# Synthesis and Structure Elucidation of New Cytotoxic Azathioxanthones



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**In memory of Professor Nicholas Alexandrou**

A series of new cytotoxic azathioxanthones **7a-h** was synthesized and characterized by their spectral data.

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## Introduction.

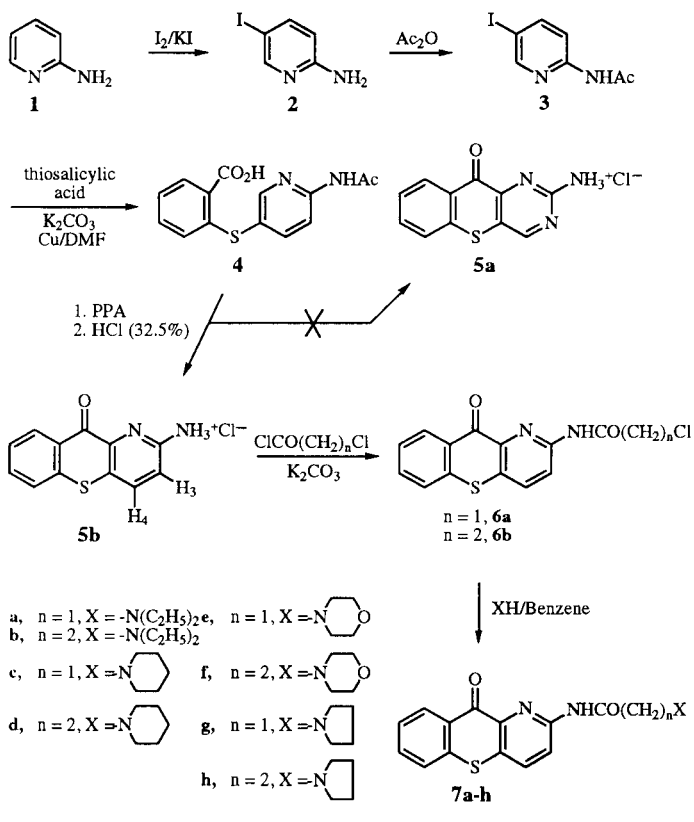
One of the most important classes of anticancer drugs in clinical use today is that of DNA-binding agents [1-4]. It has been postulated that these molecules can bind either in the major or minor grooves or that can intercalate between base pairs of duplex DNA [3]. Furthermore, there are examples of DNA-complexing agents that can bind either covalently or non-covalently to DNA [1].

As part of a continuing effort aiming at developing potential intercalators [5], we have recently reported on design rationale, preliminary synthetic work as well as tumor biology [6] of a number of potent azathioxanthones (Scheme 1).

Our design of this class of agents was based on the assumption that the presence of pyridine in the pharmacophore might lead, as in the cases of the antitumor agents aza-ellipticine and aza-anthraquinone, to improved cytotoxicity and lower toxicity [7, 8].

In general, the new azathioxanthones **7a-h** showed significant cytotoxicity in the cell lines tested and a number of them, appear to be more potent than some of the aza derinatives of the anticancer clinical agent lucanthone [9, 10].

Scheme 1




## Results and Discussion.

In this paper, we report the detailed synthetic studies on this novel series. The synthesis of the parent chromophore **5b** was effected as follows: commercially available 2-aminopyridine (**1**) was iodinated in the presence of potassium iodide to give 2-amino-5-iodopyridine (**2**) [11]. This was then acylated to **3** upon treatment with acetic anhydride [12] (Scheme 1). Ullmann condensation [13] of thiosalicylic acid with 2-acetamido-5-iodopyridine (**3**) afforded the hitherto unknown thioether **4** which was in turn converted to **5b** upon Friedel-Crafts intramolecular ring closure [14]. Although two different isomers, **5a** and **5b**, could be expected from this reaction [15,16] only the regioisomer **5b** was obtained. The structure of **5b** was fully elucidated from the nmr spectral data obtained for **7d**, which is structurally related to **5b**. Compound **7d** was used in place of **5b** as the latter decomposes upon standing.

In detail, the $^1$H nmr spectrum of **7d** showed the presence of only one isomer. The position of the ring nitrogen in ring C was deduced from the coupling constant of protons H-3 and H-4 (doublets centered at 8.31 and 8.41 ppm respectively, J = 9.0 Hz) which is characteristic of *ortho* coupling. This, of course, would not have been observed if isomer **5a** had been obtained instead. Furthermore, the C-H corr nmr spectrum of **7d** (Figure 1) shows correlation between carbon C-4 at 118.1 ppm and proton signal at 8.45 ppm corresponding to H-4. The H-3 proton at 8.31 ppm correlates with carbon C-3 at 137.6 ppm. The other characteristic correlations between the carbons and protons of ring A are also consistent with literature nmr data for xanthones [17,18] and are as follows: carbon C-6 at 132.80 ppm with proton H-6 (7.75-7.81 ppm), carbon C-7 at 126.8 ppm with proton H-7 (7.56-7.76 ppm), carbon C-8 at 130.2 ppm with proton H-8 (8.45 ppm) and finally carbon C-5 at 126.6 ppm with proton H-5 at 7.88 ppm.

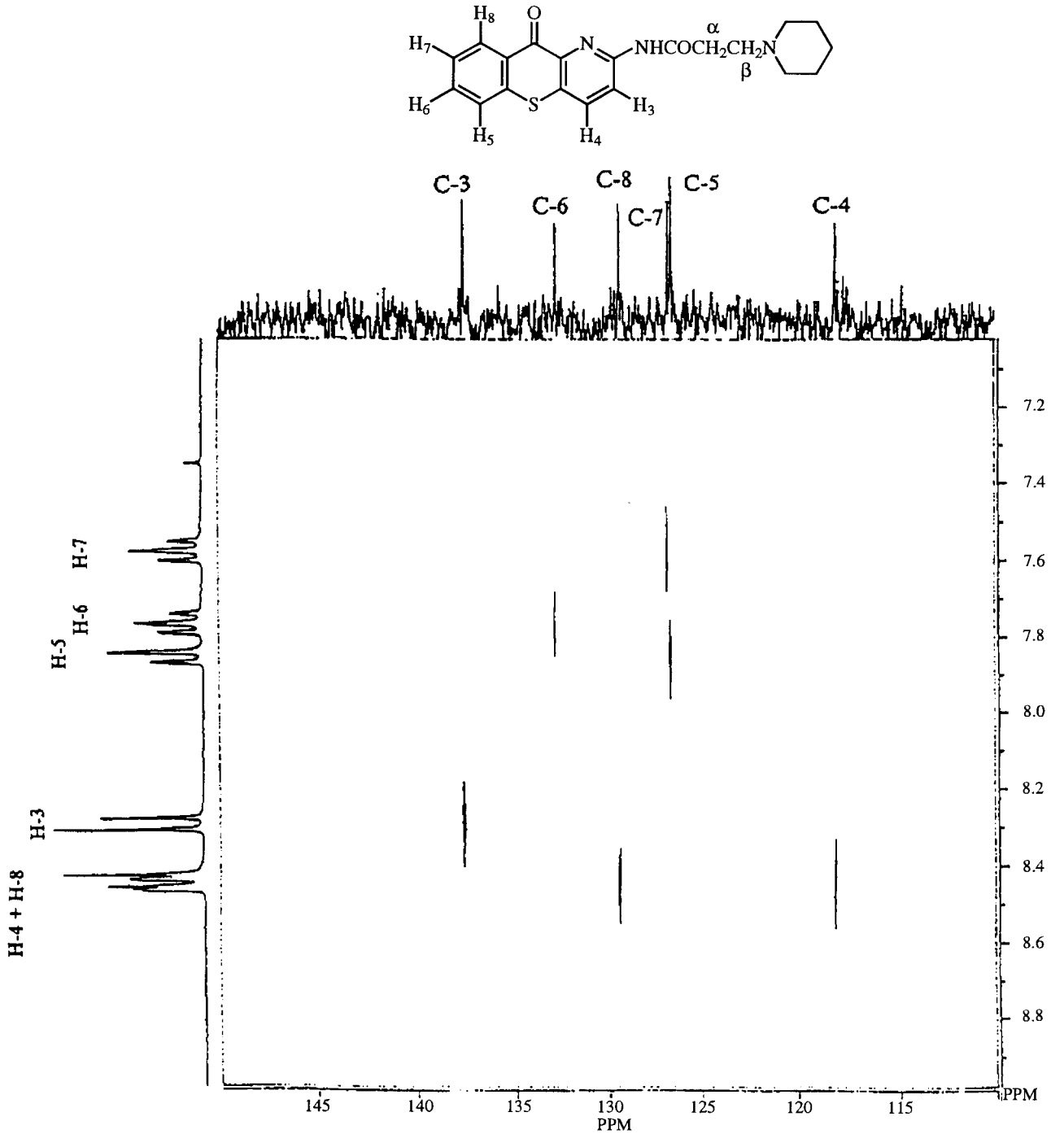



Figure 1. C-H corr nmr spectrum of compound **7d**.

## EXPERIMENTAL

Melting points were determined on a Büchi-530 melting point apparatus and are uncorrected.Infrared spectra were run on a Perkin Elmer 883 spectrophotometer. $^{1}H$, $^{13}C$ and C-H Corr nmr spectra were recorded on a Bruker AC 200 or AC 300 MHz spectrometer using tetramethylsilane as internal standard. Molecular weights were determined by DCI mass spectrometry on a VG Trio 1000 mass spectrometer. Silica gel plates (Merck $F_{254}$) were used for thin layer chromatography. Elemental analyses were performed by Service Central de Microanalyses of CNRS in Vernaison, France.

2-Amino-5-iodopyridine (**2**).

To a solution of iodine (14.0 g, 0.055 mole) and potassium iodide (14.0 g, 0.085 mole) in water (80 ml) 2-aminopyridine (**1**)

(5.0 g, 0.053 mole) dissolved in water (50 ml) was added. The mixture was allowed to stand overnight, the aqueous layer decanted and the residual oil was refluxed for a few minutes with 10% aqueous potassium hydroxide solution (50 ml). The resulting suspension was chilled (0°) and a solid precipitated. The solid was filtered and recrystallized from water to give 6.97 g (60%) of **2** as a white flaky solid, mp 128-129° (lit [8] mp 126-128°).

2-Acetamido-5-iodopyridine (**3**).

A mixture of 2-amino-5-iodopyridine (**2**) (5.0 g, 0.023 mole) and acetic anhydride (16 ml, 0.17 mole) in glacial acetic acid (13 ml) was heated at reflux for 8 hours. The reaction mixture was allowed to reach ambient temperature, cooled (0°) and then mixed with water and ice to give a yellowish solid. The solid was filtered and recrystallized from benzene to afford 5.06 g (85%) of **3**, mp 150° (benzene); $^1$H nmr (deuteriochloroform, 200 MHz): δ 2.17 (s, 3H, NHCOC$H_3$), 7.89-8.06 (m, 2H), 8.40-8.42 (m, 1H), 8.70 (s, 1H, N*H*COCH$_3$); $^{13}$C nmr (deuteriochloroform, 50 MHz): δ 24.7, 85.5, 116.0, 146.3, 150.6, 153.3, 168.9.

2-(6-Acetamido-3-pyridylthio)benzoic Acid (**4**).

A mixture of 2-acetamido-5-iodopyridine (**3**) (6.02 g, 0.027 mole), thiosalicylic acid (3.18 g, 0.020 mole), potassium carbonate (4.59 g, 0.033 mole) and a catalytic amount of copper dust (0.28 g) in *N,N*-dimethylformamide (60 ml) was heated at reflux for 16 hours. The resulting mixture was cooled to room temperature, poured to crushed ice-water and then filtered through Celite. The filtrate was extracted with diethyl ether and the aqueous layer acidified (*p*H 4) at 0° with acetic acid. The solution was left in the fridge overnight, the precipitate formed filtered and the solid was recrystallized from ethyl alcohol to give 4.28 g (91%) of **4** as a pale brown powder, mp > 240° dec (ethanol); $^1$H nmr (dimethyl sulfoxide-d$_6$, 200 MHz): δ 2.13 (s, 3H, NHCOC$H_3$), 6.68 (d, J = 7.7 Hz, 1H), 7.17-7.25 (m, 1H), 7.35-7.43 (m, 1H), 7.92-7.96 (m, 2H), 8.22 (d, J = 7.6 Hz, 1H), 8.42 (broad s, 1H), 10.78 (s, 1H, N*H*COCH$_3$), 13.27 (broad s, 1H, COOH).

*Anal.* Calcd. for $C_{14}H_{12}N_2O_3S$: C, 58.33; H, 4.17; N, 9.78; Found: C, 58.28; H, 4.47; N, 9.70.

2-Amino-9*H*-1-azathioxanth-9-one Hydrochloride (**5b**).

A mixture of acid **4** (5.0 g, 0.017 mole) and 85% polyphosphoric acid (250 g) was heated at 120° for 16 hours. Upon completion of the reaction the warm mixture was poured under stirring into ice-water, and made alkaline with saturated aqueous sodium hydroxide solution to *p*H 7-8. The precipitate formed was filtered, washed thoroughly with water and air-dried. The $^1$H nmr (dimethyl sulfoxide-d$_6$, 200 MHz) spectrum of the dried cake exhibited signals at δ 2.15 (s, 3H, NHCOC$H_3$), 7.60-7.80 (m, 1H), 7.87-7.91 (m, 1H), 8.36 (d, J = 8.7 Hz, 1H), 8.39-8.45 (m, 2H), 8.48 (d, J = 8.1 Hz, 1H) and 11.14 (s, 1H, N*H*COCH$_3$). This spectrum belongs to 2-acetamido-9*H*-1-azathioxanth-9-one which was used without any further purification for the preparation of **5b**.

A mixture of 2-acetamido-9*H*-1-azathioxanth-9-one 5.0 g (0.019 mole) and 32.5% aqueous hydrochloric acid (94 ml) was heated at reflux for 10 hours. The reaction mixture was then concentrated *in vacuo* to 50 ml and cooled (0°). The precipitated hydrochloride salt was filtered, washed with cold water and recrystallized from ethanol to give 3.38 g (74%) of **5b**, mp >240° (ethanol); $^1$H nmr (dimethyl sulfoxide-d$_6$-trifluoroacetic acid, 200 MHz): δ 7.43-7.49 (m, 1H), 7.67-7.75 (m, 1H), 7.85-7.92 (m, 1H), 8.05-8.09 (m, 1H), 8.37-8.42 (m, 1H), 8.50-8.54 (m, 1H); $^{13}$C nmr (dimethyl sulfoxide-d$_6$-trifluoroacetic acid, 75 MHz): δ 121.0, 126.4, 128.1, 129.1, 129.6, 130.1, 130.8, 134.7, 137.6, 142.1, 155.6, 173.6.

*Anal.* Calcd. for $C_{12}H_9N_2ClOS$: C, 54.44; H, 3.43; N, 10.58. Found: C, 54.87; H, 3.17; N, 10.45.

*N*-(9-Oxo-9*H*-1-azathioxanthen-2-yl)chloroacetamide (**6a**).

A mixture of the hydrochloride salt **5b** (2.10 g, 7.56 mmoles) and potassium carbonate (3.14 g, 22.68 mmoles) in chloroform (67 ml) was heated at reflux for 10 hours. The mixture was cooled to 0° and a second portion of potassium carbonate (2.09 g, 15.12 mmoles) was added followed by the dropwise addition of chloroacetyl chloride (1.81 ml, 22.68 mmoles). The reaction mixture was allowed to reach ambient temperature and stirring was continued for 15 hours. The resulting mixture was filtered and washed with warm chloroform. The filtrate was concentrated under reduced pressure to 70 ml. This solution was exhaustively washed with water till washings had neutral *p*H. The organic layer was collected, dried (sodium sulfate) and the solvent removed *in vacuo*. The residue was recrystallised from benzene to give 0.90 g (37%) of **6a**, mp 150° (benzene); $^1$H nmr (dimethyl sulfoxide-d$_6$, 200 MHz): δ 3.69, (broad s, 2H, $CH_2Cl$), 7.58-7.64 (m, 1H), 7.69-7.86 (m, 2H), 8.36-8.46 (m, 3H), 10.69 (s, 1H, NH).

*Anal.* Calcd. for $C_{14}H_9N_2ClO_2S$: C, 55.17; H, 2.98. Found: C, 55.02; H, 3.20.

*N*-(9-Oxo-9*H*-1-azathioxanthen-2-yl)-3-chloropropionamide (**6b**).

A mixture of the salt **5b** (2.23 g, 8.03 mmoles) and potassium carbonate (3.33 g, 24.05 mmoles) in dry toluene (80 ml) was heated at reflux for 10 hours. The reaction mixture was cooled to 0° and potassium carbonate (2.22 g, 16.06 mmoles) was added followed by the dropwise addition of 3-chloropropionylchloride (1.66 ml, 24.09 mmoles). The mixture was stirred for 15 hours at ambient temperature and then heated at reflux for 3 hours. The resulting mixture was filtered and washed with warm chloroform. The filtrate and the combined washings were concentrated under reduced pressure. The residue was dissolved in 50 ml of chloroform and the resulting solution was exhaustively washed with water to neutral *p*H. The organic layer was collected, dried (sodium sulfate) and the solvent removed *in vacuo*. The residue was recrystallized from benzene to give 1.37 g (51%) of **6b**, mp 250° (dec) (benzene); $^1$H nmr (dimethyl sulfoxide-d$_6$, 200 MHz): δ 2.71, (t, 2H, COC$H_2$CH$_2$Cl), 3.80 (broad s, 2H, COCH$_2$C$H_2$Cl), 7.52-7.62 (m, 1H), 7.78 -7.81 (m, 1H), 7.90-7.98 (m, 3H), 8.42-8.51(m, 1H) 11.31 (s, 1H, NH).

*Anal.* Calcd. for $C_{15}H_{11}N_2O_2SCl$: C, 56.52; H, 3.48. Found: C, 56.70; H, 3.20.

General Procedure for the Preparation of Alkanamides **7a-h**.

A mixture of the appropriate chloroalkanamide **6a** or **6b** (7.50 mmoles), the appropriate secondary amine (22.5 mmoles) and benzene (40 ml) was heated at 40-80° for 10-16 hours depending on the amine. The mixture was cooled to room temperature and filtered. The filtrate was concentrated *in vacuo* and the residue was diluted with ethyl acetate (20 ml). The organic layer was thoroughly washed with water to neutral *p*H, dried (sodium sulfate) and concentrated *in vacuo*. The solid obtained was recrystallized from benzene.

*N*-(9-Oxo-9*H*-1-azathioxanthen-2-yl)diethylaminoacetamide (**7a**).

This compound was obtained in 90% yield as a yellow powder (benzene), mp 137-140° ir (nujol) ν CO 1650, ν (C=C)CO 1540, ν (CO)NH 1460 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$, 200 MHz): δ 1.07-1.10 (m, 6H, $N(CH_2CH_3)_2$), 2.76-2.79 (m, 4H, $N(CH_2CH_3)_2$), 7.56-7.65 (m, 1H), 7.76-7.92 (m, 2H), 8.36-8.48 (m, 3H), 10.70 (s, 1H, NH); MS: m/z 341($M^+$).

*Anal.* Calcd. for $C_{18}H_{19}N_3O_2S$•0.5$H_2O$: C, 61.64; H, 5.71; N, 11.99; Found: C, 61.85; H, 5.64; N, 12.15.

*N*-(9-Oxo-9*H*-1-azathioxanthen-2-yl)-3-diethylaminopropionamide (**7b**).

This compound was obtained in 91% yield as a yellow powder (benzene), mp 121° ir (nujol) ν CO 1650, ν (C=C)CO 1520, ν (CO)NH 1452 $cm^{-1}$; $^1H$ nmr (deuteriochloroform, 200 MHz): δ 1.18 (t, J = 6.3 Hz, 6H, $N(CH_2CH_3)_2$), 2.52 (t, J = 6.4 Hz, 2H, $COCH_2CH_2N$), 2.70 (q, J = 6.3 Hz, 4H, $N(CH_2CH_3)_2$), 2.84 (t, 2H, J = 5.9 Hz, $COCH_2CH_2N$), 7.44-7.63 (m, 3H), 7.90 (d, J = 8.9 Hz, 1H), 8.54 (d, J = 8.9 Hz, 1H), 8.61-8.65 (m, 1H), 11.33 (s, 1H, NH); $^{13}C$ nmr (dimethyl sulfoxide-$d_6$, 75 MHz): δ 11.7, 33.8, 46.0, 48.2, 118.2, 126.2, 126.6, 126.8, 129.4, 130.2, 132.8, 135.6, 137.6, 140.9, 151.3, 172.3, 177.1; MS: m/z 355 ($M^+$).

*Anal.* Calcd. for $C_{19}H_{21}N_3O_2S$: C, 64.20; H, 5.95; N, 11.82. Found: C, 63.86; H, 5.84; N, 11.74.

*N*-(9-Oxo-9*H*-1-azathioxanthen-2-yl)piperidinoacetamiede (**7c**).

This compound was obtained in 94% yield as a yellow powder (benzene), mp 210-212° ir (nujol) ν CO 1645, ν (C=C)CO 1511, ν (CO)NH 1456 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$, 300 MHz): δ 1.47-1.51 (m, 2H, $N(CH_2CH_2)_2CH_2$), 1.52-1.70 (m, 4H, $N(CH_2CH_2)_2CH_2$), 2.75-2.80 (m, 4H, $N(CH_2CH_2)_2CH_2$), 7.58-7.64 (m, 1H), 7.77-7.92 (m, 2H), 8.35-8.46 (m, 3H), 11.45 (s, 1H, NH).

*Anal.* Calcd. for $C_{19}H_{19}N_3O_2S$: C, 64.57; H, 5.42; N,11.89. Found: C, 64.80; H, 5.26; N, 11.82.

*N*-(9-Oxo-9*H*-1-azathioxanthen-2-yl)-3-piperidinopropionamide (**7d**).

This compound was obtained in 80% yield as a yellow powder (benzene), mp 182-185° ir (nujol) ν CO 1708, ν (CO)NH 1594 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$, 75 MHz): δ 1.37-1.51 (m, 6H, $N(CH_2CH_2)CH_2$), 2.07 (m, 4H, $COCH_2CH_2$), 2.50 (m, 4H, $N(CH_2CH_2)_2CH_2$), 7.56-7.61 (m,1H), 7.75-7.81 (m, 1H), 7.88 (d, J = 8.1 Hz, 1H), 8.31 (d, J = 8.9 Hz, 1H), 8.45 (d, J = 8.9 Hz, 1H), 8.46 (dd, J = 1.1, 8.1 Hz, 1H), 11.32 (s, 1H, NH); $^{13}C$ nmr (dimethyl sulfoxide-$d_6$, 75 MHz): 24.0, 25.5, 33.7, 53.6, 54.2, 118.1, 126.6, 126.8, 129.0, 129.4, 130.2, 132.8, 135.6, 137.6, 140.9, 151.3, 172.1.

*Anal.* Calcd. for $C_{20}H_{21}N_3O_2S$: C, 65.37; H, 5.76; N, 11.44. Found: C, 65.20; H, 5.84; N, 11.40.

*N*-(9-Oxo-9*H*-1-azathioxanthen-2-yl)morpholinoacetamide (**7e**).

This compound was obtained in 70% yield as a yellow powder (benzene), mp 240-245° ir (nujol) ν C=O 1646, ν (C=C)CO 1546, ν (CO)NH 1463 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$, 200 MHz): δ 2.50-2.58 (m, 4H, $N(CH_2CH_2)_2O$), 3.60-3.85 (m, 4H, $N(CH_2CH_2)_2O$), 7.34-7.61 (m, 1H), 7.80-7.89 (m, 2H), 8.35-8.49 (m, 3H), 10.66 (s, 1H, NH); $^{13}C$ nmr (deuteriochloroform, 50 MHz): δ 53.8, 63.1, 66.6, 118.5, 126.0, 126.7, 126.9, 130.5, 130.6, 131.9, 132.6, 135.9, 137.2, 150.3, 170.2, 178.4; MS: m/z 268 ($M^+$-morpholine).

*Anal.* Calcd. for $C_{18}H_{17}N_3O_3S$•0.75$H_2O$: C, 58.55; H, 5.05; N, 11.39. Found: C, 58.55; H, 4.77; N, 10.71. We and other workers have encountered problems with nitrogen analyses from compounds with several nitrogen atoms [19a-c].

*N*-(9-Oxo-9*H*-1-azathioxanthen-2-yl)-3-morpholinopropionamide (**7f**).

This compound was obtained in 65% yield as a yellow powder (benzene), mp 182° ir (nujol) ν CO 1652, ν (C=C)CO 1592, ν (CO)NH 1512 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$, 300 MHz): δ 2.41-2.50 (m, 4H, $N(CH_2CH_2)_2O$), 3.54-3.59 (m, 4H, $N(CH_2CH_2)_2O$), 7.59-7.63 (m, 1H), 7.79-7.89 (m, 2H), 8.36-8.44 (m, 1H), 8.44-8.49 (m, 2H), 11.23 (s, 1H, NH); $^{13}C$ nmr (dimethyl sulfoxide-$d_6$, 75 MHz): 32.5, 52.5, 53.3, 65.2, 118.2, 126.6, 126.8, 129.4, 130.2, 132.9, 135.6, 137.7, 140.9, 151.1, 171.2, 177.1; MS: m/z 369 ($M^+$).

*Anal.* Calcd. for $C_{19}H_{19}N_3O_3S$: C, 61.76; H, 5.18; N,11.38. Found: C, 61.49; H, 5.16; N, 11.31.

*N*-(9-Oxo-9*H*-1-azathioxanthen-2-yl)pyrrolidinoacetamide (**7g**).

This compound was obtained in 56% yield as a yellow powder (benzene), mp 160° ir (nujol) ν C=O 1648, ν (C=C)CO 1586, ν (CO)NH 1512 $cm^{-1}$; $^1H$ nmr (dimethyl sulfoxide-$d_6$, 200 MHz): δ 1.73-1.75 (m, 4H, $N(CH_2CH_2)_2$), 2.80-2.83 (m, 4H, $N(CH_2CH_2)_2$), 7.55-7.63 (m, 1H), 7.75-7.91 (m, 2H), 8.30-8.48 (m, 3H), 10.49 (s, 1H, NH); $^{13}C$ nmr (dimethyl sulfoxide-$d_6$, 50 MHz): δ 28.5, 58.8, 63.8, 122.9, 131.7, 131.9, 134.4, 135.6, 138.0, 140.6, 143.0, 145.9, 155.6, 175.2, 182.1; MS: m/z 339 ($M^+$).

*Anal.* Calcd. for $C_{18}H_{17}N_3O_2S$•0.25$H_2O$: C, 62.85; H, 5.13; N, 12.22. Found: C, 63.13; H, 4.99; N, 11.91.

*N*-(9-Oxo-9*H*-1-azathioxanthen-2-yl)-3-pyrrolidinopropionamide (**7h**).

This compound was obtained in 92% yield as a yellow powder (benzene), mp 110-112° ir (nujol) ν C=O 1650, ν (C=C)CO 1550 ν (CO)NH 1463 $cm^{-1}$;$^1H$ nmr (dimethyl sulfoxide-$d_6$, 75 MHz): δ 1.67-1.69 (m, 4H, $N(CH_2CH_2)_2$), 2.51-2.53 (m, 4H, $N(CH_2CH_2)_2$), 2.65 (t, J = 6.0 Hz, 2H, $COCH_2CH_2$), 2.72 (t, J = 6.0 Hz, 2H, $COCH_2CH_2$), 7.60-7.62 (m, 1H), 780-7.91 (m, 2H), 8.32-8.33 (m, 1H), 8.46-8.49 (m, 2H), 11.23 (s, 1H, NH).

*Anal.* Calcd. for $C_{19}H_{19}N_3O_2S$•0.5$H_2O$: C, 62.91; H, 5.33; N, 11.59. Found: C, 62.74; H, 5.50; N, 11.30.

## REFERENCES AND NOTES

[1] D. E. Thurston and A. S. Thompson, *Chem. Britain*, **26**, 767 (1990).

[2] L. H. Hurley and F. L. *TIBS*, **9**, 402 (1988).

[3] Molecular Aspects of Anticancer Drug-DNA Interactions, S. Neidle and M. J. Waring, eds, The Macmillan Press Ltd, London, 1993.

[4] S. Neidle, M. S. Puvvada and D. E. Thurston, *Eur. J. Cancer*, **30-A**, 567 (1994).

[5] E . Filippatos, A. Papadaki-Valiraki, O. Todoulou, A. Jacquemin-Sablon, *Arch. Pharm. (Weinheim)*, **327** , 61 (1994).

[6] A. Varvaresou, A. Tsotinis, A. Papadaki-Valiraki and Th. Siatra-Papastaikoudi, *BioMed. Chem. Letters*, **6**, 861 (1996).

[7] R. Liderau, G. C. Chermann, J. Gruest, L. Montagnier, C. Ducrock, C. Rivalle, E. Bisagni, *Bull. Cancer*, **67**, 1 (1980).

[8] A. P. Krapcho, M. E. Petry, Z. Getahun, Jr. J. J. Landi, J. Stallman, J. F. Polsenberg, C. E. Gallagher, M. J. Maresch, M. P.Hacker,

F. C.Giuliani, G. Beggiolin, G. Pezzoni, E. Menta, C. Manzotti, O. Ambrogio, S. Spinneli, S. Tognella, *J. Med. Chem.*, **37**, 828 (1994).

[9] M. Croisy-Delsey and E. Bisagni, *J. Med. Chem.*, **26**, 1329 (1983).

[10] E. Hirschberg, A. Gellhorn, M. R. Murray and E. F. Elslager, *J. Natl. Cancer Inst.*, **22**, 567 (1959).

[11] J. R. Bochis, A. R. Dybas, P. Eskola, P. Kulsa, O. B. Linn, A. Lusi, P. E. Meitzner, J. Milkowski, H. Mrozik, E. L. Olen, H. L. Peterson, L. R. Tolman, F. A. Wagner, S. F. Waksmunski, R. J. Egerton and A. D. Ostlind, *J. Med. Chem.*, **21**, 235 (1978).

[12] R. Frampton, C. D. Johnson and A. R. Katritzky, *Liebigs Ann. Chem.*, **12**, 749 (1971).

[13] S. Archer, J. K. Miller, R. Rej, C. Periana and L. Fricker, *J. Med. Chem.*, **25**, 220 (1982).

[14] F. J. Villani, T. A. Mann, E. A. Wefer, J. Hannon, L. L. Larca, M. J. Landon, W. I. Spivak, D. Vashi, S. Tozzi, G. Danko, M. Prado and R. Lutz, *J. Med. Chem.*, **18**, 1 (1975).

[15] A. A. Goldberg and A. H. Wragg, *J. Chem. Soc.*, 4234 (1958).

[16] C. M. Passarotti, M. Valenti, M. Grianti and M. Marini, *Boll. Chim. Farmaceutico*, **133**, 592 (1994).

[17] D. Barraclough, H. D. Locksley, F. Scheinmann, M. T. Magalhaes, O. R. Gottlieb, *J. Chem. Soc.*, 603 (1970).

[18] P. W. Westerman, S. P. Gunasekera, M. Uvais, S. Sultanbawa, R. Kazlauskas, *Org. Magn.Reson.*, **9**, 631 (1977).

[19a] A. T. Nielsen, R. L. Atkins and W. P. Norris, *J. Org. Chem.*, **44**, 1181 (1979); [b] J. C. Hinshaw, W.W. Edwards, C. C. George and R. Gilardi, *J. Heterocyclic Chem.*, **29**, 1721 (1992); [c] H. Ritter and H. H. Licht, *J. Heterocyclic Chem.*, **32**, 585 (1995).