PREPARATION OF 1-HYDROXYXANTHEN-9(9*H*)-ONES AND 1-HYDROXYACRIDIN-9(10*H*)-ONES VIA CORRESPONDING 3,4-DIHYDRO-1,9(2*H*)-DIONES

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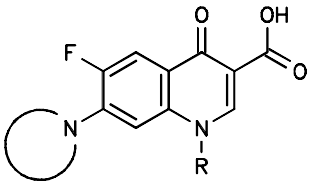
Target 10-cyclopropyl-7-fluoro-1-hydroxy-6-(4-methyl-1-piperazinyl)acridin-9(10*H*)-one (*IVc*) and 7-fluoro-1-hydroxy-6-(4-methyl-1-piperazinyl)-9*H*-xanthen-9-one (*IVd*) were obtained from corresponding difluoro derivatives *IVa* and *IVb*, respectively. These intermediates were synthesized via respective 3,4-dihydro-1,9(2*H*)-diones *Va* and *Vb*. Acridine derivative (10-cyclopropyl-6,7-difluoro-3,4-dihydro-1*H*-acridine-1,9(2*H*,10*H*)-dione, *Va*) was synthesized from 1-cyclopropyl-6,7-difluoroisatoic anhydride (*XI*) and xanthene derivative (6,7-difluoro-3,4-dihydro-1*H*-xanthen-1,9(2*H*)-dione, *Vb*) from cyclohexenone derivative *VIb*. Several unsuccessful attempts to prepare hydroxyacridone *IVc* and/or some useful intermediates of its synthesis are also described.

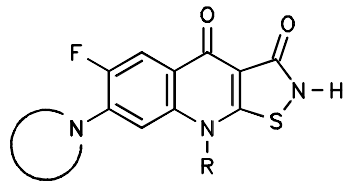
Antibacterial quinolones, which exert their activity by inhibiting bacterial DNA gyrase, have attracted increasing attention as a source of clinically useful drugs[1,2]. During our research into antibacterial quinolones we were also interested in compounds having at the position 3 various groups that could mimic the carboxylic group present in these drugs of a general formula *I*. All compounds derived by a simple replacement of the carboxy group with carboxymethyl, phosphonic, sulfonic[1], hydroxy[3], nitro[4], amino or acylamino[5] groups have been found to be virtually inactive. On the other hand, compounds of general formula *II*, having an isothiazolone ring annelated to the 2,3-position of the quinolone moiety, have been found to be extremely active DNA gyrase inhibitors[6]. Since only compounds having an unsubstituted isothiazolone nitrogen were found to be active, we envisaged that involvement of the tautomers *III* may be important to their biological action. Therefore we decided to prepare similar 1-hydroxyacridin-9(10*H*)-one (*IVc*) and investigate the biological activity of this compound. 1-Hydroxyxanthen-9(9*H*)-one derivative *IVd* was also included because some flavone DNA gyrase inhibitors have recently been reported[7]. For our initial study we chose a cyclopropyl group as the *N*-1 substituent and a 4-methyl-1-piperazinyl group as the cyclic amine residue as a typical substitution pattern present in many potent quinolones. Synthetic work connected with the preparation of these structures is reported herein.

We needed a suitable procedure for the preparation of intermediate difluoro derivatives *IVa* and *IVb*. A straightforward strategy based on dehydrogenation of the respective compounds *Va* and *Vb* was chosen. We hoped that these intermediates would be accessible by a nucleophilic cyclization of compounds *VIIIb* and *VIIb*, respectively, and that *VIIIb* could be easily prepared from *VIIb*.

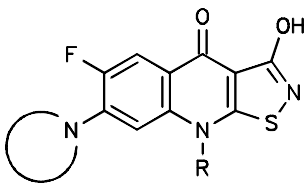
A literature procedure[8] describes a simple method for the preparation of 2-benzoylcyclohexane-1,3-dione based on the *O*-acylation of cyclohexane-1,3-dione with benzoyl chloride, followed by rearrangement of the resulting *O*-acyl derivative *VIa* to afford the corresponding *C*-acyl derivative *VIIa*. When this method was applied to the



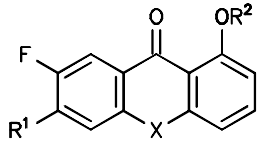
I



II



III

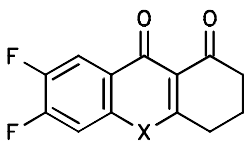


IV	X	R^1	R^2
a	N-cPr	F	H
b	O	F	H
c	N-cPr	4MeP	H
d	O	4MeP	H
e	N-cPr	4MeP	Me
f	O	F	Me

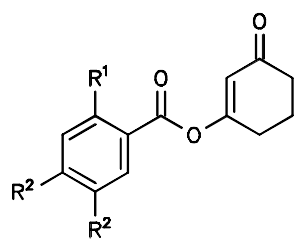
In formulae *IV* and *X*: cPr = cyclopropyl, 4MeP = 4-methylpiperazinyl

rearrangement of trifluoro derivative *VIb*, spontaneous cyclization of intermediate *VIIb* occurred providing directly *Vb***.** As we expected, compound *Vb* was easily dehydrogenated to 1-hydroxyxanthone derivative *IVb* by refluxing with palladium on carbon in ethanol. Compound *IVb* was then converted to the target structure *IVd* by treatment with *N*-methylpiperazine.

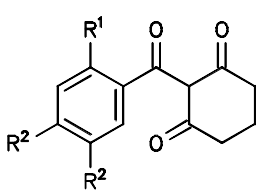
Encouraged by the easy preparation of *IVd*, we explored various ways for the preparation of analogous acridone derivatives. Since all attempts to isolate *VIIb* failed, the reactive 2-fluoro substituent was replaced by a 2-chloro atom. Application of the same reaction sequence provided *VIIc*. Compounds *VIIIa* and *VIIIc* were prepared by a treatment of *VIIa* and *VIIc*, respectively, with cyclopropylamine. Alternatively *VIIIa* was also prepared via the corresponding morpholino derivative *IXa*. Attempts to cyclize *VIIIc* to the corresponding acridinedione derivative *Va* both under nucleophilic conditions (DBU, NaH, BuLi) and with copper catalysts (Cu, CuO, Cu_2O, $Cu(OAc)_2$) failed.



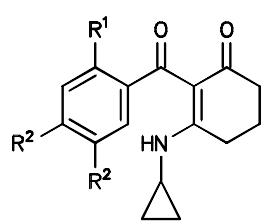
V	X
a	N–cPr
b	O



VI



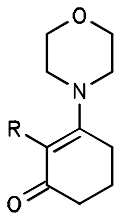
VII



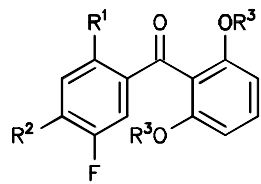
VI–VIII	R^1	R^2
a	H	H
b	F	F
c	Cl	F

We also envisaged to utilize a strategy involving the acylation of 3-(4-morpholinyl)-2-cyclohexen-1-one (*IXb*) with 2,4,5-trifluorobenzoyl chloride. 3-(4-Morpholinyl)-2-cyclohexen-1-one (*IXb*), as a representative cyclic enamino ketone, could behave either as a carbanion or as an enolate. Unfortunately, model acylation of this compound with benzoyl chloride provided, after work-up, exclusively the *O*-acyl derivative *VIa*. The reaction was monitored by TLC and none of the desired derivative *IXa* could be detected.

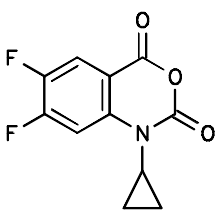
Having compound *VIIIc* we tried another approach based on a report, that treatment of 2-methoxy-2′-aminobenzophenones with sodium hydride in DMSO affords acridone derivatives[9,10]. In our case, dimethoxybenzophenone *Xd* should lead to 1-methoxyacridone *IVe*. Since a 1-methoxy group in acridones can be easily demethylated either with hydrochloric acid or by treatment with a Lewis acid as boron tribromide[11], this approach could lead to the target 1-hydroxyacridone *IVa*. Our reaction pathway starts from compound *VIIIc*. The first step was a potential source of trouble because similar 2-acylcyclohexane-1,3-diones had been found surprisingly resistant to dehydrogenation[12]. Indeed, catalytic dehydrogenation of *VIIIc* to the corresponding resorcine derivative *Xa* with palladium on carbon was unsuccessful, as well as oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The only literature method for the



IX	R
a	PhCO
b	H



X	R^1	R^2	R^3
a	Cl	F	H
b	Cl	F	Me
c	Cl	4MeP	Me
d	NH–cPr	4MeP	Me



XI

oxidation of 2-acylcyclohexane-1,3-diones to 2-acylresorcine derivatives used mercuric acetate and sodium acetate in acetic acid. Compound *Xa* was successfully prepared by this method and its methylation with iodomethane provided a mixture of the dimethoxy derivative *Xb* and 1-methoxyxanthen-9(9*H*)-one *IVf*. Compound *Xb*, when treated with *N*-methylpiperazine provided derivative *Xc*. Some copper catalysts are useful in displacement of 2-chloro atom of 2-chloroacetophenones[13] and 2-chlorobenzoic[14] acids with various amines. Unfortunately attempts to convert compound *Xc* to *Xd* by treatment with cyclopropyl amine under pressure failed with all copper catalysts tested (Cu, CuO, Cu_2O, $Cu(OAc)_2$).

Compound *Xa* can be also used as an intermediate for the synthesis of 10-hydroxyxanthones. Hydroxyxanthone *IVb* was prepared from *Xa* by a nucleophilic cyclization with sodium hydride. More surprisingly, treatment of *Xa* with *N*-methylpiperazine provided directly *IVd*.

Since we failed to construct the acridone skeleton from any intermediates we had used for the synthesis of corresponding xanthone analogs, we decided to adopt a different approach. *N*-Unsubstituted isatoic anhydrides are known to react with sodium salt of cyclohexane-1,3-dione at 50–100 °C to provide their corresponding dioxoacridine derivatives[15]. The same treatment of 1-cyclopropyl-6,7-difluoroisatoic anhydride (*XI*), which was prepared from 2-chloro-4,5-difluorobenzoic acid according to the literature procedure[14], provided a complex mixture. However, when the reaction was performed at room temperature, the desired compound *Va* was obtained in good yield. 1-Hydroxyacridone derivative *IVa* was prepared from *Va* by catalytic dehydrogenation similarly as described for analogous 1-hydroxyxanthone derivative *IVb*. Nucleophilic displacement of fluorine at position 6 in *IVa* by *N*-methylpiperazine provided the target structure *IVc*.

EXPERIMENTAL

Melting points were measured on Thomas Hoover capillary apparatus and are uncorrected. IR spectra were taken on a Digilab FTS 15E spectrophotometer (wavenumbers in cm^{-1}) and UV spectra on a Cary 17D spectrometer. ^1H NMR spectra were recorded on a Varian XL-200 instrument (200 MHz). Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. Mass spectra were obtained on a VG 7070 E-HF spectrometer. Flash and vacuum chromatography were done on silica gel 60 (230–400 mesh) from EM Science. A model 7924T Chromatotron® from Marrilon Research was used for radial chromatography.

3-(2,4,5-Trifluorobenzoyloxy)-2-cyclohexen-1-one (*VIb*)

A mixture of 2,4,5-trifluorobenzoic acid (4.40 g, 25 mmol), thionyl chloride (15 ml, 0.2 mol) and a drop of DMF was refluxed for 2 h, and then thionyl chloride was evaporated in vacuo, the residue was dissolved in dichloromethane (20 ml) and the solution was added dropwise to a stirred solution of cyclohexane-1,3-dione (2.8 g, 25 mmol) and pyridine (2 ml, 25 mmol) in dichloromethane (100 ml) and the reaction mixture was stirred at room temperature overnight. Then the reaction mixture was washed with 5 M hydrochloric acid (40 ml), saturated solution of sodium hydrogen carbonate

(2 × 20 ml), and water (2 × 20 ml) and dried with magnesium sulfate. The residue was dissolved in dichloromethane and purified by vacuum chromatography yielding 4.65 g of oily product (68%, dried under high vacuum). The compound was used for the next step without further purification. ^{1}H NMR spectrum ($CDCl_3$): 2.08–2.19 m, 2 H (CH_2); 2.45–2.65 m, 4 H (CH_2–C=O, CH_2–C=); 6.03 s, 1 H (CH); 7.00–7.15 m, 1 H (H-3); 7.76–7.90 m, 1 H (H-6).

3-(2-Chloro-4,5-difluorobenzoyloxy)-2-cyclohexen-1-one (*VIc*)

A mixture of 2-chloro-4,5-difluorobenzoic acid (9.63 g, 50 mmol), thionyl chloride (30 ml, 0.4 mol) and a drop of DMF was refluxed for 2 h, then thionyl chloride was evaporated in vacuo, the residue was dissolved in dichloromethane (40 ml) and the solution was added dropwise to a stirred solution of cyclohexane-1,3-dione (5.6 g, 50 mmol) and pyridine (4 ml, 50 mmol) in dichloromethane (200 ml) and the reaction mixture was stirred at room temperature overnight. Then the mixture was washed with 5 M hydrochloric acid (100 ml), saturated solution of sodium hydrogen carbonate (2 × 50 ml), and water (2 × 50 ml) and dried with magnesium sulfate. The residue was dissolved in dichloromethane and purified by vacuum chromatography to give 8.4 g of oily product (58.6%, dried under high vacuum) which was used for the next step without identification.

2-(2-Chloro-4,5-difluorobenzoyl)-1,3-cyclohexandione (*VIIc*)

A solution of *VIc* (2.87 g, 10 mmol) in 1,2-dichloroethane (10 ml) was added dropwise at room temperature to a stirred suspension of aluminium chloride (3 g, 22.5 mmol) in 1,2-dichloroethane (50 ml) and the mixture was stirred at room temperature overnight. Then the mixture was poured onto a mixture of ice (10 g) and concentrated hydrochloric acid (10 ml). Water layer was extracted with 1,2-dichloroethane (10 × 20 ml), organic extracts were combined, washed with water and dried with magnesium sulfate. Crystallization of the crude product from hexane–acetone (9 : 1) provided 2.35 g (82%) of white crystals, m.p. 107–108 °C. For $C_{13}H_9ClF_2O_3$ (286.7) calculated: 54.47% C, 3.16% H, 12.37% Cl, 13.25% F; found: 54.26% C, 2.92% H, 12.39% Cl, 13.54% F. ^{1}H NMR spectrum ($CDCl_3$): 2.03–2.10 m, 2 H (CH_2); 2.45–2.49 m, 2 H (CH_2); 2.78–2.81 m, 2 H (CH_2); 7.04–7.08 m, 1 H (arom. H); 7.20–7.24 m, 1 H (arom. H). IR spectrum ($CHCl_3$): 1 676 (C=O). UV spectrum, λ_{max} (log ε): 213 (4.04), 228 (4.05), 282 (4.03). Mass spectrum (*m/z*, %): 251 (M – Cl, 100).

2-Benzoyl-3-(4-morpholinyl)-2-cyclohexen-1-one (*IXb*)

A mixture of 2-benzoylcyclohexane-1,3-dione (*VIIa*) (0.4 g, 1.85 mmol), morpholine (0.26 g, 3 mmol), benzene (20 ml) and a crystal of 4-toluenesulfonic acid monohydrate was refluxed for 4 h, evaporated to dryness and the residue was crystallized from toluene; yield 0.5 g (95%) of yellow crystals, m.p. 229–230 °C. For $C_{17}H_{19}NO_3$ (285.3) calculated: 71.56% C, 6.71% H, 4.91% N; found: 71.67% C, 6.76% H, 4.88% N. ^{1}H NMR spectrum ($CDCl_3$): 1.91–2.00 m, 2 H (CH_2); 2.45 m, 4 H (CH_2–C=O, CH_2–C=); 3.60–4.00 m, 8 H (H of morpholine); 7.30–7.50 m, 5 H (H of phenyl). IR spectrum ($CHCl_3$): 1 631, 1 577 (C=O). UV spectrum, λ_{max} (log ε): 248 (4.39), 300 (3.56), 362 (3.81). Mass spectrum (*m/z*, %): 285 (M^+), 284 (100).

2-Benzoyl-3-(cyclopropylamino)-2-cyclohexen-1-one (*VIIIa*)

A) Cyclopropylamine (140 ml, 2 mmol) was added via syringe to a stirred solution of *IXb* (0.43 g, 1.5 mmol) in dichloromethane (10 ml) and the mixture was stirred at room temperature for 24 h. Then another portion of cyclopropylamine was added (20 µl, 0.3 mmol) and stirring continued for additional 24 h. The mixture was washed with water, dried with magnesium sulfate and purified by

radial chromatography on Chromatotron (hexane–ethyl acetate 1 : 1). Crystallization from hexane provided 0.36 g (95%) of white crystals, m.p. 114–115 °C. For $C_{16}H_{15}NO_2$ (253.3) calculated: 75.87% C, 5.97% H, 5.53% N; found: 75.74% C, 6.01% H, 5.41% N. ^{1}H NMR spectrum ($CDCl_3$): 0.70–0.79 m, 4 H (CH_2 of cyclopropyl); 1.86–1.89 m, 2 H (CH_2); 2.40–2.55 m, 5 H (CH_2–C=O, CH_2–C=, CH of cyclopropyl); 7.19–7.51 m, 5 H (H of phenyl). IR spectrum ($CHCl_3$): 1 643 (C=O). UV spectrum, λ_{max} (log ε): 252 (4.17), 317 (4.17). Mass spectrum (*m/z*, %): 255 (M^+, 77), 199 (100).

B) A mixture of 2-benzoylcyclohexane-1,3-dione (*VIIa*; 0.22 g, 1 mmol), cyclopropylamine (0.1 ml, 1.4 mmol) and dichloromethane (5 ml) was stirred at room temperature for 24 h, then evaporated and crystallized from hexane yielding 0.21 g (83%) of the product, m.p. 114–115 °C.

2-(2-Chloro-4,5-difluorobenzoyl)-3-(cyclopropylamino)-2-cyclohexen-1-one (*VIIIc*)

Cyclopropylamine (1.5 ml, 21.6 mmol) was added to a solution of *VIIc* (2.87 g, 10 mmol) in dichloromethane (60 ml) and the mixture was stirred at room temperature overnight, evaporated and the residue was purified by radial chromatography on Chromatotron (hexane–acetone 9 : 1) giving after crystallization from hexane 2.2 g (67%) of white crystals, m.p. 111–113 °C. For $C_{16}H_{14}ClF_2NO_2$ (325.7) calculated: 59.00% C, 4.33% H, 10.88% Cl, 11.66% F, 4.30% N; found: 58.50% C, 4.21% H, 11.18% Cl, 11.44% F, 4.44% N. ^{1}H NMR spectrum ($CDCl_3$): 0.66–0.90 m, 4 H (CH_2 of cyclopropyl); 1.86–1.99 m, 2 H (CH_2); 2.42–2.54 m, 5 H (CH_2–C=O, CH_2–C=, CH of cyclopropyl); 6.96 dd, 1 H, *J* = 8 and 10 (arom. H); 7.32 dd, 1 H, *J* = 8 and 10 (arom. H); 13.26 bs, 1 H (NH). IR spectrum ($CHCl_3$): 1 644 (C=O). UV spectrum, λ_{max} (log ε): 252 (4.13), 318 (4.23). Mass spectrum (*m/z*, %): 326 (M + H, 1), 290 (M – Cl, 100).

6,7-Difluoro-3,4-dihydro-1*H*-xanthen-1,9(2*H*)-dione (*Vb*)

Solution of *VIb* (2.3 g, 8.5 mmol) in 1,2-dichloroethane (10 ml) was added dropwise to a stirred mixture of aluminium chloride (2.5 g, 18.7 mmol) in 1,2-dichloromethane (60 ml) at 0 °C. Then the mixture was stirred at room temperature for 24 h and poured into a mixture of ice (15 g) and concentrated hydrochloric acid (15 ml). Aqueous layer was extracted with 1,2-dichloroethane (5 × 25 ml), organic solutions were combined, washed with 5 M hydrochloric acid (2 × 25 ml) and water (2 × 50 ml) and dried with magnesium sulfate. The residue after evaporation of 1,2-dichloroethane was dissolved in ethanol (25 ml) and refluxed for 1 h, evaporated and crystallized from ethanol; yield 1.35 g (54%), m.p. 203–205 °C. For $C_{13}H_8F_2O_3$ (250.2) calculated: 62.41% C, 3.22% H, 15.19% F; found: 62.20% C, 3.18% H, 14.93% F. ^{1}H NMR spectrum ($CDCl_3$): 2.10–2.26 m, 2 H (CH_2); 2.58–2.65 m, 2 H (CH_2); 2.98–3.04 m, 2 H (CH_2); 7.28 dd, 1 H, *J* = 8 and 10 (H-5); 7.94–8.07 dd, 1 H, *J* = 8 and 10 (H-8). IR spectrum ($CHCl_3$): 1 706 (C=O). UV spectrum, λ_{max} (log ε): 205 (4.27), 225 (4.24), 237 (4.27), 247 (4.24), 289 (3.74), 300 (3.74). Mass spectrum (*m/z*, %): 250 (M^+, 68), 222 (100).

6,7-Difluoro-1-hydroxy-9*H*-xanthen-9-one (*IVb*)

A) A mixture of *Vb* (0.25 g, 1 mmol), ethanol (20 ml), and 10% Pd on carbon (0.1 g) was refluxed with a stream of nitrogen bubbled through the mixture for 2 h, then the catalyst was filtered off through a cellite pad and washed with hot ethanol. The filtrate was cooled and the formed crystals were filtered off. The filtrate was concentrated to one third of its volume and another crop was obtained; yield 0.23 g (93%), m.p. 200–201 °C. For $C_{13}H_6F_2O_3$ (248.2) calculated: 62.91% C, 2.44% H, 15.31% F; found: 62.83% C, 2.39% H, 15.16% F. ^{1}H NMR spectrum ($CDCl_3$): 6.82 d, 1 H, *J* = 8 (H-2 or H-4); 6.97 d, 1 H, *J* = 8 (H-2 or H-4); 7.36 dd, 1 H, *J* = 7 and 9 (H-5); 7.64 t, 1 H, *J* = 8 (H-3); 8.06 dd, 1 H, *J* = 7 and 9 (H-8). IR spectrum ($CHCl_3$): 1 649 (C=O). UV spectrum, λ_{max} (log ε): 226 (4.37), 244 (4.41), 285 (3.88), 361 (3.72). Mass spectrum (*m/z*, %): 248 (M^+, 100).

B) A solution of DDQ (0.25 g, 1.1 mmol) in dioxane (5 ml) was added to a solution of *Vb* (0.25 g, 1 mmol) in dioxane (150 ml) and the mixture was stirred at room temperature for 24 h. Insoluble portion was filtered off, washed with dichloromethane and the combined organic solutions were evaporated and purified by radial chromatography on Chromatotron (dichloromethane) yielding 0.06 g (24%) of the product, m.p. 198–200 °C.

C) Sodium hydride (80% suspension in mineral oil, 0.1 g, 9.3 mmol) was added portionwise to a stirred solution of *Xa* (0.285 g, 1 mmol) in THF (5 ml) and the mixture was stirred at room temperature under nitrogen for 4 h, evaporated, the residue was dissolved in water and acidified with hydrochloric acid. Insoluble portion was filtered off, washed with water and dried. The crude product was dissolved in dichloromethane and purified by vacuum chromatography (dichloromethane). Crystallization from ethanol provided 0.21 g (85%) of the product, m.p. 200–201 °C.

7-Fluoro-1-hydroxy-6-(4-methyl-1-piperazinyl)-9*H*-xanthen-9-one (*IVd*)

A) A mixture of *IVb* (0.25 g, 1 mmol), acetonitrile (20 ml), triethylamine (1 ml, 7 mmol), and *N*-methylpiperazine (0.2 g, 2 mmol) was stirred at 50 °C under nitrogen for 20 h. The mixture was evaporated, the residue was triturated with water, the insoluble portion was filtered off, washed with water, dried and crystallized from ethanol; yield 0.27 g (82%), m.p. 166–168 °C. For $C_{18}H_{17}FN_2O_3$ (328.3) calculated: 65.85% C, 5.22% H, 5.79% F, 8.53% N; found: 65.66% C, 4.93% H, 6.00% F, 8.42% N. ^{1}H NMR spectrum ($CDCl_3$): 2.41 s, 3 H (CH_3); 2.68 m, 4 H (CH_2); 3.39 m, 4 H (CH_2); 6.80–6.89 m, 3 H (H-2, H-4, H-8); 7.26 s, 1 H (H-5); 7.57 t, 1 H, J = 8 (H-3); 7.81 d, 1 H, J(H,F) = 13 (H-8). IR spectrum ($CHCl_3$): 1 646 (C=O). UV spectrum, λ_{max} (log ε): 228 (4.44), 240 (4.31), 250 (4.79), 274 (3.87), 293 (3.92), 365 (4.28), λ_{infl} 340 (4.21). Mass spectrum (*m/z*, %): 328 (M^+, 55), 43 (100).

A sample was converted to its hydrochloride salt m.p. 288–295 °C (decomposition). For $C_{18}H_{17}FN_2O_3$. HCl (364.8) calculated: 59.26% C, 4.97% H, 9.72% Cl, 5.21% F, 7.68% N; found: 58.97% C, 4.81% H, 9.69% Cl, 5.34% F, 7.70% N.

B) A mixture of *Xa* (2.0 g, 7 mmol), *N*-methylpiperazine (1.5 g, 15 mmol) and acetonitrile (10 ml) was stirred under nitrogen for 5 h, the mixture was evaporated, the residue was triturated with water, the insoluble portion was washed with water and dried. Crystallization of the crude product from ethanol provided 1.6 g (69%) of *IVd*, m.p. 167–168 °C.

2-(2-Chloro-4,5-difluorobenzoyl)-1,3-dihydroxybenzene (*Xa*)

A mixture of *VIIc* (2.87 g, 10 mmol), mercuric acetate (9.6 g, 30 mmol), sodium acetate (2.5 g, 30 mmol) and acetic acid (25 ml) was stirred at 120 °C for 5 h under nitrogen. The mixture was cooled, 1 M HCl was added (50 ml) and the mixture was stirred at room temperature for 30 min. Then ethyl acetate was added (50 ml) and the mixture was filtered through a cellite pad and washed with ethyl acetate. The washings were used for extraction of the aqueous layer, organic extracts were combined, washed with 5% sodium hydrogen sulfite (100 ml), 5% sodium hydrogen carbonate (4 × 100 ml) and water (2 × 50 ml) and dried with magnesium sulfate. After evaporation, 2.7 g of yellow oil (95%) was obtained which after prolonged standing yielded yellow crystals, m.p. 66–84 °C. The crude product was used for the next step without further purification ^{1}H NMR spectrum ($CDCl_3$): 6.62 d, 2 H (arom. H); 7.15–7.46 m, 3 H (arom. H).

2-(2-Chloro-4,5-difluorobenzoyl)-1,3-dimethoxybenzene (*Xb*) and 6,7-Difluoro-1-methoxy-9*H*-xanthen-9-one (*IVf*)

A mixture of *Xa* (2.56 g, 9 mmol), potassium carbonate (5.6 g, 40 mmol) and iodomethane (5 ml, 80 mmol) in acetone (50 ml) was stirred at room temperature for 10 h. Then the mixture was evaporated, the residue was triturated with water, the insoluble portion was filtered off, washed with water and dried (2.75 g). The crude mixture was purified by flash chromatography (dichloromethane). First fraction was eluted with dichloromethane and provided after crystallization from hexane 2.1 g of *Xb* (75%), m.p. 78–79 °C. For $C_{15}H_{11}ClF_2O_3$ (312.7) calculated: 57.62% C, 3.55% H, 11.34% Cl, 12.15% F; found: 56.87% C, 3.55% H, 11.56% Cl, 11.42% F. ^{1}H NMR spectrum ($CDCl_3$): 3.74 s, 6 H (CH_3); 6.58 d, 2 H (arom. H); 7.20–7.48 m, 3 H (arom. H). IR spectrum ($CHCl_3$): 1 688 (C=O). UV spectrum, λ_{max} (log ε): 202 (4.72), 244 (3.89), 284 (3.63). Mass spectrum (*m/z*, %): 312 (M^+, 28), 165 (100). Another compound obtained by eluting with ethyl acetate and following crystallization from acetic acid (0.55 g, 23%) was identified as *IVf*, m.p. 205–207 °C. For $C_{14}H_8F_2O_3$ (262.2) calculated: 64.13% C, 3.08% H, 14.49% F; found: 61.25% C, 3.05% H, 14.48% Cl, 13.54% F. ^{1}H NMR spectrum ($CDCl_3$): 4.03 s, 3 H (CH_3); 6.82–7.07 m, 2 H (H-2, H-4); 7.20–7.24 m, 1 H (H-5); 7.63 t, 1 H, J = 8 (H-3); 8.07 dd, 1 H, J = 8 and 10 (H-8). IR spectrum ($CHCl_3$): 1 658 (C=O). UV spectrum, λ_{max} (log ε): 229 (4.37), 246 (4.38), 273 (3.84), 293 (3.69), 345 (3.84). Mass spectrum (*m/z*, %): 262 (M^+, 100).

2-[2-Chloro-5-fluorobenzoyl-4-(4-methyl-1-piperazinyl)]-1,3-dimethoxybenzene (*Xc*)

A mixture of *Xb* (0.62 g, 2 mmol), acetonitrile (5 ml), and *N*-methylpiperazine (0.5 g, 5 mmol) was stirred at room temperature for 3 days, evaporated, the residue was dissolved in dichloromethane and purified by vacuum chromatography (chloroform–methanol 95 : 5) providing after crystallization from hexane 0.75 g (96%) of yellow crystals, m.p. 96–97 °C. For $C_{13}H_9ClF_2O_3$ (286.7) calculated: 54.47% C, 3.16% H, 12.37% Cl, 13.25% F; found: 54.26% C, 2.92% H, 12.39% Cl, 13.54% F. ^{1}H NMR spectrum ($CDCl_3$): 2.42 s, 3 H (CH_3N); 2.68–2.75 m, 4 H (CH_2); 3.31–3.36 m, 4 H (CH_2); 3.78 s, 6 H (CH_3O); 6.58 d, 2 H, J = 8 (arom. H); 6.87 d, 1 H, J = 9 (arom. H); 7.28–7.42 m, 2 H, J = 8 (arom. H). IR spectrum ($CHCl_3$): 1 675 (C=O). UV spectrum, λ_{max} (log ε): 247 (3.95), 322 (4.23). Mass spectrum (*m/z*, %): 392 (M^+, 52), 165 (34), 71 (71), 70 (48), 43 (100), 42 (25), 28 (29).

10-Cyclopropyl-6,7-difluoro-3,4-dihydro-1*H*-acridine-1,9(2*H*,10*H*)-dione (*Va*)

A solution of cyclohexane-1,3-dione (0.28 g, 2.5 mmol) in DMF (2 ml) was added dropwise during 30 min to a suspension of sodium hydride (80% suspension in mineral oil, 75 mg, 2.5 mmol) in DMF (2 ml) stirred at 0 °C. Then the mixture was stirred at room temperature for 1 h, cooled to 0 °C and a solution of 1-cyclopropyl-6,7-difluoroisatoic anhydride (*XI*; 0.56 g, 2.3 mmol) in DMF (2 ml) was added and the mixture was stirred at room temperature overnight. The mixture was poured into ice water (50 ml) containing 1 M HCl (4 ml), the insoluble portion was filtered off, washed with water and dried. Crystallization from ethanol provided 0.5 g (74%) of white crystals; m.p. 270–272 °C. For $C_{16}H_{13}F_2NO_2$ (289.3) calculated: 66.43% C, 4.53% H, 13.13% F, 4.84% N; found: 66.50% C, 4.43% H, 12.96% F, 4.62% N. ^{1}H NMR spectrum ($CDCl_3$): 1.05–1.20 m, 2 H (CH_2 of cyclopropyl); 1.44–1.60 m, 2 H (CH_2 of cyclopropyl); 2.10–2.22 m, 2 H (CH_2); 2.56–2.64 m, 2 H (CH_2); 3.22–3.34 m, 3 H (CH_2, CH–N); 7.72 dd, 1 H, J = 8 and 10 (H-5); 8.15 dd, 1 H, J = 8 and 10 (H-8). IR spectrum (KBr): 1 677 (C=O). UV spectrum, λ_{max} (log ε): 217 (4.45), 255 (4.12), 264 (4.21), 316 (4.01), 355 (4.33). Mass spectrum (*m/z*, %): 289 (M^+, 100), 288 (68), 260 (28), 246 (32), 233 (32), 232 (36), 41 (28).

10-Cyclopropyl-6,7-difluoro-1-hydroxyacridin-9(10*H*)-one (*IVa*)

A solution of *Va* (0.1 g, 0.34 mmol) in ethanol (10 ml) was refluxed with 10% palladium on carbon (0.05 g) under a stream of argon for 10 h. Then the catalyst was filtered off, the filtrate was evaporated to dryness and the residue was crystalllized from ethanol to provide 0.06 g of white crystals (60%), m.p. 225–226 °C. For $C_{16}H_{11}F_2NO_2$ (287.3) calculated: 66.90% C, 3.86% H, 13.23% F, 4.88% N; found: 66.63% C, 3.56% H, 13.11% F, 4.52% N. ^{1}H NMR spectrum ($CDCl_3$): 0.95–1.01 m, 2 H (CH_2 of cyclopropyl); 1.48–1.58 m, 2 H (CH_2 of cyclopropyl); 3.20–3.30 m, 1 H (CH–N); 6.72 d, 1 H, J = 8 (H-2 or H-4); 7.28 d, 1 H, J = 7 (H-2 or H-4); 7.56–7.77 m, 2 H (arom. H); 8.14 dd, 1 H, J = 10 (H-8). IR spectrum (KBr): 1 643 (C=O). UV spectrum, λ_{max} (log ε): 213 (3.24), 241 (4.36), 264 (4.68), 300 (3.73), 309 (3.74), 403 (3.87). Mass spectrum (*m/z*, %): 287 (M^+, 100), 286 (72), 272 (34), 218 (24), 28 (36).

10-Cyclopropyl-7-fluoro-1-hydroxy-6-(4-methyl-1-piperazinyl)acridin-9(10*H*)-one (*IVc*)

A solution of *IVa* (0.1 g, 0.35 mmol) and *N*-methylpiperazine (50 µl, 0.45 mmol) in acetonitrile (10 ml) was stirred at 50 °C for 50 h under argon. The reaction mixture was evaporated, the residue was triturated with water and the insoluble portion was filtered off, dried and crystallized from ethanol providing 0.11 g of yellow crystals (86%), m.p. 216–218 °C. For $C_{21}H_{22}FN_3O_2$ (367.4) calculated: 68.65% C, 6.04% H, 5.17% F, 11.44% N; found: 68.38% C, 6.04% H, 5.19% F, 11.48% N. ^{1}H NMR spectrum ($CDCl_3$): 0.92–1.00 m, 2 H (CH_2 of cyclopropyl); 1.44–1.56 m, 2 H (CH_2 of cyclopropyl); 2.55 s, 3 H (N–CH_3); 2.78 m, 4 H (CH_2 of piperazine); 3.20–3.30 m, 1 H (N–CH); 3.47 m, 4 H (CH_2 of piperazine); 6.68 d, 1 H, J = 12 (arom. H); 7.22–7.30 m, 2 H (arom. H); 7.55 d, 1 H, J = 7 (H-5); 7.96 d, 1 H, J = 12 (H-8). IR spectrum (KBr): 1 626 (C=O). UV spectrum, λ_{max} (log ε): 251 (4.49), 264 (4.38), 293 (4.49), 341 (4.16), 398 (4.03). Mass spectrum (*m/z*, %): 367 (M^+, 94), 297 (20), 71 (50), 70 (68), 43 (100).

A sample was converted to its soluble monohydrochloride which decomposes without melting at about 310–320 °C. For $C_{21}H_{22}FN_3O_2$. HCl (403.9) calculated: 62.45% C, 5.74% H, 8.78% Cl, 4.70% F, 10.40% N; found: 62.05% C, 5.69% H, 8.67% Cl, 4.53% F, 9.91% N.

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