Synthesis of *N*-amino-3-hydroxy-2-phenyl-4(1*H*)-quinolinone

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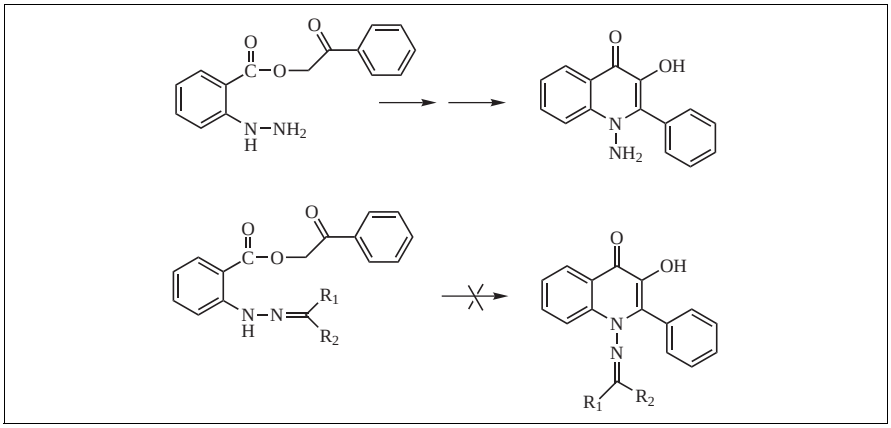

2-[(Disubstituted-methylene)-hydrazino] benzoic acid phenacylesters **2a – 2d**, prepared from anthranilic acid phenacylester **1**, were unsuccesfully tried as starting materials for the synthesis of *N*-amino-3-hydroxy-2-phenyl-4(1*H*)-quinolinone **8**. The desired compound **8** was prepared by cyclization of *N*-acetyl as well as *N*-benzoyl-hydrazinobenzoic acid phenacylester **6a** or **6b** in polyphosphoric acid to afford *N*-acylamino-3-hydroxy-2-phenyl-4(1*H*)-quinolinone **7a** or **7b**, respectively. Surprisingly, the acyl group was resistant to attack by both hydrochloric acid as well as sodium hydroxide solution. It could be removed by boiling the compounds **7a** or **7b** respectively in 50% sulphuric acid to afford the the target compound **8**.

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Introduction.

Derivatives of 4(1*H*)-quinolinones are an intensively studied group of compounds, because of their known biological activity. On the other hand, the derivatives of 3-hydroxy-2-phenyl-4(1*H*)-quinolinones have not been investigated in depth. Investigations of the biological role of some of these derivatives have been reported in only about five articles, in which the inosine monophosphate dehydrogenase [1] or topoisomerase [2,3] inhibition activity, cytostatic activity [4] and the cleavage of these quinolinones by dioxygenases [5] are discussed.

Because the derivatives of the mentioned quinolinones are sterically similar to naturally occurring flavonoids known for their anticancer activity [6,7,8], we expect this activity also for derivatives of 3-hydroxy-2-phenyl-4(1*H*)-quinolinone. The first observation of cytostatic activity against cancer lines was published for chlorine derivatives [4]. Incorporation of the amino group to nitrogen in such heterocycles can influence the biological activity and offers the possibility to enhance their solubility *via* formation of ammonium salts. An amino group is also potentially able to be involved in creation of new heterocyclic systems or to be modified into various nitrogenous substituents in position 1 of 3-hydroxy-2-phenylquinolin-4(1*H*)-one skeleton. These types of compounds have never been described. For these reasons, in this work, we have attempted to develop the methodology for preparation of *N*-amino-3-hydroxy-2-phenyl-4(1*H*)-quinolinone.

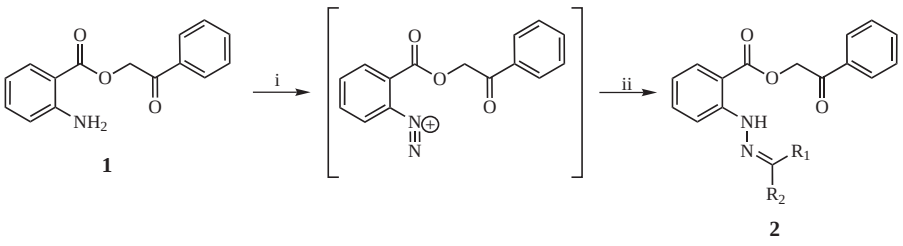
Results and Discussion.

For synthesis of the desired derivative we tried to use a modification of the widely explored cyclization reaction of anthranilic acid phenacylesters [9]. Because cyclization also takes place in phenacylesters with substituted amino groups *e.g.* by alkyl or aryl group [10], we tried to use 2-hydrazinobenzoic acid phenacylester, in which the amino group is substituted by a second amino group, for the cyclization. For preparation of the starting 2-hydrazinobenzoic acid phenacylester, an NH_2 group of hydrazine must be protected first. Otherwise, just this group was alkylated with phenacylbromide competitively. We achieved complete protection of the amino group of

hydrazine *via* transformation to the hydrazono moiety. As the protective group we chose malondinitrile, diethylmalonate, ethylcyanoacetate and ethyl-2-methyl-acetoacetate, which are suitable for subsequent formation of heterocycles, *e.g*. of the pyrazole type, in position 1 of potentially prepared quinolinones. The derivatives of quinolinones substituted in position 1 with a heterocycle have been studied intensively because of their antibacterial activity [11,12], platelet aggregation inhibition activity [12], anti-HIV activity [13], *etc*.

The incorporation of the mentioned protective group was achieved *via* diazotation of anthranilic acid phenacylester **1**, prepared by a synthesis already described [9] and subsequent coupling reaction with malondinitrile, diethylmalonate, ethylcyanoacetate and ethyl-2-methyl-acetoacetate under neutral or slightly basic conditions (Scheme 1).

Scheme1[a]



1 **2**

a) R_1 = CN; R_2 = CN
b) R_1 = CN; R_2 = $COOC_2H_5$
c) R_1 = $COOC_2H_5$; R_2 = $COOC_2H_5$
d) R_1 = CH_3; R_2 = $COOC_2H_5$

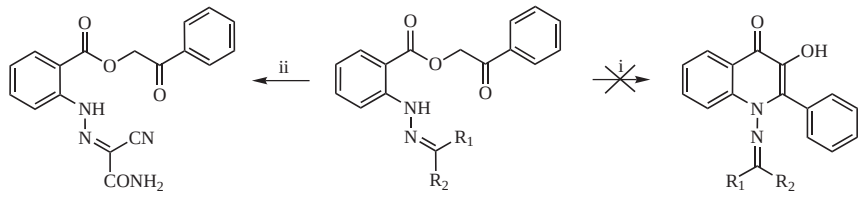
[a] Reagents: (i) $NaNO_2$, HCl, 0-5 °C ; (ii) $R_1CH_2R_2$ (for a-c) or CH_3CO-$CH(CH_3)$-$COOC_2H_5$ (for d); CH_3COONa, 0-5 °C

Cyclization of these compounds **2** to appropriate quinolinones **4** was tried in polyphosphoric acid, *N*-methylpyrrolidone and acetic acid. While the first two media afforded a mixture of numbered products in all cases, cyclization in acetic acid caused hydrolyses of one nitrile group of compound **2a** to yield hydrazone **3**, while hydrazones **2b-2d** remained unaltered. Varying the reaction temperature as well as reaction time did not lead to the target compound **4** (Scheme 2).

Probably the low basicity of nitrogen in the NH group, resulting from its mesomeric effect, is what hinders the cyclization.

In other synthetic strategy, we decided to use benzoyl as the protecting group. Esterification of benzoylhydrazonobenzoic acid **5**, prepared by a known procedure [14], proceeded without complication to afford the ester **6a**. We were interested in the rate of cyclization in comparison to competitive hydrolysis of the benzoyl group in polyphosphoric acid. If the hydrolysis had proceeded more quickly than cyclization, we could have obtained *N*-aminoquinolone **8** and probably 1,2-dihydroindazole-3-one (**9**) or some other side products. Surprisingly, we obtained *N*-benzoyl-3-hydroxy-2-phenyl-4(1*H*)-quinolinone **7a** (Scheme 3).

Scheme 2[a]

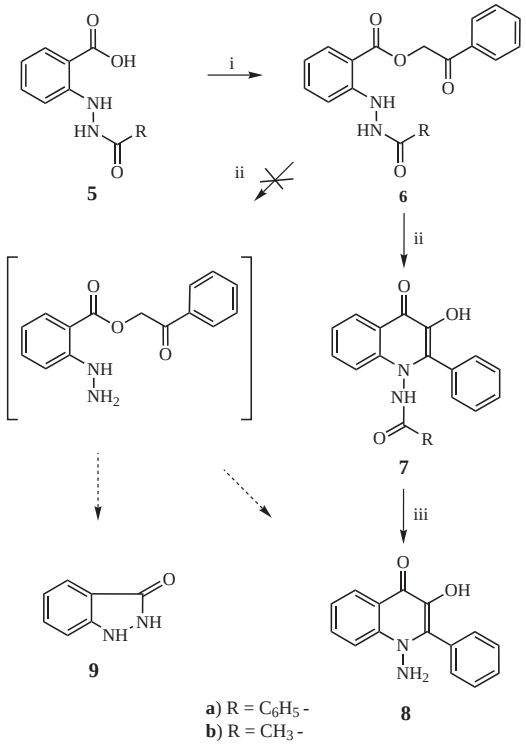


3 **2** **4**

a) R_1 = CN; R_2 = CN
b) R_1 = CN; R_2 = $COOC_2H_5$
c) R_1 = $COOC_2H_5$; R_2 = $COOC_2H_5$
d) R_1 = CH_3; R_2 = $COOC_2H_5$

[a] Reagents (i) polyphosphoric acid 120 °C, *N*-methylpyrrolidon, reflux; (ii) only for a) acetic acid, reflux

Scheme 3[a]



[a] Reagents: (i) $PhCOCH_2Br$, K_2CO_3, DMF, rt; (ii) polyphosphoric acid, 120 °C; (iii) 50% H_2SO_4, 60 °C.

Hydrolysis of the protecting benzoyl group was unsuccessful in boiling hydrochloric acid as well as in 10-15 % sodium hydroxide solution. Anticipating a more facile hydrolysis with the acetyl group (better leaving group) we prepared the *N*-acetyl derivative **7b** [14]. Unfortunately, as in case of benzoyl, it was not possible to hydrolyse this acetyl group in either hydrochloric acid or in sodium hydroxide. The unusual stability of the acyl derivatives **7a** as well as **7b** against hydrolysis and the presence of two amino groups of the hydrazine moiety able to participate in cyclization lead us to undertake a detailed study of the structures of these compounds. An elaborate NMR study including ^1H-^{13}C and ^1H-^{15}N long-range correlation techniques, was conducted for both compounds.

For compound **7a**, the ^1H signal observed at δ = 11.81 ppm was correlated with two nitrogen atoms at δ = 130.5 (multiple-bond interaction) and 139.2 ppm (one-bond interaction). The latter nitrogen atom was also correlated with two aromatic hydrogens at δ = 7.56 and 8.33 ppm. The NH proton was correlated with carbon atoms at δ = 165.6 ppm, which could be assigned to exocyclic C=O carbon, 115.3 and 131.2 ppm. In the case of compound **7b**, two nitrogen atoms were also detected. The N-H pair was proved by a one-bond correlation peak observed at 11.19 ppm (^1H) and 141.9 ppm (^{15}N). This NH nitrogen atom was also correlated with methyl protons (1.72 ppm). Another ^{15}N signal was found at 131.9 ppm correlating with two aromatic protons (7.54 and 8.27 ppm) and CH_3 protons. Thus, the presence of the $CH_3C(O)NHN$ moiety was proved. The ^1H-^{15}N gs-HMBC spectrum of compound **7b** is shown in Figure 1. ^{15}N chemical shifts determined for both nitrogen atoms correspond with literature [15]. The structure of this compound was also elucidated by its ^1H-^{13}C multiple-bond correlation spectrum, as correlation peaks between NH proton and CH_3 carbon (19.8 ppm), aromatic carbon (115.5 ppm), aromatic carbon (138.2 ppm) and C=O carbon (168.4 ppm) were observed.

Finally we tried to remove the protective group by heating compounds **7** in various concentrations of sulphuric acid. As the only effective method for the hydrolysis we found reflux in 50 % sulphuric acid, when both acetyl and benzoyl groups left the quinolone skeleton to afford the desired *N*-aminoquinolinone **8** (Scheme 3).

EXPERIMENTAL

Melting points were determined on a Boetius stage and are not corrected. Infrared spectra were measured in KBr disks and

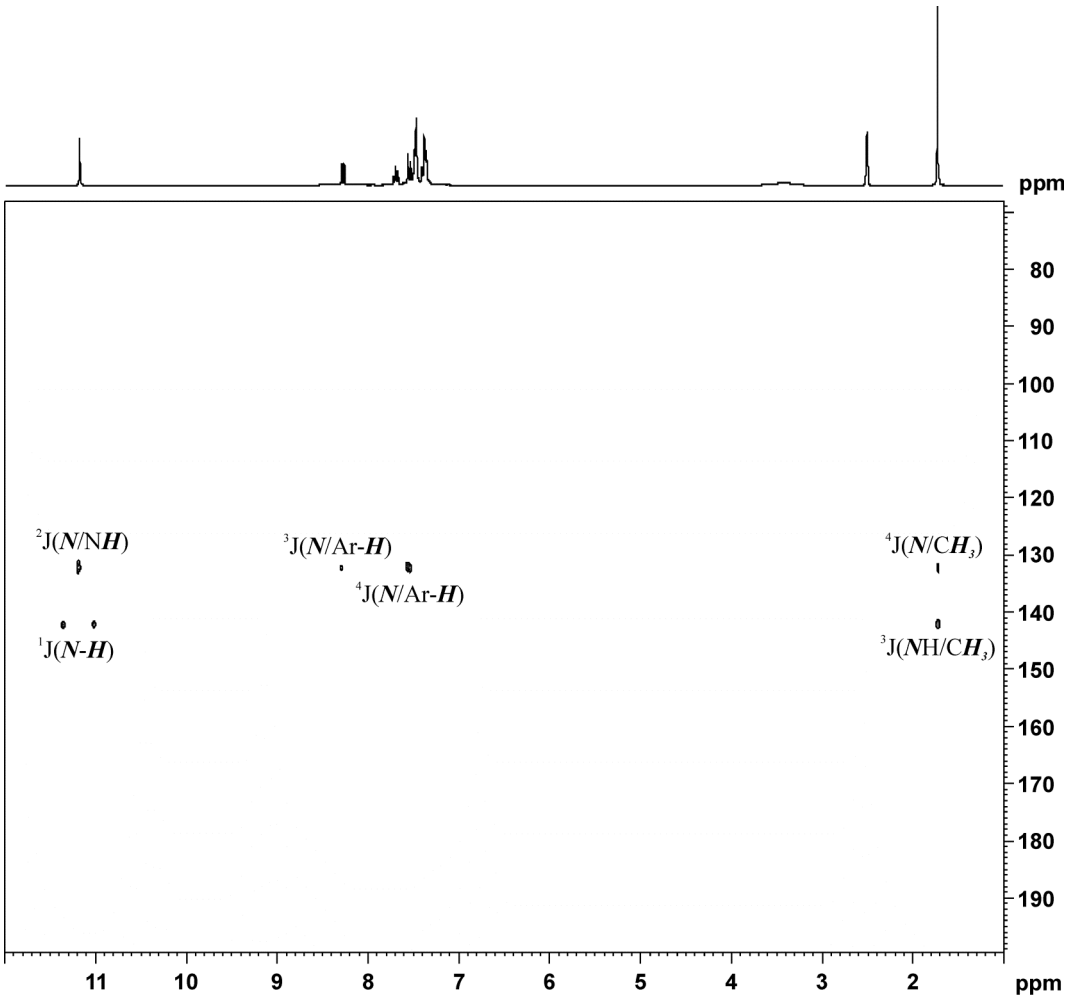


Figure 1. The ^{1}H-^{15}N gs-HMBC spectrum of compound **7b** in DMSO-d_6. A long range delay of 120 ms and a relaxation delay of 2.3 s were used.

scanned on an ATI Unicam Genesis FTIR instrument and values are described in cm^{-1}. Elemental analyses were performed by using an EA 1108 Elemental Analyzer (Fison Instrument). Mass spectrometric experiments were performed using an LCQ ion trap mass spectrometer (Finnigan MAT, San Jose, CA, USA), NMR spectra were measured with a Bruker Avance 300 spectrometer operating at 300.13 MHz (^{1}H), 75.47 MHz (^{13}C) and 30.42 MHz (^{15}N). The compounds were dissolved in DMSO-d_6 and measured at 300 K. Tetramethylsilane was used as an internal standard (^{1}H, ^{13}C). The individual ^{1}H and ^{13}C signals were assigned and refined by means of 2D correlation experiments: the gs-COSY (gradient-selected correlation) [16], gs-HMQC (gradient-selected heteronuclear multiple quantum correlation) [17] ($^{1}J_{H,C}$ = 150 Hz) and gs-HMBC (gradient-selected heteronuclear multiple bond correlation) [17] ($^{n}J_{H,C}$ = 6.0 Hz). ^{15}N NMR chemical shifts were obtained for compounds **7a** and **7b** at natural abundance by the ^{1}H-^{15}N gs-HMBC experiment ($^{n}J_{H,N}$ = 4.2 Hz) [15]. Urea (1 *M* in DMSO-d_6) was used as a secondary external standard (δ = 77.0 ppm) [15].

General Procedure for Preparation of Phenacylesters **2**.

Phenacylester of anthranilic acid (**1**) [9] (3.00 g, 11.8 mmol) was dissolved in hot acetic acid (60 ml) and 3 ml of concentrated hydrochloric acid was added to this solution. After cooling to 0 °C in an ice bath, a solution of sodium nitrite (1.05 g, 15.2 mmol) in water (30 ml) was added. The mixture was stirred in an ice bath for 30 minutes and then poured into solution of appropriate nucleophile (11.8 mmol) and sodium acetate (36.00 g, 0.4 mol) in water (300 ml). The next day, the precipitated solid was filtered, washed with water and dried.

2-[(Dicyano-methylene)-hydrazino] benzoic acid phenacylester (**2a**).

Malondinitrile (0.78 g, 11.8 mmol) was used as the nucleophile. Yield 3.48 g (96%) of yellow crystalline product, mp 169-172 °C; ir: NH 3479; CN 2231; CO 1704, 1681 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 5.86 (s, 2H, CH_2), 7.39 (t, 1H, Ar-H, J = 7.0 Hz), 7.60 (t, 2H, Ar-H, J = 7.5 Hz), 7.68-7.82 (m, 3H, Ar-H), 8.03 (d, 2H, Ar-H, J = 8.1 Hz), 8.13 (m, 1H, Ar-H), 12.88 (bs, 1H, NH); ms: m/z 333 (M^{+}).

Anal. Calcd. for $C_{18}H_{12}N_4O_3$: C, 65.06; H, 3.64; N, 16.86. Found: C, 64.97; H, 3.72; N, 16.47.

2-[(Ethoxycarbonyl-cyano-methylene)-hydrazino] benzoic acid phenacylester (**2b**).

Ethylcyanoacetate (1.25 ml, 11.8 mmol) was used as nucleophile. Yield 4.23 g (94%) of yellow crystalline product, mp 130-134 °C; ir: NH 3160; CN 2213; CO 1711, 1686, 1608 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.31 (t, 3H, CH_3, J = 7.1 Hz), 4.32 (q, 2H, CH_2, J = 7.1 Hz), 5.88 (s, 2H, CH_2), 7.35 (t, 1H, Ar-H, J = 7.0 Hz), 7.60 (t, 2H, Ar-H, J = 7.5 Hz), 7.70-7.85 (m, 3H, Ar-H), 8.04 (d, 2H, Ar-H, J = 7.7 Hz), 8.17 (d, 1H, Ar-H, J = 8.1 Hz), 12.45 (s, 1H, NH) ;ms: m/z 380 (M^+).

Anal. Calcd. for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08. Found: C, 63.62; H, 4.23; N, 10.87.

2-[(Bis-ethoxycarbonyl-methylene)-hydrazino] benzoic acid phenacylester (**2c**).

Diethylmalonate (1.78 ml, 11.8 mmol) was used as nucleophile. Yield 3.23 g (64%). Recrystallization from ethanol afforded pale yellow crystals, mp 157-161 °C; ir: NH 3362; CO 1721, 1694, 1635 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.22 (t, 3H, CH_3, J = 7.1 Hz), 1.29 (t, 3H, CH_3, J = 7.1 Hz), 4.25 (q, 2H, CH_2, J = 7.1 Hz), 4.27 (q, 2H, CH_2, J = 7.1 Hz), 5.83 (s, 2H, CH_2), 7.25 (t, 1H, Ar-H, J = 7.5 Hz), 7.60 (t, 2H, Ar-H, J = 7.5 Hz), 7.70-7.78 (m, 2H, Ar-H), 7.85 (d, 1H, Ar-H, J = 8.2 Hz), 8.04 (d, 2H, Ar-H, J = 7.5 Hz), 8.13 (d, 1H, Ar-H, J = 8.1 Hz), 13.75 (s, 1H, NH); ms: m/z 427 (M^+).

Anal. Calcd. for $C_{22}H_{22}N_2O_7$: C, 61.97; H, 5.20; N, 6.57. Found: C, 62.18; H, 5.24; N, 6.54.

2-[(Methyl-ethoxykarbonyl-methylene)-hydrazino] benzoic acid phenacylester (**2d**).

Ethyl-2-methyl acetoacetate (1.67 ml, 11.8 mmol) was used as nucleophile. Yield 4.01 g (92%) of yellow crystalline product, mp 162-168 °C; ir: NH 3413; CO 1727, 1706, 1687 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.29 (t, 3H, CH_3, J = 7.1 Hz), 2.04 (s, 3H, CH_3), 4.23 (q, 2H, CH_2, J = 7.1 Hz), 5.83 (s, 2H, CH_2), 7.06 (t, 1H, Ar-H, J = 7.5 Hz), 7.59 (t, 2H, Ar-H, J = 7.5 Hz), 7.69-7.77 (m, 2H, Ar-H), 7.82 (d, 1H, Ar-H, J = 8.6 Hz), 8.01-8.09 (m, 3H, Ar-H), 10.92 (s, 1H, NH); ms: m/z 369 (M^+).

Anal. Calcd. for $C_{20}H_{20}N_2O_5$: C, 65.22; H, 5.43; N, 7.61. Found: C, 65.24; H, 5.78; N, 7.36.

2-[*N*-(Carbamoyl-cyano-methylene)- hydrazino] benzoic acid phenacylester (**3**).

Derivative **2a** (150 mg, 0.5 mmol) was suspended in acetic acid (2 ml). This reaction mixture was refluxed for 25 hours, after which the hot solution was filtered and the yellow precipitate obtained was washed with water to yield 110 mg (70%), mp 225-229 °C; ir: NH 3481, 3364; CN 2219; CO 1705, 1685 cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.86 (s, 2H, CH_2), 7.26 (t, 1H, Ar-H, J = 7.8 Hz), 7.59 (t, 2H, Ar-H, J = 7.8 Hz), 7.70-7.76 (m, 3H, Ar-H), 8.03 (d, 2H, Ar-H, J = 7.8 Hz), 8.13 (d, 2H, Ar-H, J = 7.8 Hz), 8.23 (d, 1H, Ar-H, J = 8.4 Hz), 12.15 (s, 1H, NH); ms: m/z 351 (M^+).

Anal. Calcd. for $C_{18}H_{14}N_4O_4$: C, 61.71; H, 4.03; N, 15.99. Found: C, 61.28; H, 3.76; N, 15.76.

N-Benzoyl-hydrazinobenzoic acid phenacylester (**6a**).

To a solution of *N*-benzoyl-hydrazinobenzoic acid **5a** [14] (2.00 g, 7.8 mmol) in DMF (50 ml), solid sodium bicarbonate ($NaHCO_3$; 0.72 g, 8.6 mmol) was added. The mixture was stirred at 100 °C until the bicarbonate had dissolved. The solution was then cooled to room temperature and phenacylbromide (1.3 g, 6.5 mmol) was slowly added. The reaction mixture was stirred for 30 minutes and then poured into a 5% aqueous solution of $NaHCO_3$ (200 ml). The pale yellow precipitate was filtered, washed with water and dried to yield 1.80 g (62%), mp 160-162 °C; ir: NH 3309; CO 1705, 1690, 1650 cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.75 (s, 2H, CH_2), 6.88 (t, 1H, Ar-H, J = 7.5 Hz), 7.02 (d, 1H, Ar-H, J = 8.1 Hz), 7.47-7.54 (m, 3H, Ar-H), 7.55-7.63 (m, 3H, Ar-H), 7.71 (t, 1H, Ar-H, J = 7.4 Hz), 7.91 (d, 2H, Ar-H, J = 7.5 Hz), 7.98-8.05 (m, 3H, Ar-H), 9.00 (s, 1H, NH), 10.67 (s, 1H, NH); ms: m/z 375 (M^+).

Anal. Calcd. for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.43; H, 4.55; N, 7.36.

N-Acetyl-hydrazinobenzoic acid phenacylester (**6b**).

To a solution of *N*-acetyl-hydrazinobenzoic acid **5b** [14] (500.0 mg, 2.6 mmol) in DMF (10 ml) solid sodium bicarbonate ($NaHCO_3$; 238.1 mg, 2.8 mmol) was added. The mixture was stirred at 100 °C until the bicarbonate dissolved. Then the solution was cooled down to room temperature and phenacylbromide (428.9 mg, 2.2 mmol) was slowly added. The reaction mixture was stirred for 30 minutes and then poured into 50 ml of 5% aqueous solution of $NaHCO_3$. The white precipitate was filtered, washed with water and dried to yield 560 mg (67%), mp 166-168 °C; ir: NH 3288; CO 1705, 1691, 1658 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.93 (s, 3H, CH_3), 5.74 (s, 2H, CH_2), 6.84 (t, 1H, Ar-H, J = 7.5 Hz), 6.93 (d, 1H, Ar-H, J = 8.2 Hz), 7.49 (t, 1H, Ar-H, J = 7.9 Hz), 7.59 (t, 2H, Ar-H, J = 7.5 Hz), 7.72 (t, 1H, Ar-H, J = 7.3 Hz), 7.97 (dd, 1H, Ar-H, J = 8.1 Hz, J = 1.5 Hz), 8.02 (d, 2H, Ar-H, J = 7.5 Hz), 8.76 (d, 1H, NH, J = 2.0 Hz), 9.95 (d, 1H, NH, J = 2.0 Hz); ms: m/z 313 (M^+).

Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.13; N, 8.97. Found: C, 65.24; H, 5.43; N, 8.63.

General Procedure for Preparation of Quinolinones **7**.

Appropriate derivative **6** was suspended in polyphosphoric acid (15 ml) and heated to 120 °C. The reaction mixture was stirred at this temperature for 30 minutes and then poured onto crushed ice. The brown precipitate was filtered, washed with water and dried.

N-Benzoyl-3-hydroxy-2-phenyl-4(1*H*)-quinolinone (**7a**).

General procedure starting from derivative **6a** (1.50 g, 4.0 mmol). Yield 1.33 g (93%), mp 160-167 °C; ir: OH 3468; NH 3263; CO 1701, 1659 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.37-7.49 (m, 8H, Ar-H), 7.52-7.61 (m, 4H, Ar-H), 7.71 (t, 1H, Ar-H, J = 7.7 Hz), 8.33 (dd, 1H, Ar-H, J = 8.1 Hz, J = 1.1 Hz), 8.49 (bs, 1H, OH), 11.81 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 115.3, 122.1, 122.8, 125.1, 127.2, 127.7, 128.5, 128.8, 129.5, 130.4, 131.2, 132.0, 132.4, 137.0, 138.4, 139.7, 165.6, 170.5 ; ms: m/z 357 (M^+).

Anal. Calcd. for $C_{22}H_{16}N_2O_3 .H_2O$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.72; H, 4.68; N, 7.57.

N-Acetyl-3-hydroxy-2-phenyl-4(1*H*)-quinolinone (**7b**).

General procedure starting from derivative **6b** (1.50 g, 4.8 mmol). Yield 1.37 g (97%), mp 242-248 °C; ir: OH 3373; NH 3146; CO 1709, 1625 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.72 (s, 3H,

CH_3), 7.33-7.42 (m, 3H, Ar-H), 7.44-7.51 (m, 3H, Ar-H), 7.54 (d, 1H, Ar-H, J = 8.6 Hz), 7.70 (t, 1H, Ar-H, J = 7.9 Hz), 8.27 (d, 1H, Ar-H, J = 8.2 Hz, J = 1.1 Hz), 8.38 (bs, 1H, OH), 11.19 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 19.8, 115.5, 121.9, 122.8, 125.0, 127.7, 128.8, 129.4, 130.5, 131.9, 136.8, 138.2, 139.5, 168.4, 170.3; ms: m/z 295 (M^+).

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.11; H, 5.02; N, 9.17.

N-Amino-3-hydroxy-2-phenyl-4(1*H)*-quinolinone (**8**).

a) Derivative **7a** (186.0 mg, 0.5 mmol) was suspended in 50% solution of sulphuric acid (5 ml). The reaction mixture was refluxed for 1 hour and then poured onto ice. The solution was subsequently neutralized with aqueous ammonia and the dark brown precipitate filtered, washed with water and dried to yield 73.9 mg (56%).

b) Above mentioned procedure starting from derivative **7b** (147.0 mg, 0.5 mmol). Yield 65.5 mg (52 %); mp 199-205 °C; ir: NH 3194; CO 1719, 1694, 1607 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 5.68 (s, 2H, NH_2), 7.34 (t, 1H, Ar-H, J = 7.3 Hz), 7.42-7.52 (m, 5H, Ar-H), 7.71 (t, 1H, Ar-H, J = 7.9 Hz), 8.08 (d, 1H, Ar-H, J = 8.8 Hz), 8.12 (bs, 1H, OH), 8.25 (dd, 1H, Ar-H, J = 8.2 Hz, J = 1.3 Hz); ms: m/z 253 (M^+).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.83; H, 4.41; N, 11.03.

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REFERENCES

[1] E. J. Iwanowicz, J. Edwin, S.H. Watterson, T. G. Dhar, P. Murali, J. William, H.H. Gu, Patent WO 2001081340 (2001); *Chem. Abstr*., **135**, 44472.

[2] Z. Sui, V. N. Nguyen, J. Altom, J. Fernandez, J. J. Hilliard, J. I. Bernstein, J. F. Barrett, K. A. Ohemeng, *Eur. J. Med. Chem*., **34(5)**, 381 (1999).

[3] R. P. Verma, *Bioorg. Med. Chem.*, **13(4)**, 1059 (2005).

[4] P. Hradil, P. Krejci, J. Hlavac, I. Wiedermannova, A. Lycka, V. Bertolasi, *J. Heterocyclic Chem.*, **41(3)**, 375 (2004).

[5] U. Frerichs-Deeken, K. Ranguelova, R. Kappl, J. Huettermann, S. Fetzner, *Biochemistry*, **43(45)**, 14485 (2004).

[6] E. E. Deschner, J. Ruperto, G. Wong, H. L. Newmark, *Carcinogenesis*, **12 (7)**, 1193 (1991).

[7] V. Elangovan, N. Sekar, S. Govindasamy, *Cancer Lett*., 87, 107 (1994).

[8] S. Kuo, *Cancer Lett*., **110**, 41, (1996).

[9] P. Hradil, J. Jirman, *Collect. Czech. Chem. Commun*., **60**, 1357 (1995).

[10] P. Hradil, J. Hlavac, K. Lemr, *J. Heterocyclic Chem.*, **36(1)**, 141 (1999).

[11] E. L. Ellsworth, R. J. Sciotti, J. T. Starr, Patent WO 2005026165 (2005), *Chem. Abstr*., **142**, 336263 (2005).

[12] S. Watanuki, Y. Koga, H. Moritomo, I. Tsukamoto, D. Kaga, T. Okuda, F. Hirayama, Y. Moritani, J. Takasaki, Patent WO 2005009971 (2005); *Chem. Abstr*., **142**, 197896 (2005).

[13] O. Tabarrini, M. Stevens, V. Cecchetti, S. Sabatini, M. Dell'Uomo, G. Manfroni, M. Palumbo, C. Pannecouque, E. De Clercq, A. Fravolini, *J. Med. Chem.*, **47(22)**, 5567 (2004).

[14] R. M. Anderson, *J. Chem. Res. Synopses*, **12**, 376 (1985).

[15] R. Marek, A. Lyčka, *Curr. Org. Chem*., **6**, 35 (2002).

[16] A. L. Davis, E. D. Laue, J. Keeler, D. Moskau, J. Lohman, *Magn. Reson*., **94**, 637 (1991).

[17] W. Willker, D. Leibfritz, R. Kerssebaum, W. Bermel, *Magn. Reson. Chem*., **31**, 287 (1993).