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Research Article

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The use of pyridazine thione derivative in the preparation of some new heterocyclic compounds with expected antitumor activity

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ABSTRACT

*Pyridazine thione **1** was used as a key intermediate for the preparation of numerous pyridazine derivatives. Reaction of **1** with copper bronze, nitrous acid, anthranilic acid, acetylacetone and benzalacetophenone afforded the bis pyridazine, quinazolinone, diketo and the adduct derivatives. Condensation of the diketo and the adduct derivatives with hydrazine hydrate gave the corresponding pyrazole and hydrazone derivatives. The behaviour of **1** towards thiourea, ethyl chloroacetate and aromatic amines has also been studied. The reaction of the resulting products with diethyl malonate/acetyl chloride, aromatic amines, sodium hydroxide and hydrazine hydrate has also been taken into consideration. The antitumor activity of some of the synthesized compounds were tested*

Keywords: pyridazine and antitumor activity

INTRODUCTION

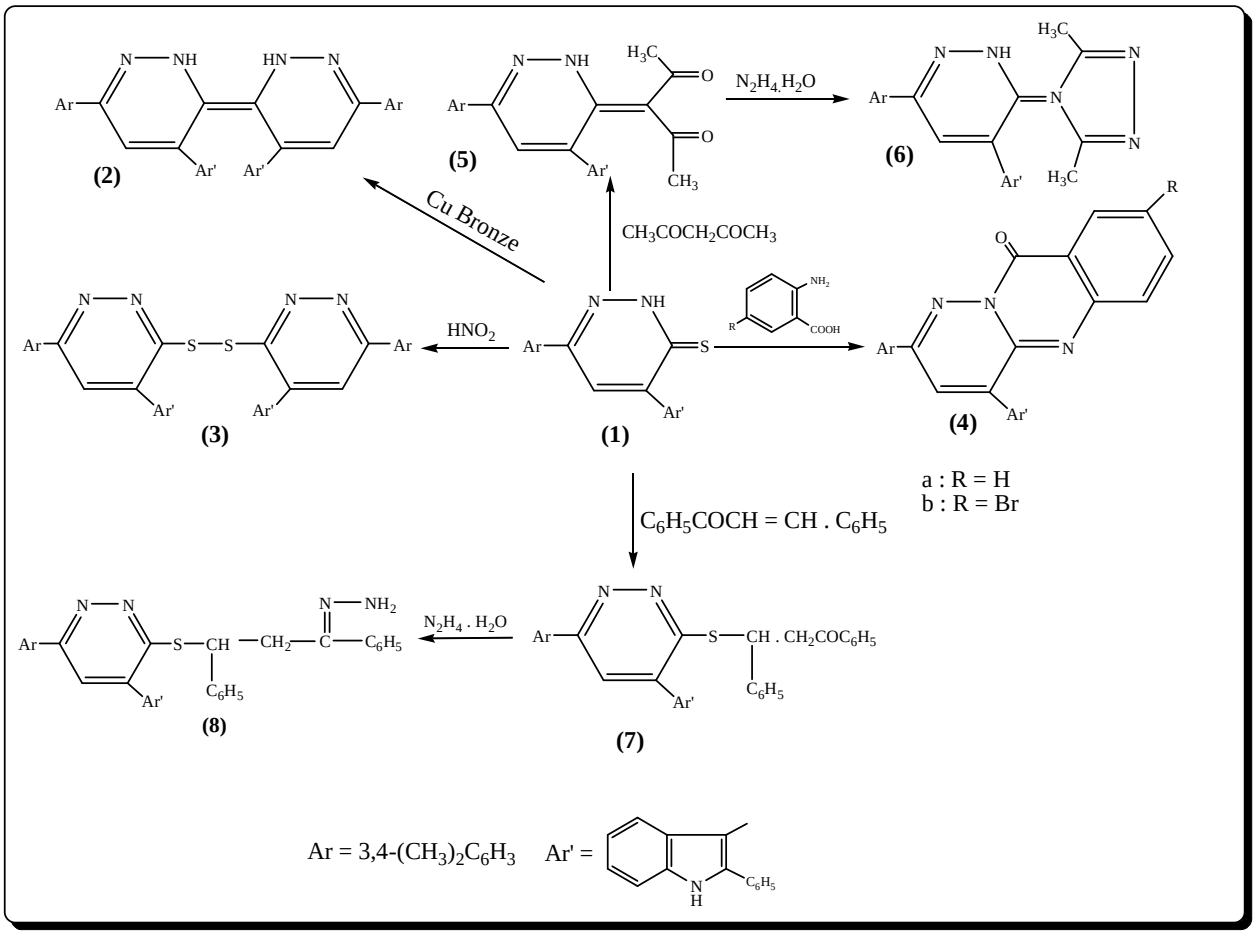
In the last several decades, pyridazine and indole derivatives have received considerable attention due to their wide-range applications Pyridazines are reported to exhibit antibacterial[(1)], antifungal[(1)], antituberculosis[(2)], antinociceptive[(3)], anthelmintic[(4)], antidiabetic[(5)] activities and also as human rhinovirus (HRV-3) inhibitors[(6)]. On the other hand indole derivatives exhibit antioxidant[(7)], antifungal[(8)], antitumor[(9)], anti-hepatitis C virus[(10)] activities.

Encouraged by these reports, we though of synthesizing a new series of pyridazines containing the 2-phenylindole at 4-position hoping to improve the antitumor activity of the new compounds.

EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra (KBr) were recorded with a Perkin Elmer Spectrum RXIFT-IR systems. ^{1}HNMR were measured with a Varian Gemini 200 MHz instrument using TMS as internal standard and mass spectra were measured with a Shimadzu GC-MS-QP 100 EX mass spectrometer.

Synthesis of 3,3'-(6,6-bis(3,4-dimethylphenyl)-3,3'-bipyridazine-4,4'-diyl)-bis (2-phenyl-1H-indole) (2)
A mixture of **1** (0.01 mol), xylene (30 mL) and copper bronze (2g) was refluxed for 6h, concentrated, cooled, the solid product separated was filtered off and recrystallized from ethanol to give **2** (m.p 200°C). Analysis for $\mathbf{C_{52}H_{42}N_6}$(%):Calcd. C 83.17, H 5.64, N 11.19; found C 83.22, H, 5.62, N11.16.

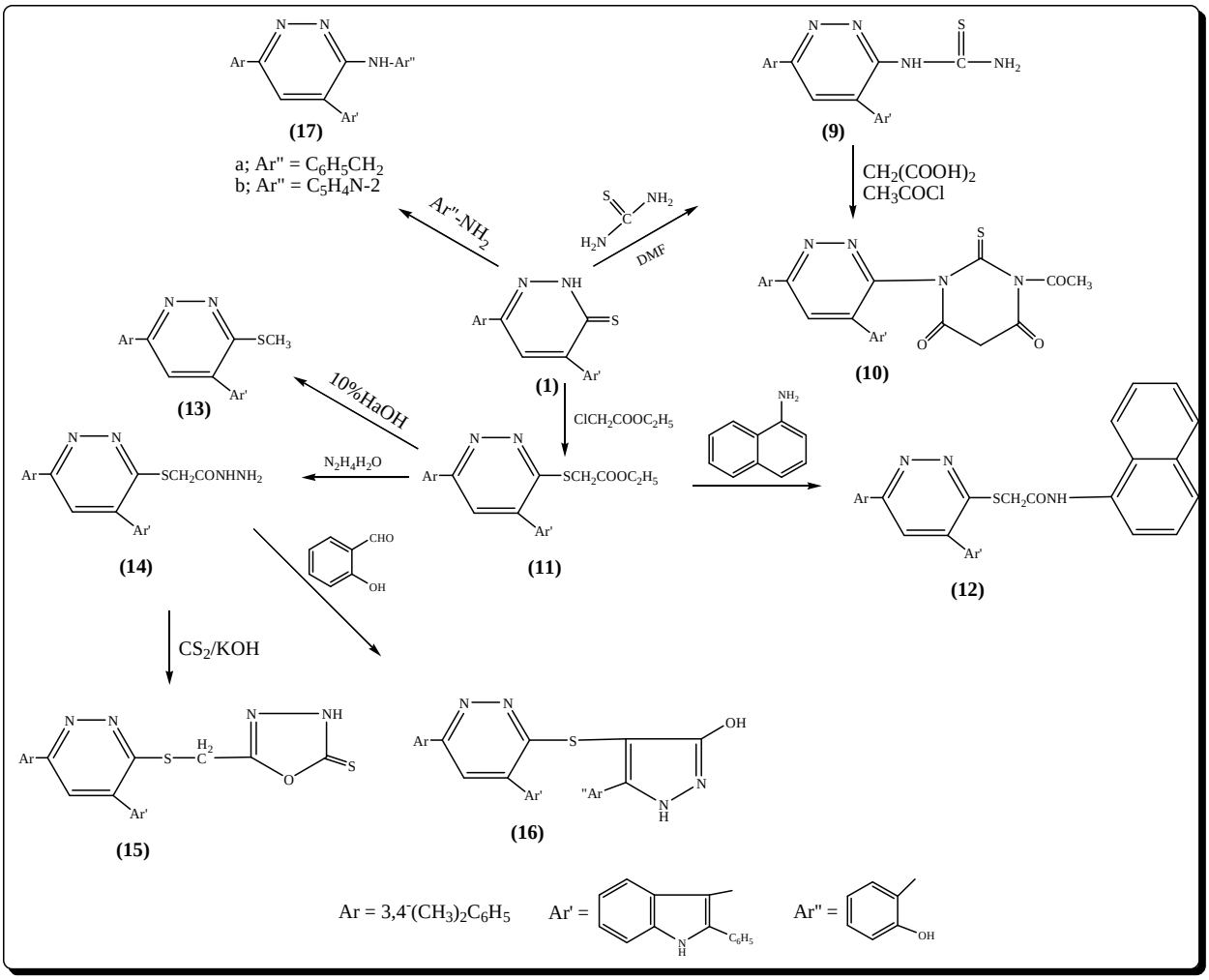


Scheme 1

Synthesis of 1,2-bis(6-(3,4-dimethylphenyl)-4-(2-phenyl-1H-indol-3-yl) pyridazin-3-yl) disulfane (3).
To a solution of **1** (0.01 mol) in ethanol (20 mL), sodium nitrite (0.01 mol) and acetic acid (3ml) were added. The mixture was stirred at room temperature for 4h. The solid product which separated out was crystallized from ethanol to give **3** (m.p. 273°C). Analysis for **$C_{52}H_{40}N_6S_2$**(%): Calcd. C 76.82, H, 4.96, N 10.34, S 7.89; found C76.80, H, 4.98, N 10.32, S, 7.91.

Synthesis of 2-(3,4-dimethylphenyl)-4-(2-phenyl-1H-indol-3-yl)-10H-pyridazino [6,1-b] quinazolin-10-one (4a) , 8-bromo-2-(3,4-dimethylphenyl)-4-(2-phenyl-1H-indol-3-yl)-10H-pyridazin[6,1-b] quinazolin-10-one (4b) , 3-(6-(3,4-dimethylphenyl)-4-(2-phenyl-1H-indol-3-yl) pyridazin-3 (2H)-ylidene) pentane - 2,4-dione (5) and 3-(6-(3,4-dimethylphenyl)-4-(2-phenyl-1H-indol-3-yl)pyridazin-3-ylthio)-1,3-diphenylpropan-1-one (7).
Solution of **1**(0.01mol), anthranilic acid, 5-bromoanthranilic acid, acetylacetone or benzalacetophenone (0.01 mol) in ethanol or butanol (30 ml) was refluxed for 6-7h. The solid separated on cooling was crystallized from ethanol (**4a** m.p. 212°C, **4b** m.p. 211°C, **5**m.p. 189°C, **7** m.p. 194°C. Analysis for **$C_{33}H_{24}N_4O$**(%): Calcd. C 80.47, H 4.91. N 11.37; Found C 80.43, H 4.90, N 11.41; for **$C_{33}H_{23}BrN_4O$**(%): Calcd. C69.36, H 4.06, Br 13.98, N 9.80; Found C 69.38, H 4.07, Br 13.97, N 9.82; for **$C_{31}H_{27}N_3O_2$**(%): Calcd. C78.62, H 5.75, N 8.87; found C 78.58, H 5.77, N 8.89; for **$C_{41}H_{33}N_5OS$**(%): Calcd. C79.79, H 5.40, N 6.82, S 5.21; Found C 79.95, H 5.41, N 6.85, S 5.19.

Synthesis of 3-(3-(3,5-dimethyl-4H-pyrazol-4-ylidene) – 6 - (3,4-dimethyl-phenyl)-2,3-dihydropyridazin-4-yl)-2-phenyl-1H-indole (6) , 3-(6-(3,4-dimethylphenyl)-3-(3-hydrazono-1,3-diphenylpropylthio) pyridazin-4-yl)-2-phenyl-1H-indole (8) and 2-(6-(3,4-dimethylphenyl)-4-(2-phenyl-1H-indol -3-yl) pyridazin-3-ylthio) aceto hydrazide (14).
To a solution of **5,7** or **11** (0.01 mol) in ethanol (20 ml), hydrazine hydrate (0.01 mol) was added and the reaction mixture was refluxed for 4-6 h. The solid separated on cooling was crystallized from ethanol (**6** m.p. 203°C,**8** m.p. 170°C, **14** m.p. 178°C. Analysis for **$C_{31}H_{27}N_5$**(%) : Calcd. C 79.29, H 5.80, N 14.91; found C79.25, H 5.82, N 14.93; for **$C_{41}H_{35}N_5S$**(%): Calcd 78.19, H 5.60, N 11.12, S 5.09; Found C 78.21, H 5.58, N 11.10, S 5.11; for **$C_{28}H_{25}N_5OS$**(%): Calcd. C70.12, H 5.25, N 14.60, S 6.69; Found C 70.02, H 5.23, N 14.62, S 6.79.



Scheme 2

Synthesis of 1-(6-(3,4-dimethylphenyl)-4-(2-phenyl-1H-indol-3-yl) pyridazin-3-yl) thiourea (9).
Solution of **1**(0.01 mol) and thiourea (0.01 mol) in dimethyl formamide (30 ml) was refluxed for 16h. The solid separated on cooling was crystallized from ethanol to give **9** (m.p 173°C). Analysis for **$C_{27}H_{23}N_5S$(**%): Calcd. C72.13, H 5.16, N 15.58, S 7.13; found C 72.10, H 5.14, N 15.60, S. 7.16.

Synthesis of 1-acetyl-3-(6-(3,4-dimethylphenyl)-4-(2-phenyl-1H- indol-3-yl) pyridazin-3-yl)-2-thioxodi hydropyrimidine-4-,6- (1H, 5H)-dione (10).
Solution of **9** (0.01 mol), malonic acid (0.01 mol) and acetyl chloride (5ml) in ethanol (20 ml) was refluxed for 2h. The solid separated on cooling was crystallized from ethanol to give **10**(m.p. 190°C). Analysis for **$C_{32}H_{25}N_5O_3S$**(%): Calcd. C 68.68, H 4.50, N 12.51, S 5.73; found: C 68.70, H 4.51, N 12.50, S 5.71.

Synthesis of ethyl 2-(6-(3,4-dimethylphenyl)-4-(2-phenyl-1H-indol-3-yl). pyridazin-3-ylthio) acetate (11).
A mixture of **1** (0.01 mol), anhydrous potassium carbonate (0.03 mol), ethyl chloroacetate (0.03 mol) and dry acetone (50 ml) was refluxed for 24 h. on a water bath. The solid product obtained after hot filtration and evaporation of the solvent was crystallized from ethanol to give **11** (m.p. 141°C). Analysis for **$C_{30}H_{27}N_3O_2S$** (%): Calcd. C 73.00, H 5.51, N 8.51. S 6.50; Found: C 72.80, H 5.71, N 8.49, S 6.52.

Synthesis of 2- (6- (3,4-dimethylphenyl -4- (2-phenyl-1H-indol-3-yl) pyridazin-3-ylthio) -N- (naphthalen-1-yl) acetamide (12) , N-benzyl -6-(3,4-dimethylphenyl) -4 - (2-phenyl-1H-indol-3-yl) pyridazine -3-amine (17a) and 6-(3,4-dimethylphenyl) – 4 - (2-phenyl-1H-indol-3-yl) – N -(pyridin-2-yl) pyridazin-3-amine (17b).
Solution of **11** or **1** (0.01 mol), α-naphthylamine, benzylamine or 2-aminopyridine (0.01 mol) in ethanol (30 ml) was refluxed for 6h. The solid separated on cooling was crystallized from ethanol (**12** m.p. 197°C, **17a** m.p. 150°C, **17b** m.p. 132°C). Analysis for **$C_{38}H_{30}N_4OS$**(%): Calcd C 77.26, H 5.12, N 9.48, S 5.43; Found C77.23, H 5.15, N 9.45,

S 5.46; for $C_{33}H_{28}N_4$(%): Calcd. C 82.47, H 5.87, N 11.66; Found C 82.43, H, 5.89, N 11.68; for $C_{31}H_{25}N_5$(%): Calcd. C 79.63, H 5.39, N 14.98; Found C 79.60, H 5.40, N 15.00.

Synthesis of 3-(6-(3,4-dimethylphenyl)-3-(methylthio) pyridazin-4-yl)-2-phenyl -1H-indole (13).
To a 10% ethanolic sodium hydroxide solution (50 ml), compound **11** was added and the reaction mixture was refluxed for 6h. The solid separated after concentration and cooling was washed well with water and crystallized from ethanol to give **13** (m.p. 160°C). Analysis for $C_{27}H_{23}N_3S$(%): Calcd. C 76.93, H 5.50, N 9.97, S 7.61; Found C 76.90, H 5.57, N 9.90, S 7.64.

Synthesis of 5-(6-(3,4-dimethyl phenyl)-4-(2-phenyl-1H-indol-3-yl) pyridazin-3-ylthio)methyl)-1,3,4-oxadiazole-2 (3H)- thione (15).
To a suspension of **14** (0.01 mol) in ethanol (15 ml), CS_2(5ml) and KOH (0.005 mol) were added. The reaction mixture was refluxed for 2h. on a water bath, cooled then poured onto ice and acidified with dil. HCl. The solid obtained was crystallized from ethanol to give **15** (m.p. 216°C). Analysis for $C_{29}H_{23}N_5OS_2$(%): Calcd. C 66.77, H 4.44, N 13.43, S 12.29; found C 66.73, H 4.47, N 13.47, S 12.25.

Synthesis of 4- (6- (3,4-dimethylphenyl) -4- (2-phenyl-1H-indol-3-yl) pyridazin-3-ylthio)-5-(2-hydroxyphenyl)-1,2-dihydro-3-H-pyrazol-3-one (16).
To a solution of **14**(0.01 mol) in ethanol (30 ml), salicylaldehyde was added dropwise while stirring at room temperature. Stirring was continued for 2h. The orange crystals formed was collected by filtration and recrystallized from ethanol to give **16** (m.p. 200°C). Analysis for $C_{35}H_{27}N_5O_2S$(%): Calcd. C 72.27, H 4.68, N 12.04, S 5.51; Found C 72.17, H 4.62, N 5.57, S 5.41.

Sulforhodamine-B(SRB) assay of cytotoxic activity.
MCF7 (breast carcinoma cell line), HEPG2 (hepatocellular carcinoma cell line), HCT 116 (colon carcinoma cell line) were obtained frozen in liquid nitrogen (-180°C) from the American type culture collection .The tumor cell line were maintained in the National Cancer Institute, Cairo, Egypt, by serial sub-culturing. Potential cytotoxicity of **4a-b, 5,7,13, 17a** and **17b**. were tested using method of Skehan *et al*.**[(11)].**

Principle
The sensitivity of the human tumor cell lines to thymoquinone was determined by the SRB assay. SRB is a brought pink aminoxanthrene dye with two sulfonic groups. It is a protein stain that binds to the amino group of intracellular proteins under mildy acidic conditions to proceed a sensitive index of cellular protein content.

Procedure
1. Cells were used when 90% confluence was reached in T25 flasks. Adherent cell lines were harvested with 0.025% trypsin .Viability was determined by trypan blue exclusion using the inverted microscope (Olympus 1 x 70, Tokyo, Japan).
2. Cells were seeded in 96- well microtiter plates at a concentration of 5 x 10^4 – 10^5 cell/well in a fresh medium and left to attach to the plates for 24h.
3. After 24 h, cells were incubated with the appropriate concentration ranges of drugs, completed to total of 200 µl volume/well using fresh medium and incubation was continued for 24, 48 and 72h. Control cells were treated with vehicle alone. For each drug concentration, 4 wells were used.
4. Following 24, 48 and 72h, treatment, the cells were fixed with 50µl cold 50% trichloroacetic acid for 1h. at 4°C.
5. Wells were washed 5 times with distilled water and stained for 30 min. at room temperature with 50 µl 0.4% SRB dissolved in 1% acetic acid.
6. The wells were then washed 4 times with 1% acetic acid.
7. The plates were air- dried and the dye was solubilized with 100µl/well or 10 mM tris base (Ph 10.5) for 5 min. on a shaker (orbital shaker 0520, Boeco, Germany) at 1600 rpm.
8. The optical density (O.D) of each well was measured spectrophotometrically at 564 nm with an ELIZA microplate reader (Meter tech Σ960, U.S.A). The mean background absorbance was automatically substracted and mean values of each drug concentration was calculated .The relation between survival fraction and compound concentration was plotted to get the survival curve of each tumor cell lines. (Fig. 1) .The IC 50 values (the concentration of thymoquinone required to produce 50% inhibition of cell growth (Fig. 2).

RESULTS AND DISCUSSION

The new derivatives were prepared following the reaction sequences depicted in Schemes **1** and **2**.

Treatment of 6-(3,4-dimethylphenyl)-4-(2-phenyl-1H-indol-3-yl) pyridazine-3(2H)-thione[12] **(1)** with copper bronze in boiling xylene yielded the bipyridazine derivative (**2)**. Its IR spectrum was devoid of υC=S and showed the C=N absorption band at 1647 and NH 3397 cm^{-1}. Its mass spectrum showed an ion peak at m/z 751 (M+1) (0.27%).

On the other hand, compound **1** was oxidized to the disulfane derivative **3** upon treatment with sodium nitrite/acetic acid mixture. Its IR spectrum showed the band of υC=N at 1644, S-S at 1349 and NH at 3243 cm^{-1}.

Reaction of **1** with anthranilic acid and 5-bromoanthranilic acid gave the quinazolinone derivatives **4a,b** through elimintation of one molecule of H_2S and H_2O. Their IR spectra exhibited bands for υC=O at 1675, 1674, υC=N at 1614, 1595 and υNH at 3379 and 3371 cm^{-1}. The ^{1}HNMR (DMSO-d_6) spectrum of **4b** exhibited signals at ð(þþm): 8.41-6.83(16H,m,Ar-H),2.28(6H,s,2xCH_3)and 11.76(1H,s,NH).The mass spectrum of **4b** showed an ion peak at m/z 572 (M+1) (0.66%).

It was stated that pyrazole derivatives showed anticancer[13-15] anti-inflammatory[16], antioxidant[16], antimicrobial[16], molluscicidal[17], anti-angiogenic[18] ,activities and as a novel carries of nitric oxide[19]. This prompted the authors to synthesize pyrazole derivative trough the reaction of the pyridazine thione with acetylacetone to give the diketo compound **5** followed by cyclization with the binucleophile hydrazine hydrate to give the pyrazole derivative **6**. The IR spectrum of **5** exhibited bands for υC=O at 1708, υC=N at 1610 and υNH at 3400 cm^{-1}(broad). Its mass spectrum showed an ion peak at m/z 474 (M+1) (0.05%). While the IR spectrum of **6** was devoid of υC=O and showed υC=N and υNH at 1582 and 3441cm^{-1}.

The nucleophilic addition of the pyridazinethione **1** to benzalace-tophenone gave the adduct **7**. Its IR exhibited bands for υC=O at 1659, υC=N at 1604 and υNH at 3432 cm^{-1}. The structure of **7** was further established by its reaction with hydrazine hydrate to give the corresponding hydrazone derivative **8**. Its IR was devoid of υC=O, while its mass spectrum showed an ion peak at m/z 630 (M+1) (6.23%).

Treatment of compound **1** with thiourea in boiling DMF gave the thiourea derivative **9** through the nucleophilic attack of the nitrogen of thiourea to the carbon of the thione moiety followed by elimination of one molecule of H_2S. Its IR spectrum exhibited absorption bands at 1594, 1402, 3373, 3261, 3162 cm^{-1} for υC=N, υC=S and υNH_2 + NH, while its mass spectrum showed the molecular ion peak at m/z 449 (0.02%).

The thioxodihydropyrimidinedione **(10)** can be prepared through the one - pot reaction of compound **9**, malonic acid and acetyl chloride. Its IR spectrum exhibited bands at 1714, 1637, 1590, 1400 and 3413 for υ$COCH_3$, υC=O, υC=N, υC=S and υNH.

The present investigation also deals with carboethyoxymethylation of the thiopyridazine **1** through its treatment with ethyl chloroacetate in dry acetone in the presence of potassium carbonate to give compound **11**. Its IR spectrum showed the characteristic for υC=O (ester) at 1729, υC=N at 1604 and υNH at 3368cm^{-1}, while its mass spectrum showed the molecular ion peak at m/z 493 (1.05).

The resulting ester **11** has been used as starting material for the preparation of a series of new compounds.

Reaction of **11** with α-naphthylamine gave the acetamide derivative **12**. Its IR spectrum showed υC=O at 1672, υC=N at 1606 and υNH at 3409 cm^{-1}, while its mass spectrum showed an ion peak at m/z 589 (M–1) (4.36%).

Alkaline hydrolysis of compound **11** using ethanolic sodium hydroxide solution afforded the S-alkylated product **13** through decarboethoxylation. Its IR spectrum was devoid of υC=O and showed υC=N at 1599 and υNH at 3434cm^{-1}, while its ^{1}HNMR (DMSO-d_6) spectrum exhibited signals at 7.84-6.87 (13H, m, Ar–H), 2.32 (6H, s, 2 x CH_3), 2.13 (3H, s, SCH_3) and 11.53 (1H, s, NH). Its mass spectrum showed the molecular ion peak at m/z 421 (4.36%).

On the other hand, reaction of **11** with hydrazine hydrate afforded the corresponding hydrazide derivative **14**, which can be used for the preparation of the oxadiazole derivative **15** and the pyrazole derivative **16**, through its reaction with carbon disulfide/ KOH and/or salicylaldehyde. The IR spectrum of **11** showed υC=O at 1658, υC=N at 1598 and υ$NHNH_2$ at 3403, 3213 and 3117cm^{-1}, its mass spectrum showed the molecular ion peak at m/z 479 (24.67%). While the IR spectrum of **14** showed υC=N at 1618, υC=S at 1402 and υNH at 3441.

Reaction of compound **1** with benzylamine and 2- aminopyridine yielded Schiff bases **17a** and **17b,** respectively. Their IR spectra were devoid of υC=S and showed υC=N at 1604-1616, υNH at 3404, 3426 cm^{-1}(broad). The ^{1}HNMR of **17a** exhibited signals at 8.35- 6.86 (18H, m, ArH), 3.98. (2H, s, CH_2), 2.25 (6H, s, 2 x CH_3) and 11.37

(2H, s, 2 x NH) ,while that of **17b** exhibited signals at 7.83-6.50 (17H, m, Ar–H), 2.47 (6H, s, $2XCH_3$) and 11.51 (2H, s, 2 xNH). The mass spectra of **17a** showed the molecular ion peak at m/z 480 (6.14%), while that of **17b** at m/z 467 (17.74%).

Cytotoxicity against different human cancer cell lines in vitro for evaluation of anti-tumor cytotoxicity of compounds **4a, 4b, 5, 7, 13,17a** and **17b**, three different human cancer cell lines were used: MCF7 (breast carcinoma cell line), HEPG2 (hepatocellular carcinoma cell line), HCT116 (colon carcinoma cell line) cytotoxicity and IC_{50} values of the tested compounds are shown in Fig. **1** and **2**. The survival fractions were gradually decreased as the concentration of the tested compounds were increased (Table 1).
From Fig. **1**, it has been shown that **5,7,13,17a** and **17b** are the compounds of lowest IC_{50} which means that they are the most effective cytotoxic drugs, accordingly compounds **13,17a** and 17b can be used as very potent cytotoxic drug for colon carcinoma cell, while **5** and **7** as moderate cytotoxic drug for colon and liver carcinoma cell respectively, while the remaining compounds are very weak cytotoxic drug.

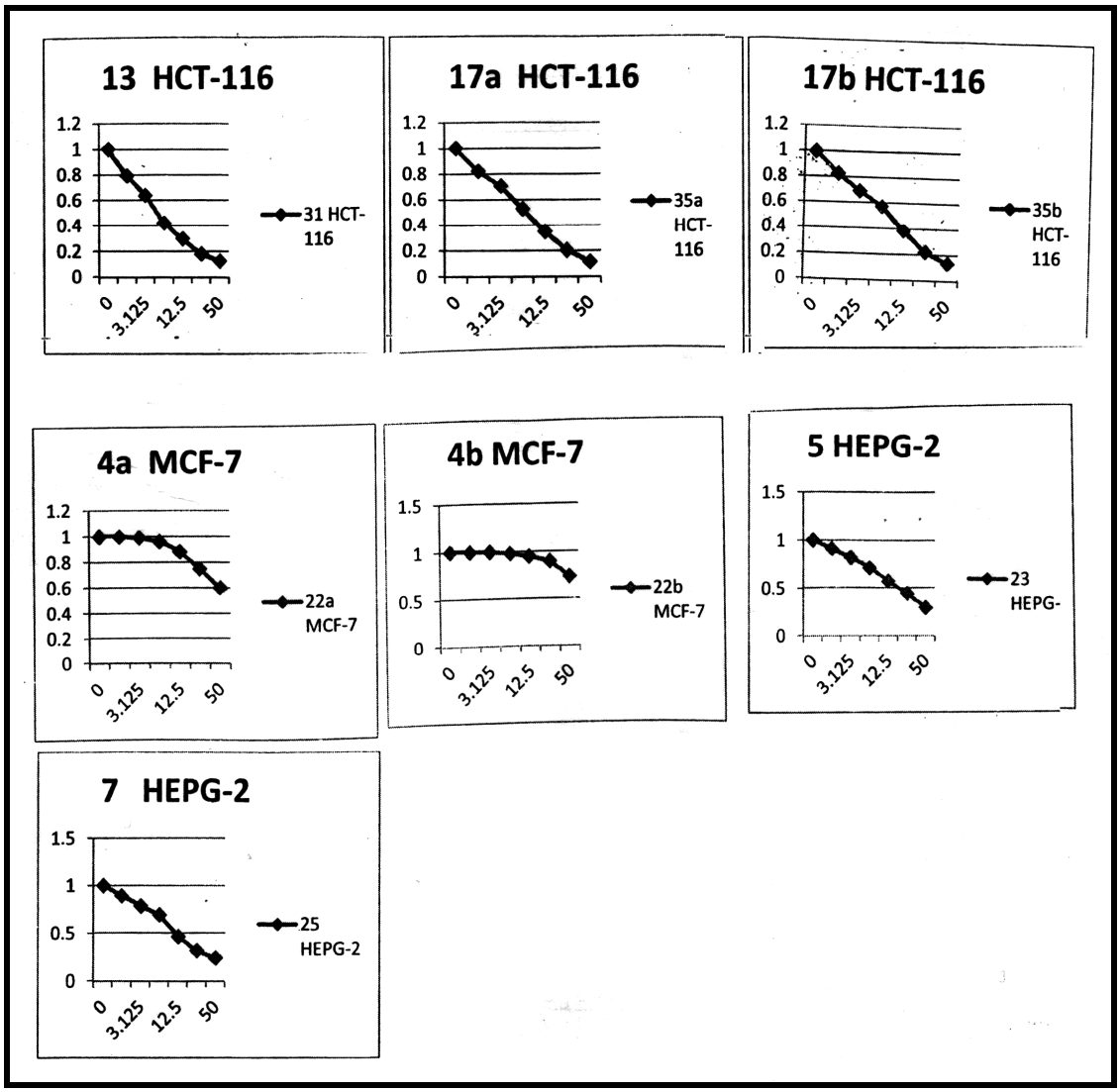


Fig. (1): Effect of some new prepared compounds on different tumor cells as cytotoxic drug

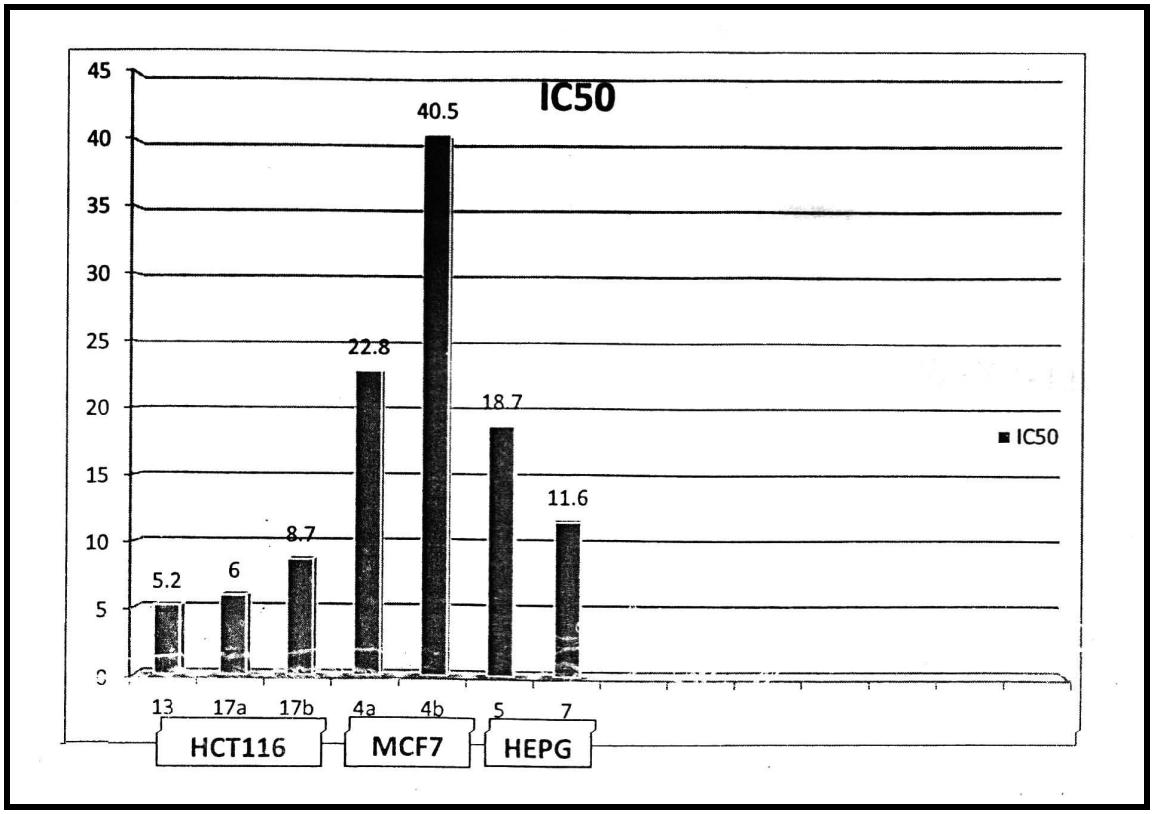


Fig. (2): 0-10 Very potent cytotoxic durg, 10-20 Moderate cytotoxic drug> 20 Very weak cytotoxic drug.

Table (1): Effect of some new prepared compounds on different tumor cells as cytotoxic drug.

Conc. µg/ml	HCT-116			MCF-7		HEPG-2	
	13	17a	17	4a	4b	5	7
0.0000	1.000000	1.000000	1.000000	1.000000	1.000000	1.000000	1.000000
1.6500	0.793800	0.819600	0.827800	0.100000	0.914800	0.914800	0.89260
3.1250	0.639400	0.705800	0.691200	0.989600	0.821500	0.821500	0.784800
6.2500	0.421200	0.526200	0.573600	0.962400	0.716600	0.716600	0.694800
12.500	0.2986800	0.348700	0.382400	0.884300	0.578200	0.578200	0.469300
25.000	0.182500	0.204800	0.221600	0.748000	0.445400	0.445400	0.317600
50.000	0.124600	0.115400	0.138000	0.601200	0.302100	0.302100	0.241400

CONCLUSION

A series of 4a, 4b, 5, 7, 13,17a and 17b compounds have different anti-tumar effects and IC_{50} values of them were discussed. Compounds 13,17a and 17b can be used as very potent cytotoxic drug for colon carcinoma cell, while 5 and 7 as moderate cytotoxic drug for colon and liver carcinoma cell respectively, while the remaining compounds are very weak cytotoxic drug.

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