# New Synthesis of Furochromenyl Imidazo [2a-1b] Thiazole Derivatives, Studies on Their Antitumor Activities.

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**Abstract** 4, 9-Dimethoxy-5-oxo-5H-furo [3, 2-g] benzopyran-6-carboxaldehyde 1 was condensed with 2-thiox-4-imidazolinone 2 to form 3. Treatment of 3 with α-chloroacetyl chloride gave 4. Cyclization of 4 with acetic anhydride took place by heating to give 5. Condensation of 5 with aromatic aldehydes gave the arylidene derivatives 6a-c. Coupling of 5 with diazonium salts gave azo derivatives 7a-c. The work was further extended to investigate the behavior of 3 with 1, 2-dichloroethane to give (4Z)-2-(2-chloroethylthio)-4-((4, 9-dimethoxy-5-oxo-5H-furo [3, 2-g] chromen-6-yl) methylene)-1H-imidazol-5(4H)-one 8. Then 8 was cyclized with acetic anhydride to give (6Z)-2, 3-dihydro-6-[(4, 9-dimethoxy-5-oxo-5H-furo-[3, 2-g] chromen-6-yl) methylene] imidazo [2, 1-b] thiazol-5-(6H)-one 9. [Journal of American Science 2010; 6(5):251-256]. (ISSN: 1545-1003).

**Key words:** Furochromon; arylidene derivatives; azo; antitumor activity

## 1. Introduction

2-Thioxo-4-imidazolinone derivatives posses mathematical correlation of plasma levels of anticonvulsant drugs in epileptic patients which introduced in 1978 by Abarbanel [(1)] and use of it as antiasthmatic drugs [(2)]. On the other hand, furochromen and flavones were known to possess coronary dilator activities [(3)]. Some derivatives of furochromen composite for treating chronic skin or eye diseases which used in ophthalmic drugs and in dermatological diseases[(4)] Recently some furochromone derivatives showed potent antispasmodic , and antitumor activities [(5-10)].

A compound having both imidazolinone and furochromone moieties could expect to posses marked biological activities. This prompted us to design and synthesis new furochromen imidazo [2, 1-b]thiazole derivatives to study their antitumor activities.

## 2. Material and Methods

### 1-Chemistry

### Experimental

All melting points were uncorrected. IR spectra recorded on a Pye Unicam SP- 1100 spectrophotometer using KBr discs. The $^1$HNMR spectra were recorded on a Varian EM-390-90 MHz spectrometer using DMSO-$d_6$ as a solvent and TMS as an internal standard. Chemical shifts expressed as δ ppm units. The micro analytical Centre at Cairo University performed the microanalysis. The antitumor activity of the newly compounds were tested at Cancer Biology Department, National Cancer Institute Cairo, Egypt.

*General procedure for preparation of 4 and 8*

A solution of *(4Z)*-2-mercapto-4-[(4,9-dimethoxy-5-oxo-*5H*-furo-[3,2-*g*]chromen-6-yl)methylene]-1-*H*-imidazol-5*(4H)* one (3) (0.01 mole) in a mixture of 2% potassium hydroxide (56 ml) and absolute ethanol(40 ml) was added α-chloroacetyl chloride (0.01 mole) The reaction mixture was reflux on a steam bath for 3hrs then left to cool at room temperature. It acidified with dilute hydrochloric acid. The solid obtain was filtered off and crystallized from ethanol as yellow crystals of 4.

*S-(4Z)-4, 5-dihydro-4-[(4, 9-dimethoxy-5-oxo-5H-fuoro [3, 2-g] chromen-6-yl) methylen]-5-oxo-1H-imidazol-2-yl-2-chloroethanethioate (4)*

4 :m.p 261$^0$C yields 75%.

Analysis : $C_{19}H_{13}ClN_2O_7S$

Calculated :C, 50.84; H, 2.92; N, 6.24; S, 7. 14; Cl, 7.90

Found : C, 50.61; H, 2.73; N, 6.11; S, 7. 31; Cl, 8.01.

IR (Cm$^{-1}$): 3380 (NH); 1720 (ring C=O); 1690 (γ-pyrone C=O); 1640 (C=N).

MS : m,z 448,450

$^1$H NMR (DMSO-$d_6$) (δ ppm): 3..8, 3.7 (2s, 6H, 2$OCH_3$); 4.5 (s, 2H, $CH_2$); 6.3-6.8 (2s, 2H, 2CH=C); 8.0, 7.2 (2d, 2H, H-2, H-3 furan); 9.2 (s, 1H, NH exchangeable with $D_2O$).

*(4Z)-2-(2-Chloroethylthio)-4-[(4, 9-dimethoxy-5-oxo-5H-furo [3, 2-g]chromen-6-yl) methylen]-1H-imidazol-5(4H)-one (8)* crystallized from ethanol as a yellowish green *of 8*.

8 : m.p. 243$^0$C yield 65%.

Analysis : $C_{19}H_{15}ClN_2O_6S$

Calculate: C, 52.46; H, 4.39; N, 6.44; S, 7, 38; Cl, 8.16

Found : C, 52.23; H, 4, 12; N, 6.23; S, 7, 50; Cl, 8.45

IR (Cm$^{-1}$): 3440 (NH); 1740 (ring C=O); 1665 (γ-pyrone C=O); 1640 (C=N); 1243 (C-S).

MS : m/z 434, 436
$^1$H NMR (DMSO-$d_6$) (δ ppm) : 3.8, 3.9 (2s, 6H, 2$OCH_3$); 3.3 (t, $CH_2$-S); 4.1 (t, $CH_2$-Cl);
6.2, 7.1 (2s, 2H, 2CH=C); 8.1, 7.2 (2d, 2H, H-2, H-3 furan); 8.7 (s, 1H, NH exchangeable with $D_2O$).

*General procedure for preparation of 5 and 9*

A suspension of each of 4, 8 (0.01mole) in acetic anhydride (30 ml) was refluxed for 4hrs. The reaction mixture allowed cooling, and then the mixture poured into cold water. The product obtained was filtered off and crystallized from ethanol as yellowish green, dark brown crystals for 5 and 9 respectively.

*(6Z)*-6-[(4,9-dimethoxy-5-oxo-*5H*-furo[3,2-*g*]chromen-6-yl)methylen]imidazo [2,1-b]thiazol-2,5(*3H*,*6H*)-dione (5) crystallized from ethanol as a yellowish green of 5.

5 : m.p. 272$^o$C yield 70%.
Analysis : $C_{19}H_{12}N_2O_7S$
Calculate : C, 55.34; H, 2.93; N, 6.79; S, 7.78
Found : C, 55.60; H, 2.72; N, 6.54; S, 8.03
IR (Cm$^{-1}$): 1720-1710(two ring C=O); 1680 (γ -pyrone C=O); 1640 (C=N).
MS : m/z 434, 436
$^1$HNMR (DMSO-$d_6$)
(δppm):3.7,3.6(2s,6H,2$OCH_3$);4.1(s,2H,$CH_2$);6.4,6.7(2s,2H,2CH=C);7.1,7.9 (2d,2H,H-2,H-3furan)

*(6Z)*-2, 3-dihydro-6-([(4, 9-dimethoxy-5-oxo-*5H*-furo [3, 2-*g*]chromen-6-yl) methylen] imidazo[2,1-b]thiazol-5(*6H)*-one (9) crystallized from ethanol as dark brown of 9.

9 : m.p. 255$^o$C yield 75%.
Analysis : $C_{19}H_{14}N_2O_6S$
Calculated : C, 62.86; H, 3.07; N, 6.11; S, 7.00
Found : C, 63.01; H, 2.93; N, 5.89; S, 7.40
IR (Cm$^{-1}$) : 1736 (ring C=O); 1655 (γ -pyronC=O); 1648(C=N); 1253(C-S
MS : m/z 398
$^1$HNMR (DMSO-$d_6$)
(δppm):3.6,3.9(2s,6H,2$OCH_3$);3.2,3.7(2t,2$CH_2$);7.O,6.3 (2s, 2H, 2CH=C);8.1,7.2 (2d,2H,H-2,H-3 furan).

*Reaction of (5) with aromatic aldehydes*

A mixture of 5 (0.005 mole) fused sodium acetate (2.5g) and a slight excess of aromatic aldehyde (0.005 mole) benzaldehyde, chlorobenzaldehyde, bromobenzaldehyde in (25ml) glacial acetic acid were refluxed for 2 hrs. The reaction mixture poured over cooled water, and then separated solid filtered off washed with water and crystallized from acetic acid to give greenish yellow, olive green and dark brown for 6a-c respectively.

*(3E,6Z)*-3-benzylidene-6-[(4,9-dimethoxy-5-oxo-*5H*-furo[3,2-*g*]chromen-6-yl)methylen] imidazo[2,1-b]thiazol-2,5(*3H*,*6H*)-dione (6a) crystallized from acetic acid as greenish yellow of 6a.

6a : m.p. 281$^o$C yield 65%.
Analysis : $C_{26}H_{16}N_2O_7S$
Calculated : C, 62.34; H, 3.19; N, 5.59; S, 6.39
Found : C, 62.50; H, 3.12; N, 5.82; S, 6.25
IR (Cm$^{-1}$) : 1715, 1700 (two ring C=O); 1680 (γ -pyron C=O); 1635(C=N)
MS : m/z 500
$^1$HNMR(DMSO-$d_6$)(δppm):
3.8,3.6(2s,6H,2$OCH_3$);6.3,6.5,6.8(3s,3H,3CH=C);7.1,7.8(2d,2H,H- 2,H-3furan);7.3-7.6 (m,5H,aromatic protons).

*(3E,6Z)*-3-(7-chlorohepta-2,4,6-triynylidene)-6-[(4,9-dimethoxy-5-oxo-*5H*-furo [3,2-*g*]chromen-6-yl)methylen]imidazo[2,1-b]thiazol 2,5(*3H*,*6H*)-dione (6b) crystallized from acetic acid as olive green of 6b.

6b : m.p. 259$^o$C yield 70 %.
Analysis : $C_{26}H_{15}ClN_2O_7S$
Calculated :C, 58.38; H, 2.83; N, 5.24; S, 5.99; Cl, 6.63
Found : C, 58.21; H, 3.10; N, 5.41; S, 6.23; Cl, 6.42
IR (Cm$^{-1}$) : 1720, 1710 (two ring C=O); 1690 (γ -pyrone C=O); 1640 (C=N).
MS : m/z 534,536

*(3E,6Z)*-3-(7-bromohepta-2,4,6 triynylidene)-6-[(4,9-dimethoxy-5-oxo-*5H*-furo [3,2-*g*]chromen-6-yl)methylen]imidazo[2,1-b]thiazol 2,5(*3H*,*6H*)-dione (6c) crystallized from acetic acid as dark brown of 6c.

6c : m.p. 247$^o$C yield 75%
Analysis : $C_{26}H_{15}BrN_2O_7S$
Calculated :C, 53.90; H, 2.61; N, 4.84; S, 5.53; Br, 13.79
Found : C, 54.17; H, 2.86; N, 5.11; S, 5.81; Br, 13.53
IR (Cm$^{-1}$) : 1715, 1705 (two ring C=O); 1685 (γ -pyrone C=O); 1635(C=N).
MS : m/z 578,580

*Reaction of 5 with diazotised aromatic amines:-*

In a very cold condition, a solution of (0.01 mole) of the appropriate diazotised aromatic amines (prepared from the equivalent amounts of the amine, HCl and $NaNO_2$) was gradually added to a cold solution of 5 (0.01 mole) in aqueous sodium hydroxide solution (2%, 20 ml) in about 15 min. The reaction mixture kept in the ice-chest for 2hrs with constant stirring; the solid product collected by filtration, washed with water then crystallized from appropriate solvent to give reddish brown, dark brown and brown crystals of compounds 7a-c respectively.

*(6Z)*-3-(2-phenyldiazenyl)-6-[(4,9-dimethoxy-5-oxo-*5H*-furo[3,2-*g*]chromen-6-yl)methylen] imidazo[2,1-b]thiazol-2,5(*3H,6H*)-dione (7a) crystallized from acetone as reddish brown of 7a.

7a : m.p. 278°C yield 70%
Analysis : $C_{25}H_{16}N_4O_7S$
Calculated :C, 58.13; H, 3.12; N, 10.84; S, 6.21
Found : C, 57.91; H, 3.32; N, 11.00; S, 6.13.
IR ($Cm^{-1}$):3370 (NH); 1720,1700 (two rings C=O);1680 (γ - pyroneC=O);1635(C=N)
MS : m/z 516
$^1$HNMR(DMSO-$d_6$)(δppm) : 3.7, 3.6(2s,6H,2$OCH_3$ ; 6.4, 6.6(2s,2H,2CH=C);7.2, 7.7(2d,2H,H-2,H-3 furan); 7.3-7.6 (m,5H,aromatic protons and 12.4(s,1H,NH).

*(6Z)*-3-(2-(6-chlorohexa-1,3,5-triynyl)diazenyl)-6-[(4,9-dimethoxy-5-oxo-*5H*-furo[3,2-*g*]chromen-6-yl)methylen]imidazo[2,1-b]thiazol-2,5(*3H,6H*)-dione (7b)crystallized from chloroform as dark brown of 7b.

7b : m.p. 263°C yield 70%
Analysis: $C_{25}H_{15}ClN_4O_7S$
Calculated: C, 54.49; H, 2.72; Cl, 6.44; N, 10.17; S, 5.82.
Found : C, 54.27; H, 2.95; Cl, 6.2;.N, 10.34; S, 6.11.
IR ($Cm^{-1}$):3390 (NH); 1725,1710 (two rings C=O);1690 (γ pyroneC=O);(C=N)
MS : m/z 551,553
*(6Z)*-3-(2-(6-bromohexa-1,3,5-triynyl)diazenyl)-6-[(4,9-dimethoxy-5-oxo-*5H*- furo[3,2-*g*]chromen-6-yl)methylen]imidazo[2,1-b]thiazol-2,5(*3H,6H*)-dione (7c) crystallized from chloroform as brown of 7c.

7c : m.p. 262°C yield 75%
Analysis : $C_{25}H_{15}BrN_4O_7S$
Calculated: C, 50.41; H,2.54; Br,13.42; N,9.41; S,5.93
Found : C, 50.67; H,2.76; Br,13.16; N,9.59; S,5.63.
IR ($Cm^{-1}$) :3380 (NH); 1716, 1700 (two ring C=O); 1685 (γ -pyrone C=O); 1635 (C=N).
MS : m/z 595,593

**2-Antitumor**

Different concentration of the tested compounds between 1-10 μg/ml were added to the cell monolayer using SRB ASSAY (Sulfrohodamine B stain), and compared with the standard drug Doxorubicin DXR[19] using the method of Skehan et al[20].
The antitumor activity of the new formed compounds were tested at Cancer Biological Department, National Cancer Institute, Cairo, Egypt .

## Results and Discussion

**1-Chemistry**

4,9-Dimethoxy-5-oxo-5H-furo[3,2-g]benzopyran-6-carboxaldehyde (1) [11] condensed with 2-thio-4-imidazolinone (2) [12] to give (4Z)-2-mercapto-4-[(4,9-dimethoxy-5-oxo-5-H-furo[3,2-g]chromen-6-yl)methylene]-1-H-imidazol-5-(4H)-one (3). The reaction product (3) was formed via the condensation of the formyl group of (1) with active methylene group of (2).

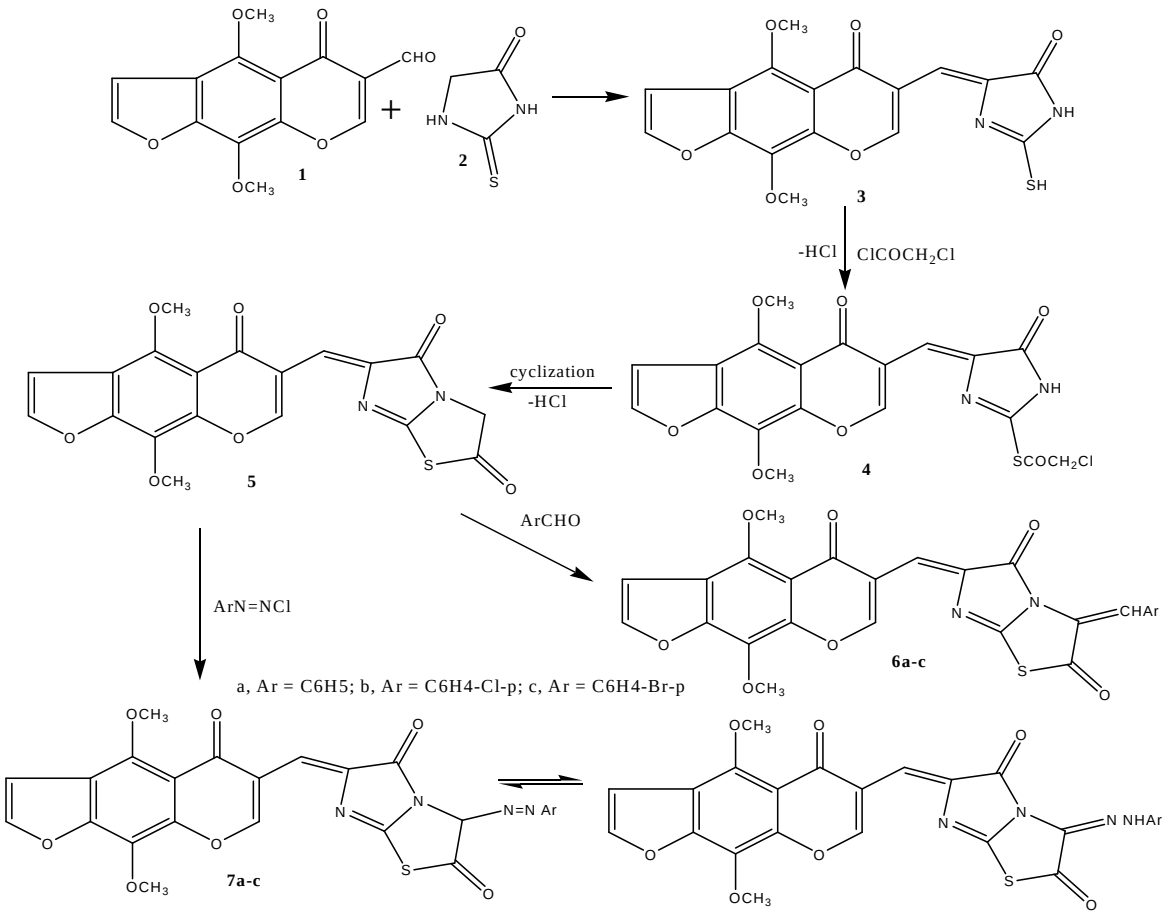
Treatment of (3) with α-chloroacetyl chloride gave S-(4Z)-4, 5-dihydro-4-[(4, 9-dimethoxy-5-oxo-5H-furo [3, 2-g] chromen-6-yl) methylene]-1H-imidazol-2-yl-2-chloro-ethanethioate (4). Compound (4) confirmed by elemental analysis and spectral data.

When compound (4) was heated with acetic anhydride, cyclization took place and (6Z)-6-[(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)methylene]imidazo[2,1-b]thiazole-2,5(3H,6H)-dione (5) was obtained via loss of HCl, the IR and $^1$H NMR spectrum of (5) was characterized by the absence of NH proton. The cyclic structure proposed for compound (5) was the favor one.

Moreover, compound (5) having an active methylene group adjacent to carbonyl group was condensed with aromatic aldehydes (benzaldehyde chlorobenzaldehyde, bromobenzabenzaldehyde in glacial acetic acid in presence of fused sodium acetate at 140°C to give (3E,6Z)-3-benzylidene)-6-[(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)methylene]imidazo[2,1-b]thiazole-2,5-(3H,6H)-dione derivatives (6a-c). The arylidene derivatives (6a-c) showed the correct analytical values, their UV absorption spectra were studied (6a) absorbed at 358 nm (ε= 1553). This absorption is compatible with the benzene ring conjugated with C=C bond which in turn is conjugated with carbonyl group[13] Exhibiting another property of active methylene groups. Compound (5) reacted in sodium hydroxide solution with aromatic diazonium compounds to give (3E,6Z)-3-(aryl-hydrazone)-6-[(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)methylene]imidazo[2,1-b]thia-zole-2,5(3H,6H)-dione derivatives (7a-c). However, it is generally assumed that hydrazon is the stable form, whenever, coupling occurs at a methylene carbon atom (Scheme 1).

Wlley and Jarboe[14] and Tanner[15] have presented the IR absorption data which corroborated the above view, and in addition the presence of maximum band at 410 nm in the UV spectrum of (7a) which proved that (7a) exists in the hydrazone form rather than the azo form [16,17] (Scheme 1).

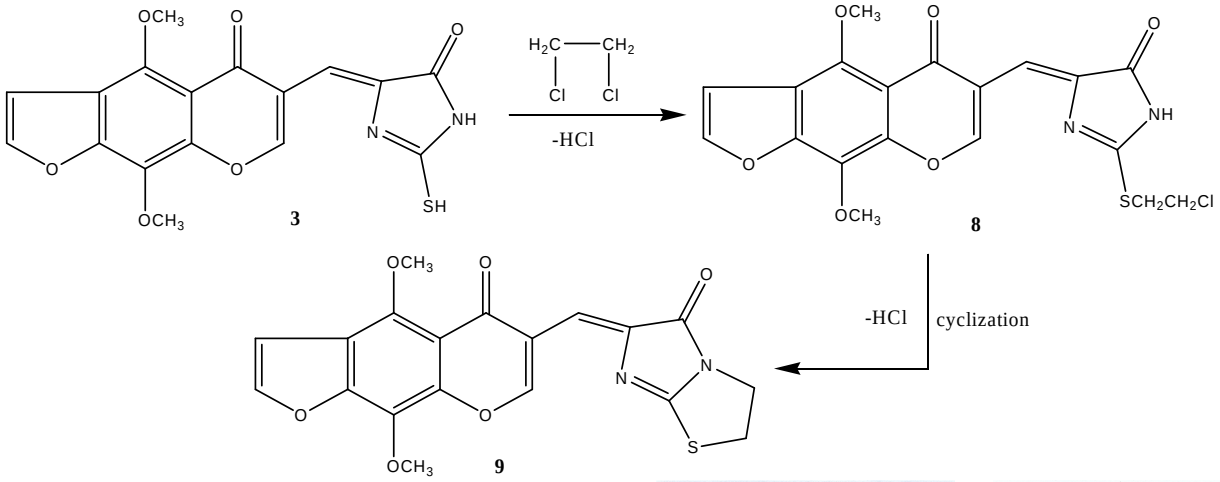
The work was further extended to investigate the behavior of 3 with 1,2-dichloroethane to give (4Z)-2-(2-chloroethylthio)-4-[(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)methylene]-1H-imidazol-5(4H)-one(8) which upon cyclization with acetic anhydride gave (6Z)-2,3-dihydro-6-[(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)methylene]imidazo[2,1-b]thiazol-5(6H)-one(9) by elemination of HCl (Scheme 2). The structure assigned for the cyclized product based on the correct analytical and spectral data. The $^{1}$HNMR spectrum of the above compound revealed the absence of the NH group.




Azo-form Hydrazo-form

a,Ar=$C_6H_5$; b,Ar=$C_6H_4$-Cl-$_p$; c,Ar=$C_6H_4$-Br-$_p$

Scheme-1-




Scheme 2

**Antitumor activity**
**The cytotoxic activity:**

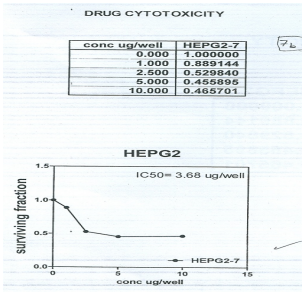
All the newly synthesized compounds were tested for their cytotoxic activity using tumor cell Lines [18] ,[HEPG2 (Human Liver Carcinoma Cell Line) and MCF7 (Human Breast Carcinoma Cell Line)].

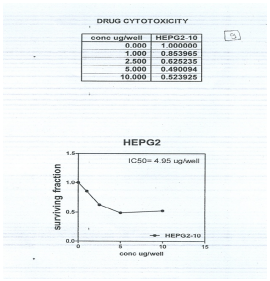
**2-Antitumor**

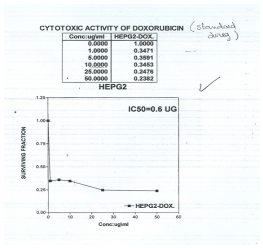
The cytotoxic activity of the tested compounds on HEPG2 and MCF7 were expressed as IC50, table (I), where IC50 (UM ) is the dose of compound which reduces survival to 50%. The relation between the surviving fraction and drug concentration plotted to get the survival curve of the tumor cell line. The tested compound showed this activity only at the specified concentration and this cell lines.c.f.Table (I)

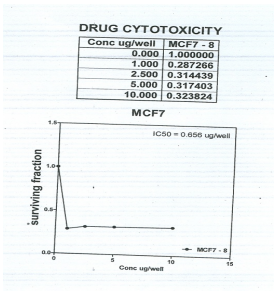
Table (I):

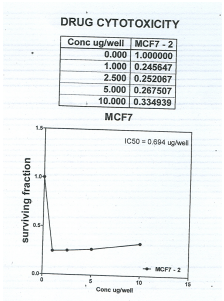
| Compound No. | Cell lines | |
|---|---|---|
| | HEPG2 IC50 | MCF7 IC50 |
| 1 | -ve | 0.769 |
| 2 | -ve | 0.694 |
| 3 | -ve | 0.731 |
| 4 | -ve | 0.769 |
| 5 | -ve | 0.694 |
| 6a | -ve | 0.656 |
| 6b | -ve | 0.806 |
| 7b | 3.68 | 0.769 |
| 8 | -ve | 0.769 |
| 9 | 4.95 | 0.731 |

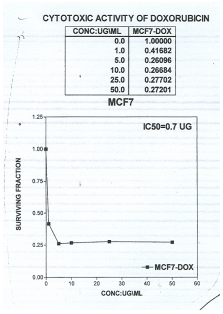



The standard curves for the most active compounds and the standard drugs Doxorubicin (DXR) are given below.

**Conclusion:**

All the tested compounds showed remarkable antitumor activity against human MCF7 cell line. Compound 6b was the most potent one comparing with the standard drug DXR.

The following compounds $6_a$<2, 5<3, 9<1,4,$7_b$,8 showed varying activity in an increasing order.

When those compounds tested against human HEPG2 cell line, compounds $7_b$, 9 showed moderate activity. Compounds 1, 2, 3, 4, 5, $6_{a,b}$, 8 has no activity, comparing with the standard drug DXR.

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