Synthesis of New 3-(4-Oxo-4*H*-chromen-3-yl)-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-dione Derivatives by 1,3-Dipolar Cycloaddition Reaction

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A series of new 3-(4-oxo-4*H*-chromen-3-yl)-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-dione have been synthesized by the reaction of *N*-arylmaleimides with nitrile oxide, prepared from α-chloro-4-oxo-4*H*-chromen-carbaldehyde oximes *in situ* through 1,3-dipolar cycloaddition reaction. The structures of all new compounds were confirmed by elemental analysis, ir, ^{1}H nmr and mass spectral data.

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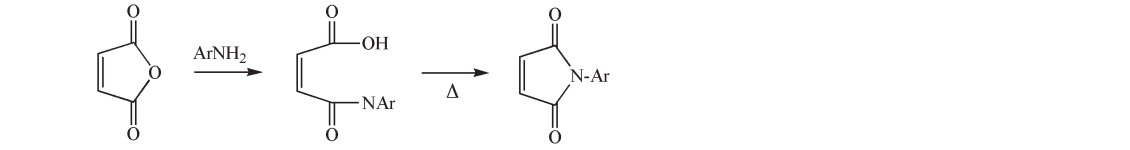
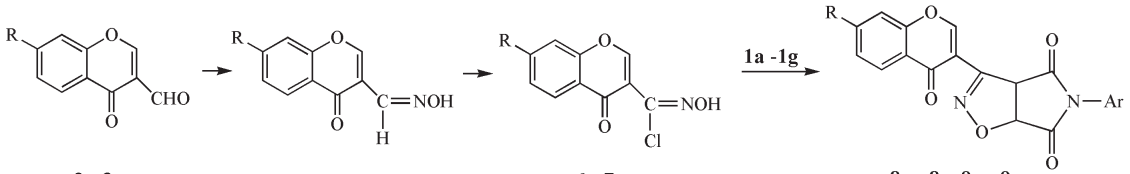
Flavones and chromones are unique molecules because of the availability of their structural framework in a variety of natural products and biologically active molecules as well as for the challenges involved in the synthesis of these structures and related molecules [1]. Isoxazoles play an important role among a wide variety of nitrogen heterocycles that have been used after developing useful herbicides [2,3]. The isoxazole and isoxazoline ring system, which is typically prepared by the 1,3-dipolar cycloaddition of a nitrile oxide with alkynes and olefins [4-7], is particularly interesting since it is ready transformed into various biodynamic agents, including those with antithrombotic. PAF antagonist, and hypolipidemic properties [8]. In the present paper we describe the synthesis of a new series of 3-(4-oxo-4*H*-chromen-3-yl)-3a,6a-dihydropyrrolo[3,4-*d*]-isoxazole-4,6-dione derivatives by 1,3-dipolar cycloaddition reaction.

The formation of chromen oximes is facile and can be readily obtained by reacting 3-formylchromones with hydroxylamine hydrochloride and using sodium acetate in ethanol-water in good yield [9], without the formation of any side products or the rupture of the chromone unit itself. Alpha haloaldoximes were prepared by alpha aldoximes with NBS in ether. In this paper, 4-oxo-4*H*-chromene-carbaldehyde oximes with $(CH_3)_3COCl$ (*tert*-butyl hypochlorite) in isopropanol and 1,2-dichloroethane as solvent at ice-salt bath gave us the desired α-chloro-4-oxo-4*H*-chromenecarbaldehyde oximes. Nitrile oxide has been widely employed in 1,3-dipolar cycloadditions, and there are several methods for its preparation [10]. Aromatic nitrile oxides are usually generated *in situ via* dehydrohalogenation of the corresponding alpha haloaldoximes. We prepared 4-oxo-4*H*-chromenecarbaldehyde nitrile oxides by dehydrohalogenation of the corresponding α-chloro-4-oxo-4*H*-chromencarbaldehyde oximes with triethylamine in chloroform at room temperature.

Compounds **8**, **9** obtained by the reaction of N-arylmaleimides with 4-oxo-4*H*-chromene-carbaldehyde nitrile oxides. All these reactions gave the desired compounds in good yields. The spectral data agree with reported structures. The structure of **8**,**9** were confirmed based upon two mutually coupled doublet peaks with chemical shifts at δ 5.60-5.65 and 5.76-5.80 with coupling constant of J = 9.6-10.4 Hz, attributable to the C_4-H and C_5-H hydrogen



1a -1g



2 - 3 **4 - 5** **6 - 7** **8a - 8g, 9a - 9g**

For compounds **2, 4, 6, 8:** R = H
For compounds **3, 5, 7, 9:** R = CH_3
Ar: **a** = Ph^- **b** = p-$ClC_6H_4^-$ **c** = o-$CH_3OC_6H_4^-$ **d** = p-$BrC_6H_4^-$
e = p-$CH_3C_6H_4^-$ **f** = p-$NO_2C_6H_4^-$ **g** = p-$CH_3OC_6H_4^-$

atoms of the pyrrolo[3,4-*d*]isoxazole ring, based on a previous report by us for similar compounds [11]. The proton H-2 in the chromone ring was observed as a single peak resonating at δ 8.35-8.47. The proton H-8 in chromone ring of compounds **8** was observed as two double peaks at δ 8.28-8.32 with a coupling constant J = 8.0-8.4 Hz and J = 0.4-1.2 Hz. The proton H-8 in the chromone ring of compounds **9** was observed as double peaks at δ 8.06-8.09, with coupling constant J = 0.4-0.8 Hz. All of the prepared compounds were evaluated *in vitro* for their antifungal activity against variant streptococcus using $CDCl_3$ as solvent at 20 μg/mL concentration. The results obtained revealed that compounds have no significant antifungal activity.

EXPERIMENTAL

Melting points were determined with a mettler FP-5 capillary melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 elemental analyzer. The ir spectra were measured as potassium bromide pellet on a Bruker FT-IR spectrophotometer. The ^{1}H nmr spectra were recorded on a Varian Inova-400 spectrometer using TMS as an internal standard. Mass spectra were performed on a HP 5890.

General Procedure for the Synthesis of 3-Chromone-5-Aryl-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-dione Derivatives.

Triethylamine (18 drops) and 10 mL chloroform was added dropwise to the mixture of α-chloro-4-oxo-4*H*-chromenecarbaldehyde oximes (2.0 mmoles) and *N*-arylmaleimides (2.5 mmoles) in chloroform, after the mixture was stirred at room temperature for 5~6 h, water was added and the aqueous phase was extracted with chloroform (3×), the combined organic layer was washed with water, then was dried over Na_2SO_4 and the solvent was removed to give crude products. The crude products were recrystallized from chloroform or chloroform and petroleum ether mixture to give pure product.

3-(4-Oxo-4*H*-chromen-3-yl)-5-phenyl-3a,6a-dihydropyrrolo-[3,4-*d*]isoxazole-4,6-dione (**8a**).

This compound was obtained as brown yellow granular crystal, yield 51%; mp 239-241°; ms: *m/z* (%) 360 (M^+, 24), 213 (45), 146 (100); ir (potassium bromide): 3064, 1711,1690,1657,1600, 1555, 1500, 1303; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 5.64 (d, 1H, J = 10 Hz), 5.80 (d, 1H, J = 10 Hz), 7.12-7.73 (m, 8H), 8.28-8.30 (dd, 1H, J = 8.0 Hz, J = 1.2 Hz), 8.40 (s, 1H).

Anal. Calad. For $C_{20}H_{12}N_2O_5$: C, 66.67; H, 3.36; N, 7.77. Found: C, 66.59; H, 3.31; N, 7.80.

5-(4-Chlorophenyl)-3-(4-oxo-4*H*-chromen-3-yl)-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-dione (**8b**).

This compound was obtained as white needles crystal, yield 78%; mp 225-226°; ms: *m/z* (%) 396 ($[M+2]^+$, 4), 394 (M^+, 16), 213 (37), 146 (100); ir (potassium bromide): 3060, 1715, 1685, 1657, 1600, 1555, 1500, 1300; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 5.63 (d, 1H, J = 10 Hz), 5.78 (d, 1H, J = 10 Hz), 7.13-7.76 (m, 7H), 8.28-8.30 (dd, 1H, J = 8.0 Hz, J = 1.2 Hz), 8.41 (s, 1H).

Anal. Calad. For $C_{20}H_{11}ClN_2O_5$: C, 60.85; H, 2.81; N, 7.10. Found: C, 60.96; H, 2.90; N, 7.18.

5-(2-Methoxyphenyl)-3-(4-oxo-4*H*-chromen-3-yl)-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-dione (**8c**).

This compound was obtained as white granular crystal, yield 48%; mp 234-237°; ms: *m/z* (%) 390 (M^+, 38), 213 (45), 146 (100); ir (potassium bromide): 3030, 2979, 1720, 1685, 1657, 1596, 1553, 1495, 1233; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 3.73 (s, 3H), 5.64 (d, 1H, J = 10.4 Hz), 5.81 (d, 1H, J = 10.4 Hz), 6.95-7.69 (m, 7H), 8.28-8.30 (dd, 1H, J = 8.0 Hz, J = 0.8 Hz), 8.41 (s, 1H).

Anal. Calad. For $C_{21}H_{14}N_2O_6$: C, 64.62; H, 3.62; N, 7.18. Found: C, 64.78; H, 3.53; N, 7.09.

5-(4-Bromophenyl)-3-(4-oxo-4*H*-chromen-3-yl)-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-dione (**8d**).

This compound was obtained as white powdery crystal, yield 60%; mp 231-233°; ms: *m/z* (%) 440 ($[M+2]^+$, 30), 438 (M^+, 34), 213 (39), 146 (100); ir (potassium bromide): 3058, 1715, 1690, 1654, 1600, 1555, 1500, 1300; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 5.63 (d, 1H, J = 10 Hz), 5.79 (d, 1H, J = 10 Hz), 7.12-7.75 (m, 7H), 8.28-8.30 (dd, 1H, J = 8.0 Hz, J = 1.2 Hz), 8.41 (s, 1H).

Anal. Calad. For $C_{20}H_{11}BrN_2O_5$: C, 54.69; H, 2.52; N, 6.38. Found: C, 54.77; H, 2.58; N, 6.43.

3-(4-Oxo-4*H*-chromen-3-yl)-5-*p*-tolyl-3a,6a-dihydropyrrolo-[3,4-*d*]isoxazole-4,6-dione (**8e**).

This compound was obtained as white crystal, yield 82%; mp 223-225°; ms: *m/z* (%) 374 (M^+, 41), 213 (62), 146 (100); ir (potassium bromide): 3047, 2960, 1725, 1688, 1665, 1600, 1555, 1500, 1311; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.46 (s, 3H), 5.62 (d, 1H, J = 10 Hz), 5.79 (d, 1H, J = 10 Hz), 7.03-7.67 (m, 7H), 8.29-8.31 (dd, 1H, J = 8.4 Hz, J = 0.4 Hz), 8.42 (s, 1H).

Anal. Calad. For $C_{21}H_{14}N_2O_5$: C, 67.38; H, 3.77; N, 7.48. Found: C, 67.26; H, 3.83; N, 7.39.

5-(4-Nitrophenyl)-3-(4-oxo-4*H*-chromen-3-yl)-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-dione (**8f**).

This compound was obtained as white pellet crystal, yield 46%; mp 185-186°; ms: *m/z* (%) 405 (M^+, 52), 213 (66), 146 (100); ir (potassium bromide): 3062, 1720, 1692, 1660, 1596, 1555, 1500, 1349; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 5.63 (d, 1H, J = 10.4 Hz), 5.78 (d, 1H, J = 10.4 Hz), 7.32-7.85 (m, 7H), 8.30-8.32 (dd, 1H, J = 8.4 Hz, J = 0.8 Hz), 8.42 (s, 1H).

Anal. Calad. For $C_{20}H_{11}N_3O_7$: C, 59.27; H, 2.74; N, 10.37. Found: C, 59.14; H, 2.82; N, 10.29.

5-(4-Methoxyphenyl)-3-(4-oxo-4*H*-chromen-3-yl)-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-dione (**8g**).

This compound was obtained as gray yellow powdery crystal, yield 67%; mp 246-248°; ms: *m/z* (%) 390 (M^+, 32), 213 (47), 146 (100); ir (potassium bromide): 3030, 2985, 1720, 1685, 1657, 1593, 1555, 1495, 1300; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 3.74 (s, 3H), 5.63 (d, 1H, J = 10.4 Hz), 5.77 (d, 1H, J = 10.4 Hz), 7.01-7.75 (m, 7H), 8.28-8.31 (dd, 1H, J = 8.4 Hz, J = 0.8 Hz), 8.41 (s, 1H).

Anal. Calad. For $C_{21}H_{14}N_2O_5$: C, 67.38; H, 3.77; N, 7.48. Found: C, 67.46; H, 3.82; N, 7.40.

3-(7-Methyl-4-oxo-4*H*-chromen-3-yl)-5-phenyl-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-dione (**9a**).

This compound was obtained as light yellow pellet crystal, yield 58%; mp 208-210°; ms: *m/z* (%) 374 (M^+, 28), 227 (45),

160 (100); ir (potassium bromide): 3054, 2986, 1723, 1685, 1662, 1586, 1555, 1500, 1305; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.35 (s, 3H), 5.63 (d, 1H, J = 10 Hz), 5.78 (d, 1H, J = 10 Hz), 7.15-7.61 (m, 7H), 8.08 (d, 1H, J = 0.8 Hz), 8.39 (s, 1H).

Anal. Calad. For $C_{21}H_{14}N_2O_5$: C, 67.38; H, 3.77; N, 7.48. Found: C, 67.43; H, 3.85; N, 7.38.

5-(4-Chlorophenyl)-3-(7-methyl-4-oxo-4*H*-chromen-3-yl)-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-dione (**9b**).

This compound was obtained as light yellow powdery crystal, yield 70%; mp 210-211°; ms: *m/z* (%) 410 ([M+2]$^+$, 5), 408 (M$^+$, 19), 227 (45), 160 (100); ir (potassium bromide): 3050, 2990, 1720, 1685, 1662, 1585, 1555, 1500, 1305; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.35 (s, 3H), 5.62 (d, 1H, J = 10 Hz), 5.81 (d, 1H, J = 10 Hz), 7.15-7.70 (m, 6H), 8.10 (d, 1H, J = 0.8 Hz), 8.40 (s, 1H).

Anal. Calad. For $C_{21}H_{13}ClN_2O_5$: C, 61.70; H, 3.21; N, 6.85. Found: C, 61.84; H, 3.12; N, 6.90.

5-(2-Methoxyphenyl)-3-(7-methyl-4-oxo-4*H*-chromen-3-yl)-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-dione (**9c**).

This compound was obtained as light yellow crystal, yield 63%; mp 215-216°; ms: *m/z* (%) 404 (M$^+$, 21), 227 (40), 160 (100); ir (potassium bromide): 3035, 2987, 1721, 1680, 1655, 1586, 1554, 1498, 1303; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.35 (s, 3H), 3.75(s, 3H), 5.63 (d, 1H, J = 10 Hz), 5.80 (d, 1H, J = 10 Hz), 7.00-7.58 (m, 6H), 8.09 (d, 1H, J = 0.8 Hz), 8.39 (s, 1H).

Anal. Calad. For $C_{22}H_{16}N_2O_6$: C, 65.34; H, 3.99; N, 6.93. Found: C, 65.44; H, 4.02; N, 7.01.

5-(4-Bromophenyl)-3-(7-methyl-4-oxo-4*H*-chromen-3-yl)-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-dione (**9d**).

This compound was obtained as white powdery crystal, yield 54%; mp 236-238°; ms: *m/z* (%) 454 ([M+2]$^+$, 25), 452 (M$^+$, 29), 227 (38), 160 (100); ir (potassium bromide): 3040, 2987, 1721, 1680, 1655, 1586, 1554, 1498, 1303; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.35 (s, 3H), 5.63 (d, 1H, J = 10 Hz), 5.83 (d, 1H, J = 10 Hz), 7.18-7.59 (m, 6H), 8.06 (d, 1H, J = 0.8 Hz), 8.39 (s, 1H).

Anal. Calad. For $C_{21}H_{13}BrN_2O_5$: C, 55.65; H, 2.89; N, 6.18. Found: C, 55.52; H, 2.80; N, 6.27.

3-(7-Methyl-4-oxo-4*H*-chromen-3-yl)-5-*p*-tolyl-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-dione (**9e**).

This compound was obtained as yellow needles crystal, yield 79%; mp 185-187°; ms: *m/z* (%) 388 (M$^+$, 34), 227 (52), 160 (100); ir (potassium bromide): 3035, 2995, 1715, 1686, 1662, 1597, 1550, 1500, 1300; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.36 (s, 3H), 2.40(s, 3H), 5.63 (d, 1H, J = 10 Hz), 5.80 (d, 1H, J = 10 Hz), 7.10-7.62 (m, 6H), 8.08 (d, 1H, J = 0.8 Hz), 8.40 (s, 1H).

Anal. Calad. For $C_{21}H_{16}N_2O_5$: C, 68.04; H, 4.15; N, 7.21. Found: C, 68.18; H, 4.21; N, 7.30.

3-(7-Methyl-4-oxo-4*H*-chromen-3-yl)-5-(4-nitrophenyl)-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-dione (**9f**).

This compound was obtained as light yellow granular crystal, yield 68%; mp 205-207°; ms: *m/z* (%) 419 (M$^+$, 30), 227 (61), 160 (100); ir (potassium bromide): 3050, 2990, 1715, 1675, 1650, 1600, 1554, 1500, 1300; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.36 (s, 3H), 5.64 (d, 1H, J = 10 Hz), 5.83 (d, 1H, J = 10 Hz), 7.18-7.71 (m, 6H), 8.09 (d, 1H, J = 0.4 Hz), 8.41 (s, 1H).

Anal. Calad. For $C_{21}H_{13}N_3O_7$: C, 60.15; H, 3.12; N, 10.02. Found: C, 60.28; H, 3.15; N, 10.08.

5-(4-Methoxyphenyl)-3-(7-methyl-4-oxo-4*H*-chromen-3-yl)-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-dione (**9g**).

This compound was obtained as light yellow powder crystal, yield 51%; mp 225-226°; ms: *m/z* (%) 404 (M$^+$, 31), 227 (49), 160 (100); ir (potassium bromide): 3035, 2985, 1718, 1676, 1649, 1600, 1550, 1498, 1301; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.35 (s, 3H), 3.76(s, 3H), 5.63 (d, 1H, J = 10 Hz), 5.80 (d, 1H, J = 10 Hz), 7.00-7.58 (m, 6H), 8.06 (d, 1H, J = 0.8 Hz), 8.40 (s, 1H).

Anal. Calad. For $C_{22}H_{16}N_2O_6$: C, 65.34; H, 3.99; N, 6.93. Found: C, 65.46; H, 3.87; N, 6.99.

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