6 (Aromatic C=C stretching); MS (ESI) (m/z): calcd for $C_{34}H_{19}Br_2NO_4$, $[M]^+$, 663.0; found, 663.6.

2.2.9. Synthesis of
3-[2,5-bis(4-methoxyphenyl)-4-(2-oxochromen-3-yl)-1H-pyrrol-3-yl]chromen-2-one (**12f**)

A mixture of 1,4-bis(4-methoxyphenyl)-2,3-bis(2-oxo-2H-chromen-3-yl)butane-1,4-dione **11c** (0.557 g, 0.950 mmol) and ammonium acetate (0.732 g, 9.50 mmol) in ethanol (47.5 mL) were heated to reflux for 15 h. The ethanol was evaporated under reduced pressure. A total of 100 mL of water was added to the reaction mixture. The solid precipitates were filtered off and recrystallized from ethanol and dried with 76% yield (0.34 g) yellow solid; M.P = 121–124 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 6H), 6.88–6.85 (d, 4H), 7.21–7.18 (t, 2H), 7.27–7.24 (m, 3H), 7.36–7.33 (m, 5H), 7.46–7.42 (t, 2H), 7.67 (s, 2H), 8.43 (broad s, 1H); FT-IR (cm^{-1}): 3015 (Aromatic C-H Stretch), 3425 (pyrrolo NH group), 3020 (Aromatic C-H Stretch), 1712.8 (Pyrano C=O group), 1602.8 (Aromatic C=C stretching); MS (ESI) (m/z): calcd. For $C_{36}H_{25}NO_6$, $[M^{+1}]^+$, 568.2; found, 568.0.

3. Results and Discussion

3.1. Spectroscopic Characterizations

The ^{1}H-NMR spectra were acquired on a Bruker (400 MHz) instrument. The $CDCl_3$ and DMSO-$_{d6}$, were used as solvents with tetramethylsilane (TMS) as the internal standard. The chemical shifts were given on the delta scale as parts per million (ppm). The majority of the 1H NMR spectra of the compounds (**12a–e**) were recorded in a $CDCl_3$ solvent over the range of 0–14 ppm. For the compounds (**11a–c**), the appearance of a singlet peak integrated two protons in the range of 6.0–6.3 ppm assignable to the -CH group, which has an isomeric position next to carbonyl, which confirms the condensation of (2a–c) with (**3a–c**). Compounds (**11a–c**), also confirmed by the disappearance of the singlet peak, integrated two protons in the range 4.0–4.5 ppm of (**2a–c**) and the disappearance of the singlet peak integrated one proton in the range of 6.5–6.7 ppm of (**3a–c**). The disappearance of the singlet peak integrated two protons in the range of 6.0–6.3 ppm, assignable to the -CH group, which has an isomeric position next to carbonyl and confirmed the formation of compounds (**12a–e**). In addition, a set of multiple singlets observed in the range 7.6–8.4 ppm were ascribed to the aromatic protons in all the synthesized compounds (**12a–e**). The ^{1}H-NMR spectral assignments with chemical shifts and coupling constants for the compounds (**12a–e**) are given in the experimental section. The electron impact ionization mass spectra were recorded on an Agilent Technologies 5975C MSD detector at 70 eV. The formation of the desired compounds was confirmed by the presence of an intense molecular ion peak in the mass spectrum. Spectral evaluation predicts the molecular weights of the synthesized compounds. The FT-IR spectrum of compound (11a–c) showed strong absorption bands in the range 1714–1717 cm^{-1}, a region that corresponds to the Pyrano C=O group, and bands in the range 1664–1666 cm^{-1}, a region that corresponds to Aryl ketone C=O stretching. The disappearance of the bands in the range 1664–1666 cm^{-1}, a region that belongs to Aryl ketone C=O stretching, confirmed the formation of the cyclized product (**12a–f**).

3.2. Antimycobacterial Activity

The antimycobacterial activities were evaluated according to the macro dilution protocol described by Abate et al. [15]. The antimycobacterial activities of some novel derivatives (**11a–c**) and (**12a–f**) were assessed at the Department of Microbiology, Maratha Mandal's NGH Institute of Dental Sciences and Research Centre, Belgaum-590010, India, against M. tuberculosis ATTC 27,294 [15] using the micro plate Alamar Blue assay (MABA) testing method for anti-TB analysis [15–39]. This methodology is nontoxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric methods [29d–e]. The mycobacterium tuberculosis stain H37Rv (ATCC 27294) was cultured at 37 °C in Lowenstein–Jensen medium until the log phase growth. Then, a cell suspension was prepared at a concentration of about 2×10^6 UFC Ml-CM and further diluted 1:20 in Middlebrook 7H9 medium. The latter was supplemented with 10% OADC (oleic acid–albumin–dextrose catalase) and 0.001% Tween 80. One mL of bacterial suspension was added to each tube (capped, glass) to gather with the sample solutions of various concentrations. The final concentrations of the compounds tested ranged from 0.8 to 100 µg per ml and were adjusted to a final 2 mL volume. After a 7-day incubation, 100 µL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (5 mg/mL) with 20% Tween 80 was added to the glass tubes. A violet colour indicated bacterial growth. The tubes were evaluated for colour change on day 8. The colour of the dye turns from blue to pink only when the organisms are alive and viable. If a compound has anti-mycobacterial activity, then it helps to determine at what concentration it exerts its bactericidal effect (at which point the blue remains unaffected); hence, it is useful to determine the MIC. For standard tests, a MIC value of Pyrazinamide-3.125 µg/mL, Streptomycin-6.25 µg/mL and Ciprofloxacin-3.125 µg/mL were determined each time. The MIC of each sample corresponded to the lowest concentration at which the bacteria tested did not show growth. The results are summarized in Table 1.

Table 1. The minimum inhibitory concentration values for (11a–c) and (12a–f).

Entry	The Minimum Inhibitory Concentration							
	100 mg/mL	50 mg/mL	25 mg/mL	12.5 mg/mL	6.25 mg/mL	3.12 mg/mL	1.6 mg/mL	0.8 mg/mL
Pyrazinamide	S	S	S	S	S	S	R	R
Ciprofloxacin	S	S	S	S	S	S	R	R
Streptomycin	S	S	S	S	S	R	R	R
11a	S	S	S	S	S	S	S	R
11b	S	S	S	R	R	R	R	R
11c	S	S	S	R	R	R	R	R
12a	S	S	S	R	R	R	R	R
12b	S	S	S	R	R	R	R	R
12c	S	S	S	R	R	R	R	R
12d	S	S	S	R	R	R	R	R
12e	S	S	S	R	R	R	R	R
12f	S	S	R	R	R	R	R	R

(S—Sensitive, R—Resistant); MICs of compounds: 11a: 1.6 µg/mL; 11b: 25 µg/mL; 11c: 25 µg/mL; 12a: 25 µg/mL; 12 b: 25 µg/mL; 12c: 25 µg/mL; 12d: 25 µg/mL; 12e: 25 µg/mL; 12f: 50 µg/mL; Pyrazinamide: 3.12 µg/mL by MABA assay.

4. Conclusions

In conclusion, novel derivatives of (**11a–c**) and (**12a–f**) have been synthesized successfully. The experimental data for the anti-tuberculosis activity of 2,3-bis(2-oxochromen-3-yl)-1,4-diphenyl-butane-1,4-dione (**11a–c**) revealed that, in this series, compound 11a showed a

better minimum inhibitory concentration of 1.6 µg/mL against *Mycobacterium tuberculosis (H37 RV strain)* ATCC No-27,294, which was better than the MIC value of Pyrazinamide-3.125 µg/mL, Streptomycin-6.25 µg/mL and Ciprofloxacin-3.125. Both compounds 11b and 11c showed moderate activity, i.e., a MIC value of 25 µg/mL. For the compounds 3,4-(dicoumarin-3-yl)-2,5-diphenyl furans and pyrroles (**12a–f**), all the compounds showed moderate activity with a MIC value of 25 µg/mL, except 12f, which showed even less value at 50 µg/mL. This study will pave the way for future development of more effective 2,3-bis(2-oxochromen-3-yl)-1,4-diphenyl-butane-1,4-dione analogs for applications in biological and material science.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ASEC2022-13851/s1, Figure S1. 1H NMR and FT-IR spectra of (**11a**); Figure S2. 1H NMR and FT-IR spectra of (**11b**); Figure S3. 1H NMR and FT-IR spectra of (**11c**); Figure S4. 1H NMR, 13C NMR and FT-IR spectra of (**12a**); Figure S5. 1H NMR and FT-IR spectra of (**12b**); Figure S6. 1H NMR, FT-IR and Mass spectra of (**12c**); Figure S7. 1H NMR, 13C NMR, FT-IR and Mass spectra of (**12d**); Figure S8. 1H NMR, FT-IR and Mass spectra of (**12e**); Figure S9. 1H NMR, FT-IR and Mass spectra of (**12e**).

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