Dihydrothienopsoralens: New Furocoumarins as Potential Photoreacting Agents

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A series of new dihydrothienopsoralen derivatives were synthesized from 6-hydroxybenzo[*b*]furan in four steps in good yield. These compounds were prepared as potential photosensitizing and chemotherapeutic agents for psoriasis. The spectroscopy study in also reported and showed an absorbance at $\lambda = 364$ nm and fluorescence at $\lambda = 440$ nm with high molar absorptivity, wave length used to perform the photochemical and photobiological experiments.

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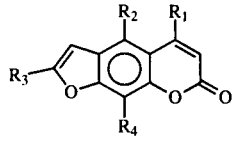
Furocoumarins, such as 8-methoxypsoralen, 5-methoxypsoralen and 4,5',8-trimethoxypsoralen, are used in photochemotherapy for the therapeutic treatment of vitiligo [1] and some skin diseases characterized by an increased reproduction activity of cutaneous cells, such as psoriasis and mycosis fungoides [2,3]. Some cutaneous lymphoma can be treated by 8-methoxypsoralen [4].

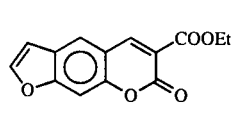
The psoralens have two photoreactives sites: the 3,4 and 4',5' double bonds. Under long wavelength ultraviolet radiation (320-400 nm) (Figure 1) they are able to photoreact with nucleic acids, especially DNA forming monoadducts to one strand of DNA or cross links between the opposite strands of native DNA [5]. Although photochemotherapy has been shown to be effective, there are some side effects with this clinical application. The short term hazards are inflammation of skin and alteration of the proliferation kinetics and viability of the cutaneous cells; the long term side effects include skin cancer and cataracts [6]. The undesired side effects are mostly attributed to the formation of cross linkages in DNA, where as a simple monoaddition would seem to be safer [7].



Psoralen	$R_1 = R_2 = R_3 = R_4 = H$
8-methoxypsoralen	$R_1 = R_2 = R_3 = H$, $R_4 = OCH_3$
5-methoxypsoralen	$R_1 = R_3 = R_4 = H$, $R_2 = OCH_3$
4,5',8-trimethylpsoralen	$R_2 = H$, $R_1 = R_3 = R_4 = CH_3$

Figure 1. Structures of psoralens used in photochemotherapy.

For this reason, much attention has been given to the development of furocoumarins which only have monofunctional photobinding with DNA and thereby reduce the undesirable side effects. This has been accomplished by using angular furocoumarins such as 4,5'-dimethylangelicin which do not have interstrand DNA cross-links for geometric reasons [8], by blocking the photoreactive α-pyrone double bond with appropriate substituents [9] such as 3-carbethoxypsoralen A and by attaching the additional aromatic ring such as pyridopsoralen B [10,11] or pyrazinopsoralen C [12] (Figure 2). These compounds can form only a 4',5'-monoadduct with DNA and have lower phototoxic effects. However, the use of these psoralens for photosensitizing drug as limited by residual problems such as photoinstabilityand the high efficiency of $^1O_2$ formation [12].Thus, the aim of this work was to synthesize and investigate another series of monofunctional furocoumarins derivatives.



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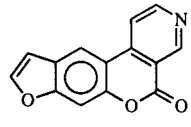

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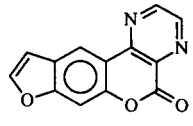

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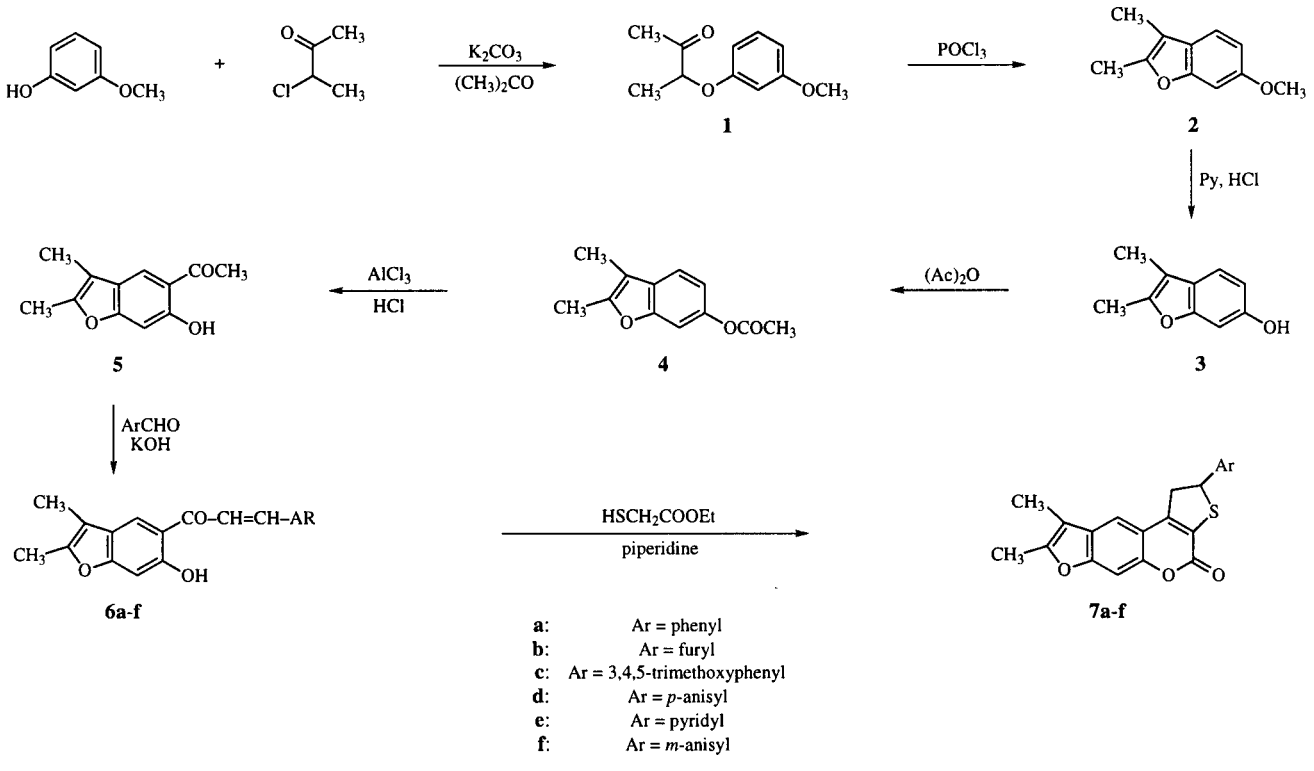
Figure 2. Structures of psoralen's analogues.

The present paper reports the synthesis of monofunctional psoralen analogues with the dihydrothienofurocoumarines **7** having a fused dihydrothiophene ring on the 3,4 site (Scheme 1).

Scheme 1



Chemistry.

The synthetic procedure of new dihydrothienopsoralens **7a-f** is shown in Scheme 1. The synthesis was carried out starting from 3-methoxyphenol on which the furan ring was built. Several halogenoketones were condensed with 3-methoxyphenol. The cyclization of intermediate **1** using phosphorus oxychloride as the catalyst, yielded 6-methoxybenzofuran **2**. The corresponding 6-hydroxybenzofuran **3** was readily obtained and isolated according to Royer's procedure using pyridine hydrochloride [13]. Acylation of **3** gave acyloxy-2,3-dimethylbenzofuran **4** which was submitted to the Fries rearrangement [14] giving 5-acetyl-6-hydroxy-2,3-dimethylbenzofuran **5**. This rearrangement was established by a ^{1}H nmr study of compound **5** which showed the loss of the proton signal in position 5. With compound **5**, appropriate aldehydes were condensed in alkaline medium, giving the corresponding orthohydroxychalcone derivatives **6a-f** [15-18]. The desired dihydrothienopsoralens **7a-f** were successfully synthesized by the condensation of ethyl thioglycolate with the corresponding orthohydroxychalcones **6a-f** using Xicluna and Ombetta's procedure [19,20].

The ultraviolet absorption spectra of several dihydrothienopsoralens dissolved in different solvents are reported in Table 1. The ε values were calculated respectively at the corresponding λ max. They show an absorption peak near 360 nm wavelength generally used to perform the photochemical and photobiological experiments.

Table 1

Spectral Data of Dihydrothienopsoralens **7a-f**

Compound	Solvent	λ_{avs}^{max} (nm)	$\varepsilon_{(c=8\ mg.l^{-1})} \times 10^4$	λ_{fluo}^{max} (nm)
7a	Methanol	364	1.79	437
	Ethanol	365	2.20	440
7b	Methanol	362	1.86	434
	Ethanol	363	1.97	442
7c	Methanol	365	1.85	438
	Ethanol	365	2.00	441
7d	Methanol	365	1.41	439
	Ethanol	365	1.70	443
7e	Methanol	364	1.67	438
	Ethanol	364	1.83	440
7f	Methanol	364	1.9	439
	Ethanol	364	2.1	440

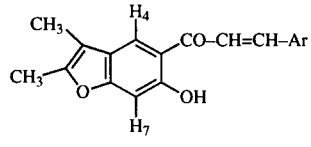
Table 2

Physical and Analytical Data of Compounds **6a-f**

Compound	Ar	Method	Yield %	mp °C	Formula	Calcd./Found (%) C	H	N
6a	Phenyl	A	62	133	$C_{19}H_{16}O_3$	78.00	5.48	-
						78.35	5.33	
6b	Furyl	B	82	157	$C_{17}H_{14}O_4$	72.34	4.96	-
						72.56	4.81	
6c	Trimethoxyphenol	B	87	168	$C_{22}H_{22}O_6$	69.10	5.76	-
						69.22	5.65	
6d	*p*-anisyl	B	75	171	$C_{20}H_{18}O_4$	75.53	5.59	-
						74.41	5.72	
6e	Pyridyl	A	45	182	$C_{18}H_{15}O_3N$	73.22	5.12	4.78
						73.27	4.96	4.82
6f	*m*-anisyl	A	58	165	$C_{20}H_{18}O_4$	74.53	5.59	-
						73.95	5.32	

Table 3

Spectral Data of Compounds **6a-f**



Compound	IR (cm^{-1})	H_4	H_7	2-CH_3	3-CH_3	CH=CH-Ar	Ar	OH	(OCH_3)
6a	1640	7.80 (s)	6.90 (s)	2.35 (s)	2.20 (s)	7.70 (m)	7.40 (m)	13.00 (s)	-
6b	1640	7.85 (s)	6.90 (s)	2.35 (s)	2.20 (s)	7.65 (m)	6.10-6.70 (m)	13.10 (s)	-
6c	1640	7.90 (s)	6.95 (s)	2.35 (s)	2.20 (s)	7.65 (m)	7.25 (s)	13.20 (s)	3.9 (s)
6d	1635	7.90 (s)	6.95 (s)	2.35 (s)	2.20 (s)	7.65 (m)	7.25 (s)	13.00 (s)	3.9 (s)
6e	1635	7.90 (s)	6.95 (s)	2.35 (s)	2.15 (s)	7.60 (m)	7.30 (m)	13.00 (s)	-
6f	1640	7.90 (s)	6.95 (s)	2.35 (s)	2.15 (s)	7.30 (d)-7.60 (d)	7.30 (m)	13.00 (s)	3.9 (s)

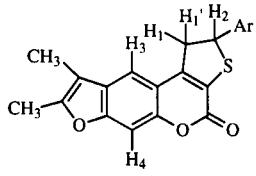
Table 4

Physical and Analytical Data of Compounds **7a-f**

Compound	Ar	Yield (%)	mp °C	Formula	Calcd./Found(%) C	H	N	S
7a	Phenyl	62	247.5	$C_{21}H_{16}O_3S$	72.41	4.60	-	9.20
					72.15	4.63		9.33
7b	Furyl	72	245	$C_{19}H_{14}O_4S$	67.45	4.14	-	9.46
					67.32	4.23		9.61
7c	Trimethoxyphenol	69	>260	$C_{24}H_{22}O_6S$	65.75	5.02	-	7.30
					65.59	5.17		7.27
7d	*p*-anisyl	54	>260	$C_{22}H_{18}O_4S$	69.84	4.76	-	8.46
					69.82	4.81		8.42
7e	Pyridyl	52	220	$C_{20}H_{15}O_3N$	68.76	4.29	4.01	9.17
					68.73	4.27	4.11	9.21
7f	*m*-anisyl	63	193	$C_{22}H_{18}O_4S$	69.84	4.76	-	8.46
					69.82	4.73		8.37

Table 5

Spectral Data of **7a-f**



Compound	IR (cm^{-1})	H_1	H_1	H_2	H_3	H_4	CH_3	CH_3	Ar	OCH_3
7a	1700	3.60 (dd)	3.90 (dd)	5.20 (dd)	7.20 (s)	7.50 (s)	2.15 (s)	2.40 (s)	7.40 (m)	-
7b	1700	3.50 (dd)	3.80 (d)	5.20 (dd)	7.20 (s)	7.40 (s)	2.15 (s)	2.40 (s)	7.30 (s)	-
7c	1705	3.70 (dd)	3.90 (dd)	5.20 (dd)	7.20 (s)	7.40 (s)	2.15 (s)	2.40 (s)	6.70 (s)	3.80 (s)
7d	1700	3.70 (dd)	3.90 (dd)	5.20 (dd)	7.30 (s)	7.30 (s)	2.15 (s)	2.40 (s)	6.90 (d)-7.40 (d)	3.80 (s)
7e	1705	4.20 (dd)	4.10 (dd)	5.30 (dd)	7.20 (s)	7.30 (s)	2.15 (s)	2.40 (s)	7.10 (d)-7.50 (d)-7.70 (dd)	-
7f	1700	3.70 (dd)	3.70 (dd)	5.20 (s)	7.20 (d)	7.30 (s)	2.14 (s)	2.45 (s)	6.90 (d)-6.80 (d)	3.80 (s)

EXPERIMENTAL

Melting points were determined on a Buchi No. 510 apparatus and are uncorrected. Infrared spectra were taken in potassium bromide pellets on a Shimadzu FTIR 800 1PC Spectrometer.

The ^1H nmr spectra were recorded on a Bruker AC 200 spectrometer at 200 MHz using tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million and signals are quoted as s (singlet), d (doublet), t (triplet), q (quadruplet) and m (multiplet). Elemental analyses were carried out at the Service Central d'Analysis. Centre National de la Recherche Scientifique, 69390 Vernaison, France.

3-Methoxyphenyloxy-3-butan-2-one (**1**).

To a stirred solution of 3-methoxyphenol (12.4 g, 0.1 mole) and potassium carbonate (13.8 g, 0.1 mole) in 70 ml of acetone, 3-chlorobutan-2-one (10.6 g, 0.1 mole) was added. The reaction mixture was heated at reflux for 24 hours, then cooled and acidified with 5*N* aqueous hydrochloric acid solution. The resulting mixture was extracted with chloroform, washed with 10% aqueous sodium hydroxide and water successively and dried over sodium sulfate, then evaporated. The compound was a dark oil yielding (17.5 g, 93%); ir (potassium bromide): ν 2950 (CH), 1720 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.30 (s, 3H), δ 2.35 (d, 3H), δ 3.70 (m, 1H), δ 3.85 (s, 3H), δ 6.60 (m, 2H), δ 7.20 (m, 2H).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.04; H, 7.20. Found: C, 67.68; H, 7.35.

6-Methoxy-2,3-dimethylbenzo[*b*]furan (**2**).

To phosphorus oxychloride (60 g, 0.4 mole) heated to 100° (30 g, 0.15 mole) of **1** was added dropwise. The reaction mixture was stirred for 15 minutes at 100°. The mixture was cooled in an ice bath and water (100 ml) was added. The resulting mixture was extracted with chloroform. The organic phase was washed with 10% aqueous sodium hydroxide and water successively, then dried over sodium sulfate and evaporated. The residue was purified by column chromatography on silica gel (eluent-dichloromethane) to give 24.6 g (90%) of **2** as a dark oil; ir (potassium bromide): ν 2920 (CH); ^1H nmr (deuteriochloroform): δ 2.15 (s, 3H), 2.30 (s, 3H), 3.85 (s, 3H), δ 6.85 (m, 2H), δ 7.20 (d, 1H).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.0; H, 6.80. Found: C, 74.5; H, 6.85.

6-Hydroxy-2,3-dimethylbenzo[*b*]furan (**3**).

A mixture of **2** (20 g, 0.11 mole) and pyridine hydrochloride (40 g, 0.35 mole) was stirred and heated to reflux for 25 minutes, then cooled and acidified with 50 ml of 5*N* aqueous hydrochloric acid solution. The resulting mixture was extracted with chloroform. The organic phase was separated and extracted with 10% aqueous sodium hydroxide. The aqueous phase was acidified with 5*N* aqueous hydrochloric acid solution and the precipitate was filtered and the product was recrystallized from cyclohexane to give yellow crystals (11.6 g, 65%) mp 112°; ir (potassium bromide): ν 3300 (OH), 2950 (CH) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.15 (s, 3H), δ 2.30 (s, 3H), δ 6.85 (d, 1H), 6.80 (d, 1H), δ 7.30 (d, 1H), δ 12.50 (s, 1H).

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.0; H, 6.17. Found: C, 73.6; H, 6.27.

6-Acetoxy-2,3-dimethylbenzo[*b*]furan (**4**).

An acetic anhydride solution (40 ml, 15 g, 0.09 mole) of **3** was stirred and heated at reflux for 30 minutes, then evaporated. The resulting residue was dissolved in chloroform (50 ml) and washed with 5% aqueous sodium carbonate solution. The organic phase was dried over sodium sulfate and evaporated. After cooling the residue crystallized to give a dark oil, yield 93%, mp 48°; ir (potassium bromide): ν 2950 (CH), 1755 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.10 (s, 3H), δ 2.35 (d, 6H), δ 6.80 (d, 1H), δ 7.10 (d, 1H), δ 7.30 (d, 1H).

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.58; H, 5.88. Found: C, 70.92; H, 5.79.

5-Acetyl-6-hydroxy-2,3-dimethylbenzo[*b*]furan (**5**).

To a stirred solution of 10 g (0.05 mole) of 6-acetoxy-2,3-dimethylbenzofuran (**4**) in benzene (50 ml), aluminium chloride (6.7 g, 0.05 mole) was added in small amounts. The reaction mixture was stirred and heated at reflux for 5 hours. Then the resulting mixture was cooled in an ice bath and acidified with

diluted hydrochloric acid. The organic phase was washed with water, dried over sodium sulfate and evaporated. The residue was crystallized from methanol to give yellow crystals, yield 63%, mp 121°; ir (potassium bromide): ν 3100 (OH), 2920 (CH), 1645 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.10 (s, 3H), δ 2.35 (s, 3H), δ 2.70 (1, 3H), δ 6.85 (s, 1H), δ 7.60 (s, 1H), δ 12.50 (s, 1H).

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.58; H, 5.88. Found: C, 70.32; H, 5.75.

General Procedure for the Preparation of Chalcones **6a-f**.

Method A.

To a stirred solution of 15 ml of 50% alcoholic potassium hydroxide, 5 mmoles of **5** was added to an equimolar amount of aldehyde. The reaction mixture was stirred for 24 hours at room temperature, then acidified with 5*N* aqueous hydrochloric acid solution. The precipitate was filtred and washed with water and recrystallized from ethanol to give orange crystals.

Method B.

To a solution of 1 g (5 mmoles) of **5** in ethanol (10 ml) was added an equimolar amount of aldehyde. The mixture was stirred and heated at 60° for 15 minutes, then 15 ml of 40 *N* aqueous sodium hydroxide solution was added in small amounts. The reaction mixture was stirred at room temperature for 5 hours, then acidified with 5*N* aqueous hydrochloric acid solution. The precipitate was filtered and washed with water and recrystallized furan-ethanol-water to give orange crystals (Tables 2 and 3).

General Procedure for the Preparation of Dihydrothienopsoralens **7a-f**.

To a stirred solution of 5 mmoles of chalcone in benzene (20 ml) ethyl thioglycolate (0.6 ml, 5 mmoles) and piperidine (1 ml) were added dropwise. The reaction mixture was stirred and heated at reflux for 8 hours. Then 5*N* aqueous hydrochloric acid solution (50 ml) was added. The resulting mixture was stirred at room temperature for 15 minutes then the organic phase was separated and washed with water, dried over sodium sulfate and evaporated. The residue was crystallized from ethanol to give yellow crystals (Tables 4 and 5).

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