

Synthesis and Proton NMR Stereochemical Study of
7,8,9-substituted-7,8-dihydro-4*H*,9*H*-furo[2',3',4':4,4a,5]-
naphth[2,1-*e*][1,3]oxazin-4-ones

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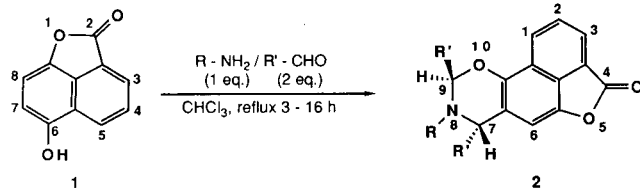
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7,8,9-Substituted-7,8-dihydro-4*H*,9*H*-furo[2',3',4':4,4a,5]naphth[2,1-*e*][1,3]oxazin-4-ones were stereospecifically obtained as a single pair of enantiomers. Their relative *trans* configuration and the conformation of the dihydro oxazine ring were established by ¹H nmr 2D NOESY experiments.

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N-Substituted 3,4-dihydro-2*H*-1,3-oxazines have been described as antitumor or antifungal agents [1] [2] [3] [4]. These observations led us to prepare some oxazines derived from 6-hydroxy-2*H*-naphtho[1,8-*bc*]furan-2-one **1** [5] [6] [7] in order to verify if the γ -lactone function would enhanced these pharmacological properties. Thus the furonaphthoxazines derivatives **2** were prepared by a Mannich type condensation of compound **1** with allyl or *p*-substituted benzylamines and two equivalents of various aldehydes (Table I).

Table I



No.	R	R'
2a	CH ₂ =CH-CH ₂	CH ₃
2b	<i>p</i> -Cl-C ₆ H ₄ CH ₂	CH ₃
2c	<i>p</i> -CH ₃ O-C ₆ H ₄ -CH ₂	CH ₃
2d	C ₆ H ₅ -CH ₂	C ₆ H ₅
2e	<i>p</i> -CH ₃ -C ₆ H ₄ -CH ₂	C ₆ H ₅
2f	<i>p</i> -CH ₃ O-C ₆ H ₄ -CH ₂	C ₆ H ₅
2g	C ₆ H ₅ -CH ₂	<i>p</i> -CH ₃ O-C ₆ H ₄
2h	CH ₂ =CH-CH ₂	<i>p</i> -Cl-C ₆ H ₄
2i	C ₆ H ₅ -CH ₂	<i>p</i> -NO ₂ -C ₆ H ₄
2j	<i>p</i> -CH ₃ -C ₆ H ₄ -CH ₂	<i>p</i> -NO ₂ -C ₆ H ₄

All compounds **2** were obtained stereospecifically as a single pair of enantiomers. Their diastereoisomeric purity was corroborated by ¹H nmr spectroscopy at 300 MHz. The relative *trans* configuration of H-7 and H-9 was established by ¹H nmr 2D phased NOESY experiments on **2a** (R = allyl, R' = methyl) and **2d** (R = benzyl, R' = phenyl).

The conformation of the dihydrooxazine ring in these compounds was discussed on the basis of their ¹H nmr 2D NOESY spectra and the literature data. Owing to the anomeric effect [8] the *N*-substituent (methyl or benzyl) in tetrahydro-1,3-oxazines seems to prefer an axial orientation; an equatorial preference being observed only for bulky groups [9] [10]. A recent ¹H and ¹³C nmr study of *N*-methyl-3,4-dihydro-2*H*-1,3-benzoxazines [11] [12] (prepared by condensation of carbonyl compounds with *ortho*-hydroxybenzylamines) has also indicated that the dihydrooxazine ring has a half-chair conformation with the *N*-methyl group predominantly axial. Our results from the ¹H nmr 2D phased NOESY experiments carried out with compounds **2a** and **2d** (Figures 1 and 2) are in good agreement with the literature data. It appears also from the spectra of **2a** and **2d**, that the 9-CH₃ or 9-C₆H₅ substituent is in an equatorial orientation, whilst the 7-CH₃ or 7-C₆H₅ substituent is pseudoaxial.

EXPERIMENTAL

Melting points were measured on a Kofler apparatus. The infra-red spectra were performed on Perkin-Elmer 1310 spectrophotometer. The ¹H nmr spectra were recorded at 300 MHz on a Bruker AM 300 Spectrometer. Elemental analysis were made at the Centre de Microanalyse du CNRS at Solaise, Lyon. Liquid aldehydes or primary amines were freshly distilled before use.

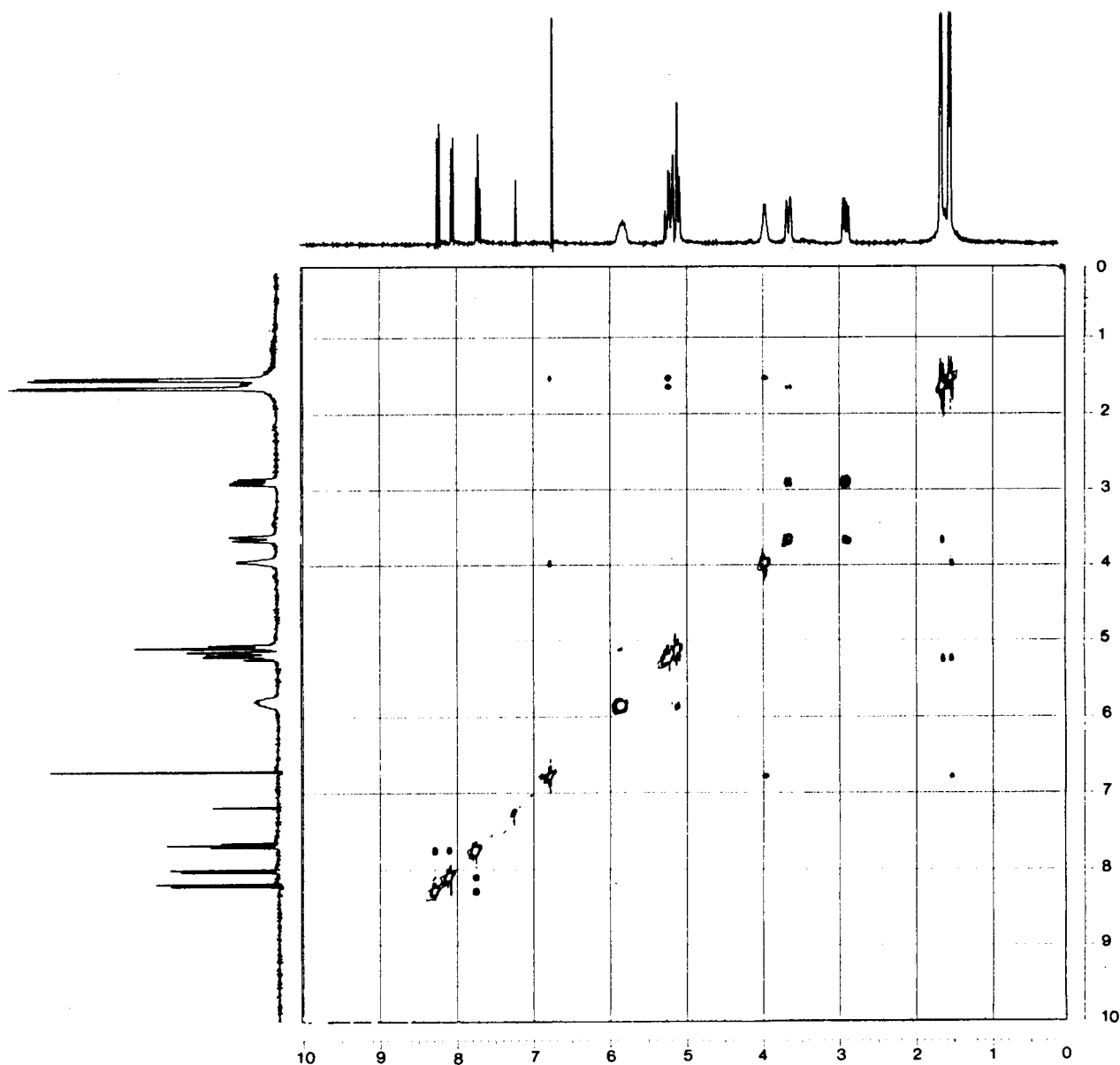


Figure 1. ^1H nmr 2D NOESY spectrum of **2a** (300 MHz, deuteriochloroform).

Proton NMR 2D NOESY Experiments.

Spectra were recorded in the phase sensitive mode [13] with the standard Bruker sequence using TPPI for quadrature detection in F1 dimension. A random variation of $\pm 1\%$ was applied to τ_m , view to attenuate zero quantum coherences between close coupled protons [14]. Prior to starting NOESY experiments, a T_1 measurement was performed. The mixing time τ_m and the relaxation delay D1 were chosen as a function of the average T_1 and fixed respectively to T_1 and $3 \times T_1$. Each spectrum was recorded in an overnight experiment on 10 mg of **2a** or **2d** in deuteriochloroform at 22° with acquisition time AQ = 0.34s, S12 = 2048, τ_m = 2s, NE = 512, NS = 16 accumulations. Prior to 2D Fourier

transformation and to attenuate the effect of signals truncation, the data were multiplied by a shifted sine-bell ($\pi/2$) and a squared shifted sine-bell ($\pi/2$) in the F2 and F1 dimension respectively [15] and zero-filled to 1K in the F1 dimension to increase digital resolution. The NOE effect is positive because of the small size of the molecules. The final matrix exhibits positives diagonals peaks and negatives cross-peaks but this detail is not visible on the Figures.

Synthesis of the 7,8,9-Substituted-7,8-dihydro-4*H*,9*H*-furo[2',3',4':4,4a,5]naphth[2,1-*e*]1,3]oxazin-4-ones **2**.

trans-8-Allyl-7,9-dimethyl-7,8-dihydro-4*H*,9*H*-furo[2',3',4':4,4a,5]naphth[2,1-*e*]1,3]oxazin-4-one (**2a**).

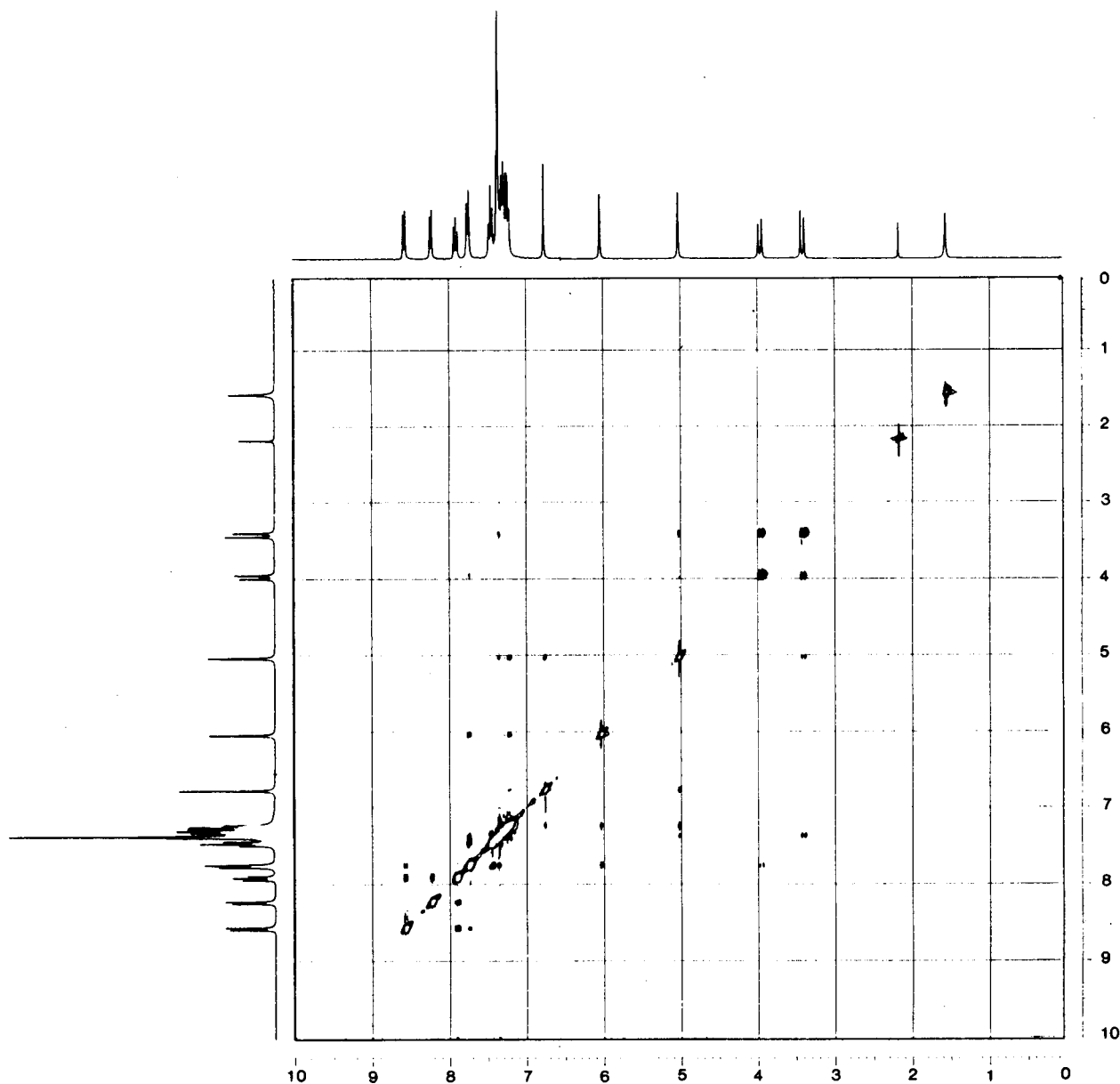


Figure 2. ^1H nmr 2D NOESY spectrum of **2d** (300 MHz, deuteriochloroform).

A solution of ethanal (0.044 g, 1 mmole) in chloroform (5 ml) was cooled in an ice bath. Then, allylamine (0.029 g, 0.5 mmole) was added and the resulting mixture was stirred at 0° for 30 minutes. Then, compound **1** [6], [7] (0.093 g, 0.5 mmole) in chloroform (15 ml) was added in one portion and the reaction mixture was heated to reflux for 5 hours. After evaporation of the solvent methanol (5 ml) was added to the residue. A yellow precipitate of compound **2a** was formed. It was recovered and recrystallized from acetone. This compound was obtained in 65% yield, mp = 135° ; ir (potassium bromide): ν cm^{-1} 1780 (CO); ^1H nmr (deuteriochloroform): δ ppm 1.54 (d, CH_3 -7, 3H, $J = 6.7$ Hz), 1.65 (d, CH_3 -9, 3H, $J = 6$ Hz), 2.9 and 3.64 (2 m, $\text{CH}_2 = \text{CH}-\text{CH}_2$ -N, 2H), 3.98 (q, H-7, 1H, $J = 6.7$ Hz), 5.1 to 5.19 (m, $\text{CH}_2 = \text{CH}-\text{CH}_2$ -N, 2H), 5.24 (q, H-9, 1H, $J = 6$ Hz), 5.85 (m, $\text{CH}_2 = \text{CH}$ -

CH_2 -N, 1H), 6.78 (s, H-6, 1H), 7.75 (dd, H-2, 1H, $J = 7.1$ and 8.1 Hz), 8.1 (d, H-3, 1H, $J = 7.1$ Hz), 8.29 (d, H-1, 1H, $J = 8.1$ Hz).

Anal. Calcd. for $\text{C}_{18}\text{H}_{17}\text{NO}_3 \cdot 0.1\text{H}_2\text{O}$: C, 72.75; H, 5.83; N, 4.71. Found: C, 72.93; H, 5.94; N, 4.42.

trans-8-*p*-Chlorobenzyl-7,9-dimethyl-7,8-dihydro-4*H*,9*H*-furo[2',3',4':4,4a,5]naphth[2,1-*e*][1,3]oxazin-4-one (**2b**).

The reaction mixture was heated to reflux for 3 hours. Compound **2b** was obtained in 80% yield, mp = 147° ; ir (potassium bromide): ν cm^{-1} 1780 (CO); ^1H nmr (deuteriochloroform): δ ppm 1.49 (d, CH_3 -7, 3H, $J = 6.71$ Hz), 1.71 (d, CH_3 -9, 3H, $J = 5.84$ Hz), 3.35 and 4.24 (2 d, CH_2 -N, 2H, $J = 14.6$ Hz), 3.77 (q, H-7, 1H, $J = 6.71$ Hz), 5.34 (q, H-9, 1H, $J = 5.84$ Hz), 6.71 (s, H-6, 1H), 7.26 to 7.29 (m, H arom, 4H), 7.78 (dd, H-2, 1H, $J = 7.35$ and 8.3

(Hz), 8.12 (d, H-3, 1H, J = 7.35 Hz), 8.32 (d, H-1, 1H, J = 8.3 Hz).

Anal. Calcd. for $C_{22}H_{18}NO_3Cl$: C, 69.56; H, 4.77; N, 3.68; Cl, 9.33. Found: C, 69.55; H, 4.83; N, 3.64; Cl, 9.41.

trans-8-*p*-Methoxybenzyl-7,9-dimethyl-7,8-dihydro-4*H*,9*H*-furo[2',3',4':4,4a,5]naphth[2,1-*e*][1,3]oxazin-4-one (**2c**).

The reaction mixture was heated to reflux for 3 hours. Compound **2c** was obtained in 80% yield, mp = 125°; ir (potassium bromide): ν cm^{-1} 1780 (CO); 1H nmr (deuteriochloroform): δ ppm 1.47 (d, CH_3 -7, 3H, J = 6.33 Hz), 1.73 (d, CH_3 -9, 3H, J = 5.46 Hz), 3.32 and 4.2 (2 d, CH_2 -N, 2H, J = 14 Hz), 3.82 (m, CH_3 O, 3H, and H-7, 1H), 5.34 (q, H-9, 1H, 6.72 (s, H-6, 1H), 6.87 and 7.24 (2 d, H arom, 4H, J = 7.5 Hz), 7.78 (dd, H-2, 1H, J = 6.6 and 7.9 Hz), 8.10 (d, H-3, 1H, J = 6.6 Hz), 8.32 (d, H-1, 1H, J = 7.9 Hz).

Anal. Calcd. for $C_{23}H_{21}NO_4 \cdot 0.25H_2O$: C, 72.71; H, 5.70; N, 3.68. Found: C, 72.32; H, 5.62; N, 3.54.

trans-8-Benzyl-7,9-diphenyl-7,8-dihydro-4*H*,9*H*-furo[2',3',4':4,4a,5]naphth[2,1-*e*][1,3]oxazin-4-one (**2d**).

The reaction mixture was heated to reflux for 5 hours. Compound **2d** was obtained in 70% yield, mp = 187°; ir (potassium bromide): ν cm^{-1} 1780 (CO); 1H nmr (deuteriochloroform): δ ppm 1.6 (water from the chloroform), 2.2 (traces of acetone), 3.41 and 3.96 (2 d, CH_2 -N, 2H, J = 14 Hz), 5.02 (s, H-7, 1H), 6.03 (s, H-9, 1H), 6.76 (s, H-6, 1H), 7.21 to 7.75 (m, H arom, 15H), 7.9 (dd, H-2, 1H, J = 8.1 and 7.1 Hz), 8.22 (d, H-3, 1H, J = 7.1 Hz), 8.57 (d, H-1, 1H, J = 8.1 Hz).

Anal. Calcd. for $C_{32}H_{23}NO_3$: C, 81.85; H, 4.93; N, 2.98. Found: C, 81.38; H, 4.94; N, 2.94.

trans-8-Methylbenzyl-7,9-diphenyl-7,8-dihydro-4*H*,9*H*-furo[2',3',4':4,4a,5]naphth[2,1-*e*][1,3]oxazin-4-one (**2e**).

The reaction mixture was heated to reflux for 5 hours. Compound **2e** was obtained in 65% yield, mp = 180°; ir (potassium bromide): ν cm^{-1} 1790 (CO); 1H nmr (deuteriochloroform): δ ppm 2.35 (s, CH_3 , 3H), 3.36 and 3.9 (2 d, CH_2 -N, 2H, J = 13.72 Hz), 5.02 (s, H-7, 1H), 6.2 (s, H-9, 1H), 6.75 (s, H-6, 1H), 7.22 to 7.86 (m, H arom, 14 H), 7.89 (dd, H-2, 1H, J = 7.1 and 8.1 Hz), 8.21 (d, H-3, 1H, J = 7.1 Hz), 8.55 (d, H-1, 1H, J = 8.1 Hz).

Anal. Calcd. for $C_{33}H_{25}NO_3 \cdot 0.33H_2O$: C, 80.96; H, 5.22; N, 2.86. Found: C, 81.19; H, 5.22; N, 2.79.

trans-8-*p*-Methoxybenzyl-7,9-diphenyl-7,8-dihydro-4*H*,9*H*-furo[2',3',4':4,4a,5]naphth[2,1-*e*][1,3]oxazin-4-one (**2f**).

The reaction mixture was heated to reflux for 16 hours. Compound **2f** was obtained in 60% yield, mp = 128°; ir (potassium bromide): ν cm^{-1} 1790 (CO); 1H nmr (deuteriochloroform): δ ppm 3.34 and 3.88 (2 d, CH_2 -N, 2H, J = 14 Hz), 3.82 (s, CH_3 O, 3H), 5.03 (s, H-7, 1H), 6.02 (s, H-9, 1H), 6.77 (s, H-6, 1H), 6.9 to 7.8 (m, H arom, 14H), 7.9 (dd, H-2, 1H, J = 7.1 and 8.1 Hz), 8.22 (d, H-3, 1H, J = 7.1 Hz), 8.56 (d, H-1, 1H, J = 8.1 Hz).

Anal. Calcd. for $C_{33}H_{25}NO_4 \cdot 0.75H_2O$: C, 77.25; H, 5.20; N, 2.73. Found: C, 77.40; H, 5.24; N, 2.58.

trans-8-Benzyl-7,9-di(*p*-methoxyphenyl)-7,8-dihydro-4*H*,9*H*-furo[2',3',4':4,4a,5]naphth[2,1-*e*][1,3]oxazin-4-one (**2g**).

The reaction mixture was heated to reflux for 5 hours. Compound **2g** was obtained in 53% yield, mp = 164°; ir (potassium bromide): ν cm^{-1} 1780 (CO); 1H nmr (deuteriochloroform): δ ppm 3.36 and 3.95 (2 d, CH_2 -N, 2H, J = 14 Hz), 3.77 (s, CH_3 O, 3H), 3.83 (s, CH_3 O, 3H), 4.95 (s, H-7, 1H), 6 (s, H-9, 1H), 6.74 (s, H-6, 1H), 6.8 to 7.65 (m, H arom, 13H), 7.89 (dd, H-2, 1H, J = 7.1 and

8.2 Hz), 8.21 (d, H-3, 1H, J = 7.1 Hz), 8.5 (d, H-1, 1H, J = 8.2 Hz).

Anal. Calcd. for $C_{34}H_{27}NO_5 \cdot 0.5H_2O$: C, 75.82; H, 5.24; N, 2.60. Found: C, 75.84; H, 5.31; N, 2.56.

trans-8-Allyl-7,9-di(*p*-chlorophenyl)-7,8-dihydro-4*H*,9*H*-furo[2',3',4':4,4a,5]naphth[2,1-*e*][1,3]oxazin-4-one (**2h**).

The reaction mixture was heated to reflux for 5 hours. Compound **2h** was obtained in 60% yield, mp = 179°; ir (potassium bromide): ν cm^{-1} 1780 (CO); 1H nmr (deuteriochloroform): δ ppm 2.9 and 3.34 (2 m, CH_2 = CH - CH_2 -N, 2H), 5.16 (s, H-7, 1H), 5.22 (m, CH_2 = CH - CH_2 -N, 2H), 5.8 (s, H-9, 1H), 5.88 (m, CH_2 = CH - CH_2 -N, 1H), 6.79 (s, H-6, 1H), 7.3 to 7.56 (m, H arom, 8H), 7.89 (dd, H-2, 1H, J = 7, and 8 Hz), 8.21 (d, H-3, 1H, J = 7 Hz), 8.49 (d, H-1, 1H, J = 8 Hz).

Anal. Calcd. for $C_{28}H_{19}NO_3Cl$: C, 68.86; H, 3.92; N, 2.86; Cl, 14.51. Found: C, 69.09; H, 3.89; N, 2.80; Cl, 14.32.

trans-8-Benzyl-7,9-di(*p*-nitrophenyl)-7,8-dihydro-4*H*,9*H*-furo[2',3',4':4,4a,5]naphth[2,1-*e*][1,3]oxazin-4-one (**2i**).

The reaction mixture was heated to reflux for 5 hours. Compound **2i** was obtained in 52% yield, mp = 189°; ir (potassium bromide): ν cm^{-1} 1790 (CO); 1H nmr (deuteriochloroform): δ ppm 3.48 and 3.83 (2 d, CH_2 -N, 2H, J = 14 Hz), 5.11 (s, H-7, 1H), 5.93 (s, H-9, 1H), 6.74 (s, H-6, 1H), 7.31 to 8.59 (m, H arom, 16H).

Anal. Calcd. for $C_{32}H_{21}N_3O_7 \cdot 0.5H_2O$: C, 67.60; H, 3.90; N, 7.39. Found: C, 67.63; H, 3.84; N, 7.11.

trans-8-*p*-Methylbenzyl-7,9-di(*p*-nitrophenyl)-7,8-dihydro-4*H*,9*H*-furo[2',3',4':4,4a,5]naphth[2,1-*e*][1,3]oxazin-4-one (**2j**).

The reaction mixture was heated to reflux for 16 hours. Compound **2j** was obtained in 70% yield, mp = 150°; ir (potassium bromide): ν cm^{-1} 1790 (CO); 1H nmr (deuteriochloroform): δ ppm 2.37 (s, CH_3 , 3H), 3.42 and 3.76 (2 d, CH_2 -N, 2H, J = 13.5 Hz), 5.1 (s, H-7, 1H), 5.91 (s, H-9, 1H), 6.72 (s, H-6, 1H), 7.15 to 8.34 (m, H arom, 12 H), 7.96 (dd, H-2, 1H, J = 7.1 and 8.1 Hz), 8.27 (d, H-3, 1H, J = 7.1 Hz), 8.56 (d, H-1, 1H, J = 8.1 Hz).

Anal. Calcd. for $C_{33}H_{23}N_3O_7 \cdot 0.25H_2O$: C, 68.57; H, 4.10; N, 7.27. Found: C, 68.37; H, 4.01; N, 7.28.

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