Synthesis of new 2-[3-aryl-5-methyl-4-isooxazolyl]-7-hydroxy-3-phenyl-4*H*-1-benzopyran-4-ones and their insect-antifeedant activity

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Abstract

Condensation of ω-substituted-2,4-dihydroxyacetophenones **(1a-c)** with 3-(2-aryl)-5-methyl-4-isoxazolecarbonyl chlorides **(2a-c)** in acetone-K_2CO_3 medium afforded 2-[3-aryl-5-methyl-4-isoxazolyl]-7-hydroxy-3-phenyl-4H-1-benzopyran-4-ones **(3a-f)** in good yields. Insect-antifeedant activity of **3a-f** against agricultural pest tobacco caterpillar larvae (*Spodoptera litura* F) showed **3e** and **3f** to be active.

Keywords: 2,4-Dihydroxyacetophenones, 3-(2-aryl)-5-methyl-4-isoxazolecarbonyl- chlorides, insect-antifeedant, *Spodoptera litura* F.

Introduction

Chromones, flavones and isoflavones are biogenetically closely related oxygen heterocyclics reported to have physiological properties. Isoxazole derivatives have been reported to exhibit antiviral,[1] antitubercular,[2] anaesthetics,[3] anticancer,[4,5] and hypolipidemic, anabolic and antiarrhythmic,[6] activities.

2-(5-Tetrazolyl)-, and 3-(5-tetrazolyl)- chromones, 2-(3-pyridyl) chromones are reported as antiallergic, [7,8] coronaryvasodilatory, [9-11] and insecticidal,[7] agents. "Isoxazole penicillins" are reported to be potent antibacterial agents. Oxacillin,[12] (5-methyl-3-phenyl-4-isoxazolyl) penicillin, cloxacillin,[13] [5-methyl-(3-o-chlorophenyl)-4-isoxazolyl] penicillin and floxacillin,[14] [3-(2-chloro-6-fluorophenyl)-5-methyl-4-isoxazolyl] penicillin are the good antibacterial "isoxazole penicillins".

The attachment of a tetrazolyl or pyridyl ring at 2-position of chromones gave compounds with antiallergic, coronaryvasodilatory and insecticidal activity,[7-11]. Therefore it is considered worthwhile to synthesize 4H-1-benzopyran-4-ones with 3, 5-disubstituted isoxazolyl heterocyclic ring attached at C-2 position and study their insect-antifeedant activity against agricultural pest tobacco caterpillar larvae (*Spodoptera litura* F) in a non-choice laboratory study.

The reaction of ω-substituted-2,4-dihydroxyacetophenones **(1a-c)** with 3-(2-aryl)-5-methyl-4-isoxazolecarbonyl chlorides **(2a-c)** in acetone-K_2CO_3 medium afforded 2-[3-aryl-5-methyl-4-isoxazolyl]-7-hydroxy-3-phenyl-4H-1-benzopyran-4-ones**(3a-f)** in good yields.

The **IR** (KBr) in cm^{-1} spectrum of **3a** showed a broad band at 3148 (OH) and at 1608 (C=O) of the 4*H*-1-benzopyran-4-ones (chromones).The other prominent bands are assigned as follows i.e. 1578 (C=N) of isoxazolyl ring, 1303 (N-O) and 1074 & 1056 due to C-O linkages.

^{1}H nmr spectrum of **3a** showed a peak at δ 2.30 as singlet due to methyl group attached to the isoxazolyl ring. The aromatic H-8 proton resonated at δ 6.50 as a doublet with coupling constant, J = 2.0 Hz and at δ 6.85 as double doublet with coupling constant, J = 10.0, 2.0 Hz, respectively. H-5 proton appeared at 7.90 as doublet with coupling constant, J = 10.0 Hz. H-2′, H-3′, H-4′ & H-5′ and H-6′ protons of 3-phenyl ring of 4H-1-benzopyran-4-one resonated at δ 7.20-7.40 as multiplet. The aromatic protons of the phenyl ring attached to the isoxazolyl ring i.e. H-3″, H-4″ & H-5″ & H-6″ resonated at δ 6.95 as multiplet.

^{13}C nmr spectrum of **3a** showed chemical shift at δ 174.8 due to carbonyl carbon of 4*H*-1-benzopyran-4-one and the methyl carbon of the isoxazolyl ring appeared at δ 11.3(C-5-$\underline{CH_3}$). The three carbons i.e. C-3, C-4, & C-5 of the isoxazolyl ring appeared at δ 162.2, 101.1 & 169.0. The phenyl carbons of the isoxazolyl ring i.e. C-1″, C-2″, C-3″, C-4″, C-5″ & C-6″ resonated at δ 131.7, 130.8, 126.6, 129.9, 126.4, and 128.6 respectively. The 3-phenyl carbons of the 4*H*-1-benzopyran-4-one ring i.e. C-1′, C-2′ & C-6′, C-3′& C-5′ and C-4′ appeared at δ 130.2, 129.5, 127.0 and 131.7 etc. Other carbons C-2, C-3, C-5, C-6, C-7, C-8, C-9, and C-10 appeared at δ 152.0, 115.2, 123.0, 114.6, 159.2, 101.1, 152.0 and 115.2 respectively.

Mass spectrum **3a** showed the molecular ion peak at m/z 429 (56%).The other prominent ion peaks are observed at m/z(%) 414 (78), 394 (12), 386 (10), 379 (6), 352 (12), 318 (10), 304 (22), 292 (20), 277 (48), 251 (12), 202 (20), 178 (12), 165 (12), 137 (14), 102 (8), 60 (10), 43 (100). The fragmentation pattern is shown in Chart-1.

Mass Fragmentation

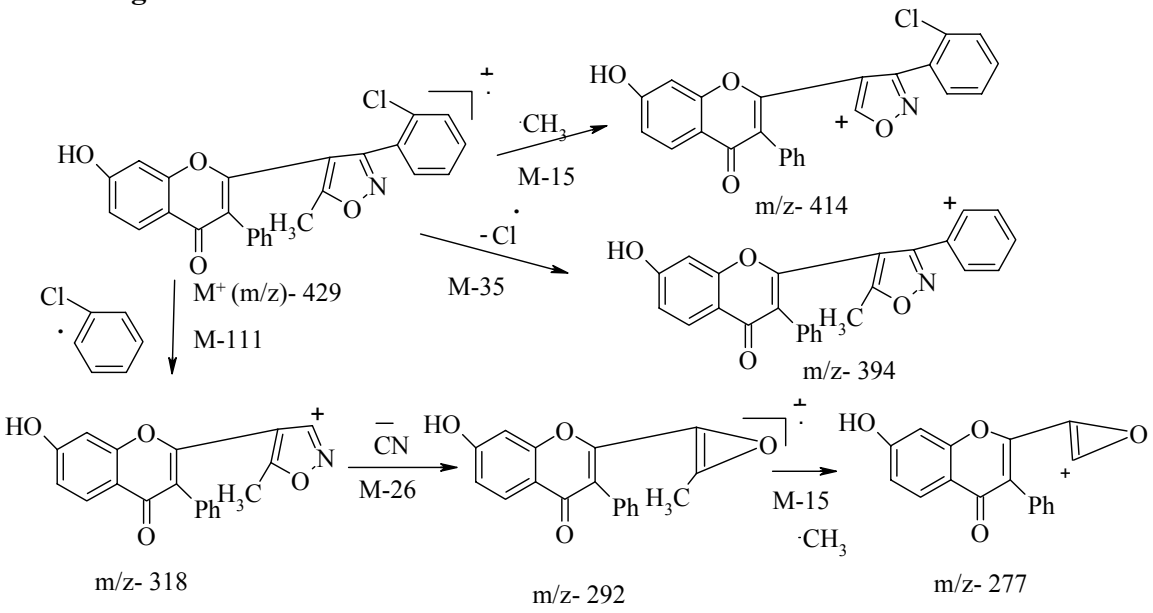


Chart 1

Insect-antifeedant activity

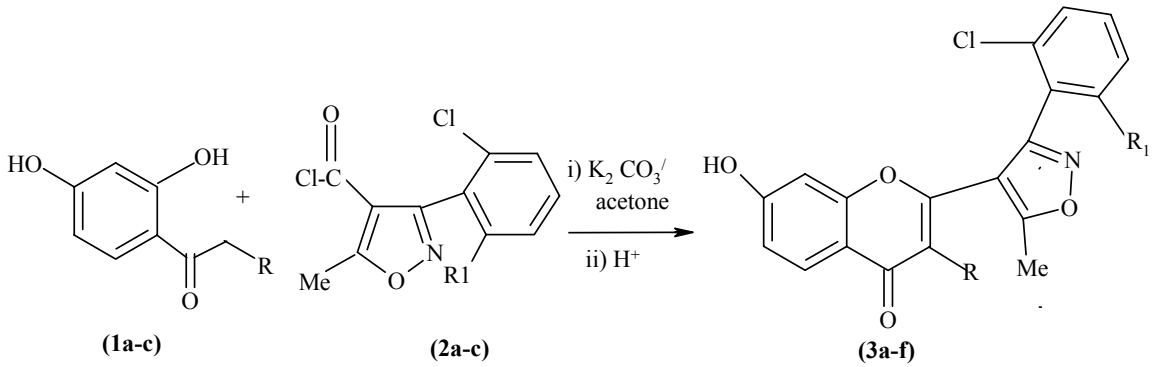
The antifeedant activities of **3a-f** were assessed by non-choice method against IV instar larvae of tobacco caterpillar (*Spodoptera litura F*). The tobacco caterpillars were reared on fresh castor leaves (*Ricinus communis*) controlled under laboratory conditions at 27 ± 1 ^{0}C, 70 ± 5% RH and 14:10 light / dark photo period. **3a-f** were diluted with acetone containing 5% Triton X-100 as sticker to 500ppm concentration. The assays were conducted as described by Ascher and Rones,[16] (1964).Test solution sprayed uniformly on either side of the castor leaf with an automizer and air dried. The sprayed castor leaf petiole was tied with wet cotton plug to maintain freshness of the leaf for a long time. Bottom of the plastic container covered with wet filter paper to maintain the microclimate inside the container and it was covered with fine muslin cloth. Before placing the leaf into jar one prestarved larva was placed inside the jar. 10 treated and 10 untreated control discs were run for each test and each test was replicated three times. The time period of the experiment was 24h and 48h. Leaf consumption was measured with the help of planimeter and the percentage of protection was calculated using the following formula adopting the method of Singh and Panth,[17] (1979).

$$\text{\% of antifeedant activity (\% Protection due to treatment)} = \left[1 - \frac{\text{\% protection in treated} - \text{\% protection in control}}{100 - \text{\% protection in control}} \right] \times 100$$

Results and Discussion

The antifeedant activity of compounds **3a-f** with 500 ppm concentration and at 24 h, and 48 h time intervals against tobacco caterpillar was presented in **Table-1.** Among all the compounds tested 2-[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]-7-hydroxy-3-methyl-4H-1-benzopyran-4-one **(3f)** and 3-(4-bromophenyl)-2-[3-(2-chloro-6-fluorophenyl)-5-methyl-4-isoxazolyl]-7-hydroxy-4H-1-benzopyran-4-one **(3e)** showed highest antifeedancy after 24h (72.10 ± 1.66%) and (66.90 ± 2.26%). After 48h the antifeedancy shown by **3f** was (55.73 ± 2.35%) and by **3e** was (50.11 ± 1.98%).

Synthesis



(1a-c) (2a-c) (3a-f)

Compound	R	Compound	R_1
1a	C_6H_5	2a	H
2a	4-Br-C_6H_4	2b	Cl
3a	Me	2c	F

Compound	R	R_1
3a	C_6H_5	H
3b	C_6H_5	Cl
3c	C_6H_5	F
3d	4-Br-C_6H_4	H
3e	4-Br-C_6H_4	F
3f	Me	Cl

Scheme 1

Table 1. Insect-antifeedant activity of 2-[3-aryl-5-methyl-4-isoxazolyl]-7-hydroxy-3-phenyl-4H-1-benzopyran-4-ones (3a-f), Non Choice method, using Castor leaf (5cm dia) against IV instar larvae of *Spodoptera litura F* (500 ppm)

S. No	Compound	Antifeedant activity	
		After 24h	After 48h
1	2-[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]-7-hydroxy-3-phenyl-4H-1-benzopyran-4-one **(3a)**	66.75 ± 2.10 (52.76)	47.86 ± 1.95 (41.50)
2	2-[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]-7-hydroxy-3-phenyl-4H-1-benzopyran-4-one **(3b)**	59.37 ± 1.88 (49.98)	45.25 ± 1.75 (41.25)
3	2-[3-(2-chloro-6-fluorophenyl)-5-methyl-4-isoxazolyl]-7-hydroxy-3-phenyl-4H-1-benzopyran-4-one **(3c)**	62.30 ± 2.15 (51.50)	43.18 ± 1.88 (40.50)
4	3-(4-bromophenyl)-2-[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]-7-hydroxy-4H-1-benzopyran-4-one **(3d)**	63.81 ± 1.98 (51.68)	40.30 ± 2.12 (37.65)
5	3-(4-bromophenyl)-2-[3-(2-chloro-6-fluorophenyl)-5-methyl-4-isoxazolyl]-7-hydroxy-4H-1-benzopyran-4-one **(3e)**	66.90 ± 2.26 (52.66)	50.11 ± 1.98 (43.68)
6	2-[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]-7-hydroxy-3-methyl-4H-1-benzopyran-4-one **(3f)**	72.10 ± 1.66 (56.36)	55.73 ± 2.35 (45.15)

* ± - Standard deviation
( ) - Arcin values (Statistical values with respect to % of antifeedant activity value)

Experimental Section

General Procedures. Melting points were determined on Polmon make instrument (Model No. MP 96). IR spectra were recorded on FT-IR perkin - Elmer 1605 spectrometer and ^{1}H NMR (200 MHz) and ^{13}C NMR (50.3 MHz)were recorded on a Varian Gemini 200 spectrometer using TMS as internal standard (Chemical shifts in δ ppm). UV-spectra were obtained on a Shimadzu UV-visible Spectrophotometer (Model UV-1601). Mass spectra were recorded on a VG micro mass 70-70H instrument.

General procedure for the Synthesis of 2-[3-aryl-5-methyl-4-isoxazolyl]-7-hydroxy-3-phenyl-4*H*-1-benzopyran-4-ones (3a-f)

To ω-substituted-2,4-dihydroxyacetophenones (10 mmoles) **(1a-c)** dissolved in acetone (50 ml) was added 3-(2-aryl)-5-methyl-4-isoxazolecarbonyl chloride (20 mmoles) **(2a-c)** and anhydrous potassium carbonate (50 mmoles). The reaction mixture was refluxed for 12 h with stirring. Acetone was distilled off and the reaction mixture was poured into ice water. The resulting solution was neutralized with dil HCl and the solid which separated out was filtered, washed with water and dried. The solid was dissolved in alcoholic KOH (5%, 50 ml) and refluxed for 30 min. The solution was distilled off and the residue was treated with ice water (500 ml). The filtrate was neutralized with cold dil HCl and filtered. The solid was washed with saturated sodium bicarbonate solution and dried to give 2-[3-aryl-5-methyl-4-isoxazolyl]-7-hydroxy-3-phenyl-4H-1-benzopyran-4-ones **(3a-f)** in 80% yield**.** These were recrystallised from methanol to give colourless crystals.

2-[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]-7-hydroxy-3-phenyl-4*H*-1-benzopyran-4-one (3a). Recrystallised from methanol as pale yellow coloured crystals, mp 251^{0}C (84%); IR (KBr) in cm^{-1} 3148 (OH), 1608 (C=O), 1578 (C=N), 1303 (N-O), 1074 (C-O) & 1056 (C-O); UV (MeOH) 217 nm (log ε 4.78), 233 nm (log ε 4.74) and 309 nm (log ε 4.39); MS (EI) M^+ m/z at 429 (56%). ^{1}H NMR (200 MHz) ($CDCl_3$): δ 7.90 (d, J=10 Hz, H-5), 7.20-7.40 (m, 5H, chromone-3-phenyl protons), 6.95 (m, 4H, isoxazolyl phenyl protons), 6.85 (dd, J=10,2 Hz, H-6), 6.50 (d, J=2 Hz, H-8), 2.30 (s, 3H, 5-CH_3), 10.36 (bs, OH). Analc.Calcd. For $C_{25}H_{16}ClNO_4$: C, 69.85; H, 3.75; N, 3.26; found C, 70.15; H, 3.97; N, 3.48%.

2-[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]-7-hydroxy-3-phenyl-4*H*-1-benzopyran-4-one (3b). Recrystallised from methanol as pale yellow coloured crystals, mp 230^{0}C (82%); IR (KBr) in cm^{-1} 3151 (OH), 1608 (C=O), 1566 (C=N), 1303 (N-O), 1075 (C-O) & 1005 (C-O); UV (MeOH) 219 nm (log ε 4.44), 237 nm (log ε 4.33) and 309 nm (log ε 4.01); MS (EI) M^+ m/z at 464 (50%). ^{1}H NMR (200 MHz) ($CDCl_3$): δ 8.00 (d, J=10 Hz, H-5), 7.10-7.50 (m, 8H, aromatic protons), 6.85 (dd, J=10,2 Hz, H-6), 6.55 (d, J=2 Hz, H-8), 2.35 (s, 3H, 5-CH_3), 10.25 (bs, OH). Analc.Calcd. For $C_{25}H_{15}Cl_2NO_4$: C, 64.67; H, 3.76; N, 3.02; found C, 64.85; H, 3.98; N, 3.25%.

2-[3-(2-chloro-6-fluorophenyl)-5-methyl-4-isoxazolyl]-7-hydroxy-3-phenyl-4*H*-1-benzopyran-4-one (3c). Recrystallised from methanol as pale yellow coloured crystals, mp 222^{0}C (80%); IR (KBr) in cm^{-1} 3316 (OH), 1607 (C=O), 1575 (C=N), 1250 (N-O), 1095 (C-O) & 1010 (C-O); UV (MeOH) 227 nm (log ε 4.48), 237 nm (log ε 4.46) and 307 nm (log ε 4.20); MS (EI) M^+ m/z at 447 (50%). ^{1}H NMR (200 MHz) ($CDCl_3$): δ 7.90 (d, J=10 Hz, H-5), 7.00-7.50 (m, 8H, aromatic protons), 6.85 (dd, J=10,2 Hz, H-6), 6.50 (d, J=2 Hz, H-8), 2.25 (s, 3H, 5-CH_3), 10.20 (bs, OH). Analc.Calcd. For $C_{25}H_{15}ClFNO_4$: C, 67.05; H, 3.38; N, 3.13; found C, 67.36; H, 3.62; N, 3.25%.

3-(4-Bromophenyl)-2-[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]-7-hydroxy-4*H*-1-benzopyran-4-one (3d). Recrystallised from methanol as pale yellow coloured crystals, mp 231^{0}C (78%); IR (KBr) in cm^{-1} 3185 (OH), 1604 (C=O), 1565 (C=N), 1261 (N-O), 1072 (C-O) & 1010 (C-O); UV (MeOH) 209 nm (log ε 4.94), 223 nm (log ε 4.86) and 308 nm (log ε 4.45); MS (EI)

M^+ m/z at 508 (50%). ^{1}H NMR (200 MHz) ($CDCl_3$): δ 7.85 (d, J=10 Hz, H-5), 7.30-7.50 (m, 4H, isoxazolyl phenyl protons), 6.80-7.20 (m, 4H, chromone-3-phenyl protons), 6.90 (dd, J=10,2 Hz, H-6), 6.55 (d, J=2 Hz, H-8), 2.30 (s, 3H, 5-CH_3), 10.45 (bs, OH). Analc.Calcd. for $C_{25}H_{15}BrClNO_4$: C, 59.02; H, 2.97; N, 2.75; found C, 59.18; H, 3.12; N, 3.06%.

3-(4-Bromophenyl)-2-[3-(2-chloro-6-fluorophenyl)-5-methyl-4-isoxazolyl]-7-hydroxy-4*H*-1-benzopyran-4-one (3e). Recrystallised from methanol as pale yellow coloured crystals, mp 289^{0}C (75%); IR (KBr) in cm^{-1} 3129 (OH), 1620 (C=O), 1584 (C=N), 1251 (N-O), 1074 (C-O) & 1013 (C-O); UV (MeOH) 217 nm (log ε 4.59), 237 nm (log ε 4.47) and 309 nm (log ε 4.15); MS (EI) M^+ m/z at 526 (50%). ^{1}H NMR (200 MHz) ($CDCl_3$): δ 7.90 (d, J=10 Hz, H-5), 7.00-7.25 (m, 4H, isoxazolyl phenyl protons), 6.90-7.30 (m, 4H, chromone-3-phenyl protons), 6.80 (dd, J=10,2 Hz, H-6), 6.55 (d, J=2 Hz, H-8), 2.30 (s, 3H, 5-CH_3), 10.30 (bs, OH). Analc.Calcd. For $C_{25}H_{14}BrClFNO_4$: C, 57.01; H, 2.68; N, 2.66; found C, 57.26; H, 2.92; N, 2.85%.

2-[3-(2,6-Dichlorophenyl)-5-methyl-4-isoxazolyl]-7-hydroxy-3-methyl-4*H*-1-benzopyran-4-one (3f). Recrystallised from methanol as pale yellow coloured crystals, mp 200^{0}C (72%); IR (KBr) in cm^{-1} 3200 (OH), 1615 (C=O), 1574 (C=N), 1308 (N-O), 1072 (C-O) & 1008 (C-O); UV (MeOH) 209 nm (log ε 4.55), 222 nm (log ε 4.48) and 297 nm (log ε 4.03); MS (EI) M^+ m/z at 402 (50%). ^{1}H NMR (200 MHz) ($CDCl_3$): δ 7.80 (d, J=10 Hz, H-5), 7.10-7.35 (m, 3H, isoxazolyl phenyl protons), 6.65 (dd, J=10,2 Hz, H-6), 6.35 (d, J=2 Hz, H-8), 2.35 (s, 3H, 5-CH_3), 1.50 (s, 3H, 3-CH_3), 9.90 (bs, OH). Analc.Calcd. For $C_{20}H_{13}Cl_2NO_4$: C, 59.72; H, 3.26; N, 3.48 ; found C, 59.88; H, 3.38; N, 3.58%.

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