Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 44 (2009) 18–24
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

Tetrahydrobenzo- and benzofurobenzopyrones as a new class of potential photoreagents toward DNA

Nahla Ahmed Hasan Farag*

Pharmaceutical Chemistry Department, Faculty of Pharmacy, Cairo University, El-Kasr El-Aini Street, Cairo 11562, Egypt

Received 26 May 2007; received in revised form 3 March 2008; accepted 6 March 2008
Available online 10 April 2008

Abstract

The synthesis and the photobiological activity of new tetrahydrobenzo- and benzofurobenzopyrone derivatives carrying at position 4 of benzopyrone ring of furobenzopyrone moiety a phenyl, or a methyl group with a linear structure or with various angular arrangements, are reported. The new compounds are characterized by having an additional cyclohexene or phenyl ring condensed at the 2, 3 double bond of the furan ring of furobenzopyrone nucleus. The syntheses were performed starting from the appropriate hydroxybenzopyrones on which the tetrahydrobenzofuran or benzofuran moiety was built, which look most promising for enhancement of photoreactivity of compounds toward DNA. All the synthesized compounds were screened for photosensitizing activity and some of them exhibited good activity also a certain effect was observed in the dark.

Keywords: Tetrahydrobenzofurobenzopyrone; Benzofurobenzopyrone; Photochemotherapeutic agents; Photobiological activity

1. Introduction

Photochemotherapy using psoralens and UVA; 320–400 nm (PUVA) is a treatment used widely in some skin diseases including vitiligo, a skin depigmentational disorder and psoriasis, a disease of accelerated epidermal cell proliferation [1], in cutaneous lymphomas and in autoimmune diseases, assuming that the major site of action is DNA [2]. The photobiological activity of furobenzo-α-pyrones (furocoumarins) is the result of the covalent bonding they undergo with nucleic acid [3–7]. The process is believed to involve three major steps: noncovalent intercalative binding to DNA helix [5], formation of a number of monoadditional products between the furobenzopyrone and DNA based upon long wave length UV-irradiation [7], absorption of a second photon by some of the mono-adducts to form bi-adducts resulting in interstrand cross-linkages [7]. Therefore, the 2, 3 and 5, 6 double bonds are the two photoreactive sites responsible for DNA photobinding and for the biological activity [8]. In addition, it is reported that, genotoxicity is the undesirable side effect of furobenzopyrones and it is developed from the formation of DNA bi-functional adducts [9–11].

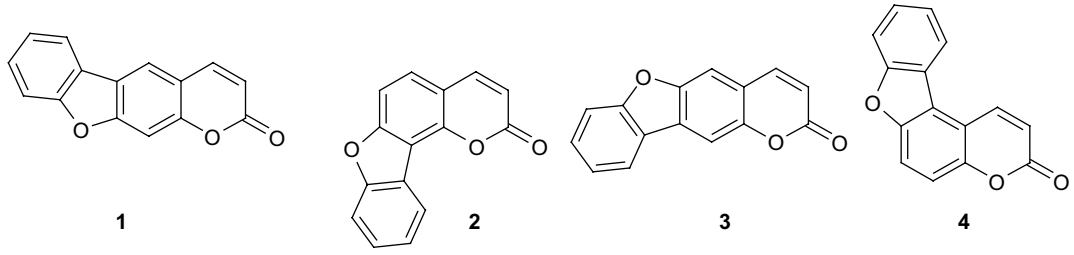
Extensive photochemical and photobiological studies have been performed mainly on two series of furobenzopyrones, that is psoralens (linear furobenzopyrone) [1,12,13] and, angelicins (angular furobenzopyrone) [14–18]. In addition, new DNA monofunctional furobenzopyrones as 6-carbethoxy analogues [19], furobenzopyrones with modified annulations geometry [20] as well as pyridopsoralen [21–23], azapsoralens [24], and furoquinolinones [25] have been prepared. They prevent interstrand cross-link formation, consequently lack skin phototoxicity [21–25], and at the same time maintain the photosensitizing activity. Synthesis of different series of tetrahydrobenzo- and benzofurobenzopyrone derivatives as new monofunctional DNA photobinding agents was reported [26,27] and it was interesting for the development of new, less phototoxic chemotherapeutic agents that interact with DNA better than 8-methoxypsoralen (8-MOP) (xanthotoxin) [28].

* Tel.: +20 24534418, 0123378871; fax: +20 23628426.
E-mail address: anahla_69@yahoo.com

0223-5234/$ - see front matter © 2008 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2008.03.041

The single-crystal structures 1FHY and 1FHZ are presented for two DNA sequences with the thymine bases covalently cross-linked across the complementary strands by 4′-hyroxymethyl-4, 5′,8-trimethylpsoralen (HMT). The HMT-adduct of d(CCGCTAGCGG) forms a psoralen-induced Holliday junction showing the effect of this important class of chemotherapeutics on the structure of the recombination intermediate. In contrast HMT-d(CCGGTACCGG) forms a sequence-dependent junction. In both structures, the DNA duplex is highly distorted at the thymine base linked to the six-membered pyrone ring of the drug. The psoralen cross-link defines the intramolecular interactions of the drug-induced junction, while the sequence-dependent structure is nearly identical to the native Holliday junction, suggesting a role for psoralen in the mechanism to initiate repair of psoralen-lesion in mammalian DNA [29].

Owing to our interest for drug molecules able to photoreact monofunctional with DNA and their biological activity, we planned to prepare a new series of tetracyclic furobenzopyrone derivatives. These new compounds derive from the condensation of a cyclohexene or phenyl ring at 2, 3 double bond of the furan ring of the furobenzopyrone nucleus and may have both a linear geometry **1**, **3** and angular structures **2**, **4**.



1 **2** **3** **4**

2. Chemistry

Generally the synthetic pathway followed by MacLeod et al. [30] to obtain the unsubstituted tetrahydrobenzofurobenzopyrone and benzofurobenzopyrone has been employed to prepare the designed compounds as illustrated by the formulae **1**, **2**, **3**, **4**.

The appropriate hydroxybenzopyrones **5**, **11** were condensed with 2-bromocyclohexanone to yield the corresponding ethers **6**, **12** [31–33], which were cyclized in alkaline medium [34] obtaining the linearly annulated **8**, **14** and the angular derivatives **7**, **13**. Dehydrogenation of the appropriate compounds **7**, **8**, **13**, **14** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [35,36] yielded the corresponding benzofurobenzopyrones **9**, **10**, **15**, **16** (Schemes 1 and 2).

In particular, the synthesis of phenyl derivatives of tetrahydrobenzofurobenzopyrones **7**, **8** was performed starting from 7-hydroxybenzopyrone derivative with phenyl group in 4-position Scheme 1. Thus, cyclization of 2′-oxocyclohexenyl ethers of 7-hydroxybenzopyrone **6**, yielded the angular structure (angelicin type, **2**) **7** which is supported by ^{1}H NMR which reveals the presence of *ortho* coupling of H-5, H-6 protons of furobenzopyrone moiety, and the linearly annulated furobenzopyrone (psoralen type, **1**) **8**, which is supported by the absence of ortho coupling of H-5, H-6 protons of furobenzopyrone moiety and the presence of separate signals for H-5, H-11 of furobenzopyrone moiety.

Analogously, the cyclized 4-methyl analogues **13**, **14** are obtained from the corresponding ether derivative **12**, Scheme 2, to yield the angular structure (isopseudopsoralen type **4**) **13** and the linearly annulated furobenzopyrone (type **3**) **14**.

3. Photosensitizing activity

The new derivatives (**7–10**, **13–16**) obtained from the reaction sequence were screened for their antimicrobial and photoreactivity toward DNA and the results are presented in Table 1.

4. Isoelectric potential studies

Chem3D Ultra-models have been simulated using ChemOffice 2004 software. First the structure models were generated then fully minimized to obtain the optimum structures with least energy. The charges were calculated by MNDO method [37].

5. Results and discussion

With dark controlled screening, data concerning antimicrobial activity which are reported in Table 1, it was noticed that compounds **8–10**, **15**, **16** are active as antimicrobial against *Bacillus subtilis* where compound **9** was the most active one, while comparing activity as photosensitizer, compounds **7**, **9**, **10**, **15**, **16** have photosensitizing activity.

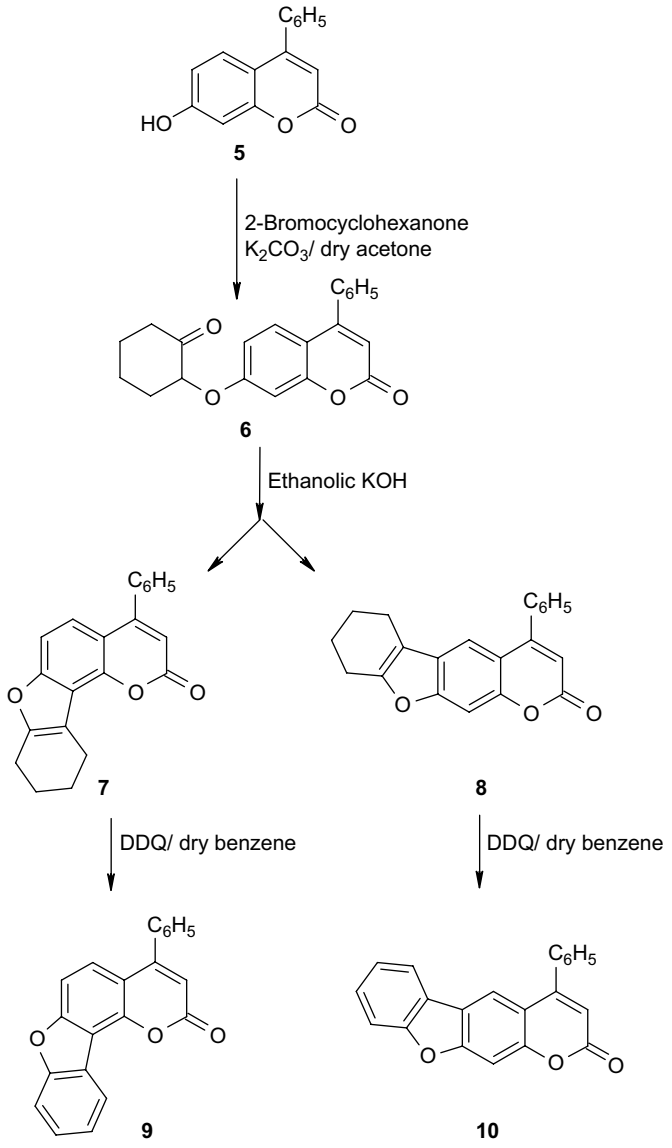
Isoelectric potential studies (Figs. 1–5) reveal that there may be a relationship between photosensitizing activity and coplanarity of the molecule may be due to its noncovalent intercalative binding with DNA helix where, benzo group is coplanar with furobenzopyrone moieties **9**, **10**, **15**, **16**.

Based on this finding, compounds **7**, **10**, **15**, **16** may be good candidates as new, monofunctional, less phototoxic chemotherapeutic agents that interact with DNA.

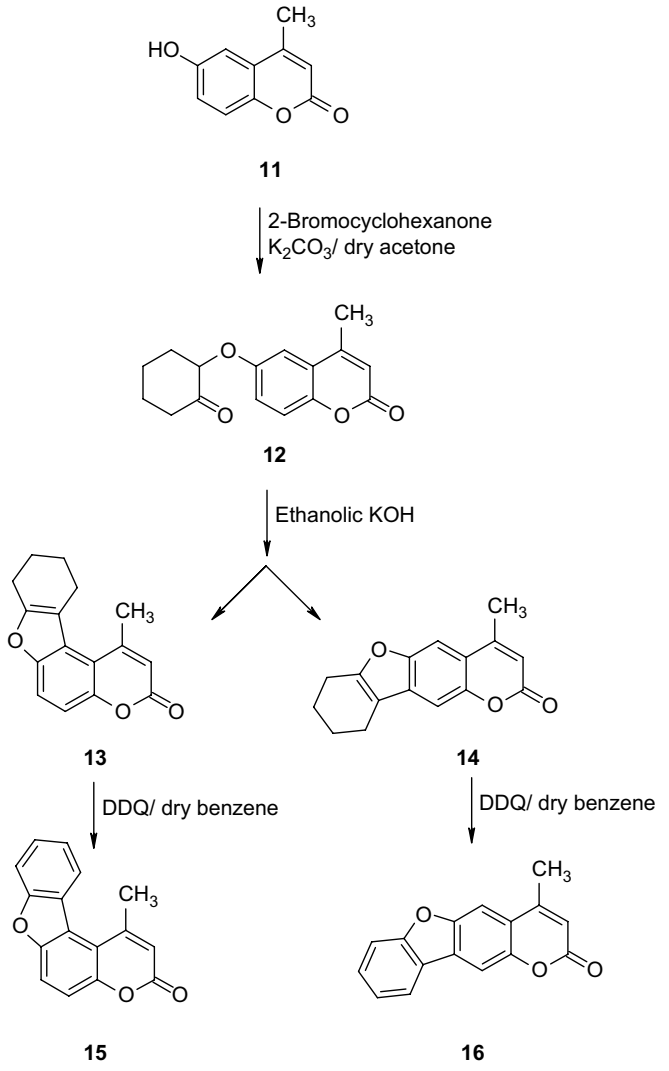
6. Experimental protocols

6.1. Chemistry

Remarks: melting points (mp) were determined in one-end open capillary tubes on Gallenkamp and Kofler melting point



Scheme 1.



Scheme 2.

apparatus and are uncorrected. Elemental analyses (C, H) were undertaken with Perkin–Elmer model 240Canalyser and performed by microanalytical center, Cairo University (within ±0.4%). Infrared spectra were determined on Shimadzu IR 435 Spectrophotometer using KBr disc. Nuclear magnetic resonance spectra were scanned on Joel NMR and Varian Gemini 300 MHz and 90 MHz spectrometer. Mass spectra were taken with a Finigan Mat 212-spectrometer (ei 120 eV, R 1000). The homogeneity of the compounds was monitored by thin-layer chromatography (TLC) using precoated silica gel-G plates 60-F-254 (Merk; 0.25 mm). Developing solvent was chloroform.

*6.1.1. Synthesis of 7-(2′-oxocyclohexyloxy)-4-phenyl-2H-1-benzopyran-2-one (**6**)*

A solution of 7-hydroxy-4-phenyl-2*H*-1-benzopyran-2-one **5** (2.38 g, 0.01 mol) in 120 ml of acetone was reacted with 2-bromo-cyclohexanone (3.52 g, 0.02 mol) in the presence of anhydrous potassium carbonate (2.76 g, 0.02 mol) by refluxing the mixture for 20 h. After chilling the potassium carbonate was filtered off and washed with acetone. The pooled filtrate and acetone washings were concentrated to dryness and the residue crystallized from methanol giving **6** as yellow crystals (2.2 g, 66%), mp 173 °C.

*Compound **6** ^1H NMR*. (90 MHz, δ): 1.80–2.65 (m, 8H, $-(CH_2)_{4-}$), 4.74–4.79 (m, 1H, =CH–O–), 6.22 (s, 1H, H-3), 6.78 (d, 1H, H-8, $J_{8,6} = 2.1$), 6.80 (d, 1H, H-6, $J_{6,8} = 2.1$), 7.37 (d, 1H, H-6, $J_{6,5} = 9.6$), 7.43 (d, 1H, H-5, $J_{5,6} = 9.6$), 7.45–7.52 (m, 5H, ar. protons). Anal. Calcd for $C_{21}H_{17}O_4$: C, 75.68; H, 5.11. Found: C, 75.60; H, 5.02.

*6.1.2. Synthesis of 4-methyl-6-(2′-oxocyclohexyloxy)-2H-1-benzopyran-2-one (**12**)*

Reaction of 6-hydroxy-4-methyl-2*H*-1-benzopyran-2-one **11** (1.76 g, 0.01 mol), and 2-bromocyclohexanone (3.52 g, 0.02 mol) as described for compound **6** was adopted, crystallization from methanol giving **12** as yellow crystals (3.5 g, 65%), mp 212 °C.

Table 1
Preliminary screening of furobenzopyrone derivatives (**7**–**10**, **13**–**16**) as antimicrobial and photosensitizing agents

Compound	Control (before UV-irradiation) inhibition zone (mm)	Test (after UV-irradiation) inhibition zone (mm)
Xanthotoxin (8-MOP)	–	12.0
7	–	5.0
8	9.0	7.0
9	13.0	14.0
10	10.0	13.0
13	–	–
14	–	–
15	11.0	14.0
16	12.0	16.0

Compound ***12*** *^1H NMR*. (90 MHz, δ): 1.15–2.64 (m, $(CH_2)_4$, 8H), 2.37 (s, 3H, CH_3-4), 4.74–4.79 (m, 1H, =CH–O–), 6.34 (s, 1H, H-3), 7.00–7.29 (m, 3H, H-6, H-5, H-8), m/z = (272.15, 25.77), (176.00, 93.96), (147.00, 100). Anal.Calcd for $C_{16}H_{15}O_4$: C, 70.85; H, 5.54. Found: C, 71.11; H, 5.36.

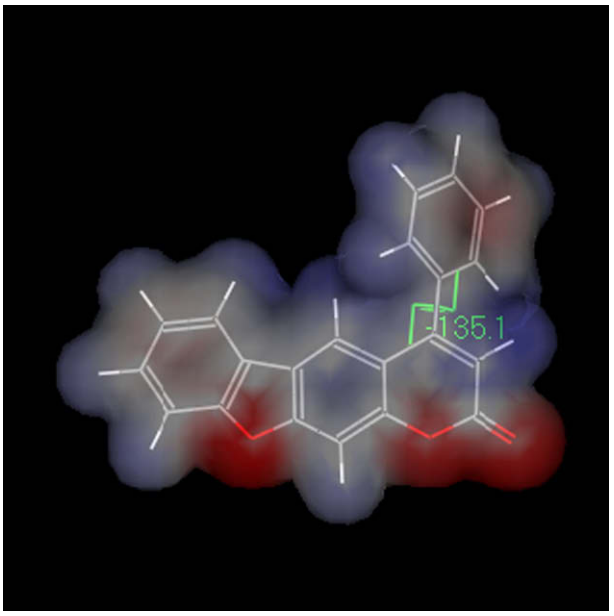


Fig. 2. Isoelectric potential of **10**.

*6.1.3. Synthesis of 4-phenyl-8,9,10,11-tetrahydro-2H-benzofuro[2,3-h]-1-benzopyran-2-one (**7**) and 4-phenyl-6,7,8,9-tetrahydro-2H-benzofuro [3,2-g]-1-benzopyran-2-one (**8**)*

7-(2′-Oxocyclohexyloxy)-4-phenyl-2*H*-1-benzopyran-2-one **6** (3.33 g, 0.01 mol) was dissolved in 0.1 N potassium hydroxide solution (0.56 g, 100 ml absolute ethanol) and was refluxed for 18 h. The reaction was TLC controlled and left overnight at room temperature, then filtered.

The residue was collected, acidified with dilute hydrochloric acid and filtered, washed with water and dried under vacuum. The crude product was crystallized from ethanol obtaining **7** as greenish brown needles (1.17 g, 37%), mp 235 °C.

Compound ***7*** *^1H NMR*. (300 MHz, δ): 1.81–1.96 (m, 4H, H-9, H-10), 2.52–2.76 (m, 4H, H-8, H-11), 6.26 (s, 1H, H-3), 7.49 (d, 1H, H-6, $J_{6,5} = 9.6$), 7.54 (d, 1H, H-5, $J_{5,6} = 9.6$), 7.56–7.57 (m, 5H, Ar-H).

Compound ***7*** *^{13}C NMR*. δ 19.5, 21.0, 23.9, 23.9 (C-11, C-9, C-10, C-8), 103.8–112.5, 112.7, 117.6, 122.1, 122.5 (C-6, C-3, C-11a, C-11b, C-5, C-4a), 126.4 (C-2′, C- 6′), 128.0 (C-3′, C-5′), 128.7(C-4′), 140 (C-1′), 148.6, 152.1, 154.0 (C-11c, C-6a, C-7a), 155.5 (C-4), 160.9 (C-2). Anal. Calcd for $C_{21}H_{16}O_3$: C, 79.75; H, 5.06. Found: C, 79.66; H, 5.35.

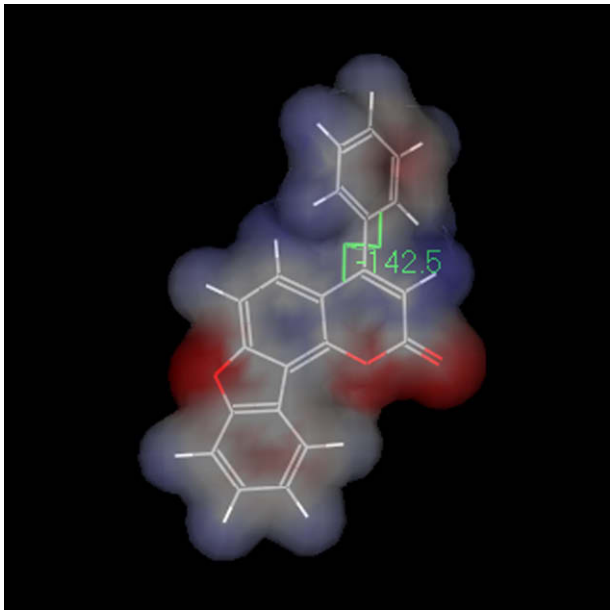


Fig. 1. Isoelectric potential of **9**.

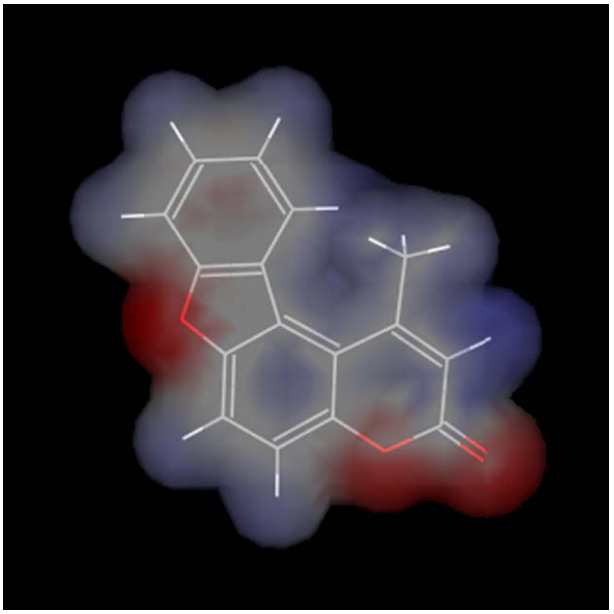


Fig. 3. Isoelectric potential of **15**.

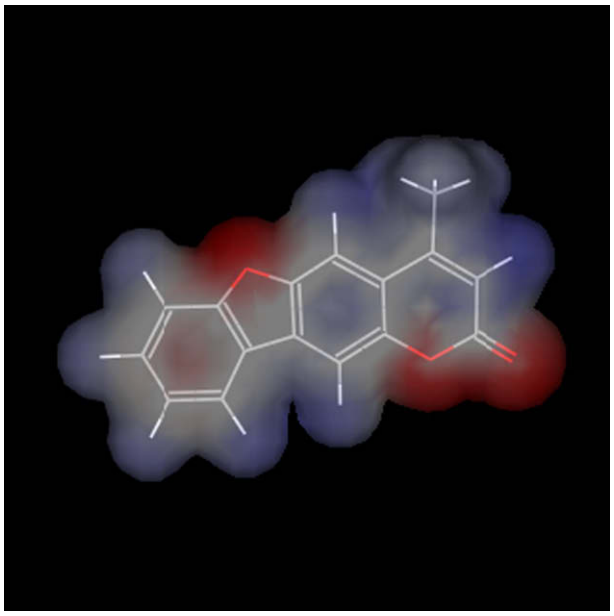


Fig. 4. Isoelectric potential of **16**.

Then, the obtained mother liquor was acidified with dilute hydrochloric acid and the precipitate obtained was filtered, washed with water and dried under vacuum. The crude product was crystallized from benzene/pet.ether obtaining **8** as light brown powder (0.95 g, 30%), mp 157 °C.

*Compound **8*** ^{1}H *NMR*. (300 MHz, δ): 1.81–1.96 (m, 4H, H-7, H-8), 2.52–2.78 (m, 4H, H-6, H-9), 6.31 (s, 1H, H-3), 7.27 (s, 1H, H-5), 7.40 (s, 1H, H-11), 7.44–7.57 (m, 5H, Ar-H).

*Compound **8*** ^{13}C *NMR*. δ 19.5, 21.0, 23.9 (C-6, C-8), 23.9 (C-7, C-9), 103.6, 112.5, 112.7, 119.5 122.5, 134.0 (C-5a, C-3, C-5b, C-5, C-4a, C-11), 126.4 (C-2′, C-6′), 128.0 (C-3′, C-5′), 128.7 (C-4′), 140 (C-1′), 151.5, 152.1, 154.6 (C-11a, C-10a, C-9a), 155.5 (C-4), 160.9 (C-2). Anal. Calcd for $C_{21}H_{16}O_3$: C, 79.75; H, 5.06. Found: C, 79.49; H, 4.83.

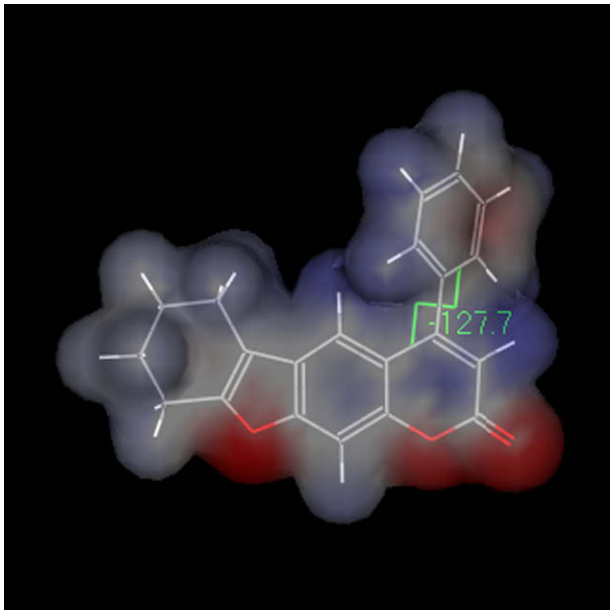


Fig. 5. Isoelectric potential of **8**.

*6.1.4. Synthesis of 4-methyl-5,6,7,8-tetrahydro-2H-benzofuro[3,2-f]-1-benzopyran-2-one (**13**) 4-methyl-7,8,9,10-tetrahydro-2H-benzofuro[2,3-g]-1-benzopyran-2-one (**14**)*

These compounds were prepared from 4-methyl 6-(2′-oxocyclohexyloxy)-2*H*-1-benzopyran-2-one **12** (2.71 g, 0.01 mol) as described for compounds **7**, **8**.

The residue was collected, acidified with dilute hydrochloric acid and filtered, washed with water and dried under vacuum. The crude product was crystallized from ethanol obtaining **13** (1.33 g, 52%), mp above 350 °C.

*Compound **13*** ^{1}H *NMR*. (300 MHz, δ): 1.74–1.98 (m, 4H, H-6, H-7), 2.39 (s, 3H, CH_3-4), 2.62–2.87 (m, 4H, H-5, H-8), 6. 33 (s, 1H, H-3), 7.26 (d, 1H, H-10, $J_{6,5} = 9.6$), 7.27 (d, 1H, H-11, $J_{5,6} = 9.6$). Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.59; H, 5.51. Found: C, 75.93; H, 5.02.

Then, the obtained mother liquor was acidified with dilute hydrochloric acid and the precipitate obtained was filtered, washed with water and dried under vacuum. The crude product was crystallized from benzene/pet.ether obtaining light brown powder (1.17 g, 46%) of **14** mp 247 °C.

*Compound **14*** ^{1}H *NMR*. (300 MHz, δ): 1.80–1.90 (m, 4H, H-8, H-9), 2.37–2.60 (m, 4H, H-7, H-10), 2.38 (s, 3H, CH_3-4), 6.34 (s, 1H, H-3), 7.00 (s, 1H, H-5), 7.30 (s, 1H, H-11), *m/z* = (256.25, 1.92), (176.00, 76.62), (147.00, 100). Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.59; H, 5.51. Found: C, 75.93; H, 5.39.

*6.1.5. Synthesis of 4-phenyl-2H-benzofuro[2,3-h]-1-benzopyran-2-one (**9**)*

A solution of 4-phenyl-8,9,10,11-tetrahydro-2*H*-benzofuro[2,3-*h*]-1-benzopyran-2-one **7** (0.60 g, 0.0018 mol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone DDQ (1.4 g, 0.007 mol) in 300 ml of benzene was refluxed for 20 h. After cooling, the solid was filtered off and the solution was concentrated to dryness. The obtained residue was collected and chromatographed on silica gel column eluting with chloroform:ethanol 8:2. From the pooled fractions containing a pure product (TLC), the solvent was evaporated and the residue crystallized from methanol/benzene giving **9** as dark red powder (0.18 g, 36%), mp 170 °C, $R_f = 0.68$.

*Compound **9*** ^{1}H *NMR*. (300 MHz, δ): 6.39 (s, 1H, H-3), 7.27 (s, 5H, C_6H_5-4), 7.04–7.08 (d, 1H, H-6, $J_{6,5} = 9.3$), 7.24–7.37 (d, 1H, H-5, $J_{5,6} = 9.9$), 7.57–7.99 (m, 9H, Ar-H).

*Compound **9*** ^{13}C *NMR*. δ 106.5, 108.3, 111.6, 112.7, 121.0, 122.1, 122.5, 123.3, 124.7 (C-11, C-9, C-10, C-8, C-6, C-3, C-11a, C-11b, C-5, C-4a), 126.4 (C-2′, C-6′), 128.0 (C-3′, C-5′), 128.7 (C-4′), 140 (C-1′), 145.8, 148.6, 155.5 (C-11c, C-6a, C-7a), 156.3 (C-4), 160.9 (C-2). Anal. Calcd for $C_{21}H_{12}O_3$: C, 80.77; H, 3.85. Found: C, 81.13; H, 3.83.

*6.1.6. Synthesis of 4-phenyl-2H-benzofuro[3,2-g]-1-benzopyran-2-one (**10**)*

This compound was prepared from 4-phenyl-6,7,8,9-tetrahydro-2*H*-benzofuro[3,2-*g*]-1-benzopyran-2-one **8** (0.50 g, 0.0016

mol) as described for the synthesis of compound **9** giving **10** as dark red powder (0.14 g, 28%), mp 123 °C, $R_f = 0.58$.

*Compound **10*** ^1H *NMR*. (300 MHz, δ): 6.39 (s, 1H, H-3), 7.27 (s, 1H, H-11), 7.35 (s, 5H, C_6H_5-4), 7.43 (m, 2H, H-7), 7.52 (s, 1H, H-8), 7.52 (s, 1H, H-6) 7.61 (s, 1H, H-5), 7.99 (s, 1H, H-9).

*Compound **10*** ^{13}C *NMR*. δ 103.6, 111.6, 112.7, 113.0, 119.5, 121.0, 122.5, 123.3, 124.7 (C-6, C-8, C-7, C-9, C-5a, C-3, C-5b, C-5, C-4a, C-11), 126.4 (C-2′, C-6′), 128.0 (C-3′, C-5′), 128.7(C-4′), 140 (C-1′), 145.8, 151.5, 155.9 (C-11a, C-10a, C-9a), 155.5 (C-4), 160.9 (C-2). Anal. Calcd for $C_{21}H_{12}O_3$: C, 80.77; H, 3.85. Found: C, 80.54; H, 3.92.

6.1.7. Synthesis of 4-methyl-2H-benzofuro [3,2-f]-1-benzopyran-2-one (*15*)

A solution of 4-methyl-5,6,7,8-tetrahydro-2*H*-benzofuro[3,2-*f*]-1-benzopyran-2-one **13** (0.6 g, 0.002 mol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone DDQ (1.4 g, 0.007 mol) in 300 ml of benzene was treated as described for the synthesis of compound **9**. Crystallization from benzene gives **15** as red needles, (0.29 g, 49%), mp 213 °C.

*Compound **15*** ^1H *NMR*. (300 MHz, δ): 2.41 (s, 3H, CH_3-4), 6.31 (s, 1H, H-3), 7.04–7.08 (d, 1H, H-11, $J_{11,10} = 9.3$), 7.22–7.25 (d, 1H, H-10, $J_{10,11}$, $= 9.9$), 7.23–7.27 (m, 4H, H-5, H-6, H-7, H-8). Anal. Calcd for $C_{16}H_{10}O_3$: C, 76.80; H, 4.00. Found: C, 76.62; H, 4.17.

6.1.8. Synthesis of 4-methyl-2H-benzofuro [2,3-g]-1-benzopyran-2-one (*16*)

This compound was prepared from 4-methyl-7,8,9,10-tetrahydro-2*H*-benzofuro[2,3-*g*]-1-benzopyran-2-one **14**(0.5 g, 0.0019 mol) as described for the synthesis of compound **9**. Crystallization from benzene gives **16** as orange red powder (0.21 g, 42%), mp 200 °C.

*Compound **16*** ^1H *NMR*. (300 MHz, δ): 2.41 (s, 3H, CH_3-4), 6.31 (s, 1H, H-3), 7.06 (d, 1H, H-11, $J_{11,5} = 1.0$), 7.08 (d, 1H, H-5, $J_{5,11} = 0.9$), 7.26–7.27 (m, 4H, H-7, H-8, H-9, H-10). Anal. Calcd for $C_{16}H_{10}O_3$: C, 76.80; H, 4.00. Found: C, 76.45; H, 4.38.

6.2. Photosensitizing activity

In this study the compounds were screened for antimicrobial and photosensitizing activities by the disc diffusion method [38] compared with reference compound as xanthotoxin, which can be clinically investigated. The test organism used was *B. subtilis*.

6.2.1. Pre-experimental procedure

(a) Nutrient agar medium: 0.3% of beef extract, 0.5% of peptone, 0.1% of dipotassium hydrogen phosphate, and 1.5% of agar.
(b) Broth culture of the organism *B. subtilis* was incubated overnight and then broth culture of the organism was prepared.
(c) Paper discs: Whatman no. 1 filter paper disc (6 mm) was sterilized and impregnated with the tested compounds 10 mg/ml dimethylformamide (DMF) and allowed to dry overnight.

6.2.2. Experimental

Prepared broth culture 0.02 ml was added carefully in the sterile Petri dishes, then 10 ml of the liquefied nutrient agar medium was added, allowed to be mixed uniformly and solidified agar layer. Each dish contains a disc impregnated with DMF (neglect effect of the solvent) and another disc impregnated with xanthotoxin and 10 mg/ml DMF as reference compound.

Two groups of plates were used, one as test plate was incubated in the dark at 37 °C for 3 h before irradiation to allow for diffusion of the tested compounds through the agar layer, and the duplicate plate was left in the incubator overnight as control to determine the antimicrobial activity.

Covers were removed from the tested Petri dishes and exposed to UV lamp (365 nm) for 20 min. After irradiation, the plates were reincubated in the dark at 37 °C overnight and examined for antimicrobial and photosensitizing activities by measuring the produced inhibition zones.

Acknowledgements

I wish to offer my deep gratitude to Yosra Ibrahim demonstrator of Microbiology, Faculty of Pharmacy, Cairo University, for carrying out the microbiological and photosensitizing activities.

References

[1] Z. Zarebaska, E. Waszkowska, S. Caffieri, F. Dall'Acqua, Farmaco 55 (8) (2000) 515.
[2] J.D. Laskin, E. Lee, E.J. Yurkow, D.L. Laskin, M.A. Gallo, Proc. Natl. Acad. Sci. U.S.A. 82 (18) (1985) 6158.
[3] F. Dall'Acqua, Furocoumarin Photochemistry and its Main Biological Implications, in: H. Hoenigsmann (Ed.), Current Problems in Dermatology, Karger, Vienna, 1985.
[4] F. Dall'Acqua, S. Caffieri, J. Photomed. Photobiol. (Japan) 10 (1988) 1.
[5] F. Dall'Acqua, New Chemical Aspects of Photoreaction between Psoralen and DNA, in: A. Catellani (Ed.), Research in Photobiology, Plenum Press, New York, 1978, p. 245.
[6] K. Straub, D. Kanne, J.E. Hearst, H. Rapoport, J. Am. Chem. Soc. 103 (9) (1981) 2347.
[7] F. Dall'Acqua, G. Jori, Principle of Medicinal Chemistry, in: W.O. Foy, T.L. Lemke, D.A. Williams (Eds.), Photochemotherapy, Press, 1995, p. 898.
[8] S.M. Desai, K.N. Trivedi, Ind. J. Chem. 24B (1985) 47.
[9] F. Dall'Acqua, QSAR on Furocoumarins, Agents for the Phototherapy of Psoriasis, in: M. Kuchar (Ed.), QSAR in Design of Bioactive Compounds, J.R. Prous, Barcelona, 1984, p. 87.
[10] F. Dall'Acqua, G. Rodighiero, Biological and Medical Aspects of Furocoumarins in Primary Photoprocess, in: R.V. Bensasson (Ed.), Biology and Medicine, Plenum Press, New York, 1985, p. 277.
[11] J.B. Hansen, P. Bjerring, O. Buchardt, P. Ebbesen, A. Kanstrup, G. Karup, P.H. Knudsen, P.E. Nielsen, B. Norden, B. Ygge, J. Med. Chem. 28 (1985) 1001.
[12] R. Rodighiero, M. Palumbo, S. Marciani Magno, P. Manzini, O. Gia, R. Piro, A. Guiotto, J. Heterocycl. Chem. 23 (1986) 1405.

[13] O. Gia, E. Uriarte, G. Zagotto, F. Baccichetti, C. Antonello, S. Marciani-Mango, J. Photochem. Photobiol. B 14 (1–2) (1992) 95.
[14] P.S. Song, K.J. Tapley, J. Photochem. Photobiol. 29 (1979) 1177.
[15] A. Guiotto, P. Rodighiero, G. Pastorini, P. Manzini, E. Bordin, F. Baccichetti, F. Carassare, D. Vedaldi, F. Dall'Acqua, Eur. J. Med. Chem. 16 (1981) 489.
[16] F. Baccichetti, F. Bordin, F. Carlassare, F. Dall'Acqua, A. Guiotto, G. Pastorini, G. Rodighiero, P. Rodighiero, D. Vedaldi, U.S. Patent 4,312,883, Jan. 26, 1982.
[17] F. Dall'Acqua, D. Vedaldi, A. Guiotto, P. Rodighiero, F. Carlassare, F. Baccichetti, F. Bordin, J. Med. Chem. 24 (1981) 806.
[18] A. Guiotto, P. Rodighiero, P. Manzini, G. Pastorini, F. Bordin, F. Baccichetti, F. Carlassare, D. Vedaldi, F. Dall'Acqua, M. Tamaro, G. Recchia, M. Cristofolini, J. Med. Chem. 27 (1984) 959.
[19] Y.B. Shi, I. Griffith, H. Gamper, J.E. Hearst, Nucleic Acid Res. 16 (18) (1988) 8945.
[20] P. Rodighiero, A. Chilin, A. Guiotto, Gazz. Chim. Ital. 114 (1984) 509.
[21] J. Blais, P. Vigny, J. Moron, E. Bisagni, J. Photochem. Photobiol. 39 (1984) 145.
[22] J.P. Dwmaret, S. Brunie, J.P. Ballini, J. Cadet, P. Vigny, J. Photochem. Photobiol. 6 (1990) 207.
[23] R. Costalat, J. Blais, J.P. Ballini, A. Moysan, J. Cadet, O. Chalvet, P. Vigny, J. Photochem. Photobiol. 51 (1990) 255.
[24] E. Bisagni, J. Photochem. Photobiol. 14 (1–2) (1992) 23.
[25] F. Bordi, F. Baccichetti, C. Marzano, F. Carlassare, G. Miolo, L.A. Chilin, A. Guiotto, J. Photochem. Photobiol. 71 (2000) 254.
[26] M. Palumbo, P. Rodighiero, O. Gia, A. Guiotto, S. Marciani Magno, J. Photochem. Photobiol. 44 (1) (1986) 1.
[27] L.D. Via, O. Gia, S.M. Magno, L. Santana, M. Teijeira, E. Uriarte, J. Med. Chem. 42 (21) (1999) 4405.
[28] O. Gia, S. Mobilio, M. Palumbo, M.A. Pathak, J. Photochem. Photobiol. 57 (1993) 497.
[29] B.F. Eichman, B.H. Mooers, M. Alberti, J.E. Hearst, P.S. Ho, J. Mol. Biol. 308 (2001) 15.
[30] J.K. MacLeod, B.R. Worth, R.J. Wells, Aust. J. Chem. 31 (1978) 1533.
[31] J.K. MacLeod, B.R. Worth, Tetrahedron Lett. (1972) 237.
[32] V.K. Ahluwalia, B. Mittal, V.D. Metha, Ind. J. Chem. 27B (1988) 179.
[33] J. Allinget, N.L. Allinget, Tetrahedron 2 (1958) 64.
[34] V.K. Ahluwalia, C.H. Khanduri, Ind. J. Chem. 28 (1989) 599.
[35] V.K. Ahluwalia, R. Adhikari, R.P. Singh, Ind. J. Chem. 27B (1988) 274.
[36] M. Udaya Bhaskar, L. Jagan Mohan Rao, N.S. Prakasa Rao, Ind. J. Chem. 32B (1993) 975.
[37] HyperChem: Release 4 for Windows, Molecular Modeling Software Serial No. 519–10007596, HyperChem. Inc., 1994.
[38] Cruickshank, J.P. Duguid, R.H.A. Swain, Medicinal Microbiology, 11th ed. E.S. Livingstone Limited, London, 1968, 899.