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Synthesis of Flavopiridol Analogues Containing 1,3-Thiazolan-4-one and Their Antibacterial Activity

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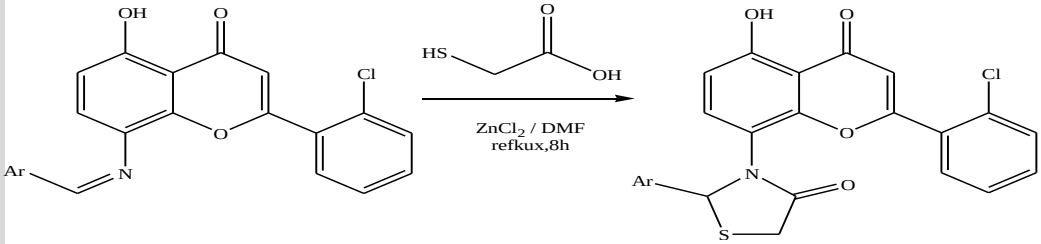
KEYWORDS
Flavopiridol, Biological Activity, 1,3-Thiazolan-4-one, Flavonoids

ABSTRACT:

The biological and pharmacological importance of flavopiridol and 1,3-thiazolan-4-one and their derivatives, contemplated to synthesize some new flavopiridol analogues containing 1,3-thiazolan-4-ones such as 3-[2-(2-chlorophenyl)-5-hydroxy-4-oxo-4*H*-8-chromenyl]-2-aryal-1,3-thiazolan-4-one **8 (a-f)** has been Synthesized by the reaction of 2-(2-chlorophenyl)-5-hydroxy-8-[(*E*)-1-arylmethylidene]amino-4*H*-4-chromenone **7** with a view to explore their potential biological activity. The antibacterial activities of these compounds have also been evaluated.



1. Introduction

The family of cyclin-dependent kinases (CDKs) is a crucial group of regulators that manages the cell cycle's timing and coordination[1-5]. With their obligatory cyclin partners, CDKs construct reversible complexes that regulate passage through critical cell cycle junctions. For instance, the CDK1-cyclin B1 complex regulates entry into the mitotic phase of the cell cycle[6], whereas the active CDK4-cyclin D1 complex regulates advancement through the G1 phase[6]. It is known that endogenous CDK's can bind either the CDK or the cyclin component and inhibit the kinase activity[7-8]. The native CDK's in many malignancies, including melanomas, pancreatic, and esophageal cancers, are either missing or mutated[9]. This means that targeted CDK inhibitors may be effective chemotherapeutic drugs.

Flavopiridol is a semi-synthetic flavonoid that is structurally related to an isolated naturally occurring alkaloid from an Indian native plant called *Dysoxylum binectariferum*[10]. It has been demonstrated that flavopiridol is a powerful cyclin-dependent kinase (CDK) inhibitor[11]. According to research done on human breast cancer cells (MCF-7), flavopiridol inhibits CDK1, CDK2, and CDK4 by attaching to the kinase's ATP-binding pocket. Additionally to inhibiting, flavopiridol lowers cyclin D1, and it was thought that cyclin D1 depletion results in the loss of CDK4 activity. Later research has demonstrated that flavopiridol induces strong cell cycle arrest and death as a result of the CDK inhibition[12].

Flavopiridol has been demonstrated to be a powerful antiproliferative medication in animal studies. Flavopiridol greatly inhibited the growth of tumours in leukaemia and lymphoma xenografts[15], as well as the

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tumours in colorectal[10], prostate[13], and head and neck carcinoma[14] xenograft models. Peak plasma concentrations of 5-8 μM, a reduction in cyclin D1, and apoptotic cell death have all been associated with flavopiridol's anticancer activity in tumour tissue[13].

It has been demonstrated to cause cell cycle arrest in both the G1 and G2 phases[16,17]. A powerful and selective CDK inhibitor, flavopiridol is now undergoing clinical trials as a cancer treatment[18,19]. Its antitumor efficacy is correlated with its CDK inhibitory activity[10]. Studies have revealed that its tumour cell growth inhibitory activity happens specifically during the cell cycle[16]. Additionally, kinetic investiga- tions have demonstrated that favopiridol binds to the CDKs[17] ATP binding site. Des-chloro favopiridol's interaction to CDK2 and its recently revealed X-ray crystal structure provide additional evidence that the favone nucleus is present in the enzyme's ATP binding pocket[20]. The total synthesis of favopiridol[21-24] and some SAR around favopiridol have been reported[10].

Because many biologically active molecules, including thiamine, penicillin, and other antibiotics[25,26], include these heterocyclic rings, the nitrogen and sulfur-containing heterocyclic compounds are important from a biological perspective. The same goes for 1,3-thiazolan-4-one and its derivatives, which are significant and exhibit the desired biological and pharmacological activities, such as hypnotic[27], antiinflammatory[28], antibacterial[29], antifungal[30], antitubercular[31], anticancer[32], antitumor[33], analgesic[34], anesthetic[35], antiproliferative[36], anti-HIV[37], and nematicidal[38]. 1,3-Thiazolan-4-one have also been utilized to treat schizophrenia[39], diabetic problems such cataract, nephropathy, and neuropathy[40], as well as selective antiplatelet activating factor (PAF)[41].Additionally, cyanine dyes, which are utilized in the photographic film industry[42], are made using 1,3-thiazolan-4-one derivatives.

2. Experimental

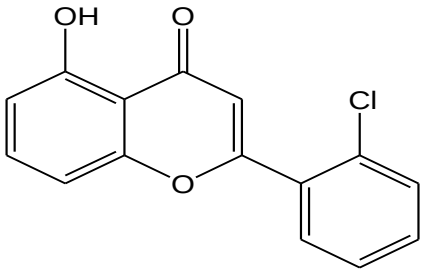
All of the reagents were of commercial grade and used exactly as directed. On pre-coated silica gel F254 plates from Merck, reactions were observed using thin-layer chromatography (TLC), and chemicals were seen using UV light. Silica gel with a mesh size of 70–230 was utilised in chromatographic columns for separations. A Varian Gemini spectrometer was used to record the ^{1}H NMR and ^{13}C NMR spectra (300 MHz for ^{1}H and 75 MHz for ^{13}C). Coupling constants (*J*) are published in Hz units, and chemical shifts are recorded in ppm units relative to TMS as the internal standard. A VG micro mass 7070H spectrometer was used to record the mass spectra.[43-61]

2.1 1-(2-chlorophenyl)-3-(2,6-dihydroxyphenyl)-1,3-propanedione (3):

2,6-dihydroxyacetophenone **1** (0.02 mol) in pyridine (25 mL) was dissolved in 2-chlorobenzoyl chloride **2** (0.02 mol), and DMAP was added as a catalytic quantity. After 3 hours of stirring at room temperature, the reaction mixture was dumped into ice water (150 mL). Ethyl acetate was used to extract the solution. Under reduced pressure, the solvent was removed. Compound **3** was produced with a 76% yield after the residue was purified using flash silica gel column chromatography (1:9 EtOAc/hexane).

2.2. 2-(2-chlorophenyl)-5-hydroxy-4H-4-chromenone (4):

DBU (0.04 mol) was added to a compound **3** (0.02 mol) in pyridine (50 mL). After 12 hours of heating at 100 ^{o}C, the reaction mixture was dumped into freezing water (150 mL). EtOAc was used to extract the solution, after which the organic layer was cleaned with diluted hydrochloric acid, dried over anhydrous Na_2SO_4, and the solvent was removed at reduced pressure. The residue obtained was purified by column chromatography (1:9 EtOAc/hexane) to afford compound **4**.



Yield: 82%, mp: 169-170 ^{o}C;^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.57 (s, 1H, 3-H), 6.80-6.85 (m, 2H, Ar), 7.10-7.15 (m, 3H, Ar), 7.45-7.50 (m, 2H, Ar), 12.72 (s, 1H,

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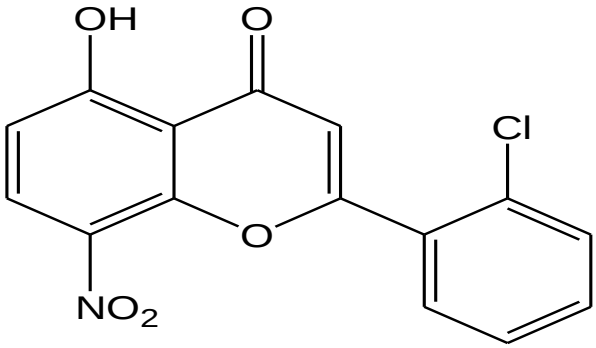
OH).^{13}C NMR (DMSO-d_6, 75 MHz): δ 109.0, 109.9, 110.3, 111.4, 127.5, 128.6, 129.9, 130.3, 132.1, 135.7, 155.2, 156.1, 158.7, 182.1,MS: *m/z* 273 [M+H].

2.3. 2-(2-chlorophenyl)-5-hydroxy-8-nitro-4H-4-chromenone (5):

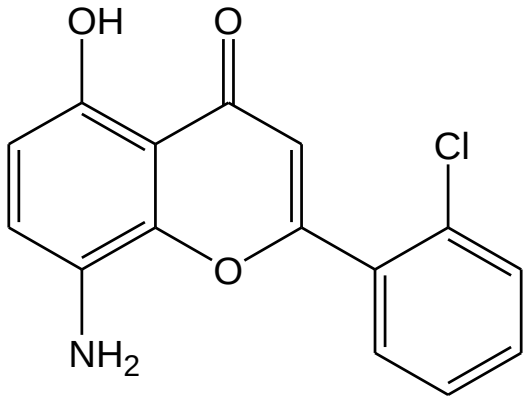
Nitric acid (5 mL) was added to a solution of **4** (0.005 mol) in glacial acetic acid (40 mL). The reaction mixture was placed in freezing water (150 mL) after being heated at 55 ºC for 5 h. EtOAc was used to extract the solution and dried over anhydrous Na_2SO_4 and removed the solvent under reduced pressure. To produce **5a** and **5b**, the residue was purified using silica gel column chromatography (1:9 EtOAc/hexane).



Yield: 42%, mp: 192-194 ºC;^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.82 (s, 1H, 3-H), 7.00-7.10 (m, 4H, ArH), 7.54 (m, 1H, ArH), 8.87 (d, *J* = 9.1 Hz, 1H, ArH), 13.1 (s, 1H, OH).^{13}C NMR (DMSO-d_6, 75 MHz): δ 108.1, 109.5; 115.1, 123.6, 127.1, 128.6, 129.7, 131.0, 131.9, 132.4, 134.3, 156.1, 156.9, 158.3, 178.3.MS: *m/z* 318 [M+H].

2.4. 8-amino-2-(2-chlorophenyl)-5-hydroxy-4H-4-chromenone (6):

Tin chloride (0.01 mol) was added to a solution of **5a** (0.002 mol) in ethanol (200 mL) and the reaction mixture was heated at 80 ºc for 5 h. The solvent was then removed under reduced pressure. The residue was dissolved in EtOAc (200 mL) and washed with water, dried the organic layer over anhydrous Na_2SO_4 and removed the solvent to get compound **6**.

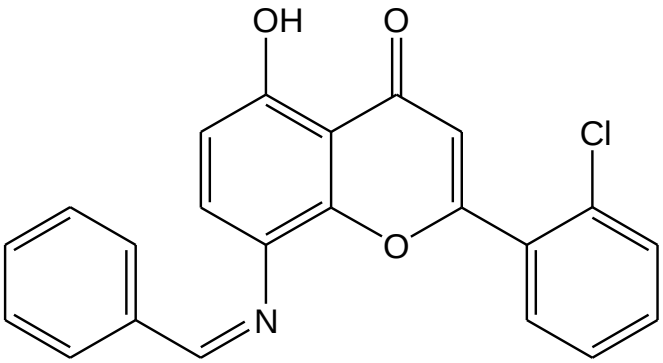


Yield: 64%, mp: 198-199 ºC;^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.21 (br s, 2H, NH_2), 6.68 (s, 1H, 3-H), 6.90-7.00 (m, 2H, ArH), 7.10-7.15 (m, 3H, ArH), 7.64 (m, *J* = 7.7 Hz, 1H, ArH), 10.57 (s, 1H, OH).^{13}C NMR (DMSO-d_6, 75 MHz): δ 108.3, 109.3, 115.1, 123.0, 123.9, 128.1, 128.7, 129.1, 130.3, 130.8, 131.0, 150.2, 152.0, 153.5, 181.2.MS: *m/z* 288 [M+H].

2.5. General procedure for the synthesis of 2-(2-chlorophenyl)-5-hydroxy-8-[(E)-1-arylmethylidene]amino-4H-4-chromenone 7(a-f):

To solution of compound **6** (0.01 mol) in toluene (20 mL), aromatic aldehyde (0.01 mol) and glacial acetic acid (0.5 mL) was added and refluxed the mixture for 4 h using a Dean–Stark apparatus. The completion of the reaction was monitore by TLC using toluene:ethyl acetate (4:1). The solvent was removed by distillation to give the solid, which was filtered, and recrystallized from ethyl alcohol to get the pure compound **7**(**a-f**).

2.5.1. 2-(2-chlorophenyl)-5-hydroxy-8-[(E)-1-phenylmethylidene]amino-4H-4-chromenone (7a):



Yield 42%; mp 245-247 °C;^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.70 (m, 1H, ArH), 6.80-6.90 (m, 2H, ArH),

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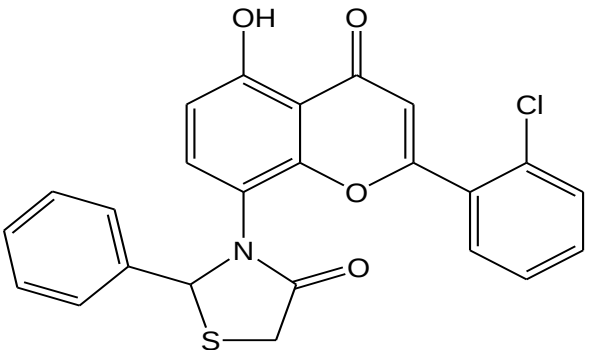
7.10-7.15 (m, 4H, ArH), 7.30-7.40 (m, 5H, ArH), 8.52 (s, 1H, CH=N), 12.84 (s, 1H, OH).^{13}C NMR (DMSO-d_6, 75 MHz): δ 107.9, 112.4, 113.0, 123.2, 126.9, 127.3, 128.9, 129.1, 130.1, 130.9, 131.2, 131.9, 132.1, 132.7, 137.6, 144.8, 153.2, 154.0, 161.1, 182.1.MS: *m/z* 375 [M^+].

2.6. General procedure for the synthesis of 3-[2-(2-chlorophenyl)-5-hydroxy-4-oxo-4H-8-chromenyl]-2-aryal-1,3-thiazolan-4-one 8 (a-f):

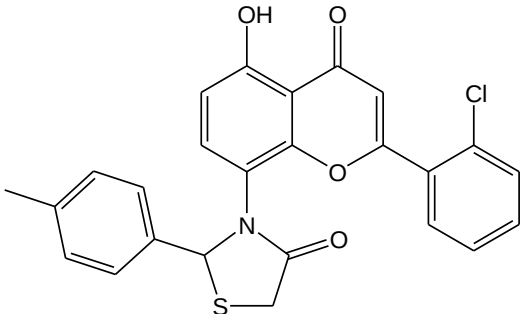
In 20 mL of DMF, together with a catalytic amount of anhydrous zinc chloride, the corresponding compound **7(a-f)** (0.01 mol), mercapto acetic acid (0.012 mol), was refluxed for 8 h. TLC was used to monitor the reaction using toluene: ether (3:1). After the reaction was completed, the mixture was cooled, put into the ice, and left at room temperature for the night. To obtain the pure compounds **8(a-f)**, the separated solid was filtered, washed with water, and subjected to column chromatography using hexane-ethyl acetate.

2.6.1. 3-[2-(2-chlorophenyl)-5-hydroxy-4-oxo-4H-8-chromenyl]-2-phenyl-1,3-thiazolan-4-one (8a):



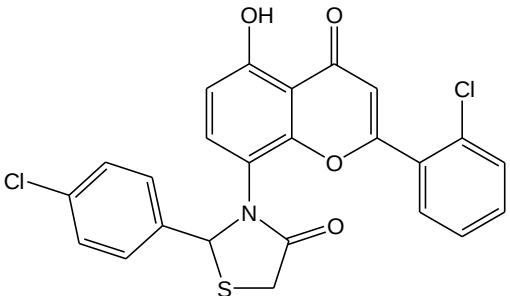
Yield: 56%, mp: 221-223 ^{o}C;^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.96 (s, 2H, CH_2-S), 5.68 (s, 1H, CH-S), 6.72 (s, 1H, 3-H), 7.10-7.20 (m, 7H, ArH), 7.50-7.55 (m, 3H, ArH), 12.78 (s, 1H, OH).^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.3, 71.3, 107.4, 112.8, 118.5, 120.3, 125.2, 126.2, 127.2, 128.9, 129.4, 130.1, 131.2, 132.3, 133.5, 134.8, 141.1, 148.7, 154.1, 154.7, 175.7, 181.1.MS: *m/z* 449 [M+].

2.6.2. 3-[2-(2-chlorophenyl)-5-hydroxy-4-oxo-4H-8-chromenyl]-2-(4-methylphenyl)-1,3-thiazolan-4-one (8b):



Yield: 61%, mp: 237-239 ^{o}C;^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.98 (s, 2H, CH_2-S), 5.66 (s, 1H, CH-S), 6.73 (s, 1H, 3-H), 7.10-7.15 (m, 8H, ArH), 7.50-7.60 (m, 2H, ArH), 12.62 (s, 1H, OH).^{13}C NMR (DMSO-d_6, 75 MHz): δ 27.2, 38.4, 71.2, 107.4, 112.7, 118.5, 120.3, 125.1, 126.4, 127.4, 129.4, 130.1, 131.2, 132.1, 133.6, 134.7, 135.2, 137.5, 148.7, 154.4, 154.7, 174.7, 182.2.MS: *m/z* 464 (M+H).

2.6.3. 2-(4-chlorophenyl)-3-[2-(2-chlorophenyl)-5-hydroxy-4-oxo-4H-8-chromenyl]-1,3-thiazolan-4-one (8c):



Yield: 63%, mp: 241-242 ^{o}C;^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.92 (s, 2H, CH_2-S), 5.69 (s, 1H, CH-S), 6.77 (s, 1H, 3-H), 7.10-7.20 (m, 6H, ArH), 7.50-7.60 (m, 4H, ArH), 12.72 (s, 1H, OH).^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.3, 71.3, 107.4, 112.8, 118.5, 120.3, 125.2, 128.5, 129.0, 129.4, 130.1, 131.2, 132.3, 132.9, 133.5, 134.8, 138.1, 148.7, 154.1, 154.7, 175.7, 181.1.MS: *m/z* 484 (M^+).

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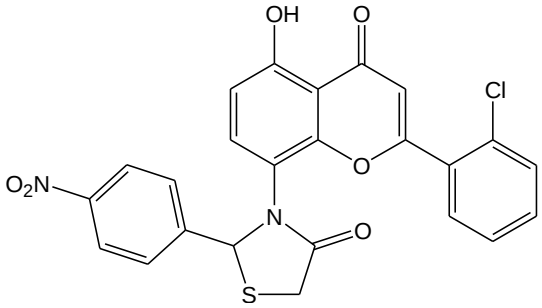
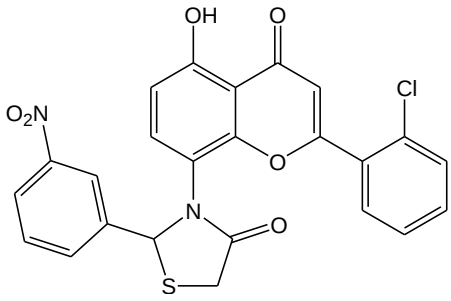
2.6.4. 3-[2-(2-chlorophenyl)-5-hydroxy-4-oxo-4H-8-chromenyl]-2-(4-nitrophenyl)-1,3-thiazolan-4-one (8d):



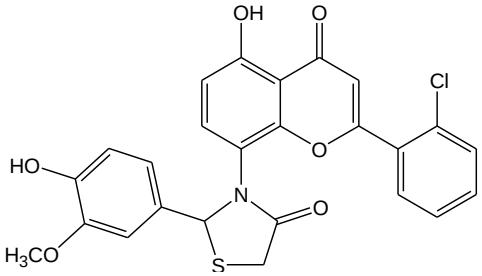
Yield: 56%, mp: 262-264 ºC;^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.95 (s, 2H, CH_2-S), 5.72 (s, 1H, CH-S), 6.74 (s, 1H, 3-H), 7.15-7.20 (m, 4H, ArH), 7.50-7.55 (m, 4H, ArH), 7.84 (d, *J* = 8.3 Hz, 2H, ArH), 12.81 (s, 1H, OH).^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.9, 71.1, 107.5, 112.7, 118.4, 120.7, 124.4, 125.2, 128.0, 129.5, 130.3, 131.7, 132.3, 133.6, 134.8, 144.8, 146.1, 148.2, 154.2, 154.5, 175.1, 181.0.MS: *m/z* 495 [M+H].

2.6.5. 3-[2-(2-chlorophenyl)-5-hydroxy-4-oxo-4H-8-chromenyl]-2-(3-nitrophenyl)-1,3-thiazolan-4-one (8e):



Yield: 52%, mp: 261-263 ºC;^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.93 (s, 2H, CH_2-S), 5.69 (s, 1H, CH-S), 6.74 (s, 1H, 3-H), 7.10-7.20 (m, 4H, ArH), 7.50-7.60 (m, 4H, ArH), 8.00-8.10 (m, 2H, ArH), 12.62 (s, 1H, OH).^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.3, 71.3, 107.4, 112.8, 118.5, 120.3, 121.0, 123.3, 125.2, 129.4, 130.1, 131.2, 131.9, 132.3, 132.9, 133.5, 134.8, 140.6, 148.7, 149.0, 154.3, 154.7, 175.2, 181.7.MS: *m/z* 494 [M^+].

2.6.6. 3-[2-(2-chlorophenyl)-5-hydroxy-4-oxo-4H-8-chromenyl]-2-(4-hydroxy-3-methoxyphenyl)-1,3-thiazolan-4-one (8f):



Yield: 66%, mp: 245-247 ºC;^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.88 (s, 3H, OCH_3), 3.92 (s, 2H, CH_2-S), 5.63 (s, 1H, CH-S), 6.70-6.75 (m, 2H, 3-H & ArH), 7.10-7.20 (m, 6H, ArH), 7.50-7.58 (m, 2H, ArH), 8.55 (s, 1H, OH), 12.71 (s, 1H, OH).^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.3, 58.7, 71.3, 107.4, 111.1, 112.8, 117.5, 118.5, 119.5, 120.3, 125.2, 129.4, 130.1, 131.2, 132.4, 133.4, 134.6, 136.2, 146.6, 148.6, 149.1, 154.3, 154.5, 174.5, 182.2.MS: *m/z* 496 [M+H].

3. Results and Discussion

The 1(2-chlorophenyl)-3-(2,6-dihydroxyphenyl)-1,3-propanedione **3** has been prepared by condensation of 2,6-dihydroxyacetophenone **1** with 2-chlorobenzoyl chloride **2** in the presence of pyridine and a catalytic amound of DMAP under stirring at room temperature for 3 h, gave compound **3** in 76% of yield.

The compound **3** was cyclised in the presence of DBU in pyridine under heating at 100 ºC for 12 h to afford 2-(2-chlorophenyl)-5-hydroxy-4*H*-4-chromenone **4** in 82% of yields. The structure was confirmed by the interpretation of its NMR and mass spectra.

Compound **4** ^{1}H NMR spectra revealed two singlets for the proton at the 3-position of the chromone ring and the OH proton, respectively, at 6.57 and 12.72 ppm. The multiplets of the other aromatic proton signals were seen at ppm 6.80-6.85, 7.10-7.15, and 7.45-7.50. The chromone ring's carbons 155.2 (C2), 109.0 (C3), 182.1 (C4), 109.9 (C5a), and 158.7 (C5b) ppm each showed signals in the sample's ^{13}C NMR spectra. A molecular ion peak at m/z 273 in the mass spectrum served as the basis for calculating its molecular weight.

Compound **4** on nitration with nitric acid in the presence of galcial acetic acid under reflux at 55 ºC for 5 h to

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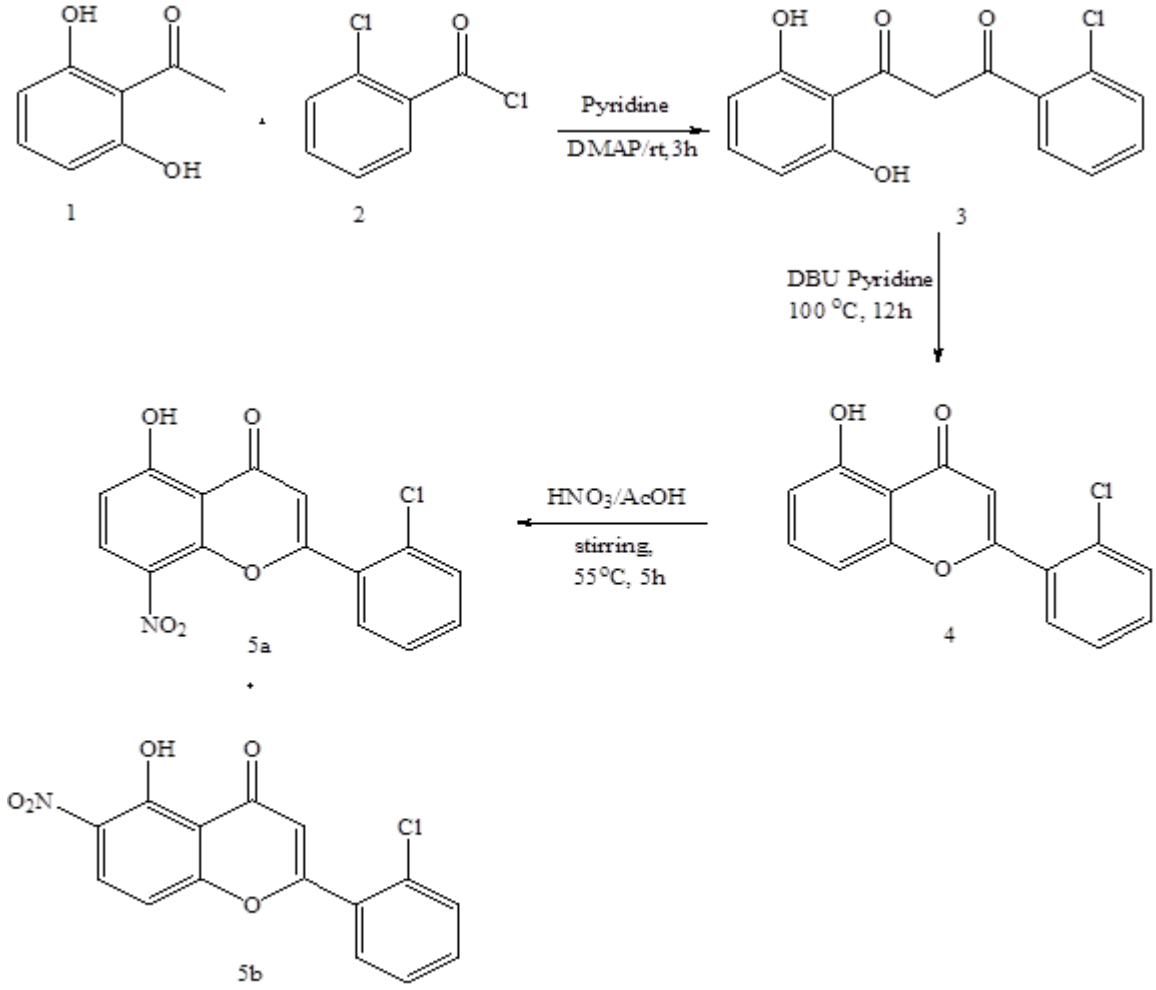
afford a mixture of 2-(2-chlorophenyl)-5-hydroxy-8-nitro-4*H*-4-chromenone **5(a)** in 42% yield and 2-(2-chlorophenyl)-5-hydroxy-6-nitro-4*H*-4-chromenone **5(b)** in 48% yield (**Scheme 1**). The structures of synthesized compound were confirmed by their EI mass, ^{1}H NMR and ^{13}C NMR spectral data.



Scheme 1

Compound **5a** ^{1}H NMR spectra revealed two singlets for the proton at the 3-position of the chromone ring and the OH proton, respectively, at 6.82 and 13.1 ppm. The multiplets of the other aromatic proton signals were seen in the predicted regions. The chromone ring's carbons

The reduction of nitro group of compound **5a** with tin chloride in the presence of ethanol under heating at 80 ^{o}C for 5 h gave 8-amino-2-(2-chlorophenyl)-5-hydroxy-4*H*-4-chromenone **6** in 64% of yield. The structure of synthesized compound was established by the interpretation of its MS and NMR spectral data.

156.1 (C2), 109.5 (C3), 178.3 (C4), 109.5 (C5a), and 158.3 (C5b) ppm each showed signals in the sample's ^{13}C NMR spectra. A molecular ion peak at m/z 318 in the mass spectrum provided evidence of the substance's molecular weight.

Two singlets were visible in the ^{1}H NMR spectra of compound **6** at 6.68 and 10.57 ppm, respectively, for the proton at the 3-position of the chromone ring and the OH proton. The amine proton signal appeared as broad at 4.21 ppm, while the other aromatic proton signals appeared as multiplets in the anticipated locations.The chromone ring's carbons 153.5 (C2), 109.3 (C3), 181.2

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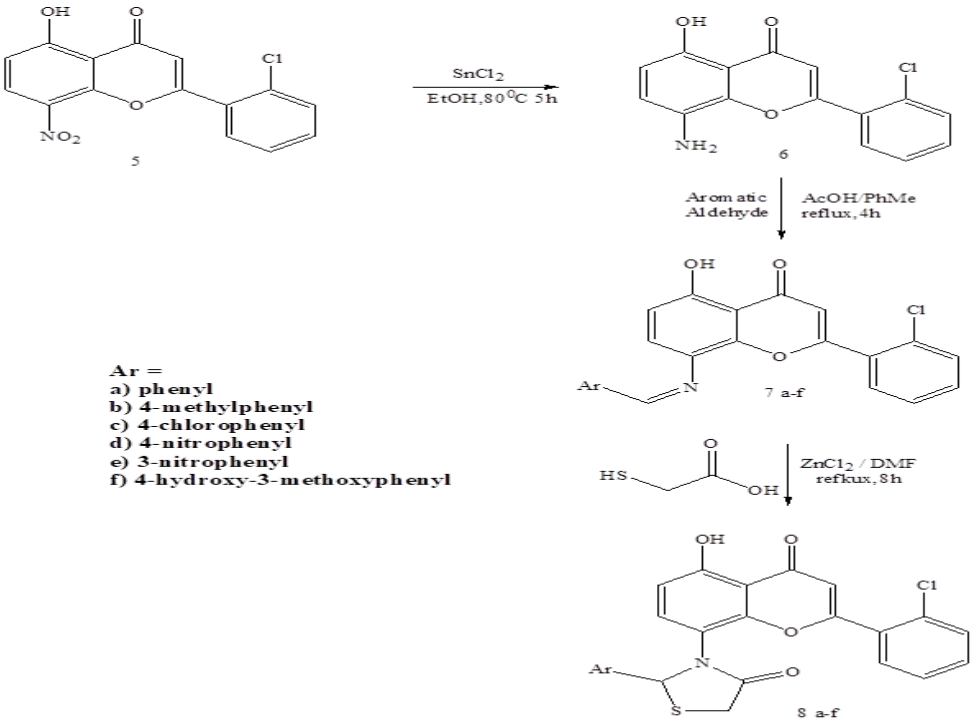
(C4), 108.3 (C5a), and 153.5 (C5b) ppm all displayed signals in the sample's ^{13}C NMR spectra. A molecular ion peak at m/z 288 in the mass spectrum provided evidence of the compound molecular weight.

Compound **6** was condensed with aromatic aldehyde in toluene using AcOH as catalyst at reflux temperature for 4 hours, furnished the corresponding 2-(2-chlorophenyl)-5-hydroxy-8-[(*E*)-1-arylmethylidene]amino-4*H*-4-chromenone **7(a-f)** in good yields. The structure of synthesized compound was established by the interpretation of its MS and NMR spectral data.

The signals for the imine proton (CH=N) emerged as singlets at 8.52 and 12.84 for the hydroxy proton as singlet, and aromatic protons as multiplets in the predicted range in the ^{1}H NMR spectrum of compound **7a**. The chromone ring's carbons 153.2 (C2), 107.9 (C3), 182.1 (C4), 112.4 (C5a), and 153.2 (C5b) ppm all showed signals in the sample's ^{13}C NMR spectra. A molecular ion peak at m/z 375 in the mass spectrum provided evidence of the substance's molecular weight.

The corresponding compound **7(a-f)** when reacted with thioglycolic acid, in the presence of catalytic amount of $ZnCl_2$ in dimethylformamide at reflux temperature for 8 h, afforded the corresponding synthesis of 3-[2-(2-chlorophenyl)-5-hydroxy-4-oxo-4*H*-8-chromenyl]-2-aryal-1,3-thiazolan-4-one **8(a-f)** in good yields (**Scheme 2**).The synthesized compound structures were established by the interpretation of their IR, MS and NMR spectral data and Antibactrial Activity.

The thiazolidinone ring protons of compound **8a** appeared as two singlets at 3.96 (CH2-S), 5.68 (CH-S), and 12.78 ppm for hydroxy proton in the proton NMR spectra. The other protons occurred in the predicted range. The thiazolidinone ring signals were detected in its ^{13}C NMR spectra at 177.7, 71.3, and 38.3 ppm, while the carbons in the chromone ring were detected at 154.1 (C2), 107.4 (C3), 181.1 (C4), 112.8 (C5a), and 154.1 (C5b) ppm. A molecular ion peak at m/z 449 in the mass spectrum provided evidence of the substance's molecular mass.



Scheme 2

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Antibacterial Activity

All the newly synthesised compounds **8(a-f)** were tested for their antibacte- rial activity against *Bacillus subtilis*, *Bacillus sphaericus*, and *Staphylococcus aureus* as well as *Pseudomonas aeruginosa*, *Klobsinella aerogenes*, and *Chromobacterium violaceum*, which are Gram-positive and Gram-negative bacteria, respectively by disc diffisionmethod[62]. At 100 μg/mL, the inhibitory zones were measured and contrasted with the reference drug streptomycin (**Table 1**).

All of the synthesised compounds **8(a-f)** demonstrated moderate to good inhibition of all of the tested organisms, according to the antibacterial screening. 4-chlorophenyl (**8c**) and 4-hydroxy-3-methoxyphenyl (**8f**) containing compounds shown greater effectiveness against Gram-positive bacterial strains and considerable activity against Gram-negative bacterial strains. Compound **8d** showed good activity against *S. aureus* and *C. violaceum* while compound **8b** showed significant activity against *B. Subtilis* only.

Table 1: Antibacterial Activity of Compounds 8(a-f)

Compound	Zone of inhibition (mm) at 100 μg/mL					
	B. subtilis	***B. sphaericus***	***S. aureus***	***P. aeruginosa***	***K. aerogenes***	***C.violaceum***
8[a]	10	12	11	9	10	9
8b	19	13	10	8	9	9
8c	21	24	22	18	19	20
8d	12	14	18	10	11	14
8e	13	11	10	9	9	8
8f	20	22	21	17	18	21
Streptomycin	25	30	30	30	25	30

4. Conclusions

A new series of 3-[2-(2-chlorophenyl)-5-hydroxy-4-oxo-4*H*-8-chromenyl]-2-aryal-1,3-thiazolan-4-one **8(a-f)** were synthesized. and tested for their antibacte- rial activity against the Gram-positive bacteria *B. subtilis*, *B. sphaericus*, and *S. aureus* as well as the Gram-negative bacteria *P. aeruginosa*, *K. aerogenes*, and *C. violaceum*, 4-chlorophenyl (**8c**) and 4-hydroxy-3-methoxyphenyl (**8f**) containing compounds shown greater effectiveness against Gram-positive bacterial strains and considerable activity against Gram-negative bacterial strains. Compound **8d** showed good activity against *S. aureus* and *C. violaceum* while compound **8b** showed significant activity against *B. Subtilis* only.

5. Conflicts of Interest

There are no conflicts to declare.

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References

1. Sherr, C. J. G1 phase progression: cycling on cue. *Cell*. 1994, *79*, 551-555.
2. Hunter, T,; Pines, J. Cyclins and cancer. II: Cyclin D and CDK inhibitors come of age. *Cell*. 1994, *79*, 573.
3. Morgan, D. O. Principles of CDK regulation. *Nature*. 1995, *374*, 131.
4. Draetta, G. Cell cycle control in eukaryotes: molecular mechanisms of cdc2 activation. *Trends Biochem. Sci.* 1990, *15*, 378.
5. Sherr, C. J. Mammalian G1 cyclins. *Cell*. 1993, *73*, 1059.
6. Draetta, G. F. Mammalian G1 cyclins. *Curr. Opin. Cell Biol*. 1994, *6*, 842.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(4), 788-798 | ISSN:2251-6727

7. Hartwell, L. H.; Kastan, M. B. "Cell cycle control and cancer" *Science*. 1994, *266*, 1821.
8. Serrano, M.; Hannon, G. J.; Beach, D. A. New regulatory motif in cell-cycle control causing specific inhibition of cyclin D/CDK4. *Nature*. 1993, *366*, 704.
9. Serrano, M. The tumor suppressor protein p16INK4a. *Exp. Cell Res.* 1997, *237*, 7.
10. Sedlacek, H. H.; Czech, J.; Naik, R.; Kaur, G.; Worland, P.; Losiewicz, M.; Parker, B.; Carlson, B.; Smith, A.; Senderowicz, A.; Sausville, E. Flavopiridol (L86 8275; NSC 649890), a new kinase inhibitor for tumor therapy. *Int. J. Oncol*. 1996, *9*, 1143.
11. Carlson, B. A.; Dubay, M. M.; Sausville, E. A.; Brizuela, L.; Worland, P. J. Flavopiridol induces G1 arrest with inhibition of cyclindependent kinase (CDK) 2 and CDK4 in human breast carcinoma cells. *Cancer Res*. 1996, *56*, 2973.
12. Parker, B. W.; Kaur, G.; Nieves, N. W.; Taimi, M.; Kohlhagen, G.; Shimizu, T.: Losiewicz, M. D.; Pommier, Y.; Sausville, E. A.; Senderowicz, A. M. Early induction of apoptosis in hematopoietic cell lines after exposure to flavopiridol. *Blood.* 1998, *91*, 458.
13. Drees, M.; Dengler, W. A.; Roth, T.; Labonte, H.; Mayo, J.; Malspeis, L.; Grever, M.; Sausville, E. A.; Fiebig, H. H. Flavopiridol (L86- 8275): selective antitumor activity *in vitro* and activity *in vivo* for prostate carcinoma cells. *Clin. Cancer Res*. 1997, *3*, 273.
14. Patel, V.; Senderowicz, A. M.; Pinto, D.; Igishi, T.; Raffeld, M.; Quintanilla M. L.; Ensley, J. F.; Sausville, E. A.; Gutkind, J. S. Flavopiridol, a novel cyclin-dependent kinase inhibitor, suppresses the growth of head and neck squamous cell carcinomas by inducing apoptosis. *J. Clinical Invest*. 1998, *102*, 1674.
15. Arguello, F.; Alexander, M.; Sterry, J. A.; Tudor, G.; Smith, E. M.; Kalaver, N. T.; Greene, J. F.; Koss, W.; Morgan, C. D.; Stinson, S. F.; Siford, T. J.; Alvord, W. G.; Klabansky, R. L.; Sausville, E. A. Flavopiridol induces apoptosis of normal lymphoid cells, causes immunosuppression, and has potent antitumor activity *in vivo* against human leukemia and lymphoma xenografts. *Blood.* 1998, *91*, 2482.
16. Kaur, G.; Stetler, S. M.; Sebers, S.; Worland, P.; Sedlacek, H.; Myers, C.; Czech, J.; Naik R.; Sausville, E. Growth inhibition with reversible cell cycle arrest of carcinoma cells by flavones L86-8275. *J. Natl. Cancer Inst*. 1992, *84*, 1736.
17. Losiewicz, M. D.; Carlson, B. A.; Kaur, G.; Sausville, E. A.; Worland, P. J. Potent inhibition of CDC2 kinase activity by the flavonoid L86-8275. *Biochem. Biophys. Res. Commun*. 1994, *201*, 589.
18. Senderowicz, A. M.; Headlee, D.; Stinson, S. F.; Lush, R. M.; Kalil, N.; Villalba, L.; Hill, K.; Steinberg, S. M.; Figg, W. D.; Tompkins, A.; Arbuck, S. G.; Sausville, E. A. Phase I trial of continuous infusion flavopiridol, a novel cyclin-dependent kinase inhibitor, in patients with refractory neoplasms. *J. Clin. Oncol*. 1998, *16*, 2986.
19. Wright, J.; Blatner, G. L.; Cheson, B. D. Clinical trials referral resource. clinical trials of flavopiridol. *Oncology*. 1998, *12*, 1023.
20. De Azevedo, W. F.; Mueller, D. H. J.; Schulze, G. U.; Worland, P. J.; Sausville, E.; Kim, S. H. Structural basis for specificity and potency of a flavonoid inhibitor of human CDK2, a cell cycle kinase. *Proc. Natl. Acad. Sci. USA*. 1996, *93*, 2735.
21. Kattige, S. L.; Naik, R. G.; Lakdawalla, A. D.; Dohadwalla, A. N.; Rupp, R. H.; Desouza, N. J. 4*H*-1-benzopyran-4-one compounds which have anti-inflamatory or immunodulating action. *U.S. Patent*. 1990, 4900727.
22. Naik, R.; Lal, B.; Rupp, R. H.; Sedlacek, H. H.; Dickneite, G.; Czech, J. Oncogene-encoded kinases inhibition using 4-H-1-benzopyran-4-one derivatives. *U.S. Patent.* 1988, 5284856.
23. Naik, R.; Lal, B.; Rupp, R. H.; Sedlacek, H. H.; Dickneite, G.; Czech, J. Use of 4*H*-1-benzopyran-4-one derivatives, 4*H*-1-benzopyran-4-one derivatives and medicines containing same. *Euro. Patent*. 1988, 0366061.
24. Naik, R. G.; Kattige, S.L.; Bhat, S. V.; Alreja, B.; de Souza, N. J.; Rupp, R.H. An antiinflammatory cum immunomodulatory piperidinylbenzopyranone from dysoxylum binectariferum: isolation, structure and total synthesis. *Tetrahedron*. 1988, *44*, 2081.
25. James, M. N. G.; Watson, K. J. Chemistry of micrococcin P. Part IX. The crystal and molecular structure of micrococcinic acid bis-4-bromoanilide. *J. Che. Soc. C.* 1966, *6*, 1361.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(4), 788-798 | ISSN:2251-6727

26. Ghazzi, N.; Perez, J. E.; Antonucci, T. K.; Driscoll, J. H.; Huang, S. M.; Faja, B. W. Cardiac and glycemic benefits of troglitazone treatment in NIDDM. The troglitazone study group. *Diabetes*. 1997, *46*, 433.
27. Ergenc, N.; Capan, G.; Bunay, N. S.; Ozkirimli, S.; Gungor, M.; Ozbay, S.; Kendi, E. Synthesis and hypnotic activity of new 4-thiazolidinone and 2-thi-oxoo-4,5-imidazolidinedione derivatives. *Archiv der Pharmazie*. 1999, *332*, 343.
28. Taranalli, A. D.; Bhat, A. R.; Srinivas, S.; Saravanan, E. Antiinflammatory, analgesic and antipyretic activity of certain thiazolidinones. *Indian J. Pharm. Sci.* 2008, *70*, 159.
29. Aakash, D.; Balasubrmanian, N.; Siong, M. L.; Kalvathy, R.; Rakesh, K. M.; Vasudevan, M. 4-Thiazolidinone derivatives: synthesis, antimicrobial, anti- cancer evaluation and QSAR studies. *RSC Advances*. 2016, *6*, 109485.
30. Marques, G. H.; Kunzler, A.; Bareno, V. D.; Drawanz, B. B.; Mastelloto, H. G.; Leite, F. R.; Nascimento, G. G.; Nascente, P. S.; Siqueira, G. M.; Cunico, W. Antifungal activity of 3-(heteroaryl-2-ylmethyl)thiazolidinone derivatives. *Med. Chem.* 2014, *10*, 355.
31. Sambhaji, T. D.; Amarsinh, R. D.; Lalit, D. K.; Manisha, A.; Dhiman, S.; Ramrao, A. M. Synthesis and antitubercular activity of new thiazolidinones with pyrazinyl and thiazolyl scaffolds. *J. Heterocy. Chem.* 2017, *54*, 125.
32. Dmytro, H.; Lundmyla, M.; Borya, Z.; Olexandr, V.; Andrzej, G.; Roman, L. Synthesis and anticancer activity evaluation of 4-thiazolidinones containing benzothiazole moiety. *Eur. J. Med. Chem.* 2010, *45*, 5012.
33. Dmytro, H.; Borys, Z.; Olexandr, V.; Andrzej, G.; Roman, L. Synthesis of new 4-thiazolidinone-, pyrazoline-, and isatin-based comjugates with promising antitumor activity. *J. Med. Chem.* 2012, *55*, 8630.
34. Vishnu, V.; Upadhyay, R. K.; Usha, G. Synthesis and analgesic activity of some new substituted aryl-4-thiazolidinones. *Biomed. Pharmacol. J.* 2009, *2*, 345.
35. Vicini, P.; Amoretti, L.; Chiavarini, M.; Impicciatore, M. Synthesis and local anesthetic activity of alkylaminoacyl derivatives of 3-amino-1,2-benzisothi- azoles. *Farmaco*. 1990, *45*, 933.
36. de Oliveira, J. F.; Lima, T. S.; Vendramini, C. D. B.; de Lacerda Pedrosa, S. C. B.; Lafayette, E. A.; da Silva, R. M. F.; de Almeida, S. M. V.; de Moura, R. O.; Ruiz, A.L.T.G.; de Carvalho, J. E.; de Lima, M.D.C.A. Thiosemicarbazones and 4-thiazolidinones indole based derivatives: Synthesis, evaluation of antiproliferative activity, cell death mechanisms and topoisomerase inhibition assay, *Eur. J. Med. Chem.* 2017, *136*, 305.
37. Ravichandran, V.; Prashantha Kumar, B. R.; Sankar, S.; Agrawal, R. K. Predicting anti-HIV activity of 1,3,4-thiazolidinone derivatives: 3D-QSAR approach. *Eur. J. Med. Chem.* 2009, *44*, 1180.
38. Srinivas, A.; Nagaraj, A.; Sanjeeva Reddy, Ch. Synthesis and biological evaluation of methylene-bis-thiazolidinone derivatives as potential nematicidal agents. *J. Heterocy. Chem.* 2008, *45*, 999.
39. Hrib, N. J.; Jurcak, J. G.; Bregna, D. E.; Geyer III, H. M.; Hartman, H. B.; Roehr, J. E.; Rogers, K. L.; Rush, D. K. 3[4-[1[(6-Fluorobenzo[b]thiophen-3-yl)-4-piperazin yl]butyl]-2,5,5-trimethyl-4-thiazolidinone: a new atypical antipsy- chotic agent for the treatment of schizophrenia. *J. Med. Chem.* 1992, *35*, 2712.
40. Lesyk, R. B.; Zimenkovskv, B. S. 4-thiazolidones: centenarian history, current status and perspectives for modern organic and medicinal chemistry. *Curr. Org. Chem.* 2004. *8*, 1547.
41. Tanabe, Y.; Yamamoto, H.; Murakami, M.; Yanagi, K.; Kubota, Y.; Okumura, H.; Sanemitsu, Y.; Suzukamo, G. Synthetic study of the highly ptent and selective anti-platelet activating factor thiazolidin-4-one agents and related compounds. *Journal of the Chemical Society. Perkin Transactions I.* 1995, *1995*, 935.
42. Abd E1-Aal, R. M. Spiro-azoles thiazolidinone in the synthesis of polymethine cyanine dyes. *Phosphorus, Sulphur, and Silicon and the Related Elements*. 2003, *178*, 681.
43. Rout, M. K.; Mahapatra, G. N. 2-β-Naphthylimino-4-thiazolidone and its derivative. *J. Am. Chem. Soc.* 1955, *77*, 2427.
44. Adele, A.; Suhas, A. S.; Aishwarya, B.; Chunderika, M.; Neil, A. K. Synthesis and antibacterial activity

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(4), 788-798 | ISSN:2251-6727

of series of 2-trifluoromethylbenzimidazole-thiazolidi- none derivatives. *J. Heterocy. Chem.* 2020, *57*, 299.

45. Roda, K. P.; Vansdadia, R. N.; Pareskh, H. Studies on 1,3,4-oxadiazoles. part 2. preparation and antimicrobial activity of 2-benzoylamino-5-(2-isopropyl-5-methylphenoxymethyl)-1,3,4-oxadiazoles. *J. Indian Chem. Soc*. 1989, *66*, 113.
46. Diurno, M. V.; Mazzoni, O.; Piscopo, E.; Caliganao, A.; Giordano, F.; Bolognese, A.Synthesis and antihistaminic acitivity of some thiazolidin-4-ones. *J. Med. Chem.* 1992, *35*, 2910.
47. Anthi, P.; Phaedra, E.; Athina, G.; Melpomeni, G. A.; Loannis, V. Novel thiazolidin-4-one as potential non-nucleoside inhibitors of HIV-1 reverse transcriptase. *Molecules*. 2019, *24*, 3821.
48. Zychowski, K. A.; Leja, M. L.; Kaminskyy, D. V.; Kryshchyshyn, A. P.; Binduga, U. E.; Pinyazhko, O. R.; Lesyk, R. B.; Tobiasz, J.; Gminski, J. Anticancer properties of 4-thiazolidinone derivatives depend on peroxisome proliferator-activated receptor gamma (PPARγ). *Eur. J. Med. Chem*. 2017, *141*, 162-168.
49. Bhatt, B. R.; Shah, H. P.; Shah, P. B.; Trivedi, N. K.; Undavia, N. C. Desai. Synthesis of anti-HIV, anticancer and antitubercular 4-oxothiazolidines, 2-imino-4-oxo-thiazolidines and their 5-arylidine derivatives. *Indian J. Chem.* 1994, *33B*, 189.
50. Kucukguzel, I.; Satilmis, G.; Gurukumar, K. R.; Basu, A.; Tatar, E.; Nichols, D. B.; Talele, T. T.; Kaushik Basu, N. 2-Heteroarylimino-5-arylidene-4-thiazolidi- nones as a new class of non-nucleoside inhibitors of HCV NS5B polymerase. Eur. J. Med. Chem. 2013, 69, 931.
51. Veeresa, G.; Eunju, H.; James, T. D.; Duane, D. M. Synthesis and antiprolife- rative activity of 2-aryl-4-oxo-thiazolidin-3-yl-amides for prostate cancer. *Bioorg. Med. Chem. Lett.* 2004, *14*, 5289.
52. Rosaria, O.; Stefania, C.; Rosanna, M.; Ida, L.; Enrico, M. In vitro antiprolifera tive activity against human colon cancer cell lines of representative 4-thiazolidinones, Part I. *Bioorg. Med. Chem. Lett.* 2005, *15*, 3930.
53. Pradeep Kumar, M. R.; Malleshappa, N. N.; Sheetal, S.; Satyanarayana, D.; Veeresh, S. M. Synthesis and antimicrobial activity of 7-(2-substituted phenylthiazolidinyl)-benzopyran-2-one derivatives. *Eur. J. Med. Chem.* 2010, *45*, 85.
54. Kumar, V.; Sharma, S. K.; Singh, S.; Kumar, A.; Sharma, S. Synthesis and evaluation of novel indolylthiadiazinoazetidinones and indolylthiadiazino thiazolidinones as antimicrobial agents. *Archiv Der Pharmazie.* 2010, *343*, 98.
55. Volynets, G. P.; Bdzhola, V. G.; Golub, A. G.; Synyugin, A. R.; Chekanova, M. A.; Kukharenko, O. P.; Yarmoluk, S. M. Rational design of apoptosis signal-regulating kinase 1 inhibitors: Discovering novel structural scaffold. *Eur. J. Med. Chem.* 2013, *61*, 104.
56. Desai, K.G.; Raval, J.P.; Desai, K. R. Neat reaction technology for the synthe- sis of 4-oxo-thiazolidines derived from 2-SH-benzothiazole and antimicrobial screening of some synthesized 4-thiazolidinones. *J. Iranian Chem. Soc.* 2006, *3*, 233.
57. Tao, J.; Cao, L. H.; Wang, C. F.; Wang, D. Z. Synthesis of 1,3,4-oxadiazoles and 1,3-thiazolidinones containing 1,4,5,6-tetrahydro-6-pyridazinone. *Journal of the Chinese Chemical Society*. 2006, *53*, 1193.
58. Parekh, H. H.; Parikh, K. A.; Parikh, A. R. Synthesis of some 4-thiazolidnone derivatives as anti-tubercular agents. *J. Sci. Islamic Rep. Iran.* 2004, *15*, 143.
59. Patel, N. B.; Patel, V. N. Synthesis and antimicrobial evaluation of new (4-oxo-thiazolidinyl) quinazolin-4(3H)ones of 2-[(2,6-dichlorophenyl)amino]phenyl acetic acid. *Iranian J. Pharm. Res.* 2007, *6*, 251.
60. Kucukguzel, G.; Kocatepe, A.; De Clercq, E.; Şahin, F.; Gulluce, M. Synthesis and biological activity of 4-thiazolidinones, thiosemicarbazides derived from diflunisal hydrazide. *Eur. J. Med. Chem.* 2006, *41*, 353.
61. Panwar, H.; Verma, R. S.; Srivastava, V. K.; Kumar, A. Synthesis of some substituted azetidinonyl and thiazolidinonyl-1,3,4-thiadiazino[6,5-*b*]indoles as prospective antimicrobial agents. *Indian J. Chem.* 2006, *45B*, 2099.
62. Seely, H. W.; Van, D. P. J. Microbes in action: A laboratory manual of microbiology. D. B. Taraporevala Sons & Co Pvt. Ltd. Bombay. 1975, pp. 55.