An Aminoisoflavone – Salicyloylindole Ring Transformation

Werner Löwe*, Sonja Witzel, Silvia Tappmeyer and Rica Albuschat

Institute of Pharmacy, Free University of Berlin, Königin-Luise-Strasse 2+4, 14195 Berlin, Germany

Received October 27, 2003

A series of 2'-nitroisoflavones **8**-**10**, **15**, **22**, **27** and **28** was prepared *via* the (2-nitro-phenyl)-acetic acids **1**, **13**, **19** and **25**. In order to obtain the corresponding 2'-aminoisoflavones the reduction of **8**-**10**, **15**, **22**, **27** and **28** was undertaken. Surprisingly, new 3-salicyloylindoles instead of the expected 2'-aminoisoflavones were the main reduction products. In the following paper the preparation of the 2'-nitroisoflavones **8**-**10**, **15**, **22**, **27** and **28** as well as the reduction experiments obtaining the 2'-aminoisoflavones **33** and **35** and the 3-salicyloylindoles **29**-**32**, **34** and **36** will be described. Furthermore, a possible mechanism responsible for the formation of the 3-salicyloylindoles from 2'-nitroisoflavones under reductive conditions will be discussed.

J. Heterocyclic Chem., **41**, 317 (2004).

In view of useful biological activities of isoflavones as selective estrogen receptor modulators (SERMs) [1] experiments were undertaken to obtain 2'-amino-isoflavones from the corresponding 2'-nitroisoflavones. It was observed that the 2'-nitroisoflavones as precursors of 2'-aminoisoflavones are of special interest since they provide access to a variety of 3-salicyloylindoles *via* a ring transformation reaction. The 2'-nitroisoflavones described in this paper were prepared from different starting materials.

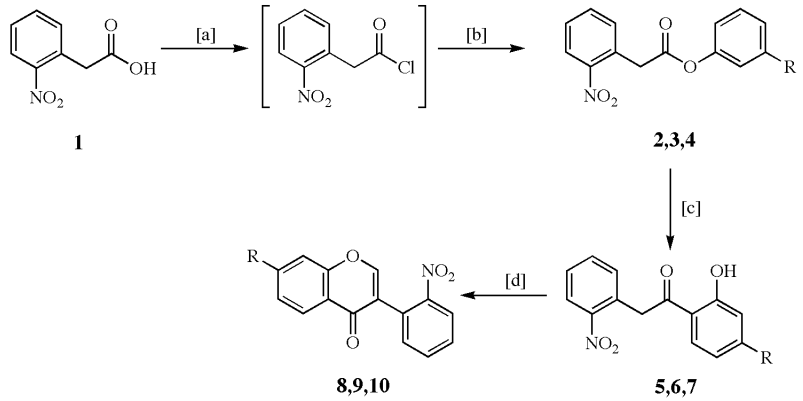
In the case of the 2'-nitroisoflavones **8**-**10** with different substituted chromone rings the synthesis starts with the commercially available (2-nitrophenyl)-acetic acid **1**, which was converted into the corresponding phenacylchloride by reaction with oxalylchloride. The following esterification of the phenacylchloride with 3-methyl-, 3-chloro- or 3-fluoro-phenol, respectively, led to the phenyl acetates **2**-**4**. The compounds **2**-**4** were subsequently converted into the corresponding ethanone derivatives **5**-**7** by a Fries rearrangement reaction in the presence of aluminium chloride. Finally, the 2'-nitroisoflavones **8**-**10** were obtained by reflux heating of the ketones **5**-**7** in the presence of *N,N*-dimethylformamide dimethyl acetal (Scheme 1).

In the case of the 2'-nitroisoflavones **15**, **22** and **27** with different substituted 3-phenyl rings the substituted (2-nitrophenyl)-acetic acid derivatives **13**, **19** and **25** were needed, which had to be prepared first. Therefore the corresponding phenylacetonitriles **12**, **18** and **24** were synthesized and afterwards hydrolyzed to the desired phenylacetic acids **13**, **19** and **25**.

As starting material for the synthesis of the 2'-nitroisoflavone **15** the phenylacetonitrile **12** had to be prepared by the reaction of 1-chloro-4-nitrobenzene (**11**) with chloroacetonitrile (Scheme 2) [2]. The hydrolysis of **12** under acid conditions led to the chlorine substituted phenylacetic acid **13**. The ethanone **14** was then obtained by the Friedl-Crafts alkanoylation of **13** and resorcinol in the presence of boron trifluoride diethylether complex. The ring closure of the ketone **14** by reaction with *N,N*-dimethylformamide dimethyl acetal produced the desired 2'-nitroisoflavone **15** (Scheme 2).

In the case of the 2'-nitroisoflavone **22** the synthesis starts with the phenylacetonitrile **18**, which had to be prepared in a multistage procedure according to *Vlattas* [3] as follows: reaction of 4-chloro-2-nitrotoluene (**16**) with diethyloxalate in the presence of sodium methoxide led to

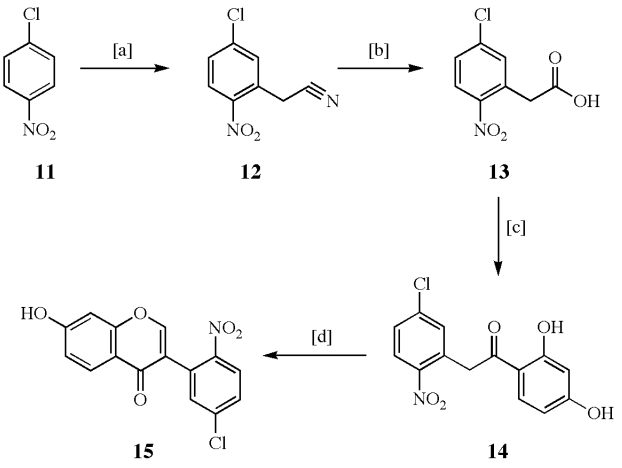
Scheme 1



1 **2,3,4** **5,6,7** **8,9,10**

[a] $ClCOCOCl/CH_2Cl_2$, r.t.; [b] phenol derivative/$N(Et)_3$/$O(Et)_2$, reflux; [c] $AlCl_3$, 80 °C up to 120-160 °C; [d] DMF-acetal/THF, reflux
2,5,8: R = CH_3; **3,6,9**: R = Cl; **4,7,10**: R = F

Scheme 2

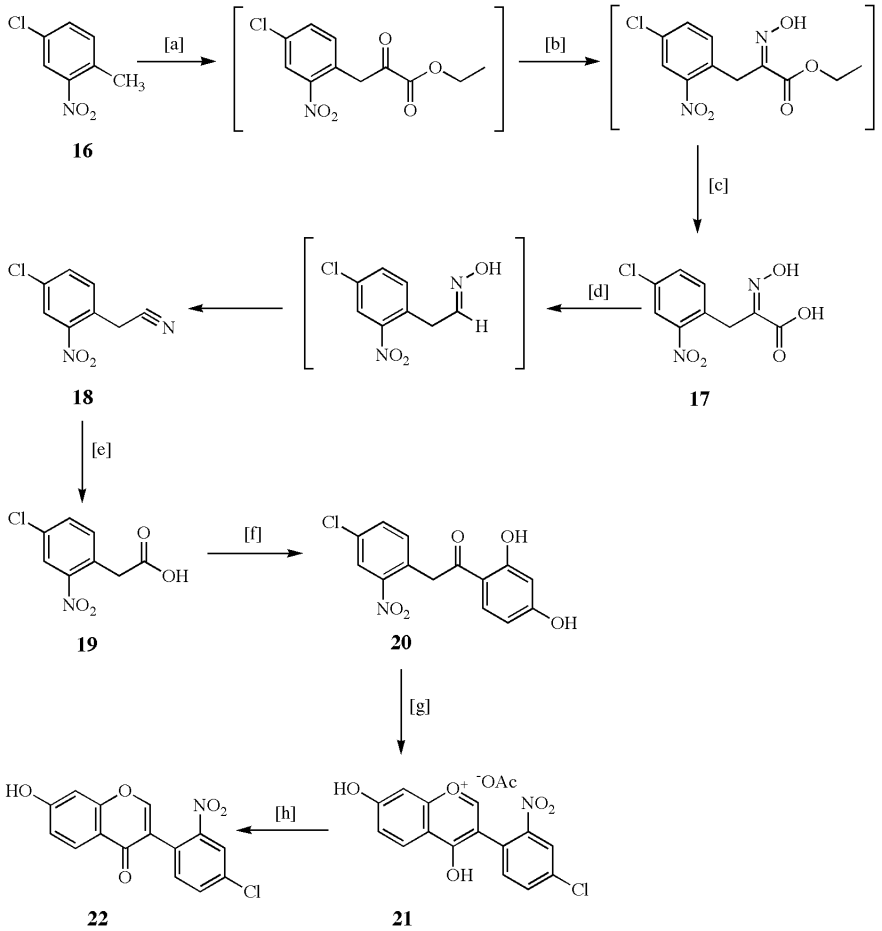


[a] $ClCH_2CN/tBuOK/THF$, -20 °C; [b] H_2SO_4/H_2O, reflux; [c] resorcinol/$BF_3{\cdot}O(Et)_2$, 90 °C; HF, reflux/AcOH, reflux

the 2-oxo-propionate ester. The *in situ* addition of hydroxylamine yielded the corresponding 2-hydroxyimino derivative and the following *in situ* saponification of the ester moiety gave the 2-hydroxyiminopropionic acid derivative **17**. The heating of **17** at reflux in acetic acid led to the desired phenylacetonitrile **18**, which was subsequently hydrolyzed to obtain the corresponding phenylacetic acid derivative **19**.

The Friedel-Crafts alkanoylation of **19** and resorcinol again produced the ethanone **20**. Subsequently, the ring closure reaction to obtain the isoflavone **22** was carried out by reaction of the ketone **20** with *N,N*-dimethylformamide dimethyl acetal. Surprisingly, the following heating of the resulting reaction mixture in acetic acid according to the synthesis of the related isoflavone **15** to obtain the isoflavone **22** only yielded the isoflavylium acetate **21**. The corresponding free isoflavone **22** could only be obtained by extraction of the reaction mixture with ethyl acetate after neutralization (Scheme 3).

Scheme 3



[a] $(CO_2Et)_2$/MeONa/EtOH, reflux; [b], H_2NOH, 50 °C/pH7, r.t.; [c] H_2SO_4, pH1, r.t.; [d] AcOH/H_2O, 90 °C; [e] H_2SO_4/H_2O, reflux; [f] resorcinol/$BF_3{\bullet}O(Et)_2$, 90 °C; [g] DMF-acetal/THF, reflux/AcOH, reflux; [h] aq Na_2CO_3/pH6-7/AcOEt

The methoxy substituted 2'-nitroisoflavone **27** was prepared starting with the commercially available 4-chloro-3-nitroanisole (**23**). For that purpose **23** first was converted into the corresponding ethyl cyano-phenyl-acetate derivative by reflux heating with ethyl cyanoacetate in the presence of sodium hydride and cesium fluoride. The desired nitrile **24** was obtained by the following heating of the ethyl cyano-phenyl-acetate in a saturated aqueous solution of sodium carbonate [4]. Subsequently, the phenylacetonitrile **24** was hydrolyzed by reflux heating in sulfuric acid to obtain the corresponding phenylacetic acid **25**.

According to the syntheses of ketones **14** and **20** the ethanone **26** could be obtained by the Friedel-Crafts alkanoylation of the phenylacetic acid **25** and resorcinol in the presence of boron trifluoride diethylether complex. Finally, the ketone **26** was converted into the 2'-nitroisoflavone **27** by reflux heating in the presence of *N,N*-dimethylformamide dimethyl acetal (Scheme 4).

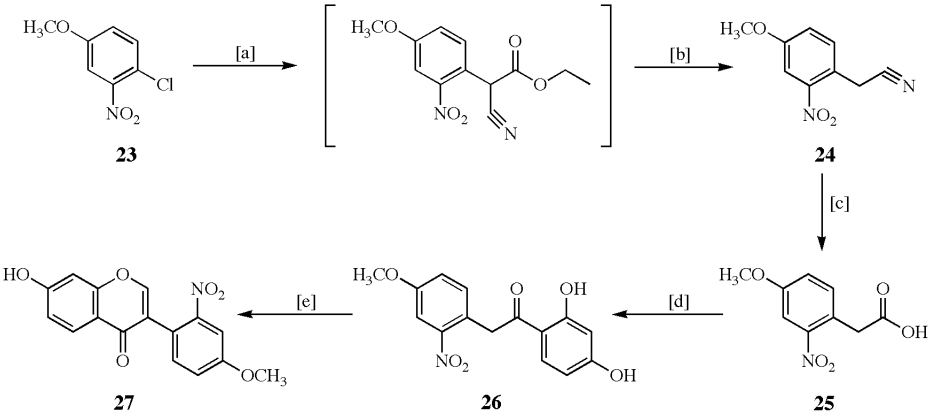
For the reduction of the 2'-nitroisoflavones **8**-**10**, **15**, **22**, **27** and **28** two different methods were used. The isoflavones **8**-**10** as well as **27** were reduced using palladium on carbon in ethanol in the presence of cyclohexene [5]. The reduction of **8**-**10** only yielded the 3-salicyloylindoles **29**, **30** and **31** (Scheme 6).

By the reduction of **15** and **21** using palladium on carbon a cleavage of the chlorine substituent was examined. Because of that, the reduction of **15** and **21** was carried out in acetic acid using zinc dust to give the 3-salicyloylindoles **32** and **34** (Scheme 6).

Surprisingly, the reduction of the 2'-nitroisoflavone **27** with palladium on carbon led to the *N*-alkylated 3-salicyloylindole **36** as well as the corresponding 2'-aminoisoflavone **35**. Longer reaction time led to a higher yield of the desired indole derivative **36** (Scheme 6).

The 2'-aminoisoflavone **33** was obtained by the reduction of the isoflavylium acetate **21**. After a reduction time

Scheme 4



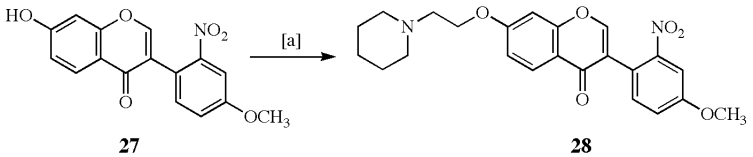
23 **24** **25** **26** **27**

[a] NaH/$NCCH_2CO_2Et$/DMF/CsF, 70 °C, r.t./H_2O/H_2SO_4/pH4/AcOEt;
[b] Na_2CO_3, 55 °C; [c] H_2SO_4/H_2O, reflux;
[d] resorcinol/BF_3·$O(Et)_2$, 90 °C ; [e] DMF-acetal/THF, reflux/AcOH, reflux

The 7-(2-piperidin-1-yl-ethoxy)-isoflavone **28** was easily obtained by the selective alkylation of the 7-hydroxy function of **27** with 1-(2-chloroethyl)-piperidinium chloride in acetonitrile in the presence of potassium carbonate (Scheme 5).

of 30 minutes only the 2'-aminoisoflavone **33** was detectable (Scheme 7). A reduction time of 75 minutes produced both: the 2'-aminoisoflavone **33** as well as the 3-salicyloylindole **34**, which could be separated by a combination of column chromatography and recrystallization.

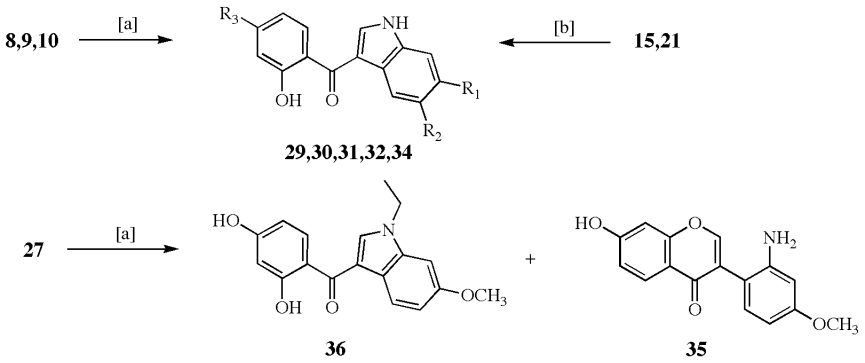
Scheme 5



27 **28**

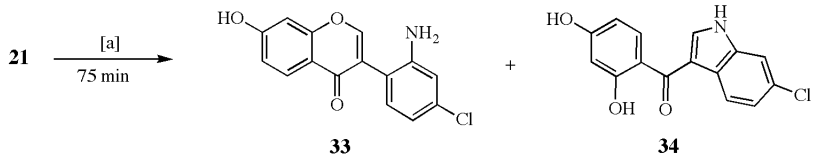
[a] 1-(2-chloro-ethyl)-piperidinium chloride/K_2CO_3/MeCN, reflux

Scheme 6



[a] Pd/C (10%)/EtOH/cyclohexene, reflux; [b] Zn/AcOH, reflux
29: $R_1 = R_2 = H$, $R_3 = CH_3$; **30**: $R_1 = R_2 = H$, $R_3 = Cl$; **31**: $R_1 = R_2 = H$, $R_3 = F$;
32: $R_1 = H$, $R_2 = Cl$, $R_3 = OH$; **34**: $R_1 = Cl$, $R_2 = H$, $R_3 = OH$

Scheme 7

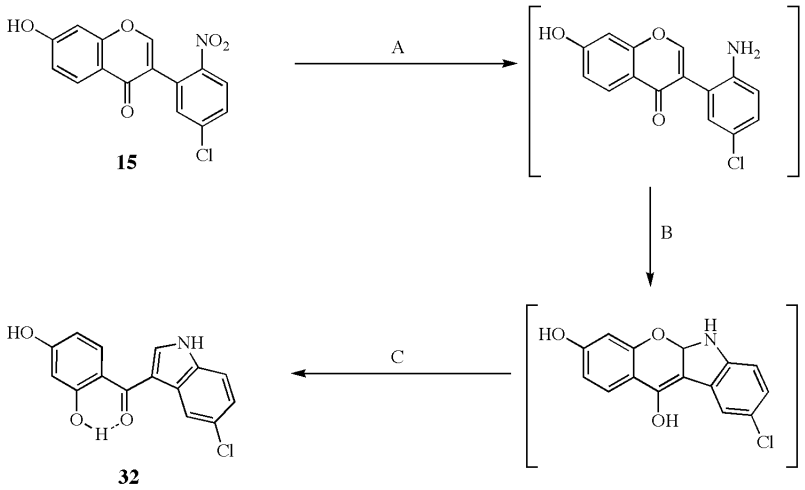


[a] Zn/AcOH, reflux

The ring transformation probably proceeds as follows: The first intermediate product occurring during the reduction of 2'-nitroisoflavones has to be the corresponding 2'-aminoisoflavone (Scheme 8: *A*). In two cases (reduction of **21** and **27**) the 2'-aminoisoflavones **33** and **35** could be separated as reduction products. For the first step of the ring transformation to salicyloylindoles we discuss an intramolecular Michael-type reaction between the aromatic amino function of the intermediate 2'-aminoisoflavone and the electrophilic C2-position of the 4*H*-chromone system (Scheme 8: *B*). The postulated intermediate tetracyclic benzopyranoindoles undergo ring opening to the energetic more convenient 3-salicyloylindoles (Scheme 8: *C*), which are additionally stabilized by the intramolecular hydrogen bond of the salicylic moiety (illustrated by a dashed line in Scheme 8).

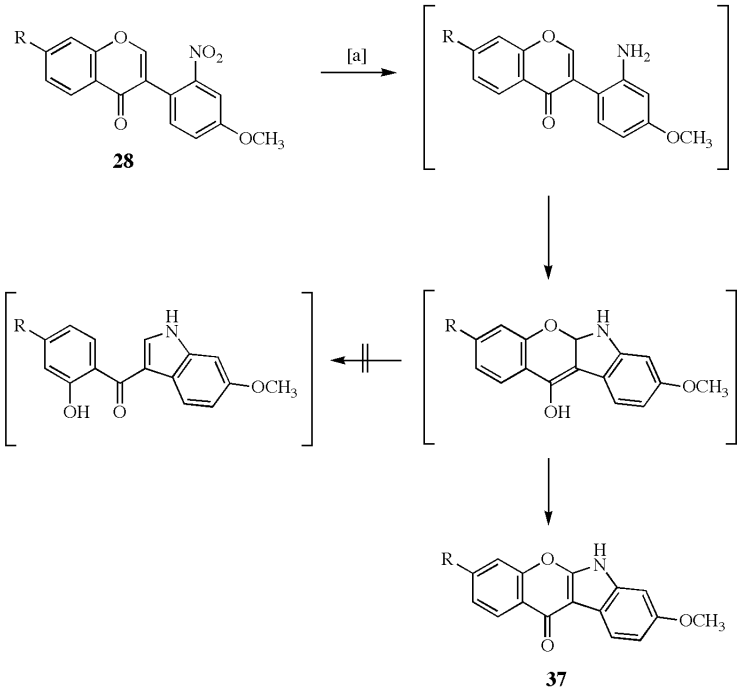
The postulated mechanism of the ring transformation is illustrated in Scheme 8 taking the reduction of **15** resulting

Scheme 8



A reduction of the 2'-nitro group
B ring closure (Michael-type reaction between the 2'-amino group and the chromone-C2)
C ring opening

Scheme 9



[a] Zn/AcOH, reflux
R = (2-piperidin-1-yl-ethoxy)

in the formation of the 3-salicyloylindole **32** as an example.

An oxidation product of the postulated tetracyclic intermediate benzopyranoindole (Scheme 8) could actually be separated after the reduction of the 7-(2-piperidin-1-yl-ethoxy)-isoflavone derivative **28** with zinc dust. Surprisingly, the reduction of **28** neither yielded the expected 3-salicyloylindole nor the 2'-aminoisoflavone, but only the tetracyclic compound **37** (Scheme 9).

Of course, the formation of **37** is not possible under reductive conditions; therefore we assume that **37** can be formed during the isolation process by the reaction of the first resulting benzopyranoindole with oxygen (Scheme 9).

EXPERIMENTAL

Melting points (mp) were determined on a Lindström apparatus and are uncorrected. The infrared (ir) spectra were recorded on a Perkin-Elmer 297 spectrometer. The nuclear magnetic resonance (^{1}H nmr) spectra were recorded at 400 MHz on a Bruker AC 300 spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to tetramethyl silane as the internal standard. The coupling constants (J) are quoted in Hz. The ^{13}C nmr spectra were recorded on a DPX 400 BRUKER. The mass spectra (electron impact) were obtained on a CH-7A-Varian MAT (70 eV) and the mass spectra (fast atom bombardment) were obtained on a CH-5-DF-MAT-Varian (80 eV). Elementar analyses were performed on Perkin-Elmer Elementar-Vario EL.

All reagents were fresh, commercial grade chemicals. The compounds 2-(2-nitro-phenyl)-acetic acid (**1**), 1-chloro-4-nitro-benzene (**11**), 4-chloro-2-nitro-toluene (**16**) as well as 4-chloro-3-nitro-anisole (**23**) were commercially available reagents.

(3-Methyl-phenyl)-2-nitro-phenyl Acetate (**2**).

Oxalyl chloride (42.0 g, 0.3 mole) was added to a dilution of 20.0 g (0.1 mole) 2-(2-nitro-phenyl)-acetic acid (**1**) in 200 mL dry dichloromethane and the mixture was stirred for 15 hours at room temperature. Subsequently, the solvent was removed in vacuo. The raw product was dissolved in 75 mL dry diethyl ether and added dropwise to a mixture of 3-methylphenol derivative (11.9 g, 0.1 mole) and 11.1 g (15 mL, 0.1 mole) triethylamine in 150 mL diethyl ether. The mixture was then heated at reflux for an hour. The precipitate was filtered off and the organic phase was washed with a saturated solution of sodium bicarbonate and then again with water. After drying (magnesium sulfate) the solvent was removed in vacuo. Compound **2** was obtained as brown oil, yield 24.4 g (82%); ir (sodium chloride): CO 1758 cm^{-1}; ^{1}H nmr (deuterochloroform): δ 8.20 (d, 1H, J = 12.4 Hz, phenyl), 7.63 (dt, 1H, J = 0.9, 7.5 Hz, phenyl), 7.43, 7.52 (m, 2H, phenyl), 7.21, 7.25 (m, 1H, phenyl), 6.98 (d, 1H, J = 7.9 Hz, phenyl), 6.90 (d, 1H, J = 11.1 Hz, phenyl), 6.60, 6.63 (m, 1H, phenyl), 4.24 (s, 2H, CH_2), 2.33 ppm (s, 3H, CH_3); ms (electron impact, 70 eV): m/z 271 (M^+, 1.2%).

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.36; H, 4.95; N, 5.27.

(3-Chloro-phenyl)-2-nitro-phenyl Acetate (**3**).

Compound **3** was obtained similarly to compound **2** from 20.0 g (0.1 mole) 2-(2-nitro-phenyl)-acetic acid (**1**) and 14.2 g (0.1 mole) 3-chloro-phenol. Compound **3** was obtained as brown crystals, yield 25.5 g (79%), mp 85 ºC; ir (potassium bromide): CO 1768 cm^{-1}; ^{1}H nmr (deuterochloroform): δ 8.19 (dd, 1H, J =

8.1, 0.9 Hz, phenyl), 7.65 (dt, 1H, J = 7.5, 1.2 Hz, phenyl), 7.53 (dt, 1H, J = 7.9, 1.3 Hz, phenyl), 7.44 (d, 1H, J = 7.4 Hz, phenyl), 7.25.7.31 (m, 1H, phenyl), 7.19.7.22 (m, 1H, phenyl), 7.15 (t, 1H, J = 1.9 Hz, phenyl), 7.03 (td, 1H, J = 8.0, 0.9 Hz, phenyl), 4.24 ppm (s, 2H, CH_2); ms (electron impact, 70 eV): m/z 291 (M^+, 1.2%, ^{35}Cl).

Anal. Calcd. for $C_{14}H_{10}ClNO_4$: C, 57.65; H, 3.46; N, 4.80. Found: C, 57.75; H, 3.47; N, 5.04.

(3-Fluoro-phenyl)-2-nitro-phenyl Acetate (**4**).

Compound **4** was obtained similarly to compound **2** from 10.0 g (55.2 mmoles) 2-(2-nitro-phenyl)-acetic acid (**1**) and 6.3 g (55.2 mmoles) 3-fluoro-phenol. Compound **4** was obtained as pale brown crystals, yield 14.1 g (93%), mp 83 ºC; ir (potassium bromide): CO 1769 cm^{-1}; ^1H nmr (deuterochloroform): δ 8.20 (d, 1H, J = 7.0 Hz, phenyl), 7.65 (t, 1H, J = 7.5 Hz, phenyl), 7.55 (t, 1H, J = 8.0 Hz, phenyl), 7.46 (d, 1H, J = 8.0 Hz, phenyl), 7.36 (m, 1H, phenyl), 6.86.7.00 (m, 3H, phenyl), 4.22 ppm (s, 2H, CH_2); ms (electron impact, 70 eV): m/z 275 (M^+, 3.2%).

Anal. Calcd. for $C_{14}H_{10}FNO_4$: C, 61.09; H,3.66; N, 5.09. Found: C, 61.05; H, 3.71; N 4.95.

1-(2-Hydroxy-4-methyl-phenyl)-2-(2-nitro-phenyl)-ethanone (**5**).

At a temperature of 80 ºC 1.0 g (7.4 mmoles) aluminium chloride was added to compound **2** (1.0 g, 3.7 mmoles). Subsequently, the temperature was raised to 160 ºC and maintained for 90 minutes. After cooling it was hydrolyzed with ice/hydrochloric acid. The precipitate was sucked off, removed with 10 mL ethyl acetate and filtered. The filtrate was constringed under vacuum by half and subsequently purified by flash chromatography (silica gel, ethyl acetate). Compound **5** was obtained as beige crystals, yield 0.7 g (23%), mp 134 ºC; ir (potassium bromide): CO 1624 cm^{-1}; ^1H nmr (deuterochloroform): δ 11.83 (s, 1H, OH, deuterium oxide-exchangeable), 8.17 (d, 1H, J = 8.1 Hz, phenyl), 7.77 (d, 1H, J = 8.1 Hz, phenyl), 7.63 (t, 1H, J = 7.4 Hz, phenyl), 7.51 (t, 1H, J = 7.5 Hz, phenyl), 7.35 (d, 1H, J = 7.5 Hz, phenyl), 6.79 (t, 2H, J = 8.4 Hz, phenyl), 4.74 (s, 2H, CH_2), 2.40 ppm (s, 3H, CH_3); ms (electron impact, 70 eV): m/z 271 (M^+, 3.4%, ^{35}Cl).

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.29; H, 4.82; N, 5.01.

1-(4-Chloro-2-hydroxy-phenyl)-2-(2-nitro-phenyl)-ethanone (**6**).

Compound **6** was obtained similarly to **5** from 1.0 g (7.4 mmoles) aluminium chloride and 1.0 g **3** (3.4 mmoles) as pale brown crystals, yield 120 mg (12%), mp 117 ºC; ir (potassium bromide): CO 1650 cm^{-1}; ^1H nmr (deuterochloroform): δ 11.94 (s, 1H, OH, deuterium oxide-exchangeable), 8.20 (d, 1H, J = 5.3 Hz, phenyl), 7.83 (d, 1H, J = 8.6 Hz, phenyl), 7.66 (dt, J = 7.5, 0.8 Hz, 1H, phenyl), 7.54 (t, 1H, J = 8.2 Hz, phenyl), 7.36 (d, 1H, J = 7.5 Hz, phenyl), 7.03 (d, 1H, J = 2.0 Hz, phenyl), 6.96 (dd, 1H, J = 1.9, 8.6 Hz, phenyl), 4.74 ppm (s, 2H, CH_2); ms (electron impact, 70 eV): m/z 291 (M^+, 2.5%, ^{35}Cl).

Anal. Calcd. for $C_{14}H_{10}ClNO_4$: C, 57.65; H, 3.46; N, 4.80. Found: C, 57.42; H, 3.55; N, 4.61.

1-(4-Fluoro-2-hydroxy-phenyl)-2-(2-nitro-phenyl)-ethanone (**7**).

At a temperature of 85 ºC 0.92 g (6.8 mmoles) alumiunium chloride was added to **4** (1.0 g, 3.6 mmoles). Subsequently, the temperature was raised to 120 ºC and maintained for 40 minutes. After cooling it was hydrolized with ice/hydrochloric acid. The resulting solid was collected, suspended in a solution of sodium hydroxide (10%) and filtered off again. The filtrate was neutralized with acetic acid (50%). The obtained beige crystals were collected and purified by flash chromatography (silica gel, ethyl acetate) to yield 0.4 g (40%) **7** as beige crystals, mp 117 ºC; ir (potassium bromide): CO 1638 cm^{-1}; ^1H nmr (deuterochloroform): δ 12.14 (s, 1H, OH, deuterium oxide-exchangeable), 8.20 (d, 1H, J = 8.0 Hz, phenyl), 7.95 (m, 1H, phenyl), 7.66 (t, 1H, J = 6.0 Hz, phenyl), 7.56 (t, 1H, J = 7.0 Hz, phenyl), 7.37 (d, 1H, J = 6.0 Hz, phenyl), 7.73 (m, 2H, phenyl), 4.74 ppm (s, 2H, CH_2); ms (electron impact, 70 eV): m/z 275 (M^+, 3.5%).

Anal. Calcd. for $C_{14}H_{10}FNO_4$: C, 61.09; H, 3.66; N, 5.09. Found C, 61.16; H, 3.76; N, 5.11.

7-Methyl-3-(2-nitro-phenyl)-chromen-4-one (**8**).

The ethanone **5** (0.6 g, 2.2 mmoles) was heated at reflux in 15 mL N,N-dimethylformamide dimethyl acetale for a few minutes. After cooling the resulting solid was collected and recrystallized from methanol. Compound **8** was obtained as beige crystals, yield 0.4 g (71%), mp 188 ºC; ir (potassium bromide): CO 1641 cm^{-1}; ^1H nmr (deuterochloroform): δ 8.12 (d, 1H, J = 8.1 Hz, chromone), 8.09 (d, 1H, J = 8.4 Hz, phenyl), 8.00 (s, 1H, chromone), 7.67 (dt, 1H, J = 0.7, 6.7 Hz, chromone), 7.56 (dt, 1H, J = 0.9, 7.7 Hz, phenyl), 7.37 (dd, 1H, J = 0.7, 7.5 Hz, chromone), 7.24 (d, 2H, J = 10.1 Hz, phenyl), 2.51 ppm (s, 3H, CH_3); ms (electron impact, 70 eV): m/z 281 (M^+, 0.5%).

Anal. Calcd. for $C_{16}H_{11}NO_4$: C, 68.32; H, 3.94; N,4.98; Found: C, 68.14; H, 4.03; N, 4.81.

7-Chloro-3-(2-nitro-phenyl)-chromen-4-one (**9**).

The ethanone **6** (1.3 g, 4.4 mmoles) was heated at reflux in 20 mL N,N-dimethylformamide dimethyl acetale for a few minutes. After cooling the resulting solid was collected and recrystallized from methanol. Compound **9** was obtained as beige crystals, yield 0.9 g (71%), mp 163 ºC; ir (potassium bromide): CO 1648 cm^{-1}; ^1H nmr (deuterochloroform): δ 8.18 (d, 1H, J = 8.5 Hz, chromone), 8.12 (d, 1H, J = 8.2 Hz, phenyl), 8.01 (s, 1H, chromone), 7.68 (d, 1H, J = 0.8, 7.5 Hz, chromone), 7.59 (dd, 1H, J = 1.1, 7.8 Hz, chromone), 7.53 (d, 1H, J = 1.7 Hz, phenyl), 7.39 ppm (dt, 2H, J = 1.8, 8.6 Hz, phenyl); ms (electron impact, 70 eV): m/z 301 (M^+, 0.3%, ^{35}Cl).

Anal. Calcd. for $C_{15}H_8Cl\,NO_4$: C, 59.72; H ,2.67; N, 4.64. Found: C, 59.47; H, 2.66; N 4.72.

7-Fluoro-3-(2-nitro-phenyl)-chromen-4-one (**10**).

The ethanone **7** (360 mg, 1.4 mmoles) was heated at reflux in 10 mL N,N-dimethylformamide dimethyl acetale for a few minutes. After cooling the resulting solid was collected and recrystallized from methanol. Compound **10** was obtained as yellow crystals, yield 0.3 g (80%), mp 208 ºC; ir (potassium bromide): CO 1649, 1618 cm^{-1}; ^1H nmr (deuterochloroform): δ 8.27 (dd, 1H, J = 6.3, 2.5 Hz, chromone), 8.12 (dd, 1H, J = 1.2, 8.1 Hz, phenyl), 8.02 (s, 1H, chromone), 7.69 (dd, 1H, J = 1.2, 7.5 Hz, chromone), 7.59 (dd, 1H, J = 1.4, 7.9 Hz, chromone), 7.38 (ddd, 1H, J = 1.3, 6.2 Hz, phenyl), 7.14,7.21 ppm (m, 2H, phenyl); ms (electron impact, 70 eV): m/z 285 (M^+, 0.2%).

Anal. Calcd. for $C_{15}H_8FNO_4$: C, 63.15; H, 2.83; N, 4.91. Found: C, 63.21; H, 2.98; N 4.89.

(5-Chloro-2-nitro-phenyl)-acetonitrile (**12**).

A mixture of 1.6 g (10 mmoles) 1-chloro-4-nitro benzene (**11**) and 0.8 g (10 mmoles) chloro-acetonitrile was dissolved in 20 mL tetrahydrofuran and added dropwise to a cooled (–20 ºC) sus-

pension of 2.5 g (20 mmoles) potassium tert-butylate in dry tetrahydrofuran (20 mL). The reaction was quenched by adding 80 mL of aqueous sulfuric acid (10%, v/v) and the mixture was extracted with dichloromethane. The combined organic layers were washed with water, dried (sodium sulfate) and evaporated. The oily raw product was purified by column chromatography on silica gel (ethyl acetate/n-hexane 1:1, v/v) to give 820 mg (41%) of **12** as pale yellow crystals, mp 87 ºC; ir (potassium bromide): CN 2250 cm^{-1}; ^1H nmr (deuterochloroform): δ 8.20 (d, 1H, J = 8.8 Hz, phenyl), 7.84 (d, 1H, J = 2.2 Hz, phenyl), 7.76 (dd, 1H, J = 2.2, 8.8 Hz, phenyl), 4.34 ppm (s, 2H, CH_2); ms (electron impact, 70 eV): m/z 196 (M^+, 78%, ^{35}Cl).

Anal. Calcd. for $C_8H_5ClN_2O_2$: C, 48.88; H, 2.56; N, 14.25. Found: C, 48.86; H, 2.56; N, 14.25.

(5-Chlor-2-nitro-phenyl)-acetic Acid (**13**).

The nitrile **12** (6.0 g, 31 mmoles) was heated at reflux in a mixture of 90 mL water and 60 mL conc. sulfuric acid water for 20 minutes. The reaction mixture was then poured onto ice. The solid was collected, washed with water and purified by flash chromatography (silica gel, ethyl acetate/ethanol 9:1, v/v). Compound **13** was obtained as white crystals, yield 4.0 g (61%), mp 159 ºC; ir (potassium bromide): OH 3551, 3467, 3413, CO 1709 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.63 (s, 1H, COOH, deuterium oxide-exchangeable), 8.12 (d, 1H, J = 8.7 Hz, phenyl), 7.73 (s, 1H, phenyl), 7.65 (d, 1H, J = 8.7 Hz, phenyl), 4.01 ppm (s, 2H, CH_2); ms (electron impact, 70 eV): m/z 215 (M^+, 3.4%, ^{35}Cl).

Anal. Calcd. for $C_8H_6ClNO_4$: C, 44.57; H, 2.81; N, 6.50. Found: C, 44.62; H, 2.77; N, 6.53

2-(5-Chloro-2-nitro-phenyl)-1-(2,4-dihydroxy-phenyl)-ethanone (**14**).

The phenylacetic acid **13** (5.0 g, 23 mmoles) and resorcinol (3.0 g, 27 mmoles) were ground together to a fine powder and added to 220 mL boron trifluoride diethyl ether complex. The mixture was heated at reflux at a temperature of 100 ºC for 90 minutes. After cooling it was slowly poured into 1000 mL of an aqueous solution of sodium acetate (12%) and extracted with diethyl ether. The combined organic layers were washed with a solution of sodium acetate (12%), dried over anhydrous sodium sulfate and evaporated. The brown oily raw product was purified by column chromatography (silica gel, dichloromethane/methanol 9:1, v/v). Compound **14** was obtained as pale pink crystals, yield 2.4 g (34%), mp 180-181 ºC; ir (potassium bromide): OH 3412, CO 1631 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 11.89 (s, 1H, OH, deuterium oxide-exchangeable), 10.68 (s, 1H, OH, deuterium oxide-exchangeable), 8.15 (d, 1H, J = 8.8 Hz, phenyl), 7.89 (d, 1H, J = 8.9 Hz, phenyl), 7.73 (d, 1H, J = 2.2 Hz, phenyl), 7.67 (dd, 1H, J = 2.2, 8.8 Hz, phenyl), 6.45 (dd, 1H, J = 2.3, 8.9 Hz, phenyl), 6.30 (d, 1H, J = 2.3 Hz, phenyl), 4.82 ppm (s, 2H, CH_2); ms (electron impact, 70 eV): m/z 307 (M^+, 3.1%, ^{35}Cl).

Anal. Calcd. for $C_{14}H_{10}ClNO_5$: C, 54.65; H, 3.28; N, 4.55. Found: C, 54.65; H, 3.24; N, 4.57.

3-(5-Chloro-2-nitro-phenyl)-7-hydroxy-chromen-4-one (**15**).

An amount of 430 mg (1.4 mmoles) of compound **14** was dissolved in 30 mL tetrahydrofuran, 1 mL of N,N-dimethylformamide dimethyl acetale was then added and the mixture was heated at reflux for 90 minutes. After removing the solvent in vacuum the residual oil was heated at reflux in 20 mL acetic acid (50%) for 5 minutes and subsequently filtered. After cooling the solid was collected. Compound **15** was obtained as yellow crystals, yield 300 mg (68%), mp 223 ºC; ir (potassium bromide): OH 3385, 3189, CO 1629 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 10.96 (s, 1H, OH, deuterium oxide-exchangeable) 8.61 (s, 1H, chromone), 8.11 (d, 1H, J = 8.5 Hz, phenyl), 7.90 (d, 1H, J = 8.6 Hz, phenyl), 7.76 (dd, 1H, J = 1.9, 10.9 Hz, chromone), 7.74 (d, 1H, J = 2.1 Hz, phenyl), 6.96 (d, 1H, J = 8.8 Hz, chromone), 6.94 ppm (s, 1H, chromone); ms (electron impact, 70 eV): m/z 317 (M^+, 3.3%, ^{35}Cl), 271 (100%, ^{35}Cl).

Anal. Calcd. for $C_{15}H_8ClNO_5$: C, 56.71; H, 2.54; N, 4.41. Found: C, 56.73; H, 2.60; N, 4.38.

3-(4-Chloro-2-nitro-phenyl)-2-hydroxyimino-propionic Acid (**17**).

A mixture of 400 mL dry ethanol and 13.2 g (244 mmoles) sodium methoxide was stirred for 5 minutes under nitrogen. Then a mixture of 35.7 g (244 mmoles) diethyl oxalate and 41.9 g (244 mmoles) 4-chloro-2-nitro toluene (**16**) was added dropwise and the resulting mixture was heated at reflux for 25 minutes at 90 ºC under nitrogen. After cooling to 60 ºC an amount of 300 mL water was carefully added and the mixture was heated at reflux for another hour at 90 ºC. The ethanol was removed in vavuo and then a solution of 17.5 g (244 mmoles) hydroxylamine hydrochloride in 100 mL water was added dropwise to the residual mixture at a temperature of 50 ºC. Afterwards the mixture was neutralized by adding a 10 M solution of sodium hydroxide and stirred at room temperature overnight. It was then standardized on pH1 with 12 M hydrochloric acid and stirred again at room temperature overnight. The solid was collected, washed with water, dried and resuspended in toluene. The resulting suspension was stirred under nitrogen for an hour. The solid was collected by filtration again, washed several times with toluene and once with petrol ether, dried in vacuo and recrystallized from ethanol to give 12.5 g (20%) of **17** as pale beige crystals, mp 176 ºC; ir (potassium bromide): OH 3235, 3079, 2851, CO 1710, CN 1588 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 11.88 (s, 1H, COOH, deuterium oxide-exchangeable), 8.01 (d, 1H, J = 2.0 Hz, phenyl), 7.70 (dd, 1H, J = 2.0, 8.3 Hz, phenyl), 7.38 (d, 1H, J = 8.4 Hz, phenyl), 3.99 (s, 2H, CH_2), 3.34 ppm (s, 1H, NOH, deuterium oxide-exchangeable); ms (electron impact, 70 eV): m/z 258 (M^+, 9%, ^{35}Cl).

Anal. Calcd. for $C_9H_7ClN_2O_5 \cdot H_2O$: C, 39.08; H, 3.01; N, 10.13. Found: C, 38.88; H, 2.48; N, 9.95.

(4-Chloro-2-nitro-phenyl)-acetonitrile (**18**).

The propionic acid derivative **17** (13.0 g, 50 mmoles) was heated at reflux in a mixture of 280 mL acetic acid and 50 mL water for two hours at a temperature of 90 ºC and afterwards stirred on at room temperature overnight. Then the mixture was extracted with dichloromethane. The combined organic layers were washed with water, dried (sodium sulfate) and evaporated. The residual oil was chromatographed (silica gel, ethyl acetate) to yield 7.9 g (80%) of **18** as white crystals, mp 85 ºC; ir (potassium bromide): CN 2250 cm^{-1}; ^1H nmr (deuterochloroform): δ 8.20 (s, 1H, phenyl), 7.71 (m, 2H, phenyl), 4.19 ppm (s, 2H, CH_2); ms (electron impact, 70 eV): m/z 196 (M^+, 34%, ^{35}Cl).

Anal. Calcd. for $C_8H_5ClN_2O_2$: C, 48.88; H, 2.56; N, 14.25. Found: C, 48.76; H, 2.54; N, 14.27.

(4-Chloro-2-nitro-phenyl)-acetic Acid (**19**).

The nitrile **18** (6.0 g, 31 mmoles) was heated at reflux in a mixture of 90 mL water and 60 mL conc. sulfuric acid for 20 min-

utes. The reaction mixture was then poured onto ice. The solid was collected, washed with water and purified by flash chromatography (silica gel, ethyl acetate/ethanol 9:1, v/v). Compound **19** was obtained as white crystals, mp 155 ºC, yield 3.3 g (50%). ir (potassium bromide): OH 3426, 3092, 3033, 2943, CO 1697 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.62 (s, 1H, COOH, deuterium oxide-exchangeable), 8.16 (d, 1H, J = 2.2 Hz, phenyl), 7.82 (dd, 1H, J = 2.3, 8.3 Hz, phenyl), 7.60 (d, 1H, J = 8.3 Hz, phenyl), 3.98 ppm (s, 2H, CH_2); ms (electron impact, 70 eV): m/z 215 (M^+, 5.8%, ^{35}Cl).

Anal. Calcd. for $C_8H_6ClNO_4$: C, 44.57; H, 2.81; N, 6.50. Found C, 44.62; H, 2.83; N, 6.30.

2-(4-Chloro-2-nitro-phenyl)-1-(2,4-dihydroxy-phenyl)-ethanone (**20**).

The ethanone **20** was prepared similarly to **14** from 5.0 g (23 mmoles) **19** and 3.0 g (27 mmoles) resorcinol and was obtained as pale yellow crystals, yield 0.6 g (8.4%), mp 177 ºC; ir (potassium bromide): OH 3445, 3418, CO 1629 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 11.91 (s, 1H, OH, deuterium oxide-exchangeable), 10.69 (s, 1H, OH, deuterium oxide-exchangeable), 8.19 (d, 1H, J = 2.2 Hz, phenyl), 7.91 (d, 1H, J = 8.9 Hz, phenyl), 7.84 (dd, 1H, J = 2.1, 8.2 Hz, phenyl), 7.61 (d, 1H, J = 8.33 Hz, phenyl), 6.44 (dd, 1H, J = 2.3, 8.8 Hz, phenyl), 6.30 (s, 1H, phenyl), 4.81 ppm (s, 2H, CH_2); ms (electron impact, 70 eV): m/z 307 (M^+, 7.7%, ^{35}Cl).

Anal. Calcd. for $C_{14}H_{10}ClNO_5$: C, 54.65; H, 3.28; N, 4.55. Found: C, 54.65; H, 3.38; N, 4.56.

3-(4-Chloro-2-nitro-phenyl)-4,7-dihydroxy-chromenylium Acetate (**21**).

An amount of 0.9 g (3 mmoles) of compound **20** was dissolved in 50 mL tetrahydrofuran, 2 mL of N,N-dimethylformamide dimethyl acetale was then added and the mixture was heated at reflux for 90 minutes. After removing of the solvent in vacuum the residual oil was heated at reflux in 30 mL acetic acid (50%) for 5 minutes and subsequently filtered. After cooling the solid was collected. Compound **21** was obtained as pale brown crystals, yield 0.9 g (81%), mp 250 ºC; ir (potassium bromide): OH 3423, CO 1711 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 11.94 (s, 1H, OH, deuterium oxide-exchangeable), 10.96 (s, br, 1H, OH, deuterium oxide-exchangeable), 8.58 (s, 1H, chromenylium), 8.19 (d, 1H, J = 2.2 Hz, phenyl), 7.94 (dd, 1H, J = 2.2, 8.3 Hz, phenyl), 7.90 (d, 1H, J = 8.7 Hz, chromenylium), 7.62 (d, 1H, J = 8.3 Hz, phenyl), 6.97 (dd, 1H, J = 2.1, 8.7 Hz, chromenylium), 6.95 (d, 1H, J = 2.1 Hz, chromenylium), 1.91 ppm (s, 3H, CH_3); ms (electron impact, 70 eV): m/z 317 (1.9%, ^{35}Cl), 271 (100%, ^{35}Cl].

Anal. Calcd. for $C_{17}H_{12}ClNO_7$: C, 54.05; H, 3.20; N, 3.71. Found: C, 54.27; H, 3.19; N, 3.77.

3-(4-Chloro-2-nitro-phenyl)-7-hydroxy-chromen-4-one (**22**).

The isoflavone **22** was prepared in a similar procedure as described for compound **21**, but after heating of the residual oil in acetic acid, the mixture was allowed to cool to room temperature, then it was neutralized with sodium carbonate and extracted with ethyl acetate. The combined organic layers were washed with water, dried (sodium sulfate) and evaporated. The resulting raw product was purified by column chromatography (silica gel, ethyl acetate) to yield 320 mg (34%) of **22** as pale yellow to brown crystals, mp 248 ºC, ir (potassium bromide): OH 3207, CO 1628 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 10.96 (s, 1H, OH, deuterium oxide-exchangeable), 8.58 (s, 1H, chromone), 8.19 (d, 1H, J = 2.2 Hz, phenyl), 7.94 (dd, 1H, J = 2.2, 8.4 Hz, phenyl), 7.90 (d, 1H, J = 8.7 Hz, chromone), 7.63 (d, 1H, J = 8.3 Hz, phenyl), 6.98 (dd, 1H, J = 2.3, 8.8 Hz, chromone), 6.94 ppm (d, 1H, J = 2.1 Hz, chromone); ms (electron impact, 70 eV): m/z 317 (M^+, 1%, ^{35}Cl), 271 (100%, ^{35}Cl).

Anal. Calcd. for $C_{15}H_8ClNO_5$: C, 56.71; H, 2.54; N, 4.41. Found: C, 56.64; H, 2.55; N, 4.30.

(4-Methoxy-2-nitro-phenyl)-acetonitrile (**24**).

A solution of 30 mL (0.3 mole) ethyl cyanoacetates was added dropwise to a solution of 10.0 g sodium hydride (50% suspension in mineral oil) in 100 mL dimethylformamide. After adding of 0.5 g (3.3 mmoles) cesium fluoride and a solution of 25.0 g (0.13 mole) 4-chloro-3-nitro-anisole (**2 3**) in 100 mL dimethylformamide the mixture was heated at reflux for 24 hours at 70 ºC. Subsequently, the mixture was cooled to room temperature and poured into 200 mL water. It was standardized on pH3-4 with 10 N sulfuric acid and extracted with ethyl acetate. The combined organic layers were dried (sodium sulfate) and evaporated. The solid was purified by flash chromatography (diethyl ether/n-hexane 1:1, v/v). The residual oil was dissolved in 300 mL of a saturated solution of sodium carbonate and the mixture was heated overnight at 55 ºC. After cooling to room temperature the mixture was extracted with ethyl acetate. The combined organic layers were dried (sodium sulfate) and the solvent was removed in vacuo. The solid was recrystallized from diethyl ether to give 5.5 g (22%) of **24** as pale yellow crystals, mp 151 ºC; ir (potassium bromide): CN 2248 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 7.66 (d, 1H, J = 2.6 Hz, phenyl), 7.63 (d, 1H, J = 8.6 Hz, phenyl), 7.33 (dd, 1H, J = 2.5, 8.6 Hz, phenyl), 4.20 (s, 2H, CH_2), 3.74 ppm (s, 3H, OCH_3); ms (electron impact, 70 eV): m/z 192 (M^+, 74%).

Anal. Calc. for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.18; H, 4.23; N, 14.57.

(4-Methoxy-2-nitro-phenyl)-acetic Acid (**25**).

The nitrile **24** (5.5 g, 28.6 mmoles) was heated at reflux in a mixture of 60 mL water and 40 mL conc. sulfuric acid water for 20 minutes. The reaction mixture was then poured onto ice. The solid was collected, washed with water and purified by flash chromatography (silica gel, ethyl acetate). Compound **25** was obtained as pale yellow crystals, yield 4.8 g (76%), mp 152 ºC; ir (potassium bromide): OH 3454, 3430, CO 1698 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.29 (s, 1H, COOH), 7.57 (d, 1H, J = 2.6 Hz, phenyl), 7.45 (d, 1H, J = 8.5 Hz, phenyl), 7.26 (dd, 1H, J = 2.7, 8.5 Hz, phenyl), 3.92 (s, 2H, CH_2), 3.82 ppm (s, 3H, OCH_3); ms (electron impact, 70 eV): m/z 211 (M^+, 28%).

Anal. Calcd. for: $C_9H_9NO_5$: C, 51.18; H, 4.26; N, 6.63. Found: C, 51.36; H, 4.26; N, 6.70.

1-(2,4-Dihydroxy-phenyl)-2-(4-methoxy-2-nitro-phenyl)-ethanone (**26**).

The ethanone **26** was prepared similarly to **14** from 2.2 g (10.4 mmoles) **25** and 1.1 g (10 mmoles) resorcinol and was obtained as pale yellow crystals, yield 2.1 g (67%), mp 155 ºC; ir (potassium bromide): OH 3434, 3410, CH 2928, CO 1630 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.04 (s, 1H, OH), 10.63 (s, 1H, OH), 7.92 (d, 1H, J = 8.8 Hz, phenyl), 7.61 (d, 1H, J = 2.6 Hz, phenyl), 7.47 (d, 1H, J = 8.5 Hz, phenyl), 7.34 (dd, 1H, J = 2.6, 8.5 Hz, phenyl), 6.41 (dd, 1H, J = 2.2, 8.8 Hz, phenyl), 6.25 ppm (d, 1H, J = 2.2 Hz, phenyl); ms (electron impact, 70 eV): m/z 303 (M^+, 2.6%).

Anal. Calcd for $C_{15}H_{13}NO_6$: C, 61.34; H, 3.51; N, 4.57. Found: C, 59.31; H, 4.33; N, 4.61.

7-Hydroxy-3-(4-methoxy-2-nitro-phenyl)-chromen-4-one (**27**).

An amount of 0.7 g (2.2 mmoles) of compound **26** was dissolved in 40 mL tetrahydrofuran, 1.5 mL of N,N-dimethylformamide dimethyl acetale was then added and the mixture was heated at reflux for 90 minutes. After removing of the solvent in vacuum the residual oil was heated at reflux in 25 mL acetic acid (50%) for 5 minutes and subsequently filtered. After cooling the solid was collected. Compound **27** was obtained as pale yellow crystals, yield 0.6 g (84%), mp 245 ºC; ir (potassium bromide): OH 3432, 3391, CO 1625 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 10.86 (s, 1H, OH) 8.46 (s, 1H, chromone), 7.88 (d, 1H, J = 8.8 Hz, chromone), 7.58 (d, 1H, J = 2.5 Hz, phenyl), 7.47 (d, 1H, J = 8.5 Hz, phenyl), 7.37 (dd, 1H, J = 2.5, 8.5 Hz, phenyl), 6.97 (dd, 1H, J = 2.1, 8.8 Hz, chromone), 6.85 (d, 1H, J = 2.0 Hz, chromone), 3.85 ppm (s, 3H, OCH_3); ms (electron impact, 70 eV): m/z 313 (M^+, 0.4%).

Anal. Calcd for $C_{16}H_{11}NO_6$: C, 61.34; H, 3.51; N, 4.47. Found: C, 61.17; H, 3.78; N, 4.41.

3-(4-Methoxy-2-nitro-phenyl)-7-(2-piperidin-1-yl-ethoxy)-chromen-4-one (**28**).

A mixture of 0.5 g (1.6 mmoles) **27**, 0.3 g (1.6 mmoles) 1-(2-chloro-ethyl)-piperidinium chloride and 0.2 g (2.0 mmoles) potassium carbonate in 70 mL acetonitrile was heated at reflux for 2 hours at 80 ºC and subsequently filtered while hot. The solvent was removed in vacuo and the raw product was purified by flash chromatography (silica gel, dichloromethane/methanol 9:1, v/v) to give 630 mg (93%) of **28** as pale yellow crystals, mp 144 ºC; ir (potassium bromide): CH 2940, CO 1644 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.55 (s, 1H, chromone), 7.93 (d, 1H, J = 8.9 Hz, chromone), 7.62 (d, 1H, J = 2.7 Hz, phenyl), 7.50 (d, 1H, J = 8.5 Hz, phenyl), 7.40 (dd, 1H, J = 2.6, 8.5 Hz, phenyl), 7.23 (d, 1H, J = 2.3 Hz, chromone), 7.09 (dd, 1H, J = 2.3, 8.8 Hz, chromone), 4.24 (t, 2H, J = 5.8 Hz, CH_2), 3.86 (s, 3H, OCH_3), 2.72 (t, 2H, J = 5.8 Hz, CH_2), 2.39.2.48 (m, 4H, piperidine), 1.44.1.56 (m, 4H, piperidine), 1.32.1.44 ppm (m, 2H, piperidine); ms (electron impact, 70 eV): m/z 424 (M^+, 0.7%).

Anal. Calcd for $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6,60. Found: C, 65.14; H, 5.71; N, 6.50.

(2-Hydroxy-4-methyl-phenyl)-(1H-indol-3-yl)-methanone (**29**).

Compound **8** (0.4 g, 1.0 mmoles) was dissolved in 50 mL ethanol. Palladium on carbon (10%, 0.1 g) and 5 mL cyclohexene were added and the mixture was heated to reflux for 16 hours. Then it was filtered hot and the filtrate was evaporated. The raw product was recrystallized from dichloromethane/methanol (9:1, v/v) to yield 194 mg (54%) of **2 9** as yellow crystals, mp 162 ºC; ir (potassium bromide): OH, NH 3257 cm^{-1}; ^1H nmr (deuterochloroform): δ 12.12 (s, 1H, OH, deuterium oxide-exchangeable), 11.38 (s, 1H, NH, trifluoroacetic acid-exchangeable), 8.16 (dd, 1H, J = 2.0, 7.0 Hz, phenyl), 8.02 (s, 1H, indole), 7.65 (d, 1H, J = 8.0 Hz, phenyl), 7.52 (dd, 1H, J = 1.0, 6.0 Hz, phenyl), 7.21,7.28 (m, 2H, indole), 6.78,6.81 (m, 2H, indole), 2.33 ppm (s, 3H, CH_3). ^{13}C nmr (deuterochloroform): δ 194.0, 162.3, 146.4, 136.2, 132.0, 131.6, 126.4, 124.1, 122.6, 122.1, 119.9, 118.8, 118.3, 116.3, 111.5, 21.8 ppm; ms (electron impact, 70 eV): m/z 251 (M^+, 26%).

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.21; N, 5.57. Found: C, 76.77; H, 5.12; N, 5.43.

(4-Chloro-2-hydroxy-phenyl)-(1H-indol-3-yl)-methanone (**30**).

Compound **9** (250 mg, 0.8 mmole) was dissolved in 50 mL ethanol. Palladium on carbon (10%, 0.1 g) and 5 mL cyclohexene were added and the mixture was heated to reflux for 14 hours. Then it was filtered hot and the filtrate was evaporated. The raw product was recrystallized from dichloromethane/methanol (9:1, v/v) to yield 54 mg (23%) of **30** as violet crystals, mp 146 ºC; ir (potassium bromide): OH, NH 3397 cm^{-1}; ^1H nmr (deuterochloroform): δ 12.24 (s, 1H, OH, deuterium oxide-exchangeable), 8.75 (s, 1H, NH, trifluoroacetic acid-exchangeable), 8.23 (d, 1H, J = 3.7 Hz, phenyl), 7.76,7.82 (m, 2H, indole, phenyl), 7.46,7.48 (m, 1H, indole), 7.33,7.35 (m, 2H, indole), 6.99 (d, 1H, = 2.5 Hz, phenyl), 6.78,6.91 ppm (m, 1H, indole); ms (electron impact, 70 eV): m/z 271 (M^+, 12%, ^{35}Cl).

Anal. Calcd. for $C_{15}H_{10}ClNO_2$: C; 66.31; H, 3.71; N, 5.16. Found: C, 66.72; H, 4.05; N, 5.13.

(4-Fluoro-2-hydroxy-phenyl)-(1H-indol-3-yl)-methanone (**31**).

Compound **10** (0.3 g, 1.0 mmole) was dissolved in 50 mL ethanol. Palladium on carbon (10%, 0.1 g) and 5 mL cyclohexene were added and the mixture was heated to reflux for 20 hours. Then it was filtered hot and the filtrate was evaporated. The raw product was recrystallized from dichloromethane/methanol (9:1, v/v) to yield 70 mg (27%) of **31** as yellow crystals, mp 191 ºC; ir (potassium bromide): OH, NH 3430 cm^{-1}; ^1H nmr (deuterochloroform): δ 12.47 (s, 1H, OH, deuterium oxide-exchangeable), 8.70 (s, 1H, NH, trifluoroacetic acid-exchangeable), 8.22 (dd, 1H, J = 2.9, 8.8 Hz, phenyl), 7.89 (dt, 1H, J = 2.1, 6.6 Hz, phenyl), 7.76 (d, 1H, J = 2.9 Hz, phenyl), 7.46.7.48 (m, 1H, indole), 7.31.7.36 (m, 2H, indole), 6.75 (dd, 1H, J = 2.4, 10.4 Hz, indole), 6.63 ppm (dt, 1H, J = 2.3, 8.5 Hz, indole); ms (fast atom bombardment, 80 eV, pos., dimethyl sulfoxide/glycerol): m/z 256 ($[M-H]^+$, 100%).

Anal. Calcd. for $C_{15}H_{10}FNO_2$: C, 70.58; H, 3.95; N, 5.49. Found: C, 70.23; H, 3.94; N, 5.35.

(5-Chloro-1H-indol-2-yl)-(2,4-dihydroxy-phenyl)-methanone (**32**).

A mixture of **1 5** (250 mg, 0.8 mmole) and zinc dust (0.6 g) was heated at reflux in 50 mL acetic acid (50%) for 2.5 hours. After cooling the mixture was poured onto ice and extracted with ethyl acetate. The combined organic layers were washed with water, dried over anhydrous sodium sulfate and evaporated. The oily raw product was chromatographed (silica gel, dichloromethane/methanol 9:1, v/v) to yield 70 mg (31%) of **32** as yellow powder, mp 205 ºC; ir (potassium bromide): OH, NH 3411, CO 1628 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.48 (s, br, 1H, OH, deuterium oxide-exchangeable), 12.27 (s, 1H, NH, deuterium oxide-exchangeable), 10.40 (s, 1H, OH, deuterium oxide-exchangeable), 8.17 (s, 1H, indole), 8.10 (s, 1H, indole)**,** 7.79 (d, 1H, J = 8.8 Hz, phenyl), 7.53 (d, 1H, J = 8.6 Hz, indole), 7.26 (d, 1H, J = 9.0 Hz, indole), 6.41 (d, 1H, J = 8.6 Hz, phenyl), 6.33 ppm (d, 1H, J = 1.9 Hz, phenyl); ms (electron impact, 70 eV): m/z 287 (M^+, 3%, ^{35}Cl).

Anal. Calcd. for $C_{15}H_{10}ClNO_3$_$0.5H_2O$: C,60.72; H, 3.74; N, 4.72. Found: C, 60.65; H, 3.79; N, 4.61.

3-(2-Amino-4-chloro-phenyl)-7-hydroxy-chromen-4-one (**33**).

Compound **21** (1.0 g, 3 mmoles) and 2.0 g zinc dust were heated at reflux in 50 mL acetic acid (50%) for 75 minutes. After cooling the

mixture was poured onto ice and extracted with ethyl acetate. The combined organic layers were washed with water, dried (sodium sulfate) and evaporated. The resulting raw product was purified by column chromatography (silica gel, dichloromethane/methanol 9:1, v/v). The collected fractions (Rf-ethyl acetate 0.88-0.90) were evaporated and the resulting residue was redissolved in a mixture of ethyl acetate and n-hexane (1:1, v/v) and the resulting solid was collected to obtain **33** as pale beige powder, yield 0.2 g (26%), mp 193 ºC, ir (potassium bromide): OH, NH_2 3425, CO 1624 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 10.78 (s, br, 1H, OH), 8.15 (s, 1H, chromone), 7.94 (d, 1H, J = 8.7 Hz, chromone), 6.93 (dd, 1H, J = 2.1, 8.7 Hz, phenyl), 6.92 (d, 1H, J = 8.1 Hz, phenyl), 6.87 (d, 1H, J = 2.0 Hz, phenyl), 6.74 (d, 1H, J = 1.9 Hz, chromone), 6.57 (dd, 1H, J = 1.9, 8.0 Hz, chromone), 5.17 ppm (s, 2H, NH_2, deuterium oxide-exchangeable); ms (electron impact, 70 eV): m/z 287 (M^+, 31%, ^{35}Cl).

Anal. Calcd. for $C_{15}H_{10}ClNO_3$•0.5H_2O: C, 60.72; H, 3.74; N, 4.72. Found: C, 61.39; H, 3.66; N, 4.50.

(6-Chloro-1H-indol-3-yl)-(2,4-dihydroxy-phenyl)-methanone (**34**).

Compound **34** was obtained similarly to compound **33**, but the ethyl acetate/n-hexane (1:1, v/v) filtrate - resulting after compound **33** was removed by filtration - was evaporated and the residue was dried in vacuum to obtain 210 mg (28%) of **34** as yellow powder, mp 178 ºC; ir (potassium bromide): OH, NH 3395, CO 1627 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.51 (s, 1H, OH, deuterium oxide-exchangeable), 12.19 (s, 1H, NH, deuterium oxide-exchangeable), 10.41 (s, 1H, OH, deuterium oxide-exchangeable), 8.13 (s, 1H, indole), 8.09 (d, 1H, J = 8.6 Hz, indole), 7.79 (d, 1H, J = 8.7 Hz, phenyl), 7.56 (d, 1H, J = 1.9 Hz, indole), 7.23 (dd, 1H, J = 1.9, 8.6 Hz, indole), 6.41 (dd, 1H, J = 2.4, 8.8 Hz, phenyl), 6.33 ppm (d, 1H, J = 2.4 Hz, phenyl); ^{13}C nmr (dimethyl sulfoxide-d_6, 400 MHz): δ 191.6, 163.5, 163.4, 136.8, 134.9, 133.5, 127.4, 125.1, 122.6, 121.8, 114.2, 113.8, 111.8, 107.6, 102.7 ppm; ms (electron impact, 70 eV): m/z 287 (M^+, 3%, ^{35}Cl).

Anal. Calcd. for $C_{15}H_{10}ClNO_3$•0.5H_2O: C, 60.72; H, 3.74; N, 4.72. Found: C, 61.20; H, 3.88; N, 4.49.

3-(2-Amino-4-methoxy-phenyl)-7-hydroxy-chromen-4-one (**35**).

Compound **27** (1.0 g, 3.2 mmoles) was dissolved in 120 mL ethanol. Palladium on carbon (10%, 1.0 g) and 6 mL cyclohexene were added and the mixture was heated to reflux for 2 hours. Then it was filtered hot and the filtrate was evaporated. The raw product was resuspended in dichloromethane/methanol (9:1, v/v) and 410 mg (45%) of **35** as pale yellow crystals could collected by filtratoin, mp 205 ºC; ir (potassium bromide): OH, NH 3321, 3262, $ArOCH_3$ 2837, CO 1623 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 10.73 (s, 1H, OH), 8.08 (s, 1H, chromone), 7.94 (d, 1H, J = 8.7 Hz, chromone), 6.93 (dd, 1H, J = 2.2, 8.7 Hz, chromone), 6.87 (d, 1H, J = 2.3 Hz, chromone), 6.85 (d, 1H, J = 8.4 Hz, phenyl), 6.31 (d, 1H, J = 2.5 Hz, chromone), 6.19 (dd, 1H, J = 2.5, 8.3 Hz, phenyl), 4.81 (s, 2H, NH_2), 3.70 ppm (s, 3H, OCH_3); ms (electron impact, 70 eV): m/z 283 (M^+, 10%).

Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.77; H, 4.40; N, 4.80.

(2,4-Dihydroxy-phenyl)-(1-ethyl-5-methoxy-1H-indol-3-yl)-methanone (**36**).

Compound **27** (0.2 g, 0.6 mmole) was dissolved in 50 mL ethanol. Palladium on carbon (10%, 0.2 g) and 3 mL cyclohexene were added and the mixture was heated to reflux for 4 hours. Then it was filtered hot and the filtrate was evaporated. The raw product was purified by flash chromatography (silica gel, dichloromethane/methanol 9:1, v/v). Compound **36** was obtained as green powder, yield 19 mg (9.5%), mp 184 ºC; ir (potassium bromide): OH 3404, 3191, CH 2930, $arOCH_3$ 2855, CO 1621 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.64 (s, 1H, OH), 10.36 (s, 1H, OH), 8.08 (s, 1H, indole), 8.00 (d, 1H, J = 8.7 Hz, phenyl), 7.80 (d, 1H, J = 8.7 Hz, indole), 7.15 (d, 1H, J = 2.1 Hz, indole), 6.87 (dd, J = 2.1, 8.9 Hz, indole), 6.42 (dd, 1H, J = 2.3, 8.8 Hz, phenyl), 6.30 (d, 1H, J = 2.3 Hz, phenyl), 4.28 (q, 2H, J = 7.1 Hz, CH_2), 3.84 (s, 3H, OCH_3), 1.40 ppm (t, 3H, J = 7.11 Hz, CH_3); ms (electron impact, 70 eV): m/z 311 (M^+, 49%).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.38; H, 5.70; N, 4.44.

8-Methoxy-3-(2-piperidin-1-yl-ethoxy)-benzopyrano[2,3-b]-indol-11-one (**37**).

Compound **28** (400 mg, 0.9 mmole) and 0.8 g zinc dust were heated at reflux in 25 mL acetic acid (50%) for 2 hours at 100 ºC. After cooling the mixture was poured onto 100 mL ice and standardized on pH 8 with 10 N solution of sodium carbonate. The solution was first extracted with dichloromethane, afterwards with ethyl acetate. The combined organic layers were dried (sodium sulfate) and the solvent was evaporated. The raw product was purified by flash chromatography (silica gel, dichloromethane/methanol 9:1, v/v) to obtain compound **39** as white powder, yield 11 mg (2.9%), mp 263 ºC; ir (potassium bromide): NH 3433, CH 2933, $ArOCH_3$ 2853, CO 1630 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.64 (s, 1H, NH), 8.10 (d, 1H, J = 8.8 Hz, phenyl), 7.93 (d, 1H, J = 8.6 Hz, phenyl), 7.25 (d, 1H, J = 2.2 Hz, phenyl), 7.09 (dd, 1H, J = 2.2, 8.8 Hz, phenyl), 6.98 (d, 1H, J = 2.2 Hz, phenyl), 6.88 (dd, 1H, J = 2.2, 8.5 Hz, phenyl), 4.23 (t, 2H, J = 5.8 Hz, CH_2), 3.81 (s, 3H, OCH_3), 2.72 (t, 2H, J = 5.8 Hz, CH_2), 2.39,2.48 (m, 4H, piperidine), 1.44,1.58 (m, 4H, piperidine), 1.32,1.44 ppm (m, 2H, piperidine); ^{13}C nmr (dimethyl sulfoxide-d_6, 400 MHz): δ 171.0, 161.8, 156.6, 155.3, 154.9, 132.8, 126.5, 120.9, 116.9, 115.4, 113.4, 110.2, 101.6, 98.2, 96.1, 66.3, 57.0, 55.3, 54.2, 25.4, 23.7 ppm; ms (electron impact, 70 eV): m/z 392 (M^+, 8%).

Anal. Calcd. For $C_{23}H_{24}N_2O_4$•H_2O: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.81; H, 6.25; N, 6.60

REFERENCES AND NOTES

[*] Corresponding Author: Werner Löwe, Institute of Pharmacy, Free University of Berlin, Königin-Luise-Strasse 2+4, 14195 Berlin, Germany; Telephone number: 0049-30-83858250; Fax number: 0049-30-83853854; e-mail: wloewe@zedat.fu-berlin.de

[1] A. Brzezinski, A. Debi, *Eur. J. Obstetrics Gyn Reprod. Biol.*, **85**, 47 (1999)

[2] M. Makosza, M. Wenäll, M. Golinski, A. Kinowski, *Bull. Soc. Sci. Chim. Polon.*, **33**, 427 (1985)

[3] I. Vlattas, Eur. Pat. Appl., Europäisches Patentamt, 56 pp., EP 81461 A2 19830615, (1983), *Chem. Abstr.*, **99**,158476 (1983).

[4] W. Löwe, R. Gust, S. Witzel, C. Dietrich, German Offen., 12pp., DE 19947863 A1 20010405, (2001), *Chem. Abstr.*, **134**, 280704 (2000).

[5] I. D. Entwistle, R. A. W. Johnstone, T. J. Povall, *J. Chem. Soc., Perkin Trans. I*, 1300 (1975).