Synthesis of [2-Aryl-6-oxo-6*H*-chromeno[6,7-*d*]oxazol-8-yl]-acetic Acid Ethyl Esters

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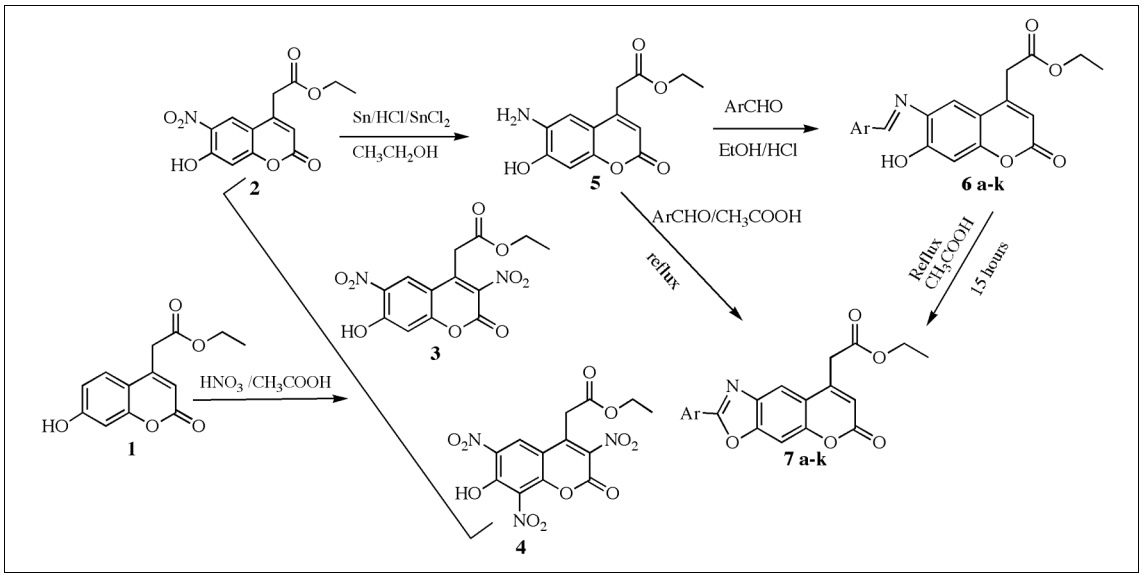

A number of coumarino[6,7-*d*]oxazoles (nitrogen analogs of psoralens) have been synthesized from (7-hydroxy-2-oxo-2*H*-chromen-4-yl) acetic acid ethyl ester **1**. The synthetic route began with the nitration of **1** with nitric acid in acetic acid to give (6-nitro-7-hydroxy-2-oxo-2*H*-chromen-4-yl) acetic acid ethyl ester **2**; (3,6-dinitro-7-hydroxy-2-oxo-2*H*-chromen-4-yl) acetic acid ethyl ester **3** and (3,6,8-trinitro-7-hydroxy-2-oxo-2*H*-chromen-4-yl) acetic acid ethyl ester **4**. The reduction of **2** was accomplished with tin(II) chloride, tin, and concentrated hydrochloric acid in ethanol giving (6-amino-7-hydroxy-2-oxo-2*H*-chromen-4-yl) acetic acid ethyl ester **5**. After the condensation of aminocoumarin **5** with aromatic aldehyde in glacial acetic acid medium, followed the dehydrocyclization to coumarino[6,7-*d*]oxazoles **7a-k**. The intermediate Schiff's bases **6a-k** have been obtained from **5** with aromatic aldehyde in ethanol. Antibacterial and antifungal activities of the compounds have been evaluated.

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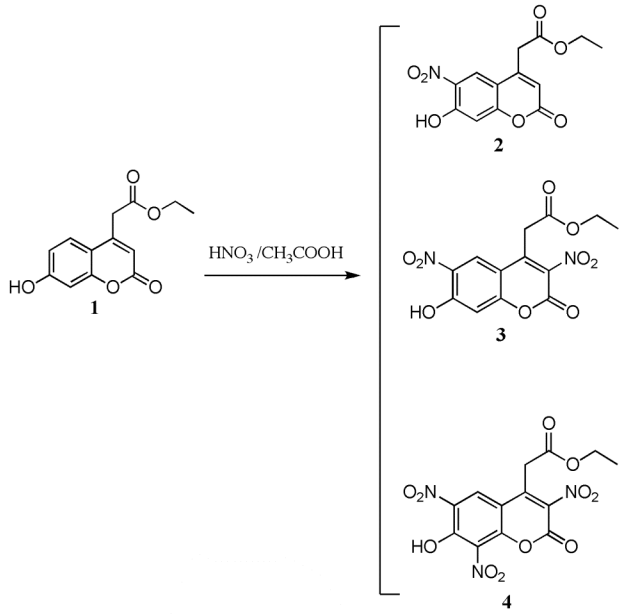
Various physiological activities of coumarine derivatives (anticoagulant, antibacterial, antihelmetic, hipothermal and vasodilatatory actions) described by Soine in his review article [1]. Some derivatives of 3-amino-4,7-dihydroxy-8-methylcoumarin (AHC), a structural component of the antibiotic novobiocin as well as AHC itself, have been reported as bactericidal and fungicidal agents [2]. Also, the publication by Ichikawa and Ichibagase [3] on the preparation of oxazolocoumarins [4-6] from the nitro derivatives of 4,7-dihydroxycoumarin encouraged us to report our results on this subject.

Different methods have been reported describing the nitration of closely related compounds of the coumarin type [7]. In general, mixtures of mono-, di- and trinitro products resulted in nonequal amounts and were separated by chromatographic methods or recrystallisation [7-13]. The nitration of compound **1** with concentrated nitric acid and acetic acid at room temperature, afterwards heated up to 80 ºC, gave (6-nitro-7-hydroxy-2-oxo-2*H*-chromen-4-yl) acetic acid ethyl ester **2**, (3,6-dinitro-7-hydroxy-2-oxo-2*H*-chromen-4-yl) acetic acid ethyl ester **3**, and (3,6,8-trinitro-7-hydroxy-2-oxo-2*H*-chromen-4-yl) acetic acid ethyl ester **4**. The separation of these three nitro derivatives was carried out by column chromatography using silica gel. The mixture of nitration products was first eluted with petroleum ether/ benzene (1:1) to isolate the 6-nitro product **2**, followed by methanol to isolate 3,6-dinitro product **3**, and methanol/acetone (1:10) to isolate 3,6,8-trinitro product **4** (Scheme I). The reduction of **2** was accomplished with tin(II) chloride, tin, and concentrated hydrochloric acid in ethanol, giving (6-amino-7-hydroxy-2-oxo-2*H*-chromenyl) acetic acid ethyl

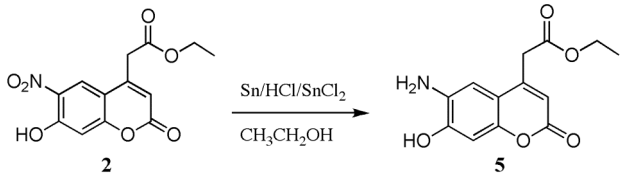
ester **5**, with yield of 76%, (Scheme II). The reduction of **2** was attempted unsuccessfully with palladium on carbon in cyclohexane as well as with ammonium hydroxide/ sodium bisulfite in isopropyl alcohol. Amino derivatives were synthesized by electrochemical reduction of 3-nitro-4-hydroxy-2-oxo-2*H*-chromen at a constant potential [14,15].

Highly coloured Schiff's bases **6a-k** (Scheme III) were first prepared by condensing equimolar proportions of different aromatic aldehydes in alcoholic medium by refluxing for 2 hours. It has been observed by Subba Rao and coworkers [5,6] that coumarino[3,4-*d*]oxazoles formed in some cases by boiling the mixture of a 3-amino-4-hydroxycoumarin derivative and an aromatic aldehyde in nitrobenzene. However, we achieved this dehydro-cyclization [16,17] merely by heating the mixture of reactants during reflux in glacial acetic acid to yield the coumarino[6,7-*d*]oxazoles **7a-k** (Scheme IV). Under these conditions Shiff's bases **6a-k** also yielded oxazoles, indicating that they are intermediates in the formation of coumarino[6,7-*d*]oxazoles (**7a-k**) from (6-amino-7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic acid ethyl ester (**5**).

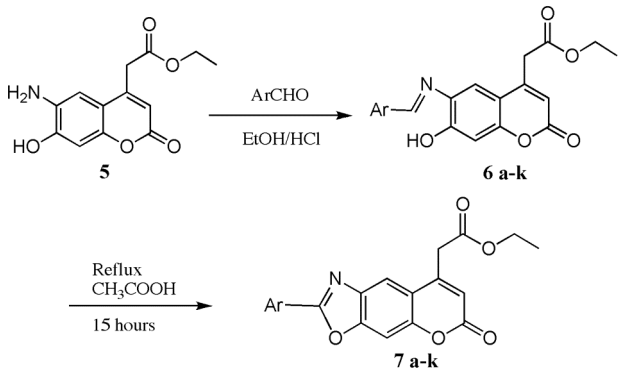
Scheme I



Scheme II

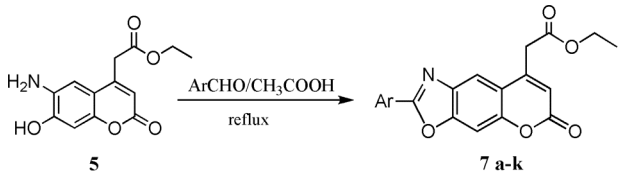


Scheme III



Ar- a-phenyl, **b**-2-hydroxyphenyl , **c**-2-chlorophenyl , **d**-3-chlorophenyl, **e**-2,3-dihydroxyphenyl , **f**-2,4-dihydroxyphenyl , **g**-2,5-dihydroxyphenyl, **h**-3,5dihydroxyphenyl, **i**-3-phenoxyphenyl , **j**-3-methoxy-4-hydroxyphenyl, **k**-4-N,N-dimethylphenyl

Scheme IV



Ar- a-phenyl, **b**-2-hydroxyphenyl, **c**-2-chlorophenyl, **d**-3-chlorophenyl, **e**-2,3-dihydroxyphenyl , **f**-2,4-dihydroxyphenyl, **g**-2,5-dihydroxyphenyl, **h**-3,5-dihydroxyphenyl, **i**-3-phenoxyphenyl, **j**-3-methoxy-4-hydroxyphenyl, **k**-4-N,N-dimethylaminophenyl

Biological Screening.

Newly synthesized compounds **6a-k** and **7a-k**, were examined for their antimicrobial activity. The best results were obtained in the case of **7e**, **7f** and **7g**. These compounds were found to possess high antimicrobial activity against *Staphylococcus pneumoniae* and were slightly less active against *Bacillus subtillus, Bacillus cereus and Salmonella panama*. In the case of **7a-d**, and **7h-k**, we have found them to have weak, but **6a-k**, very weak activity against all tested microorganisms.

EXPERIMENTAL

General Information.

The melting points were recorded with Electrothermal Capillary melting point apparatus and are uncorrected. For thin-layer chromatography fluorescent silica gel plates HF_{254} Merck were used, and plates were viewed by UV light at 254 and 265 nm. Silica gel (230-400 mesh) was used for flash chromatography separations. The elemental analysis of C, H and N were carried out on a Perkin-Elmer Analyzer 2440. Infrared spectra (ν-cm^{-1}) were recorded on a Beckman FT-IR 3303, using KBr disks. ^{1}H NMR spectra were recorded on JEOL EX-270 MHz NMR Spectrophotometer at 293 °K in DMSO-d_6. Spectra

were internally referenced to TMS. Peaks are reported in ppm downfield of TMS.

(6-Nitro-7-hydroxy-2-oxo-2*H*-chromen-4yl)-acetic acid ethyl-ester (**2**).

To a suspension of 44.0 g of **1** in 100 ml of acetic acid, 20 ml 70% nitric acid dissolved in 30 ml acetic acid was added slowly, accompanied with vigorous stirring. The temperature was kept at 0-5 °C during the period of addition, and the mixture was then placed on a steam-bath to raise the temperature to 90 ºC, when the nitration suddenly began. From that moment the flask was cooled in ice to keep the reaction under control. The reaction mixture was poured into ice-cold water the precipitate that formed was collected by filtration, dried, and purified. For that purpose a column chromatography using silica gel was used; to isolate compounds **2**, dinitro **3** and trinitro **4**, the column was eluted with petroleum ether/benzene (1:1), methanol and methanol/aceton (1:10).

Compound **2** was obtained in 60% yield; mp: 213-214 °C; IR(KBr):

3307 (-OH), 3075, 2990 (-CH), 1748, 1724 (›C=O), 1557 (-C=C-), 1295 (-CO-O) and 1136 cm^{-1}; ^1H NMR: δ 1.2 (t, J=7.1Hz, 3H, CH_3), δ 4.12 (s, 2H, CH_2-4), δ 4.14 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.46 (s, 1H, H-3), δ 7.01 (s, 1H, H-8), δ 8.30 (s, 1H, H-5) and δ 12.0 (s, 1H, OH-7); ^{13}C NMR (DMSO-d_6): δ 165.4; 160.9; 157.8; 154.8; 147.4; 141.4; 123.1; 119.2; 113.7; 112.3; 62.4;35.2;14.8.

Anal. Calcd. For $C_{13}H_{11}NO_7$: C, 53.25; H, 3.78; N, 4.78. Found: C, 53.27; H, 3.82; N, 4.75.

(7-Hydroxy-3,6-dinitro-2-oxo-2*H*-chromen-4-yl)-acetic Acid Ethyl Ester (**3**).

Compound **3** was obtained in 21% yield; mp: 225-226 °C; IR(KBr):

3233 (-OH), 2986, 2930 (›CH), 1720, 1623 (›C=O), 1547 (-C=C-), 1356 (-CO-O) and 1089 cm^{-1}; ^1H NMR: δ 1.08 (t, J=7.1Hz, 3H, CH_3), δ 3.48 (s, 2H, CH_2-4), δ 4.04 (q, J=7.1Hz, 2H, CH_2-Et), δ 8.15 (s, 1H, H-5), δ 7.03 (s, 1H, H-8) and δ 12.10 (s, 1H, OH-7). ^{13}C NMR (DMSO-d_6): δ 165.4; 161.2; 157.8; 154.8; 147.4; 141.4; 137.8; 123.1; 117.2; 110.7; 62.4;35.2; 14.8.

Anal. Calcd. For $C_{13}H_{10}N_2O_9$: C, 46.16; H, 2.98; N, 8.28. Found: C, 46.14; H, 2.94; N, 8.25.

(7-Hydroxy-3,6,8-trinitro-2-oxo-2*H*-chromen-4-yl)-acetic Acid Ethyl Ester (**4**).

Compound **4** was obtained in 8% yield; mp: 180-181 °C. IR(KBr)

3448 (-OH), 3100 (›CH), 1682 (›C=O), 1610 (-C=C-), 1367 (›CO-O) and 1906 cm^{-1}; ^1H NMR: δ 1.10 (t, J=7.1Hz, 3H, CH_3), δ 3.50 (s, 2H, CH_2-4), δ 4.10 (q, J=7.1Hz, 2H, CH_2-Et), δ 8.32 (s, 1H, H-5) and δ 12.70 (s, 1H, OH-7). ^{13}C NMR (DMSO-d_6): δ 165.4; 162.0; 157.8; 154.8; 147.4; 144.3; 141.4; 137.8; 123.1; 119.2; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{13}H_9N_3O_{11}$: C, 40.74; H, 2.37; N, 10.96. Found: C, 40.71; H, 2.33; N, 11.00.

(6-Amino-7-hydroxy-2-oxo-2*H*-chromen-4-yl)acetic Acid Ethyl Ester (**5**).

Finely powdered **2** 10.9 mmol, tin 27.3 mmol, tin(II)chloride 16.0 mmol, 9 ml of concentrated hydrochloric acid and 200 ml of ethanol were stirred overnight to dissolve all tin. Most of the ethanol was removed *in vacuo*. The solution was allowed to cool, and the gel that formed was collected by filtration, to recover a small amount of pearly crystals (the hydrochloride salt). Water and a drop of isoamyl alcohol were added to prevent frothing after the addition of solid sodium bicarbonate (accompanied by stirring) until the solution became basic. Ether was added to the filtrate and a precipitate formed. The precipitate was collected by filtration and rinsed with ether to remove tin (II) chloride. The solids were dried and extracted with hot ethanol on the funnel of a filtration flask. Evaporation of the ethanol gave a crude product that was recrystallized from ethanol to provide bright mustard yellow crystals of compound **5**.

Compound **5** was obtained in 76% yield; mp: 229-230 °C; IR(KBr):

3446, 3359 (-NH), 3207 (-OH), 3009, 2993 (-CH), 1712, 1675 (›C=O),

1596, 1577 (-C=C-), 1369 (-CO-O) and 1032 cm^{-1}; ^1H NMR: 1.2 (t, J=7.1Hz, 3H, CH_3), δ 3.35 (s, 2H, NH_2), δ 3.84 (s, 2H, CH_2-4), δ 4.14 (q, J=7.1Hz, 2H,CH_2-Et), δ 6.16 (s, 1H, H-3), δ 6.68 (s, 1H, H-8), δ 6.74 (s, 1H, H-5) and δ 12.0 (s, 1H, OH-7); ^{13}C NMR (DMSO-d_6): δ 165.4; 159.9; 157.8; 154.8; 147.4; 138.2; 123.1; 119.2; 113.7; 112.3; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.29; H, 5.01; N, 5.29.

General Procedure.

[6-(Arilidene-amino)-7-hydroxy-2-oxo-2*H*-chromen-4-yl]-acetic Acid Ethyl Ester (**6a-k**).

The aminocoumarin **5** free base or its hydrochloride salt was reacted with ethanol solutions of various aromatic aldehydes in equimolar amounts. The reaction mixture was submitted to refluxing for 1-2 hours, when highly coloured Schiff's bases were separated. The precipitates that formed were collected by filtration and recrystallized from ethanol.

(6-(Phenylidene-amino)-7-hydroxy-2-oxo-2*H*-chromeno-4-yl)-acetic Acid Ethyl Ester (**6a**).

Compound **6a** was obtained in 62% yield; mp: 134-135 °C; IR(KBr): 3313 (-OH), 3065, 2927 (-CH), 1724 (›C=O), 1637, 1572 (-C=C), 1347 (-CO-O) and 1047 cm^{-1}; ^1H NMR: δ 1.5 (t, J=7.1Hz, 3H, CH_3-Et), δ 4.0 (s, 2H, CH_2-4), δ 4.14 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.3 (s, 1H, H-3), δ 6.91 (s, 1H, H-8), δ 7.0-7.5 (m, 5H, aromatic), δ 7.69 (s, 1H, H-5), δ 8.5 (s, 1H, CH-N-) and δ 11.8 (s, 1H, OH-7). ^{13}C NMR (DMSO-d_6): δ 165.4; 160.2; 159.9; 157.8; 154.8; 147.4; 138.2; 134.8; 132.2; 129.9; 129.8; 127.9; 127.9; 123.1; 119.2; 113.7; 112.3; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.34; H, 4.89; N, 4.01.

(7-Hydroxy-6-((2-hydroxy-bezylidene)-amino)-2-oxo-2*H*-chromen-4-yl)-acetic Acid Ethyl Ester (**6b**).

Compound **6b** was obtained in 71 % yield; mp: 181 °C. IR(KBr):

3423 (-OH), 3068, 2926 (-CH), 1702 (›C=O), 1620, 1569 (-C=C-), 1392 (-CO-O) and 1204 cm^{-1}; ^1H NMR: δ 1.20 (t, J=7.1 Hz, 3H, CH_3-Et), δ 4.13 (s, 2H, CH_2-4), δ 4.15 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.30 (s, 1H, H-3), δ 6.92 (s, 1H, H-8), δ 7.0-7.7 (m, 4H, aromatic), δ 7.89 (s, 1H, H-5), δ 8.9 (s, 1H, CH-N), δ 12.7 (s, 1H, OH-7) and δ 13.35 (s, 1H, OH-2). ^{13}C NMR (DMSO-d_6):

δ 165.4; 161.2; 160.9; 158.8; 157.8; 154.8; 147.4; 138.2; 134.8; 132.2; 121.8; 128.9; 127.9; 123.1; 119.2; 113.7; 112.3; 64.4; 36.2; 14.9.

Anal. Calcd. For $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.42; H, 4.69; N, 3.80.

(6-((2-Chloro-benzylidene)-amino)-7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic Acid Ethyl Ester (**6c**).

Compound **6c** was obtained in 81% yield; mp: 164 °C. IR(KBr):

3422 (-OH), 3062, 2981 (-CH), 1724 (›C=O), 1626, 1570 (-C=C-), 1343 (-CO-O) 1155 cm^{-1}; ^{1}H NMR: δ 1.18 (t, J=7.1Hz, 3H, CH_3-Et), δ 4.12 (s, 2H, CH_2-4), δ 4.14 (q, J=7.1 Hz, 2H, CH_2-Et), δ 6.30 (s, 1H, H-3), δ 6.90 (s, 1H, H-8), δ 7.48-7.59 (m, 4H, arom.), δ 8.3 (s, 1H, H-5), δ 9.0 (s, 1H, CH-N) and δ 10.7 (s, 1H, OH-7). ^{13}C NMR (DMSO-d_6): δ 165.4; 161.0; 160.9; 157.8; 154.8; 147.4; 138.2; 135.5; 134.8; 132.2; 129.8; 128.9; 127.4; 123.1; 119.2; 113.7; 112.3; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{20}H_{16}ClNO_5$: C, 62.26; H, 4.18; N, 3.63. Found: C, 62.23;H, 4.19; N, 3.59.

(6-((3-Chloro-benzylidene)-amino)-7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic acid ethyl ester (**6d**).

Compound **6d** was obtained in 74% yield; mp: 177 °C. IR(KBr):

3387 (-OH), 3068, 2926 (-CH), 1719 (›C=O), 1630, 1570 (-C=C-), 1342 (-CO-O) and 1153 cm^{-1}; ^{1}H NMR: δ 1.18 (t, J=7.1 Hz, 3H, CH_3-Et), δ 4.01 (s, 2H, CH_2-4), δ 4.12 (q, J=7.1 Hz, 2H, CH_2-Et), δ 6.29 (s, 1H, H-3), δ 6.90 (s, 1H, H-8), δ 7.55-7.64 (m, 4H, arom.), δ 8.2 (s, 1H, H-5), δ 8.75 (s, 1H, CH-N) and 10.4 (s, 1H, OH-7). ^{13}C NMR (DMSO-d_6): δ 165.4; 161.0; 160.9; 157.8; 154.8; 147.4; 138.2; 135.5; 134.8; 131.8; 130.8; 129.9; 127.9; 123.1; 119.2; 113.7; 112.3; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{20}H_{16}ClNO_5$: C, 62.26; H, 4.18; N, 3.63. Found: C, 62.23; H, 4.20; N, 3.64.

(6-((2,3-Dihydroxy-benzylidene)-amino)-7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic Acid Ethyl Ester (**6e**).

Compound **6e** was obtained in 42% yield; mp: 229°C. IR(KBr):

3409 (-OH), 3064, 2980 (-CH), 1713 (›C=O), 1625 (-C=C-), 1395 (-CO-O) and 1019 cm^{-1}; ^{1}H NMR: δ 1.19 (t, J=7.1Hz, 3H, CH_3-Et), δ 4.04 (s, 2H, CH_2-4), δ 4.13 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.31 (s, 1H, H-3), δ 6.8 (s, 1H, H-8), δ 6.9-7.1 (m, 3H, arom.), δ 7.9 (s, 1H, H-5), δ 8.9 (s, 1H, CH-N), δ 9.8 (s, 1H, OH-7), δ 11.1 (s, 1H, OH) and δ 12.7 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ165.4; 161.0; 160.7; 155.8; 154.8; 150.4; 148.2; 135.5; 134.8; 126.8; 123.8; 123.1; 122.9; 122.6; 119.2; 113.7; 112.3; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{20}H_{17}NO_7$: C, 62.66; H, 4.47; N, 3.65. Found: C, 62.64; H, 4.45; N, 3.66.

(6-((2,4-Dihydroxy-benzylidene)-amino)-7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic Acid Ethyl Ester (**6f**).

Compound **6f** was obtained in 40% yield; mp: 158 °C; IR(KBr):

3447, 3352 (-OH), 3073, 2971 (-CH), 1712 (›C=O), 1605 (-C=C-), 1402 (-CO-O) and 1012 cm^{-1}; ^{1}H NMR: δ 1.20 (t, J=7.1Hz, 3H, CH_3-Et), δ 4.02 (s, 2H, CH_2-4), δ 4.12 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.29 (s, 1H, H-3), δ 6.9 (s, 1H, H-8), δ 6.9-7.1 (m, 3H, arom.), δ 7.6 (s, 1H, H-5), δ 8.8 (s, 1H, CH-N), δ 10,1 (s, 1H, OH-7), δ 11.4 (s, 1H, OH) and δ 13.7 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ 165.4; 162.8; 162.4 161.0; 160.7; 155.8; 154.8; 135.5; 134.8; 132.8; 126.8; 123.9; 123.1; 122.4; 119.2; 113.7; 112.3; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{20}H_{17}NO_7$: C, 62.66; H, 4.47; N, 3.65. Found: C, 62.64; H, 4.48; N, 3.62.

(6-((2,5-Dihydroxy-benzylidene)-amino)-7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic Acid Ethyl Ester (**6g**).

Compound **6g** was obtained in 62% yield; mp: 230 °C; IR(KBr):

3433, 3246 (-OH), 3000, 2959 (-CH), 1724, 1677 (›C=O), 1606 (-C=C-), 1391 (-CO-O) and 1018 cm^{-1}; ^{1}H NMR: δ 1.20 (t, J=7.1Hz, 3H, CH_3-Et), δ 4.03 (s, 2H, CH_2-4), δ 4.13 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.3 (s, 1H, H-3), δ 6.8 (s, 1H, H-8), δ 6.83-7.1 (m, 3H, arom.), δ 7.62 (s, 1H, H-5), δ 8.85 (s, 1H, CH-N), δ 9.1 (s, 1H, OH-7), δ 10.93 (s, 1H, OH) and δ 12.49 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ165.4; 161.0; 160.7; 155.8; 154.8; 153.8; 151.3; 137.5; 134.8; 132.8; 125.8; 123.9; 122.1; 121.4; 119.2; 113.7; 112.3; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{20}H_{17}NO_7$: C, 62.66; H, 4.47; N, 3.65. Found: C, 62.63; H, 4.46; N, 3.62.

(6-((3,5-Dihydroxy-benzylidene)-amino)-7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic Acid Ethyl Ester **(6h**).

Compound **6h** was obtained in 51% yield; mp: 256 °C; IR(KBr):

3413, 3250(-OH), 3020, 2919 (-CH), 1734, 1697 (›C=O), 1601 (-C=C-), 1390 (-CO-O) and 1023 cm^{-1}; ^{1}H NMR: δ 1.20 (t, J=7.1Hz, 3H, CH_3-Et), δ 4.03 (s, 2H, CH_2-4), δ 4.14 (q, J=7.1 Hz, 2H, CH_2-Et), δ 6.3 (s, 1H, H-3), δ 6.8 (s, 1H, H-8) 6.83-7.1 (m, 3H, arom.), δ 7.64(s, 1H, H-5), δ 8.85 (s, 1H, CH-N), δ 9.1 (s, 1H, OH-7), δ 11.0 (s, 1H, OH) and δ 12.50 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ 165.4; 161.0; 160.4; 160.2; 160.2; 155.8; 137.5; 136.8; 134.6; 125.8; 123.9; 119.2; 113.7; 112.3; 111.2; 110.9; 108.2; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{20}H_{17}NO_7$: C, 62.66; H, 4.47; N, 3.65. Found: C, 62.64; H, 4.45; N, 3.63.

(7-Hydroxy-2-oxo-6((3-phenoxy-bezylidene)-amino)-2*H*-chromen-4yl)-acetic Acid Ethyl Ester (**6i**).

Compound **6i** was obtained in 38% yield; mp: 166-167 °C; IR(KBr):

3422 (-OH), 3067, 2926 (-CH), 1726 (›C=O), 1631, 1591 (-C=C-), 1268 (-CO-O) and 1022 cm^{-1}; ^{1} H NMR: δ 1.21 (t, J=7.1Hz, 3H, CH_3-Et), δ 4.0 (s, 2H, CH_2-4), δ 4.13 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.3 (s, 1H, H-3), δ 6.8 (s, 1H, H-8), δ 6.83-7.1 (m, 9H, arom.), δ 7.64 (s, 1H, H-5), δ 8.85 (s, 1H, CH-N) and δ 11.0 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ 165.4; 161.0; 160.4; 157.2; 157.0; 155.8; 153.4; 152.2; 137.5; 136.8; 134.6; 128.2; 128.0; 127.8; 122.9; 121.2; 119.2; 117.7; 117.0; 116.4; 114.9; 114.3; 112.2;62.4; 35.2; 14.8.

Anal. Calcd. For $C_{26}H_{21}NO_6$: C, 70.42; H, 4.77; N, 3.17. Found: C, 70.40; H, 4.75; N, 3.14.

(7-Hydroxy-6-((4-hydroxy-3-methoxy-benzylidene)-amino)-2-oxo-2*H*-chromen-4-yl)-acetic Acid Ethyl Ester (**6j**).

Compound **6j** was obtained in 68% yield; mp: 181-182 °C; IR(KBr):

3485, 3294 (-OH), 3073, 2984 (-CH), 1731 (›C=O), 1631,

1597, 1574 (-C=C-), 1293 (-CO-O) and 1049 cm^{-1}; ^1H NMR: δ 1.19 (t, J=7.1Hz, 3H, CH_3-Et), δ 3.87 (s, 3H, OCH_3), δ 4.01 (s, 2H, CH_2-4), δ 4.13 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.28 (s, 1H, H-3), δ 6.88 (s, 1H, H-8), δ 6.92 (d, 1H, arom), δ 7.36 (d, 1H, arom.), δ 7.44 (s, 1H, arom.), δ 7.70 (s, 1H, H-5), δ 8.7 (s, 1H, CH-N), δ 9.8 (s, 1H, OH) and δ 10.2 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ 165.4; 161.0; 160.7; 155.8; 151.8; 149.2; 138.6; 135.5; 134.8; 127.8; 126.8; 123.9; 123.1; 122.4; 119.2; 116.8; 112.3; 62.4; 57.6; 35.2; 14.8.

Anal. Calcd. For $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.48; H, 4.80; N, 3.53.

(6-((4-Dimethylamino-benzylidene)-amino)-7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic Acid Ethyl Ester (**6k**).

Compound **6k** was obtained in 65% yield; mp: 201 °C; IR(KBr):

3445, 3358, 3215 (-OH), 2994 (-CH), 1714, 1676 (›C=O), 1598, 1597, 1575 (-C=C-), 1295 (-CO-O) and 1031 cm^{-1}; ^1H NMR: δ 1.22 (t, J=7.1Hz, 3H, CH_3-Et), δ 3.60 (s, 6H, $N(CH_3)_2$, δ 4.0 (s, 2H, CH_2-4) δ, δ 4.12 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.20 (s, 1H, H-3), δ 6.69 (s, 1H, H-8), δ 6.9 (d, 2H, arom), δ 7.31 (d, 2H, arom.), δ 7.8 (s, 1H, H-5), δ 8.6 (s, 1H, CH-N) and δ 9.9 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ 165.4; 161.0; 160.7; 155.8; 153.8; 150.2; 138.6; 135.5; 132.1; 132.0; 126.8; 123.9; 123.1; 117.2; 114.9; 114.8; 112.3; 62.4; 44.3; 44.3; 35.2; 14.8.

Anal. Calcd. For $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.96; H, 5.60; N, 7.09.

General Procedure.

(6-Oxo-2-aryl-6*H*-chromeno[6,7-*d*]oxazol-8-yl)-acetic Acid Ethyl Ester (**7a-k**).

The solutions of compounds **6a-k** (2 mmol) in glacial acetic acid (15 ml) were refluxed for 15 hours, cooled and poured into ice-cold water. The precipitates that formed were collected by filtration and recrystallized from ethanol.

General Procedure.

(6-Oxo-2-aryl-6*H*-chromeno[6,7-*d*]oxazol-8-yl)-acetic Acid Ethyl Ester (**7a-k**).

To a solution of compound **5** (0.57 g, 2 mmol) in glacial acetic acid (15 ml), the appropriate aromatic aldehyde (Ar-CHO, **a-k**, 2 mmol) was added and the mixture was refluxed for 12-15 hours, cooled and poured into ice-cold water. The precipitate formed was collected by filtration and recristallyzed.

(6-Oxo-2-phenyl-6*H*-chromeno(6,7-*d*)oxazol-8-yl)-acetic Acid Ethyl Ester (**7a**).

Compound **7a** was obtained in 52% yield; mp: 227 °C; IR(KBr):

3065, 2927 (-CH), 1724 (›C=O), 1637, 1572 (-C=C-), 1347 (-CO-O) and 1047 cm^{-1}; ^1H NMR: δ 1.15 (t, J=7.1Hz, 3H, CH_3-Et), δ 4.0 (s, 2H, CH_2-4), δ 4.14 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.3 (s, 1H, H-3), δ 6.91 (s, 1H, H-8), δ 7.0-7.5 (m, 5H, aromatic) and δ 7.69 (s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 165.4; 162.9; 160.7; 155.8; 151.8; 147.2; 138.6; 132.5; 132.5; 129.0; 127.8; 127.9; 126.1; 124.8; 117.2; 112.4; 104.2; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{20}H_{15}NO_5$: C, 68.76; H, 4.33; N, 4.01. Found: C, 68.72; H, 4.30; N, 3.98.

(2-(2-Hydroxy-phenyl-6-oxo-6*H*-chromeno(6,7-*d*)oxazol-8-yl)-acetic Acid Ethyl Ester (**7b**).

Compound **7b** was obtained in 46% yield; mp: 211 °C; IR(KBr):

3068, 2926 (-CH), 1702 (›C=O), 1620, 1569 (-C=C-), 1392 (-CO-O) and 1204 cm^{-1}; ^1H NMR: δ 1.20 (t, J=7.1Hz, 3H, CH_3-Et), δ 4.13 (s, 2H, CH_2-4), δ 4.15 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.30 (s, 1H, H-3), δ 6.92 (s, 1H, H-8), δ 7.0-7.7 (m, 4H, aromatic), δ 7.89 (s, 1H, H-5), δ 8.9 (s, 1H, CH-N) and δ 12.7 (s, 1H, OH-2'). ^{13}C NMR (DMSO-d_6): δ 165.4; 162.9; 160.7; 155.8; 155.3; 151.8; 147.2; 138.6; 131.5; 130.5; 124.1; 122.9; 121.8; 117.2; 114.6; 112.4; 104.2; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{20}H_{15}NO_6$: C, 65.75; H, 4.14; N, 3.83. Found: C, 65.73; H, 4.11; N, 3.80.

(2-(2-Chloro-phenyl)-6-oxo-6*H*-chromeno(6,7-*d*)oxazol-8-yl)-acetic Acid Ethyl Ester (**7c**).

Compound **7c** was obtained in 57% yield; mp: 182-183 °C; IR(KBr):

3062, 2981 (-CH), 1724 (›C=O), 1626, 1570 (-C=C-), 1343 (-CO-O) 1155 cm^{-1}; ^1H NMR: δ 1.18 (t, J=7.1Hz, 3H, CH_3-Et), δ 4.12 (s, 2H, CH_2-4), δ 4.14 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.30 (s, 1H, H-3), δ 6.90 (s, 1H, H-8), δ 7.48-759 (m, 4H, arom.) and δ 8.3 (s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 165.4; 162.9; 160.7; 155.3; 151.8; 147.2; 138.6; 137.5; 132.5; 130.6; 129.4; 128.7; 127.4; 124.1; 117.2; 112.4; 104.2; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{20}H_{14}ClNO_5$: C, 62.59; H, 3.68; N, 3.65. Found: C, 62.57; H, 3.65; N, 3.62.

(2-(3-Chloro-phenyl)-6-oxo-6*H*-chromeno(6,7-*d*)oxazol-8-yl)-acetic Acid Ethyl Ester (**7d**).

Compound **7d** was obtained in 62% yield; mp: 198 °C; IR(KBr):

3068, 2926 (-CH), 1719 (›C=O), 1630, 1570 (-C=C-), 1342 (-CO-O) and 1153 cm^{-1}; ^1H NMR: δ 1.18 (t, J=7.1Hz, 3H, CH_3-Et), δ 4.01 (s, 2H, CH_2-4), δ 4.12 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.29 (s, 1H, H-3), δ 6.90 (s, 1H, H-8), δ 7.55-7.64 (m, 4H, arom.) and δ 8.2 (s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 165.4; 162.9; 160.7; 155.3; 151.8; 147.2; 138.6; 135.5; 131.4; 130.2; 128.8; 128.3; 126.4; 124.1; 117.2; 112.4; 104.2; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{20}H_{14}ClNO_5$: C, 62.59; H, 3.68; N, 3.65. Found: C, 62.56; H, 3.64; N, 3.62.

(2-(2,3-Dihydroxy-phenyl)-6-oxo-6*H*-chromeno(6,7-*d*)oxazol-8-yl)-acetic Acid Ethyl Ester (**7e**).

Compound **7e** was obtained in 43% yield; mp: 257 °C; IR(KBr):

3409 (-OH), 3064, 2980 (-CH), 1713 (›C=O), 1625 (-C=C-), 1395 (-CO-O) and 1019 cm^{-1}; ^1H NMR: δ 1.19 (t, J=7.1 Hz, 3H, CH_3-Et), δ 4.04 (s, 2H, CH_2-4), δ 4.13 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.31 (s, 1H, H-3), δ 6.8 (s, 1H, H-8), δ 6.9-7.1 (m, 3H, arom.), δ 7.9 (s, 1H, H-5), δ 11.1 (s, 1H, OH) and δ 12.7 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ 165.4; 162.9; 160.7; 155.3; 151.8; 148.2; 147.2; 143.8; 138.6; 124.1; 123.4; 121.7; 117.8; 117.2; 113.9; 112.4; 104.2; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{20}H_{15}NO_7$: C, 62.99; H, 3.96; N, 3.67. Found: C, 62.96; H, 3.94; N,3.68.

(2-(2,4-Dihydroxy-phenyl)-6-oxo-6*H*-chromeno(6,7-*d*)oxazol-8-yl)-acetic Acid Ethyl Ester (**7f**).

Compound **7f** was obtained in 52% yield; mp: 225 °C; IR(KBr):

3447, 3352 (-OH), 3073, 2971 (-CH), 1712 (›C=O), 1605 (-C=C-), 1402 (-CO-O) and 1012 cm^{-1}; ^1H NMR: δ 1.20 (t, J=7.1Hz, 3H, CH_3-Et), δ 4.02 (s, 2H, CH_2-4), δ 4.12 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.29 (s, 1H, H-3), δ 6.9 (s, 1H, H-8), δ 6.9-7.1 (m, 3H, arom.), δ 7.6 (s, 1H, H-5), δ 11.4 (s, 1H, OH) and δ 13.7 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ 165.4; 162.9; 160.7; 159.8; 156.9; 155.3; 151.8; 148.2; 138.6; 130.4; 124.1; 123.4; 117.8; 110.8; 108.5; 105.4; 104.2; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{20}H_{15}NO_7$: C, 62.99; H, 3.96; N, 3.67.Found: C, 62.97; H, 3.95; N, 3.63.

2-(2,5-Dihydroxy-phenyl)-6-oxo-6*H*-chromeno(6,7-*d*)oxazol-8-yl)-acetic Acid Ethyl Ester (**7g**).

Compound **7g** was obtained in 38% yield; mp: 243 °C; IR(KBr):

3433, 3246 (-OH), 3000, 2959 (-CH), 1724, 1677 (›C=O), 1606 (-C=C-), 1391 (-CO-O) and 1018 cm^{-1}; ^1H NMR: δ 1.20 (t, J=7.1 Hz, 3H, CH_3-Et), δ 4.03 (s, 2H, CH_2-4), δ 4.13 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.3 (s, 1H, H-3), δ 6.8 (s, 1H, H-8), δ 6.83-7.1 (m, 3H, arom.), δ 7.62 (s, 1H, H-5), δ 10.93 (s, 1H, OH) and δ 12.49 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ 165.4; 162.9; 160.7; 155.3; 151.8; 151.6; 148.4; 148.2; 138.6; 123.4; 117.8; 117.8; 117.3; 114.4; 110.8; 105.4; 104.2; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{20}H_{15}NO_7$: C, 62.99; H, 3.96; N, 3.67. Found: C, 62.96; H, 3.92; N, 3.66.

(2-(3,5-Dihydroxy-phenyl)-6-oxo-6*H*-chromeno(6,7-*d*)oxazol-8-yl)-acetic Acid Ethyl Ester (**7h**).

Compound **7h** was obtained in 54% yield; mp: 256 °C; IR(KBr):

3413, 3250 (-OH), 3020, 2919 (-CH), 1734, 1697 (›C=O), 1601 (-C=C-), 1390 (-CO-O) and 1023 cm^{-1}; ^1H NMR: δ 1.20 (t, J=7.1Hz, 3H, CH_3-Et), δ 4.03 (s, 2H, CH_2-4), δ 4.14 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.3 (s, 1H, H-3), δ 6.8 (s, 1H, H-8), δ 6.83-7.1 (m, 3H, arom.), δ 7.64 (s, 1H, H-5), δ 11.0 (s, 1H, OH) and δ 12.50 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ 165.4; 162.9; 160.7; 155.3; 151.8; 151.6; 148.4; 148.2; 138.6; 123.4; 117.8; 117.8; 117.3; 114.4; 110.8; 105.4; 104.2; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{20}H_{15}NO_7$: C, 62.99; H,3.96; N,3.67. Found: C, 62.97; H, 3.94; N, 3.67.

(6-Oxo-2-(3-phenoxy-phenyl)-6*H*-chromeno(6,7-*d*)oxazol-8-yl)acetic Acid Ethyl Ester (**7i**).

Compound **7i** was obtained in 60% yield; mp: 237 °C; IR(KBr):

3067, 2926 (-CH), 1726 (›C=O), 1631, 1591 (-C=C-), 1268 (-CO-O) and 1022 cm^{-1}; ^1H NMR: δ 1.21 (t, J=7.1Hz, 3H, CH_3-Et), δ 4.0 (s, 2H, CH_2-4), δ 4.13 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.3 (s, 1H, H-3), δ 6.8 (s, 1H, H-8), δ 6.83-7.1 (m, 9H, arom.) and δ 7.64 (s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 165.4; 161.0; 160.4; 157.7; 157.7; 155.8; 153.4; 152.2; 137.5; 136.8; 129.6; 128.8; 126.8; 124.8; 122.4; 121.6; 117.9; 117.7; 117.5; 116.4; 114.9; 114.8; 112.2; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{26}H_{19}NO_6$: C, 70.74; H, 4.34; N, 3.17. Found: C, 70.71; H, 4.32; N, 3.13.

(2-(4-Hydroxy-3-methoxy-phenyl)-6-oxo-6*H*-chromeno(6,7-*d*)oxazol-8-yl)-acetic Acid Ethyl Ester (**7j**).

Compound **7j** was obtained in 62% yield; mp: 260 °C; IR(KBr):

3485 (-OH), 3073, 2984 (-CH), 1731 (›C=O), 1631, 1597, 1574 (-C=C-), 1293 (-CO-O) and 1049 cm^{-1}; ^1H NMR: δ 1.19 (t, J=7.1Hz, 3H, CH_3-Et), δ 3.87 (s, 3H, OCH_3), δ 4.01 (s, 2H, CH_2-4), δ 4.13 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.28 (s, 1H, H-3), δ 6.88 (s, 1H, H-8), δ 6.92 (d, 1H, arom.), δ 7.36 (d, 1H, arom.), δ 7.44 (s, 1H, arom.), δ 7.7 (s, 1H, H-5) and δ 10.2(s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ 165.4; 162.9; 160.7; 155.3; 152.2; 151.8; 148.2; 145.7; 138.6; 130.4; 124.1; 121.4; 119.9; 117.8; 112.8; 108.5; 105.4; 104.2; 62.4; 35.2; 14.8.

Anal. Calcd. For $C_{21}H_{17}NO_7$: C, 63.80; H, 4.33; N, 3.54. Found: C, 63.77; H, 4.30; N, 3.51.

(2-(4-Dimethylamino-phenyl)-6-oxo-6*H*-chromeno(6,7-*d*)oxazol-8-yl)-acetic Acid Ethyl Ester (**7k**).

Compound **7k** was obtained in 65% yield; mp: 268 °C; IR(KBr):

2994(-CH), 1714, 1676 (›C=O), 1598, 1597, 1575 (-C=C-), 1295 (-CO-O) and 1031 cm^{-1}; ^1H NMR: δ 1.22 (t, J=7.1Hz, 3H, CH_3-Et), δ 3.60 (s, 6H, $N(CH_3)_2$, δ 4.0 (s, 2H, CH_2-4), δ 4.12 (q, J=7.1Hz, 2H, CH_2-Et), δ 6.20 (s, 1H, H-3), δ 6.69 (s, 1H, H-8), δ 6.9 (d, 2H, arom.), δ 7.31 (d, 2H, arom.) and δ 7.8 (s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 165.4; 161.0; 160.7; 155.8; 150.8; 150.2; 146.9; 138.6; 128.9; 128.9; 124.3.1; 119.2; 116.7; 115.9; 115.8; 112.3; 104.8; 62.4; 44.3; 44.3; 35.2; 14.8.

Anal. Calcd. For $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14. Found: C, 67.31; H, 5.12; N, 7.11.

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