Antitumor and Synthesis of Furochromenly Pyrazoles, and Thiosemicarbazide Derivatives

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Abstract: 4,9-Dimethoxy-5-oxo-5*H*-furo[3,2-*g*]benzopyran-6-carboxaldehyde III react with diethylmalonate in pyridine to give furochromen ethylacrylate IV, which in turn react with Hydrazines to form furochromen pyrazole derivatives (Va,b and VIIIa,b) by refulex in absolute ethanol, and on the other hand gave 3- hydrazinyl ethyl acrylate derivatives (VIIa,b), by stirring at room temperature. Pyrazole-3-hydrazaid (Va) react with Isothiocyanate derivatives upon heating in chloroform in presence of catalytic amount of Triethylamine to give thiosemicarbazide derivatives (VIa-d). Also 3- Hydrazinyl ethyl acrylate react with aromatic aldehydes by stirring at room temperature in absolute ethanol to give arylidene derivatives IXa-c. The work was further extended to react IV with hydroxylaminehydrochloried in absolute ethanol lead to the formation of furochromen isoxazole derivative X. Then IV react with both malonitrile and cyanoactamaide in ethanol in presence of catalytic amount of pipredine, lead to the formation of 3- cyano- 6- pyridone derivative (XI) and 3- cyano -2- pyridone derivative (XII) respectively. [Nature and Science 2010;8(9):12-22]. (ISSN: 1545-0740).

Key Words: Furochromen ethylacrylate, Thiosemicarbazide, Pyrazole, Arylidene , Oxazole, Pyridine and Antitumor.

1. Introduction

It has been reported that furochromones possess spasmolytic [(1-3)] andantimicrobial activity [(4)]. Moreover, benzofuran derivatives have antimicrobial activity [(5-7)],bacteriostatic, bactericidal, fungistatic and fungicidal activities[(8-10)] . Some derivatives of furochromen composite for treating chronic skin or eye diseases which used in ophthalmic furochromone drugs and in treatment of dermatological diseases[(11)] Recently some derivatives showed potent antitumor ~~activity~~ [(12-14)]. Accordingly compounds having furochromone moieties expected to posses marked pharmacological activities. This prompted us to design and synthesize new furochromen derivatives to study their antitumor activity.

On the other hand, pyrazoles are biologically interesting heterocyclic compounds and their chemistry has received considerable attention, in the last few decades. Several pyrazoles are reported to have useful biological effects such as analgesic and anti-inflammatory activities [(15-17)]. In this work, it is interesting to synthesize such type of substituted compounds which having both furochromone and pyrazoles moieties to react with isothiocyanates, arylidenes, hydroxylamine and active methylene derivatives forming newly synthesized products to study their antitumor activities.

2. Material and Methods

Experimental:

All melting points were uncorrected. IR spectra were 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. Microanalysis were performed by the microanalytical Centre at Cairo University. The antitumor activity of the newly compounds were tested at Cancer Biology Department, National Cancer Institute Cairo, Egypt.

Preparation of ethyl (2E)-3-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl) acrylate (IV):

A mixture of 6-formylkhllin (III)(0.01 mole) and diethylmalonate (0.02 mole in pyridine (7ml) was refluxed for 3 hour, then left to cool overnight. The mixture treated with dilute hydrochloric acid and the solid so obtained Filtered off.

As yellow powder crystallized from benzene, m.p 178-180^0 C, yields 75%.

(IV): IR (cm^{-1}): 1735 (acrylate C=O); 1662 (γ-pyrone C=O); 1540 (C=C olifinic). MS: m/z 344. ^{1}H NMR (DMSO-d_6) (δ ppm): 1.2 (t, 3H, $OCH_2\underline{CH_3}$);.3.6- 4.1 (2s, 6H, $2OCH_3$); 4.3(q, 2H,$O\underline{CH_2}CH_3$); 7.08,7.45 (2d .2H,acrylic proton

CH=CH, J=16.5Hz); 7.1,8.2 (2d, 2H, H-2, H-3 furan, J=2.6Hz); 8.8 (s, 1H, H-7).
Anal. Form: $C_{18}H_{16}O_7$ Calculated: C, 62.79; H, 4.68
Found: C, 62.93; H, 4,57

General Synthetic procedure for 6-(5-hydrazino or phenylazino -1H-pyrazol-3-yl)-4,9-dimethoxy-5H-furo[3,2-g]chromen-5-one(Va,b):

To a solution of (0.1mole) of (IV) in absolute ethanol with (0.2mole) of hydrazine compounds (such as hydrazine hydrate, phenyl hydrazine) boiled under reflux for 2hr.The separated solid upon storing the reaction mixture to cool at room temperature, collected and crystallized from suitable solvent, affording the corresponding 1*H*-pyrazol derivatives (Va,b).

6-(5-hydrazino-1H-pyrazol-3-yl)-4,9-dimethoxy-5H-furo[3,2-g]chromen-5-one(Va):

As brown powder crystallized from ethanol, m.p. 280 ^{0}C yields 70%. IR (cm^{-1}): broad band at (3300-3520) (2NH); 2924(NH_2); 1662 (γ-pyrone C=O); 1618, 1539 (C=N, C=C pyrazol ring). MS: m/z 343. ^{1}H NMR (DMSO-d_6) (δ ppm): 1.9 (s, 2H, NH_2), 3.7,3.9 (2s, 6H, $2OCH_3$); 4.1, (s, 1H, NH);6.9, 7.8 (2d, 2H, H-2, H-3 furan J=2.6Hz); 7.9,8.1(2d, 2H, pyrazole), 8.3 (s, 1H, H-7 of pyrane); 12.3 (s,1H, NH pyrazol)
Anal. Form: $C_{16}H_{14}N_4O_5$ Calculated: C, 56.14; H, 4.12; N, 16.37.
Found: C, 56.18; H, 3.97; N, 16.24.

6-(5-phenylazino-1H-pyrazol-3-yl)-4,9-dimethoxy-5H-furo[3,2-g]chromen-5-one (Vb):

As orange powder crystallized from ethanol, m.p. 170 ^{0}C yields 70%. IR (cm^{-1}): broad band at 3245-3500 (3NH); 1662 (γ-pyrone C=O); 1600, 1553 (C=N, C=C pyrazol ring). MS : m/z 418.
Anal. Form: $C_{22}H_{18}N_4O_5$ Calculated: C, 62.15; H, 4.34; N, 13.39.
Found: C, 62.36; H, 4.13; N, 13.25.

General reaction of 5-hydrazino-1H-pyrazol with isothiocyanate derivatives (VIa-d)

To a suspension of (0.01mole) of (Va) in chloroform with (0.1mole) of appropriate isothiocyanate derivatives namely (ethylisothiocyanate, benzylisothiocyanate, benzoylisothiocyanate and phenylisothiocyanate) the reaction refluxed for 4h and then left overnight at room temperature. The solid so obtained was filtered off and crystallized from ethanol to give (VIa-d).

4-ethyl-1-(3-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-1H-pyrazol-5-yl)thiosemicarbazide(VIa):

As buff spongy crystals, crystallized from ethanol, m.p. 290 ^{0}C yields 70%.
IR (cm^{-1}): broad band at 3343-3515(4NH); 1668 (γ-pyrone C=O); 1617,1527 (C=N, C=C pyrazole ring), 1480 (C=S). MS: m/z 429.^{1}H NMR (DMSO-d_6)
(δ ppm): 1.2 (t, 3H, $CH_2\underline{CH_3}$);.3.9- 4.1 (2s, 6H, $2OCH_3$); 4.26 (q, 2H, $\underline{CH_2}CH_3$); 7.1, 8.05 (2d, 2H, H-2, H-3 furan, J=1.8Hz); 7.39 (s 1H, pyrazole), 8.17 (s, 1H, H-7 of pyrane); 9.2-9.5 (m 4H, NH).
Anal. Form: $C_{19}H_{19}N_5O_5S$ Calculated: C, 53.14; H, 4.46; N, 16.13; S, 7.47
Found: C, 53.23; H, 4.31; N, 16.08; S, 7.52

4-benzyl-)1-(3-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-1H-pyrazol-5-yl)thiosemicarbazide(VIb):

As black crystals, crystallized from ethanol, .p.m. 175 ^{0}C yield 75%. IR (cm^{-1}): broad band at 3450-3213(4NH) ;1617(γ-pyrone C=O); 1617, 1527 (C=N, C=C pyrazole ring), 1468(C=S). MS: m/z 491.
Anal. Form:$C_{24}H_{21}N_5O_5S$ Calculated: C, 58.65; H, 4.31; N,14.25;S,6.52
Found : C, 58.83: H, 4.11; N, 14.09; 6.64

4-benzoyl-1-(3-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-1H-pyrazol-5-yl)thiosemicarbazide(VIc):

As grey powder, crystallized from ethanol, m.p.160 ^{0}C yield 75%. IR (cm^{-1}): broad band at 3455-3162 (4NH); 1671(γ-pyrone C=O); 1620,1551(C=N, C=C pyrazole ring);1456 (C=S). MS: m/z 505
Anal.Form: $C_{24}H_{19}N_5O_6S$ Calculated: C, 57.02; H, 3.79; N,13.85; S,6.34
Found: C, 57.33; H, 3.54; N, 13.65; S, 6.46

1-(3-4,9-dimethoxy-5-oxo-5H-furo [3,2-g]chromen -6-yl)-1H-pyrazol-5-yl)-4-(-phenylthiosemicarbazide(VId):

As dark brown powder crystallized from ethanol, m.p.250 ^{0}C yield 75%. IR (cm^{-1}): broad band at 3452-3184 (4NH);1690(γpyronC=O);1435(C=S);1597,1540(C=N, C=C). MS:m/z 477
Anal. Form: $C_{23}H_{19}N_5O_5S$ Calculated: C, 57.85; H,4.01; N,14.67; S,6.72
Found: C, 57.96; H, 3.89; N, 14.45; S,6. 84

Preparation of 6-[3-(ethylperoxy)-1- hyzinopropyla or phenylzinopropyl] ethyl 3-(4, 9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-3-hydrazinopropanoate(VIIa,b).

A mixture (0.1mole) of (IV) in absolute ethanol with (0.Imole) of hydrazines (such as hydrazine hydrate, phenyl hydrazine) stirred at room temperature for about 5 hours. The solid was filtered off crystallized from suitable solvent, affording the corresponding 3-hydrazinopropanoates

6-[3-(Ethylperoxy)-1- hydrazinopropyl] ethyl 3-(4, 9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-3-hydrazinopropanoate(VIIa):

As a yellow powder, crystallized from ethanol m.p. 150 ^{0}C yields 70 %. IR (cm^{-1}): 3307 (NH); 2978 (NH_2); 1728 (C=O ester); 1662 (γ-pyrone C=O); MS: m/z 376. ^{1}H NMR (DMSO-d_6) (δ ppm): 1.04 (s,2H, NH_2);1,23 (t,2H, $OCH_2\underline{CH_3}$); 3.6, 3.8 (2s, 6H, $2OCH_3$); 4.0(d, 2H, CH_2 olifinic proton); 4.21 (q,2H, O $\underline{CH_2}CH_3$); 5.1(t, 1H, NH $\underline{CH}CH_2$); 7.1,7.8 (2d, 2H, H-2, H-3 furan, J=2.6Hz); 8.26 (s, 1H, H-7); 9.5 (s, 1H, NH).
Anal. Form: $C_{18}H_{20}N_2O_7$ Calculated: C, 57.44; H, 5.36; N, 7.44
Found: C, 57.61; H, 5.12; N 7.23

6-[3-(ethylperoxy)-1- phenylzinopropyl] ethyl 3-(4, 9-dimethoxy-5-oxo-5H-furo [3,2-g]chromen-6-yl)-3-hydrazinopropanoate(VIIb)

As a orange powder, crystallized from ethanol, m.p. 130 0C yields 70%. IR (cm^{-1}): broad band at 3324-3560 (2NH); 1730 (C=O ester); 1662 (γ-pyrone C=O); MS: m/z 452. ^{1}H NMR (DMSO-d_6) (δ ppm): 1,25 (t,2H, $OCH_2\underline{CH_3}$); 4.1 (d, 2H, CH_2 olifinic proton) 3.7- 3.9 (2s, 6H, $2OCH_3$); 4.3 (q,2H, O $\underline{CH_2}CH_3$); 5.3(t, H, NH $\underline{CH}CH_2$); 7.2, 7.6 (m, 5H, arom.H); 6.9,7.8 (2d, 2H, H-2, H-3 furan, J=2.6Hz); 8.4 (s, 1H, H-7); 9.4,9.8 (2s, 2H, 2NH).
Anal. Form: $C_{24}H_{24}N_2O_7$ Calculated: C, 63.71; H, 5.35; N, 6.19

Found: C, 63.84; H, 5.12; N, 6.01

Preparation of 5-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-2,4-dihydro or 2,4-phenylhydro-3H-pyrazol-3-one (VIIIa,b)

Refluxed (0.1mole) of VIIa,b in absolute ethanol for 2hr.The reaction mixture left to cool at room temperature, the separated ppt. collected and crystallized from suitable solvent, affording the corresponding (VIIIa,b)

5-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-2,4-dihydro-3H-pyrazol-3-one (VIIIa).

As yellow powder crystallized from ethanol, m.p. 205 ^{0}C yields 70%. IR (cm^{-1}): 3393 (NH); 1717(C=O of amid in pyrazole ring); 1664 (γ-pyrone C=O); 1618 (C=N, pyrazoel ring). MS: m/z 328. ^{1}H NMR (DMSO-d_6) (δ ppm): 3.9- 4.05 (2s, 6H, $2OCH_3$); 5.2 (s, 2H, CH_2 pyrazole); 7.2, 8.1 (2d, 2H, H-2, H-3 furan J=2.6Hz); 8.7 (s, 1H, H-7); 11.7 (s, 1H, NH exchangeable with D_2O).
Anal. Form: $C_{16}H_{12}N_2O_6$ Calculated: C, 58.54; H, 3.68; N, 8.53
Found: C, 58.66; H, 3.36; N, 8.28

5-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-2-hydro-4-phenyl-3H- pyrazol-3-one (VIIIb).

As orange powder crystallized from ethanol, m.p. 200 ^{0}C yields 70%. IR (cm^{-1}): 1715(C=O pyrazole);1662 (γ-pyrone C=O); 1630 (C=N of pyrazole).
MS: m/z 404.
Anal. Form: $C_{22}H_{16}N_2O_6$ Calculated: C,65.34; H, 3.99; N, 6.93
Found: C,65.61; H, 3.75; N, 6.64

General reaction of 1- hydrazinopropyl with aromatic aldehyde formed IXa-c

To a solution of (0.05mole) of VIIa in absolute ethanol (40ml) and appropriate aromatic aldehyde (0.01mole) namly (benzaldehyed, anisaldehyed and bromobenzaldehyed) was stirred at room temperature for 4 -5 hr. The precipitate collected and crystallized from suitable solvent, affording the corresponding (IXa-c).

Ethyl3-((z)-2-(2-phenylethylidene)hydrazinyl)-3-(5,8-dihydro-4,9-dimethoxy-5-oxonaphthol[2,3-b]furan-6-yl)propanoate(Ixa)

As yellowish brown powder crystallized from ethanol, m.p. 220 ^{0}C yields 70%.
IR (cm^{-1}): 3124 (NH); 1728 (C=O of ester); 1662 (γ-pyrone C=O); 1620 (C=N) MS: m/z 476. ^{1}H NMR (DMSO-d_6) (δ ppm): 1.2(t,2H, $OCH_2\underline{CH_3}$); 3.6 (d, 2H, $CH\underline{CH_2}$ of olefinic protons) 3.7, 4.05 (2s, 6H, $2OCH_3$); 3.2 (t, 1H, $\underline{CH}CH_2$ of olefinic proton); 4.21(q,2H, O $\underline{CH_2}CH_3$); 6.8 (s, 1H,$\underline{CH}$=N); 7.3-7.9 (m, 7H, arom.H); 8.5 (s, 1H, H-7); 12.5 (s,1H, NH exchangeable with D_2O).
Anal. Form: $C_{27}H_{28}N_2O_6$ Calculated: C, 68.05; H,5.92; N,5.88
Found: C, 68.30; H,5.72; N,5.69

Ethyl3-((E)-2-(4-methoxybenzylidene)hydrazinyl)-3-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)propanoate(IXb)

As dark grey powder, crystallized from ethanol m.p. 210 0C yields 70%. IR (cm^{-1}): 3274(NH); 1725 (C=O of ester); 1663 (γ-pyrone C=O); 1613 (C=N).
MS: m/z 494.

Anal. Form: $C_{26}H_{26}N_2O_8$ Calculated: C, 63.15; H,5.30; N,5.67
Found: C, 63.32; H, 5.18; N, 5.48

Ethl-3-((E)-2-(4-bromobenzylidene)hydrazinyl)-3-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)propanoate (IXc)

As brown powder, crystallized from ethanol m.p. 180 ^{0}C yields 70%. IR (cm^{-1}): 3141(NH);1725 (C=O of ester);1617 (γ-pyrone C=O);1634 (C=N)).
MS: m/z 542, 544.
Anal. Form: $C_{25}H_{23}BrN_2O_7$ Calculated: C, 55.26; H,4.27; Br,14.71; N,5.16
Found: C, 55.78; H,4.05; Br,14.50; N,4.93

Preparation of 3-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)isoxazol-5(4H)-one (X).

To a solution of (0.1mole) of IV in absolute ethanol with hydroxylamine hydrochloride (0.1mole) added few drop of tri-ethyl amine as catalyst, was refluxed for 2hr.The separated solid upon storing the reaction mixture to cool at room temperature, collected and crystallized from benzene, affording the corresponding (X) as yellowed crystal; m.p. 180 ^{0}C
IR (cm^{-1}): 1728(C=O laktone); 1662 (γ-pyrone C=O); 1625 (C=N, pyrazole ring). MS: m/z 329
^{1}H NMR (DMSO-d_6) (δ ppm): 3.83, 3.87 (2s, 6H, 2OCH$_3$); 4.4 (s, 2H, CH$_2$ oxazole ring); 7.1, 7.8 (2d, 2H, H-2, H-3 furan J=2.6Hz); 8.7 (s, 1H, H-7).
Anal. Form: $C_{16}H_{11}NO_7$ Calculated: C, 58.36; H, 3.37; N, 4.25
Found: C, 58.91; H,3.12; N, 4.02

Preparation of 4-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-6-oxo-5,6-dihydropyridine-3 carbonitrile(XI) A mixture (0.1mole) of IV in absolute ethanol (20 ml) with (0.Imole) malonitrile was boiled under reflux for 3hr. The product separated left to cool at room temperature, collected and crystallized from ethanol, affording the corresponding 3- cyano 6- pyridone (XI)
As orange crystal; crystallized from ethanol m.p.150 ^{0}C IR (cm^{-1}): 2203 (CN);1710(C=O pyridine ring);1662 (γ-pyrone C=O); 1617,1538 (C=N,C=C pyridine ring). MS: m/z 364. ^{1}H NMR (DMSO-d_6) (δ ppm): 3.8, 4.2 (2s, 6H, 2OCH$_3$); 4.3 (s, 2H, CH$_2$ pyridine ring); 7.2, 7.9 (2d, 2H, H-2, H-3 furan J=2.6Hz); 8.1 (s, 1H, CH=N pyridine ring); 8.7 (s, 1H, H-7).
Anal. Form: $C_{19}H_{12}N_2O_6$ Calculated: C, 62.64; H, 3.32; N, 7.69
Found: C, 62.86; H, 3.17; N, 4.05

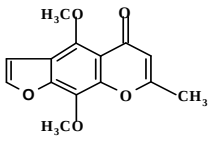
Preparation of 4-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile(XII)

A mixture (0.1mole) of IV in absolute ethanol (20 ml) with (0.Imole) cyanoacetamide was boiled under reflux for 3hr. The product separated left to cool at room temperature, collected and crystallized from ethanol, affording the corresponding 3- cyano 2- pyridone (XII)
As greenish yellow crystal; crystallized from ethanol m.p. 175^{0}C IR (cm^{-1}): 3436(NH); 2217 (CN); 1705(C=O pyridine ring); 1670 (γ-pyrone C=O) and1525,1539(2C=C of pyridine ring). MS: m/z 364. ^{1}H NMR (DMSO-d_6) (δ ppm): 3.9, 4.3 (2s, 6H, 2OCH$_3$); 6.7, 6.9 (2d, 2H, CH=CH pyridine ring); 7.3, 7.9 (2d, 2H, H-2, H-3 furan J=2.6Hz); 8.1 (s, 1H, H-7); 11.5 (s, 1H, NH exchangeable with D_2O).
Anal. Form: $C_{19}H_{12}N_2O_6$ Calculated: C, 62.64; H, 3.32; N, 7.69
Found: C, 62.77; H, 3.08; N, 7.19

3. Results and Discussion

Chemistry:

The naturally occurring furochromone of khellin I upon hydrolysis with aqueous potassium hydroxide afforded the corresponding khellinone II. The lattres via Vilsmeier-Haack reaction gave directly the corresponding 5-oxo-5*H*-furo [3,2-*g*]benzopyran-6-carboxaldehyde III. [18]



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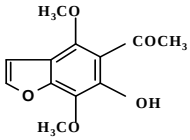

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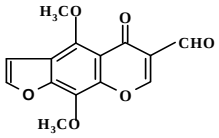
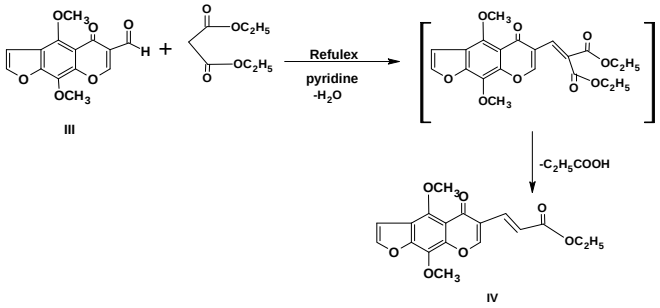


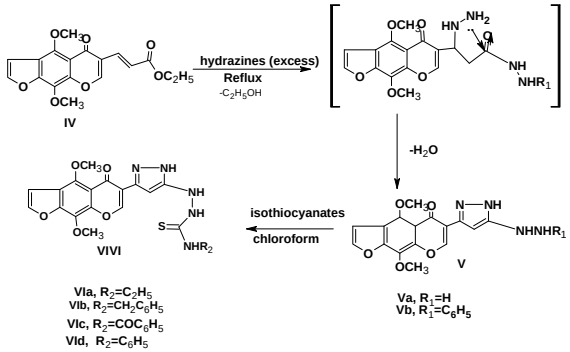
(III)

Refluxing of 4,9-Dimethoxy- 5-oxo-5*H*-furo [3,2-*g*]benzopyran-6-carboxaldehyde (6-formylkhellin) (III) With diethylmalonate in the presence of pyridine, the product occurring by hydrogenation under reaction condition formed (IV) ethyl (2*E*)-3-(4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl) acrylate (IV) derivative which showed correct analytical and spectral data values. The IR spectrum of (IV) showed (C=O) of ester at v =1735Cm$^{-1,}$ ^{1H} NMR characterized by the presence (CH =CH) olfinic protons as two d at δ =7.08, and7.45 ppm respectively.



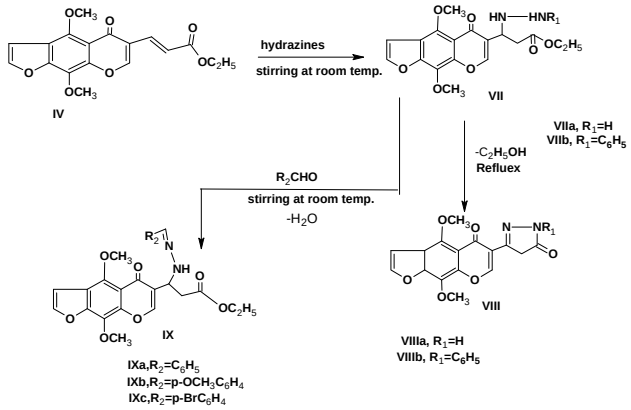
Furochromen ethyl acrylate (IV) refluxed with hydrazines (as hydrazine hydrate and phenyl hydrazine) formed 6-(5-hydr or phenyl azino-1*H*-pyrazol-3-yl)-4,9-dimethoxy-5*H*-furo[3,2-*g*]chromen-5-one(Va,b) derivatives which confirmed by elemental analysis and spectral data. Where the IR spectrum of (Va) was characterized the absence of (C=O) of ester and the presence of (2NH) broad band at v= (3300-3520) ; (NH_2) at v =2924 and (C=N, C=C of pyrazol ring) at v =1618, 1539 Cm^{-1} respectively, ^1H NMR characterized by presence of at δ = 1.9(s,2H, NH_2); 4.1 (NH azino); 7.9, 8.1(2d, 2H, CH=CH of pyrazole)and NH in pyrazole at 12.3ppm.

Pyrazol-3-yl-5-hydrazino compound (Va) reacted with isothiocyanate namely (ethylisothiocyanate, benzylisothiocyanate, benzoylisothiocyanate and phenylisothiocyanate) yielded pyrazole thiosemicarbazide derivatives (VIa-d) the structure assigned for the products were based in correct analytical and spectral data. Where(VIa): IR characterized by the presence of (C=S) at v=1480 Cm^{-1}.

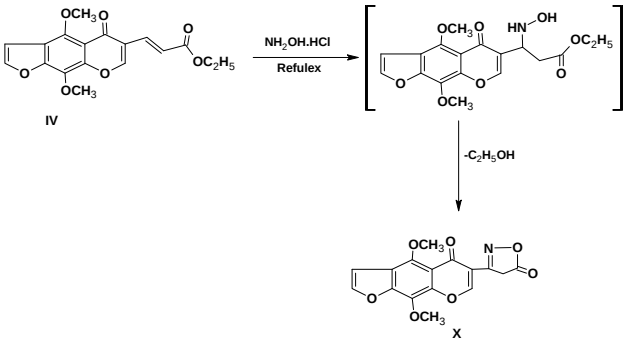


On the other hand furochromen ethyl acrylate (IV) stirred at room temperature with hydrazines (as hydrazine hydrate, phenyl hydrazine) In absolute ethanol yielded 6-[3-(ethylperoxy)-1- hydrazinopropyl or phenylazinopropyl] ethyl 3-(4, 9-dimethoxy-5-oxo-5*H*-furo [3,2-*g*]chromen-6-yl)-3-hydrazinopropanoate (VIIa,b) derivatives which confirmed by elemental analysis and spectral data.. Where (VIIa): IR spectrum showed the presence of (NH) at v =3307,(NH_2) at v =2978 and (C=O) of ester at v =1728 Cm^{-1} and ^1H NMR characterized by the presence of (t,3H, of CH_3 protons of ester) at δ =1,23 (q, 2H, CH_2 protons of ester) at δ = 4.21ppm.Then compounds (VIIa,b) were refluxed in absolute ethanol to give 5-(4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)-2,4-dihydro or 2-phenylhydro-3*H*-pyrazol-3-one (VIIIa,b) derivatives which confirmed by elemental analysis and spectral data. Where (VIIIa):IR spectrum characterized by the presence of (C=O) of amid in pyrazole ring at v =1717 Cm^{-1} and ^1H NMR characterized by the presence of (s,1H,NH) at δ = 11.7 (s,2H, CH_2 proton of pyrazole ring) at δ = 5,2 ppm.

While 1- hydrazinopropyl (VIIa) reacted with aromatic aldehyde namly (benzaldehyed ,anisaldehyed and p-bromobenzaldehyed) formed arylidene derivatives (IXa-c) the structure assigned for arylidenes were based in correct analytical and spectral data.Where (IXa): IR characterized by the presence of (2C=O)of ester and pyrane ring at v =1728 ,1662 Cm^{-1} respectively and ^1H NMR characterized by the presence of (t,3H, of CH_3 protons of ester) at δ =1,2, (q, 2H, CH_2 protons of ester) at δ = 4.21ppm.

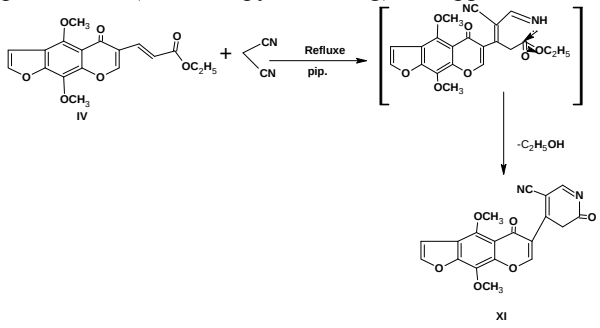


Refluxing of furochromen ethyl acrylate (IV) with hydroxylamine hrdrochloride formed 3-(4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)isoxazol-5(4*H*)-one (X) which confirmed by elemental analysis and spectral data. The IR spectrum characterized by the presence of (C=O) of laktone at v =1728 Cm^{-1} and ^1H NMR characterized by absence of ester protons.



IV X

Refluxing of furochromen ethyl acrylate (IV) in ethanol with malonitrile in presence of catalytic amount of pipredine formed 4-(4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)-6-oxo-5,6-dihydropyridine-3-carbonitrile (XI) which confirmed by elemental analysis and spectral data. The IR spectrum characterized by the presence of (CN) at v =2203, (C=O in pyridine ring) at v =1710 and (C=N, C=C of pyridine ring) at v =1617, 1538 Cm^{-1} respectively. ^{1}H NMR characterized by presence of (s, CH_2 in pyridine ring) at 4.3ppm.

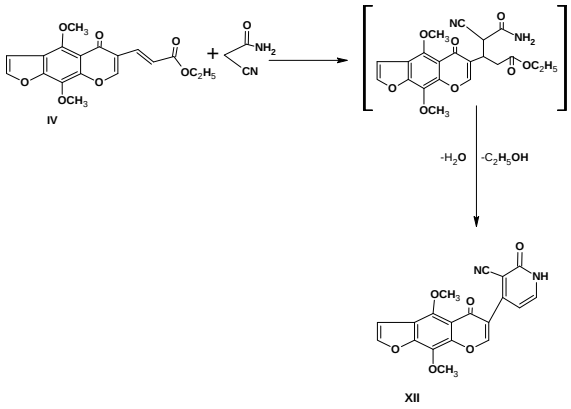


IV XI

Refluxing of furochromen ethyl acrylate (IV) with cyanoactamaide formed 4-(4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (XII) which confirmed by elemental analysis and spectral data. The IR spectrum characterized by the presence of (CN) at v =2217, (C=O in pyridine ring) at v =1705 and (2C=C of pyridine ring) at v =1525 1539 Cm^{-1} respectively, and ^{1}H NMR characterized by presence of (s,1H, NH) at 11.5 ppm.

Antitumor activity

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[20] using the method of Skehan et al [21]. The antitumor activity of the new formed compounds were tested at Cancer Biological Department, National Cancer Institute , Cairo Egypt.



IV XII

The cytotoxic activity:

Most of the newly synthesized compounds were tested for their cytotoxic activity using tumor cell Lines [19], HEPG2 (Human Liver Carcinoma Cell Line) and MCF7 (Human Breast Carcinoma Cell Line).

Results

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 is plotted to get the survival curve of the tumor cell line. The tested compounds showed this activity only at the specified concentration and this cell lines.c.f.Table I

Table (I):

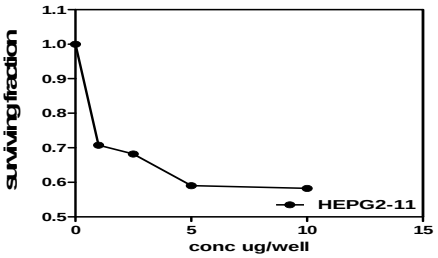
Compound No.	Cell lines	
	HEPG2 IC50	MCF7 IC50
IV	-ve	0.694
Va	-ve	0.656
VIa	2.91	0.619
VIb	2.23	0.769
VIc	2.42	0.656
VIIa	3.47	0.731
IXa	3.99	0.656

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

DRUG CYTOTOXICITY

conc ug/well	HEPG2-11
0.000	1.000000
1.000	0.707669
2.500	0.682234
5.000	0.590516
10.000	0.582548

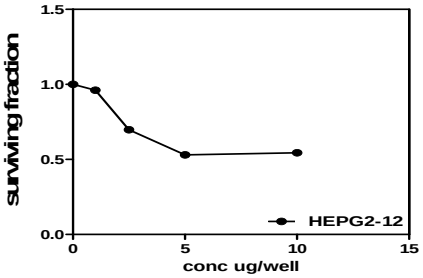
HEPG2



DRUG CYTOTOXICITY

conc ug/well	HEPG2-12
0.000	1.000000
1.000	0.960913
2.500	0.698384
5.000	0.530545
10.000	0.544457

HEPG2



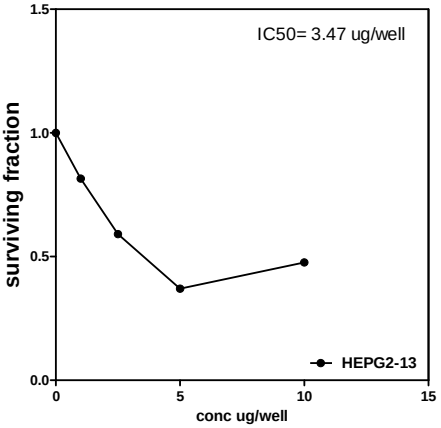
11=IV

12=Va

DRUG CYTOTOXICITY

conc ug/well	HEPG2-13
0.000	1.000000
1.000	0.815507
2.500	0.590691
5.000	0.370057
10.000	0.476290

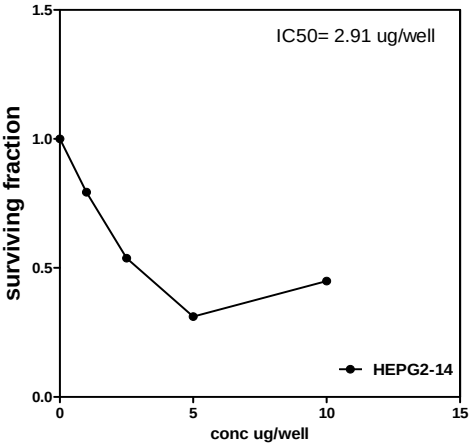
HEPG2



DRUG CYTOTOXICITY

conc ug/well	HEPG2-14
0.000	1.000000
1.000	0.793584
2.500	0.537697
5.000	0.311459
10.000	0.449205

HEPG2



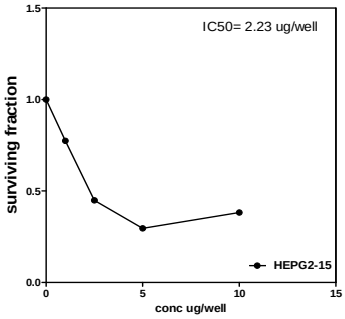
13=VIIa

=VIa 14

DRUG CYTOTOXICITY

conc ug/well	HEPG2-15
0.000	1.000000
1.000	0.774462
2.500	0.448974
5.000	0.296050
10.000	0.381964

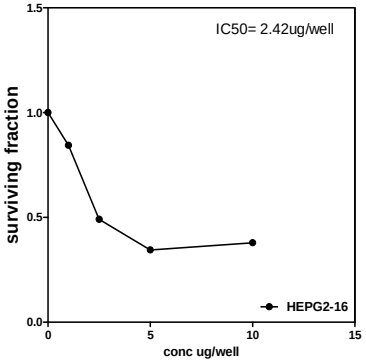
HEPG2



DRUG CYTOTOXICITY

conc ug/well	HEPG2-16
0.000	1.000000
1.000	0.844225
2.500	0.490768
5.000	0.344610
10.000	0.378931

HEPG2



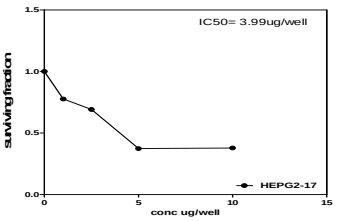
15=VIb

=VIc 16

DRUG CYTOTOXICITY

conc ug/well	HEPG2-17
0.000	1.000000
1.000	0.776984
2.500	0.691791
5.000	0.374259
10.000	0.379162

HEPG2

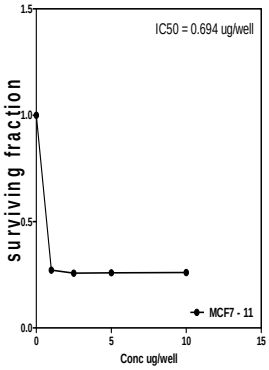


17=IXa

DRUG CYTOTOXICITY

Conc ug/well	MCF7 - 11
0.000	1.000000
1.000	0.272201
2.500	0.257625
5.000	0.259974
10.000	0.261208

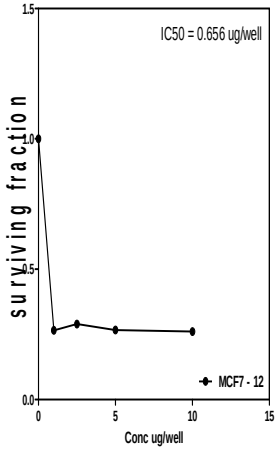
MCF7



DRUG CYTOTOXICITY

Conc ug/well	MCF7 - 12
0.000	1.000000
1.000	0.265406
2.500	0.289489
5.000	0.266766
10.000	0.261086

MCF7



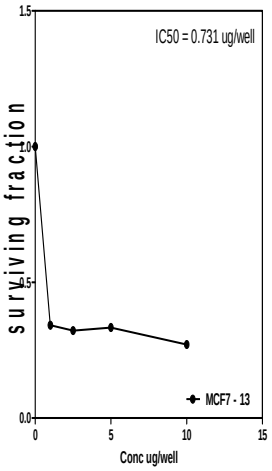
11=IV

12=Va

DRUG CYTOTOXICITY

Conc ug/well	MCF7 - 13
0.000	1.000000
1.000	0.342101
2.500	0.322093
5.000	0.333335
10.000	0.270841

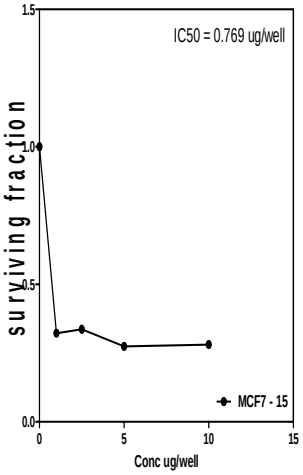
MCF7



DRUG CYTOTOXICITY

Conc ug/well	MCF7 - 15
0.000	1.000000
1.000	0.321971
2.500	0.336791
5.000	0.273927
10.000	0.281093

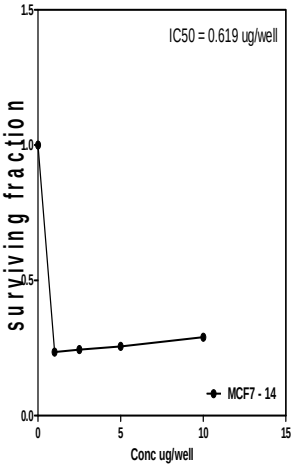
MCF7



DRUG CYTOTOXICITY

Conc ug/well	MCF7 - 14
0.000	1.000000
1.000	0.234531
2.500	0.244042
5.000	0.255773
10.000	0.289615

MCF7

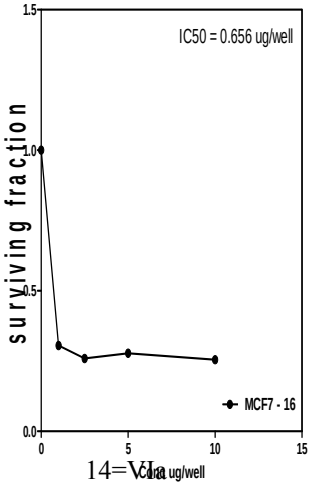


13=VIIa

DRUG CYTOTOXICITY

Conc ug/well	MCF7 - 16
0.000	1.000000
1.000	0.305050
2.500	0.259233
5.000	0.277758
10.000	0.254539

MCF7



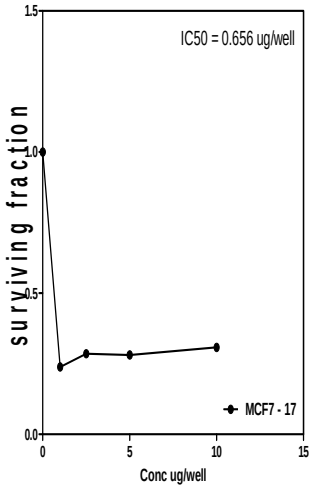
14=VIa

15=VIb

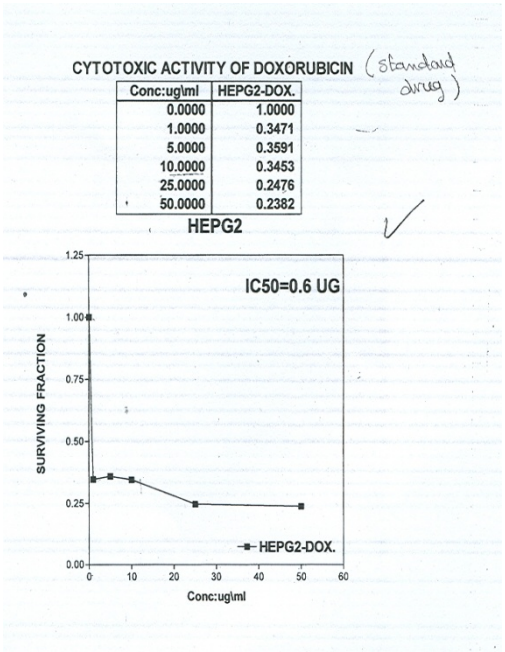
DRUG CYTOTOXICITY

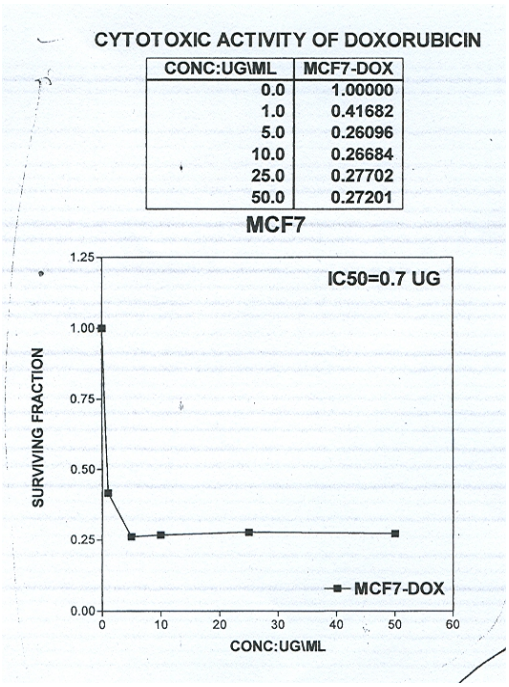
Conc ug/well	MCF7 - 17
0.000	1.000000
1.000	0.238236
2.500	0.285539
5.000	0.281215
10.000	0.307770

MCF7



17=IXa





Conclusion:

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

The following compounds VIIa,IV, Va, VIc, IXa and VIa showing varying activity in a decreasing order comparing with the standard drug DXR.

On the other hand when the following compounds where tested against human HEPG2 cell line.Compounds IXa was the most potent one comparing with the standard drug DXR.Then the following compounds VIa, VIIa, VIc and VIb showing varying activity in a decreasing order comparing with the standard drug DXR ,and compounds IV and Va have no activity.

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4. References

1. K.Ogura, K. Hasimoto, Jap. J pharmacol., 24, 227 (1974).
2. K.Ogura,K. Kubota, T. Kimwra, K. Hasimoto, Jap J pharmacol., 23, 459 (1973)..
3. N.M. Fawzy, S.A. Swelam, S.A.Batran, *Boll.Chim.farm*.143, 24-33 (2004).

4. H. Regaila, A. Gohar, G. Abdel Sadek, Egypt. J Pharm. Sci., 29, 343 (1988).
5. K. Chamberlain, G. A. Carter, Pestic. Sci. 12,539: Chem.Abstr., 96,175951v.
6. O. H. Hishmat, A. H. Abdel Rahman, N. M. A El-Ebrashi and H. I. El- Diwani, Indian J. Chem. Sec.B, 27, 313 (1983).
7. E. R.El-Sawy, A.H.Mandour, I.E.Islam, H. M.Abo-Salem, *Egypt. J Chem.*51, No.*4, 523-538 (2008).*
8. K. Formamek, H. Holler, HJanish, Kowac,Pharm. Ac. Helv., 33,437 (1958).
9. R. Lalibeerte, D. Campbell, F. Burderlin, Can. J. Pharm. Sci., 2(2), 37 (1967)
10. A. M. Packmann, N. Rubin, An. J. Pharm., 134, 35 (1962).
11. Bell,John Howard, Clarke, Clifford, Walter Fred, Taylor, James Edward and Sullivan Thomas James (Fisons Ltd.): *Ger. Offen*. 14 Apr., 2, 634, 908 (1977) (CIA61K31/35); *Brit. Appl.* 03 Oct.,507, 75/40(1975).
12. Atassi, Ghanem, Briet, Philipe, Berthelon, Jean Jaques, Collonges, Francois: *Eur. J. Med. Chem. Chim. Ther,* 20, 393-402(1985).
13. J.Hudson, G.H.N.Towers, phytomedicines as antivirals : *drugs Future* , , 24, 295(1999).
14. S. A. Galal, A. S. Abd El All, M. M. Abdallah and H. I. El-Diwan: *Med. Chem. Lett.,* 19, 2420-2428(2009).
15. S. G. Kuo, L. J. Huang, H. J. Nakamura, *J. Med. Chem*., 27,539 (1984).
16. M. A. Abdel-Aziz, O. H. Hishmat, Sh. I. El-Naem, N. M. fawzy, *Sulfur Lett.,*10, 255(*1990*).
17. O. H. Hishmat, N. M. fawzy, D. S.farrg, A.S. Abd El All, A. H. Abdel-Rahman, *Boll. Chim .Farma*., 138, 427-431(1999).
18. F. Eidin, J.Schlemann, Arch. Pharma. (Weinheim), 201, 316, (1983).
19. R. Macleod, et al. Skehan, *International Journal Cancer*. 83, 555-563 (1999).
20. Groopman, E.Jerome, *How Doctors Think. Boston: Houghton Mifflin. ISBN,* 49, 6018-61003 (2007).
21. A. Monks, D. Scudiero, P. Skehan, R. Shoemaker, K. Paull, D.Vistica, C. Hose, J.Langley, P. Cronise, A. Vaigro-wolff, M.Gray-Goodrich, H.Campbell, J. Mayo, and M. Boyd, *J. Nat. Cancer* Inst. 83, 757-766(1991).

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