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Synthesis of New 2-Thiouracil-5-Sulfonamide Derivatives with Biological Activity

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2-Thiouracil-5-sulfonylchloride **1** reacted with a series of aromatic and heterocyclic amines to give **2a-j.** The same compound **1** was reacted with a series of sulphonamides giving different sulphonamides of type **3a-e**. On the other hand compound **1** was allowed to react with p-aminoacetophenone givining compound **4** which in turn was allowed to react with derivatives of alkyl thiosemicarbazides to give thiosemicarbazones of type **5a-e**, also compound **4** was monobrominated to give compound **6** which in turn was reacted thiosemicarbazones of some aldehydes to give the corresponding thiazole derivatives **7a-f**. In the same time compound **4** was reacted with a series of aromatic and heterocyclic aldehydes givining chalcones **8a-g** (Claisen-Schemidt reaction). Also compound 4 was allowed to react with a series of aromatic and heterocyclic aldehydes, ethyl cyano acetate and/or malononitrile, and ammonium acetate giving pyridine derivatives **9a-d** and **10a-e** respectively. The biological effects of some of the new synthesized compounds was also investigated.

Key words: Thiouracil-5-sulphonamide-*p*-phenyl derivatives, Anti-microbial, Anti-viral, and anti-cancer activity

INTRODUCTION

It has been found that 2-thiouracil in conentration of 25 and 50 mg/100 ml media completely inhibits the growth of staphylococcus, the antibiotic effect was 50 times greater than that of thiourea Wyrzykiewicz *et al.* (1993), E-coli, Lactobacillus arabinosus, L. Leichmannii, L. Casei were inhibited by 2-thiouracil, Lang (1975), the inhibitory action could be increased by addition of uracil Naakamura .M and Jonsson (1957).

Influenza virus could be inhibited by 2-thiouracil, Crithidia Fasiculata was inhibited by 5-amino-2-thiouracil Naakamura and Jonsson (1957).

Several 5-substituted thiouracils possess chemotherapeutic importance especially against cancer, bacteria parasites Abdel-Hamid and Fathall (1993), Fathalla (1992), Fathalla (1999) and Fathalla *et al.* (2000). It was found that α,β-unsaturated ketones and clalcones have chemotherapeutic activity Kamell *et al.*, (1985) and Ebied *et al.* (1991). Besides it has been reported that thiosemicarbazones Hassaneen *et al.* (1995) possess strong biological activity against microorganism. Synthesis and biological evaluation of certain substituted thiazoles were also studied. The chemistry of pyridons and aminopyridines has been investigated and many of these compounds were found to have useful applications as chemotherapeutic agents.

We developed here a program aimed to synthesize novel 2-thiouracil derivatives hoping that these compounds might possess certain biological activity.

MATERIALS AND METHOD

All melting points are uncorrected and were determined in capillary tube. On Boetius melting point microscope, IR spectra were recorded in KBr on a Beckman Infrared Spectrophotometer PU 9712 using KBr discs. ^{1}H NMR spectra were obtained on Joel EX 270 MHz Spectrometer with TMS as internal standard. Mass spectra were recorded on SSQ 7000 Mass Spectrometer at 70 eV. All reactions were followed and cheked by T.L.C using chloroform/methanol (3:1) and spots were examined by UV lamp.

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4-Oxo-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-sulphonyl chloride 1

It was prepared by the procedure described in literature Fathalla (1992).

4-Oxo-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-sulphonic acidN-(substituted) amide derivatives 2a-i

General procedure: **A**: A mixture of **1** (1.13 mole) and the proper amino compound (1.13 mole), namely aniline p-toluedine, p-bromoaniline 3-fluoroaniline, 2-methyl-5-chloroanline, 2-methyl-5-nitroaniline, 2,4-dichloroaniline, 4-chloroaniline 3,5-dichloroaniline, 5-aminouracil and pyridine (0.016 mole) in absolute methanol (50 ml) was heated under reflux for 12~16 hr, then cooled and filtered off and recrystallized from DMF/water.

B The same mixture especially in case of using halogenated amines was stirred in 50 ml pyridine for 48 hr, then poured into ice water and the solid was filtered off and washed several times with water then washed with acidified ethanol till neutralized, dried and recrystallized from DMF/water.

4-Oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-sulphonicacid-N-(N'-subdtituted benzene sulphonamide) amide derivatives 3a-e

A mixture of **1** (1.13 g, 0.005 mol), the appropriate sulphonamide (0.005 mol) and 30 ml of anhydrous pyridine was stirred at room temperature for 48 hr, then the reaction mixture was poured into ice/HCl. Thus the solid formed was filtered off ,washed with water, dried and recrystallized from DMF/ H_2O.

4-Oxo-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-sulphonic acid-N-(acetyl phenyl) 4

It was prepared by the procedure described in literature Fathalla (1992).

4-Oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-sulphonamide-phenyl-thiosemicarbazone derivatives 5a-e

General procedure

A mixture of **4** (1.1 g of 0.003 mol) and the appropriate substituted thio semicarbazide (0.003 mol) was refluxed in 30 ml absolute ethanol for 12~15 hr. Then cooled, filtered off, dried and recrystallized from DMF/H_2O.

4-oxo-thiooxo-1,2,3,4-tetrahydropyrimidine-5-sulphonic acid-N-(p-bromoacetyl-phenyl)amide 6

A mixture of 4 (1.13 g, 0.005 mol) and bromine (0.005 mol) in 30 ml glacial acetic acid was stirred at room temperature for 48 hr, then filtered. The filterate was alkalinized with ammonia, the precipitate was collected, dried and recrystallized from DMF/ H_2O.

Reaction of 6 with thiosemicarbazones of some aldehydes : 7a-f

General procedure

A mixture of **6** (1.1 g, 0.003 mol) and the desired thiosemicarbazone derivatives (0.003 mol) in absolute ethanol 40 ml was refluxed for 15~17 hr, then the reaction mixture was cooled and the formed solid was filtered off, dried and recrystallized from DMF/H_2O.

Condensation of 4 with some aldehydes : Formation of Schoff's bases : 8a-g

Procedure

A mixture of **4** (1.01 g, 0.003 mol) and the appropriatearomatic and/or heterocyclic aldehydes (0.003 mol) in 50 ml ethanolic sodium hydroxide solution was shaken at room temperature for 24 hr, then refluxed for 1 hr, cooled and poured into ice-cold water. The precipitate that appeared after neutralization with dil, HCl was filtered off and recrystallized from DMF/H_2O.

4-oxo-20thioxo-1,2,3,4-tetrahydro pyrimidine-5-sulphonic acid-N-{4-[6-amino or oxo 5-cyano-4-substituted pyridine-2-yl]phenyl}amid derivatives 9 a-e and 10a-e

Procedure Fathalla *et al.* (2000)

A mixture of (1,1 gm, 0.003 mol) of **4**, the appropriate aldehydes (0.003 mol), ammonuium acetate (1.89 gm, 8 mol), and ethyl cyanoacetate (0.35 gm, 0.003 mol) or malononitrile (0.2 gm, 0.003 mol) in 50 ml absolute ethanole was refluxed for about 6~10 hs. The reaction mixtures was concentrated to its half volume, filtered, and the filterate was poured into ice/water and the precipitate was filtered off ,dried and recrystallized from DMF/H_2O.

The biological effects of some of the new synthesized compounds

A-Antibacterial Activity

The tested compounds were **2-a, 2-b, 2-c, 2-d, 2-e, 2-f, 2-g, 2-h, 2-J, 3-a, 3-b, 3-d, 3-e, 5-a, 5-b, 5-c, 6, 7-a, 7-c, 7-d, 7-e, 8-d, 8-f, 9-a, 9-b, 9-d and 10-b.**

Bacteria. The Following microorganisms were used for the determination of bacteriostatic and/or bactericidal concentrations.

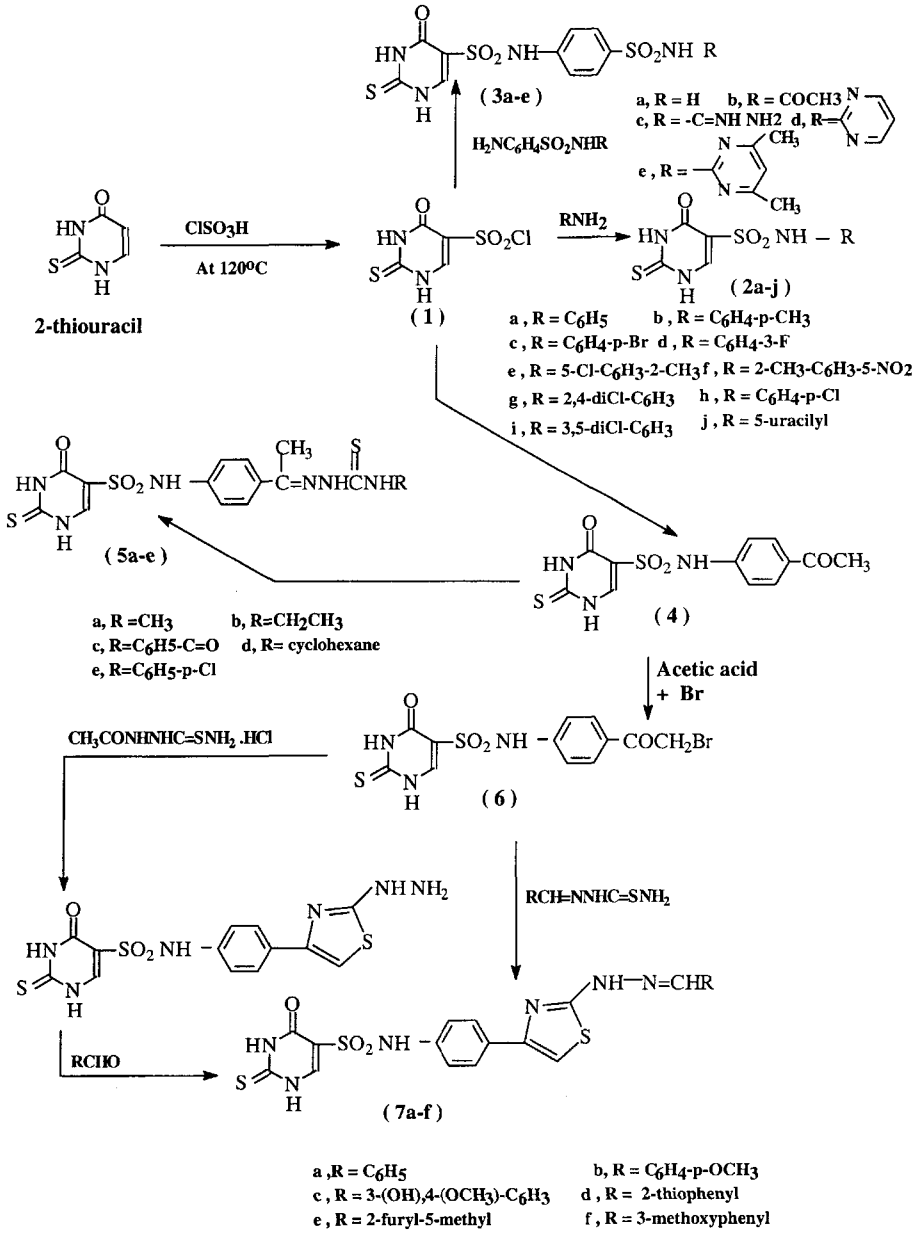
Escherichia coli, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Bacillus subtilis*, *Mycobacterium phlei*, and *Candida albicans*. All

microorganisms used were obtained from the culture collection of the department of microbiology and immunology, faculty of pharmacy, Helwan university. Compounds were tested against *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* in nutrient broth, pH 7.0; and against *Streptococcus pyogenes*, *Bacillus subtilis*, and *Mycobacterium phlei* in bacto brain hart infusion broth, *pH* 7.0; and against *Candida albicans* in broth containing 1% neo peptone, 2% dextrose with pH 5.7. A strain of *Escherichia coli* of known antibiotic sensitivity served for control purposes.

Media disc sensitivity test were nutrient agar and Muller-Hinton agar (MHA) were purchased from Difco. The disc diameter was 10 mm; the compounds with inhibition zone diameter more than 10 mm were subjected to determination of MIC by serial dilution method.

Nonsterile powder of the tested compounds and standards of guanidine, sulfanilamide, sulphadimidine sulphacetamide thiourea and thiouracile were dissolved in sterile DMSO to yield 2,000 μg/ml, passed through 0.2 μm membrane filters (Millipore Corp. Bedford, Mass). The filtrates were dispensed as 2-ml samples into sterile, small screwcapped vials, and frozen and kept stored at -15°C. The vials were never refrozen after thawing.

Sensitivity tests. Disc diffusion sensitivity tests were



Scheme 1. Preparation of compounds **1~7a-f**

done in a manner identical to that of (Bauer *et al.* 1966). Broth dilution tests, utilizing serial log2 dilutions of the testec compounds over the range of 50 to 0.025 μg/ml, were performed by using liquid media and a bacterial inoculum standardized to yield 1.5×10^6 organisms/ml at 0 time. For this purpose, organisms in the exponential growth phase (pregrown for 6 hr at 35°C in liquid media) were adjusted to McFarland $BaSO_4$ standard no. 0.5, the turbidity of which corresponds to that of 1.5×10^8 organisms/ml. The adjusted suspension of organisms was further diluted 50 fold in the selected liquid medium (corresponding to $3 < 10^6$ organisms/ml) Assay tubes re- ceived 1 ml of the respective double-strength dilution of antibiotic and 1 ml of bacterial inoculum. Control tubes received 1 ml of MHB and 1 ml of bacterial inoculum. The assay and control tubes were incubated at 35°C for 18 hr. The minimal inhibitory concentration (MIC) of tested compounds were defined as the lowest concentration of antibiotic completely inhibiting growth as judged by visual inspection. The minimal bactericidal concentration (MBC) of the drug was determined through subculture of one 3-mm loopful from clear tubes to quarter sectors of 5% sheep blood-agar plates which were incubated at 35°C for 24 hr. The MBC was defined as the lowest concentration of gentamicin yielding no growth after subculture to blood agar.

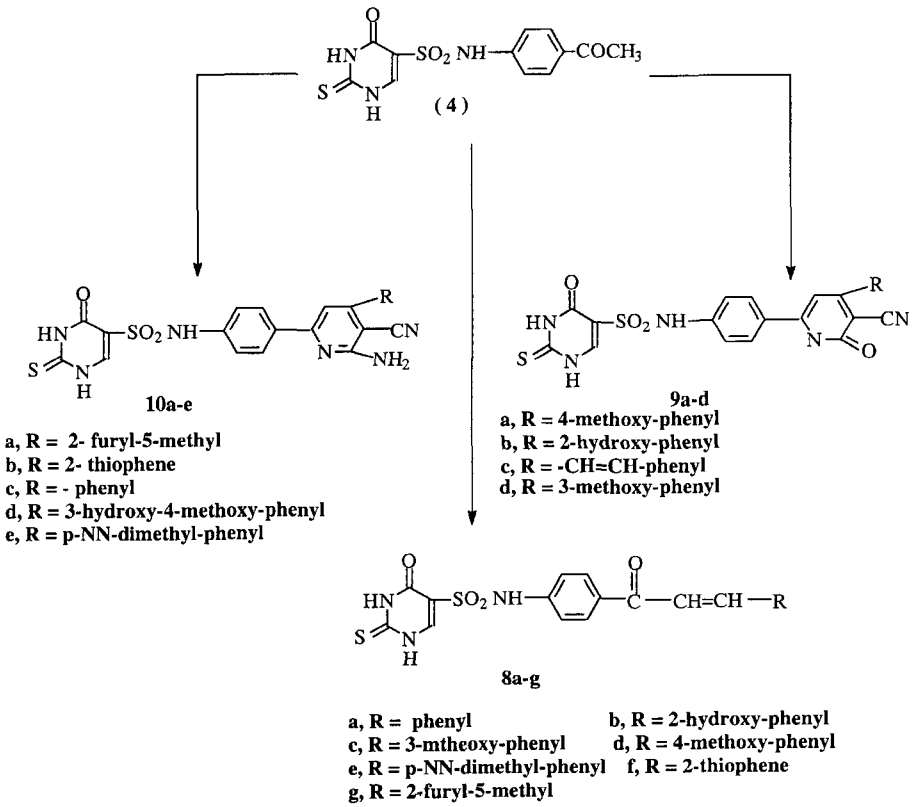
B- Antiviral activity *in vitro*

Preliminary *in vitro* Antiviral Testing:

Experiment:

The tested compounds were 2-a, 2-b, 2-d, 2-e, 2-f, 2-h, 2-J, 3-a, 3-b, 3-d, 3-e, 5-a, 5-b, 5-c, 6, 7-a, 7-c, 7-d, 7-e, 8-d, 8-f, 9-a, 9-d, 10-b. All compounds that contain 2-thiouracil nucleus were tested against a DNA baclerio-phage No PE112 obtained from ATCC and grow on E. coli k12 ATCC. The tested compounds were compared to standard 2-thiouracil and guanidine.

The test was carried out by applying viral plaque technique and the antiviral activity was expressed as percent reduction in total plaque count, medium com-position was nutrient agar (gm/100 ml, beef extract 0.3%, peptone, 0.5% agar, equal volumes of baclerial seed layer which contain to 6 E. coli K12/ml was dispensed in stenilized petn dishes. 1 ml of the virus suspension ($1\text{-}2 \times 10^2$) in sten'le saline solution was inoculated to the surface of the solidified E. coli nutnent agar plates. After 24 hr incubation at 37°C the number of viral plaques were counted, the tested compounds were dissolved in DMF and 5ml containing 5mg of the compounds were added to 1ml the viral suspension and incubated for 1 hr at 30°C priorto surface inculation on E-coli plates, the percent reduction in the plaques number were calculated as follow:



Scheme 2. Preparation of compounds **8a-g, 9a-d, 10a-e**

Table I. Physical and analytical data of the prepared compounds

Comp No	Yield (%) M.P (°C)	Formula Mol. Wt	Analysis (Calcd/Found) % C	H	N	Comp No	Yield (%) M.P (°C)	Formula Mol. Wt	Analysis (Calcd/Found) % C	H	N
2a	65 256	$C_{10}H_9N_3O_3S_2$ (283.3)	42.39 42.25	3.20 3.40	14.13 14.12	7b	59 253	$C_{21}H_{18}N_6O_4S_3$ (514.60)	49.01 48.87	3.52 3.48	16.33 16.52
2b	71 298	$C_{11}H_{10}N_3O_3S_2$ (297.35)	44.43 44.33	3.37 3.55	14.13 14.11	7c	64 261	$C_{21}H_{18}N_6O_5S_3$ (530.60)	47.50 47.30	3.42 3.75	15.84 16.12
2c	60 280	$C_{10}H_8N_3O_3BrS_2$ (362.23)	33.16 33.25	2.13 2.17	11.60 11.40	7d	60 275	$C_{18}H_{14}N_6O_3S_4$ (490.60)	44.06 44.33	2.88 2.63	17.13 17.08
2d	62 250	$C_{10}H_8N_3O_3FS_2$ (301.37)	39.86 39.65	2.68 2.51	13.95 13.72	7e	60 285	$C_{19}H_{16}N_6O_4S_3$ (488.)	48.88 48.51	2.37 2.42	17.98 17.32
2e	69 310	$C_{11}H_{10}N_3O_3ClS_2$ (331.80)	39.82 39.65	3.04 3.11	12.66 12.51	7f	61 258	$C_{21}H_{18}N_6O_4S_3$ (514.60)	49.01 49.25	3.52 3.58	16.33 16.09
2f	75 317	$C_{11}H_{10}N_4O_5S_2$ (342.35)	38.59 38.33	2.94 2.85	16.37 16.17	8a	57 325	$C_{19}H_{15}N_3O_4S_2$ (413.46)	55.19 55.39	3.66 3.29	10.16 9.98
2g	58 290	$C_{10}H_7N_3O_3Cl_2S_2$ (352.22)	34.10 34.20	2.00 2.03	11.93 11.84	8b	62 340	$C_{19}H_{15}N_3O_5S_2$ (429.46)	53.13 53.32	3.52 3.59	9.78 9.48
2h	60 305	$C_{10}H_8N_3O_3ClS_2$ (317.78)	37.79 37.53	2.54 2.44	13.22 13.13	8c	65 280	$C_{20}H_{17}N_3O_5S_2$ (443.49)	54.16 54.27	3.86 3.58	9.47 9.33
2i	62 275	$C_{10}H_7N_3O_3Cl_2S_2$ (352.22)	34.10 34,04	2.00 2.03	11.93 11.71	8d	62 255	$C_{20}H_{17}N_3O_5S_2$ (443.49)	54.16 54.03	3.86 3.57	9.47 9.13
2j	58 315	$C_8H_7N_5O_5S_2$ (317.31)	30.28 30.43	2.22 2.19	22.07 21.98	8e	63 344	$C_{21}H_{20}N_4O_4S_2$ (456.53)	55.25 55.31	4.42 4.68	12.27 12.02
3a	58 315	$C_{10}H_{10}N_4O_5S_3$ (362.41)	33.14 33.24	2.48 2.13	15.46 15.11	8f	61 310	$C_{18}H_{15}N_3O_5S_2$ (417.45)	51.79 51.48	3.62 3.42	10.07 10.02
3b	62 280	$C_{12}H_{12}N_4O_6S_3$ (404.45)	35.63 35.36	2.99 2.71	13.85 13.74	8g	60 295	$C_{17}H_{13}N_3O_4S_3$ (419.49)	48.67 48.61	3.12 3.34	10.02 10.48
3c	57 278	$C_{14}H_{12}N_6O_5S_3$ (440.49)	38.17 38.03	2.75 2.43	19.08 19.01	9a	71 295	$C_{23}H_{17}N_5O_5S_2$ (507.54)	54.43 54.31	3.38 3.24	13.89 13.76
3d	59 271	$C_{16}H_{16}N_6O_5S_3$ (435.46)	44.10 44.51	3.40 3.18	19.30 19.15	9b	69 322	$C_{22}H_{15}N_5O_5S_2$ (493.51)	53.59 53.42	3.06 3.12	14.19 14.06
3e	63 290	$C_{11}H_{12}N_6O_5S_3$ (404.46)	32.66 32.37	2.99 2.64	20.78 20.51	9c	65 285	$C_{24}H_{17}N_5O_4S_2$ (503.51)	57.34 57.31	3.40 3.21	13.91 13.74
5a	64 255	$C_{14}H_{16}N_6O_3S_3$ (412.52)	40.76 40.56	3.91 3.77	20.37 20.16	9d	66 310	$C_{23}H_{17}N_5O_5S_2$ (507.54)	54.43 54.26	3.38 3.04	13.89 13.71
5b	61 281	$C_{15}H_{18}N_6O_3S_3$ (426.54)	42.24 42.54	4.25 4.43	19.70 19.09	10a	64 319	$C_{21}H_{16}N_6O_4S_2$ (480.52)	52.49 52.34	3.36 3.23	17.49 17.43
5c	65 278	$C_{20}H_{18}N_6O_4S_3$ (502.59)	47.79 47.62	3.60 3.45	16.72 16.63	10b	65 330	$C_{20}H_{14}N_6O_3S_3$ (482.56)	49.78 49.62	2.92 2.71	17.42 17.34
5d	68 271	$C_{19}H_{17}N_6O_3ClS_3$ (509.04)	44.83 44.99	3.37 3.65	16.51 16.28	10c	70 299	$C_{22}H_{16}N_6O_3S_2$ (476.53)	55.45 55.34	3.38 3.12	17.64 17.53
5e	62 271	$C_{19}H_{23}N_6O_3S_3$ (331.80)	47.48 47.21	5.03 5.14	17.49 17.31	10d	61 310	$C_{23}H_{18}N_6O_5S_2$ (522.55)	52.86 52.71	3.47 3.31	16.08 16.03
6	60 260	$C_{12}H_{10}BrN_3O_4S_2$ (404.27)	35.65 35.91	2.49 2.17	10.39 10.13	10e	60 338	$C_{24}H_{21}N_7O_3S_2$ (519.50)	55.48 55.35	4.08 3.92	18.86 18.62
7a	55 243	$C_{20}H_{16}N_6O_3S_3$ (484.58)	49.57 49.18	3.33 3.25	17.34 17.51						

All compounds crystallized from DMF/H_2O.

% plaque reduction = Mean value of the number of plaque of the test/Mean value of the number of plaque of the control

C-Anticancer activity

In vitro test for cytotoxic effect

The tested compounds were 2a, 2f, 3e, 5a, 7b, 7c, 8f, 9a and10a respectively.

Experiment

A set of sterile test tubes was used, where 2.5×10^5 tumour cells per ml were suspended in phosphate buffer saline, then 0.1 ml of each of total DMSO containing the tested compounds and DMSO free liquid were separately added to the suspensions, kept at 37°C for 2 hours.

Trypan blue dye exclusion test was then carried out to calculate the percentage of nonviable cells (Mclimans *et al.*, 1957).

Four compounds showed inhibition of the viability of EAC cells at different doses while DMSO free liquid (control) showed no activity as in (Table IV).

Table II. The 1H-NMR and TR and Mass of Some of the prepared compounds

Comp No.	1H-NMR (DMSO-d6) ppm	IR (KBr) Cm-1	Mass Fragments %
2a	7-7.7 (5H,m,aromatic), 8.1 (1H, s, thiouracil), 10.5-11.2 (2H, s, NH exchangeable with D_2O).	3126, 3040 (NH, b), 2600 (SH), 1710 (CO) of thiouracil, 1680 (-C=N thiouracil, 1610, 1420 -C=C aromatic, 1320 (SO_2), 1130 (SO_2)	284 (M^{+1})
2b	2.1 (3H, s, CH3), 6.8, 7.1 (4H, d, aromatic), 8.1 (1H, s, thiouracil), 11-11.6 (3NH, s, exchangeable with D_2O).	3160, 3045 (NH, b), 3056, 2960 (CH, aliphatic),1720, 1670 (CO of thiouracil), 1320, 1120 (SO_2), 1270 (C=S of thiouracil).	298 (M^{+1}) 0.2% 64 (1.78%), 52 (4%), 79 (3.9%), 91 (1.6%), 108 (6.4%), 254 (0.1%)
2c	7.2, 7.5 (4H, dd, aromatic), 8.1 (1H, s, thiouracil), 11-11.5 (3H, s, 3NH exchange -able with D_2O).	3160, 3045 (NH, b), 3050 (CH, aromatic), 1670 (CO of thiouracil), 1320, 1170 (SO_2), 1270 (C=S of thiouracil), 560 (C-Br).	364 (M^{+2}) 3.69% 70 (13%), 112 (29.5%), 144 (24%), 184 (12%), 298 (1.6%)
2d	7.3, 7.8 (4H, m, aromatic), 8.1 (1H, s, thiouracil), 11.1-11.6 (3H, s, 3NH exchange able with D_2O).	3150, 3050 (NH, b), 3055 (CH, aromatic), 1670 (CO of thiouracil), 1375 (C=S of thiouracil), 1320, 1140 (SO_2), 1220 (C-F).	301 (M)
2e	2.1 (3H, s, CH_3), 6.8 (1H, s, aromatic), 7.1 (2H , d, -CH=CH-), 7.6 (4H, d, aromatic), 8.2 (1H, s, of thio uracil), 11, 11.3 (2 NH exchangeable with D_2O)	3150, 3045 (NH, b), 3020 (CH, aromatic), 1675 (CO of thiouracil), 1320, 1140 (SO_2), 1270 (C=S of thiouracil), 760 (C-Cl).	331, 333 (M, M^{+2})
2f	7.5, 7.9 (4H, dd, aromatic), 8.1 (1H, s, thiouracil),11.2-11.6 (3H, s, 3NH exchange -able with D_2O).	3142 (NH, b), 3063 (CH, aromatic), 1677 (CO of thiouracil), 1322, 1174 (SO_2), 1323, 1605 (NO_2), 1270 (C=S of thiouracil).	343 (M^{+1}), 1.6% 64 (59%), 73 (45%), 79 (33%), 144 (40%), 151 (3%), 155 (20%), 185 (8%), 191 (3%), 281 (2%)
2g	6.8 (1H, s, aromatic), 7.2 (2H, d, CH=CH), 7.7 (4H, d, aromatic), 8.2 (1H, s, of thiouracil), 11.2, 11.6 (2 NH exchangeable with D_2O)	3154 (NH, b), 3020 (CH, aromatic), 1675 (CO ofthiouracil), 1320, 1140 (SO_2), 1270 (C=Sof thio -uracil) 760 (C-Cl).	352.22 (M), 0 (5%), 70 (13%), 79 (10%), 91 (14%), 128 (21%), 155 (8.7% 0, 210 (2%), 280 (3%), 325 (3%)
2h	7.1, 7.5 (4H, dd, aromatic), 8.2 (1H, s, thiouracil), 11-11.4 (3H, 3NH exchange-able with D_2O).	3156 (NH, b), 3020 (CH, aromatic), 1675 (CO of thiouracil), 1321, 1140 (SO2), 1270 (C=S of thio-uracil) 1000 (C-Cl).	317, 319 (M, M^{+2})
2i	6.9-7.3 (3H, m, aromatic), 8.1 (1H, s, thiouracil), 11.2-11.6 (3H, 3NH exchange-able with D_2O).	3066 (NH, b), 3015 (CH, aromatic), 1680 (CO of thiouracil), 1320, 1175 (SO_2), 1170 (C=S of thio-uracil), 708 (C-Cl).	352, 354 (M, M^{+2}), 356, 358 (M^{+4},M^{+6})
2j	7.2 (4H, d, aromatic), 8.2 (1H, s, of thiouracil), 8.4 (1H, s, of uracil), 11, 11.6 (2 NH exchangeable with D_2O)	3166, 3060 (NH, b) 1677, 1613 (CO of uracil and thiouracil), 1320, 1216 (SO_2) 1217 (C=S of thiouracil).	319 (M^{+2}), 284 (0.1%), 244 (0.7 %), 235 (0.5%), 155 (61%).
3a	6.8 (2H, s, NH_2 exchange able with D_2O), 7.5, 7.7 (4H, d, aromatic), 8.2 (1H, s, thiouracil), 11.2-11.6 (3 NH exchangeable with	3520 (NH_2), 3164 (NH, b), 3040 (CH aromatic), 1660 (CO of thio -uracil), 1320, 1180 (SO_2), 1116 (C=S of thiouracil).	362 (M).
3b	3.2 (3H, s, -$COCH_3$), 7.5- 7.8 (4H, dd, aromatic), 8.2 (1H, s, thiouracil), 11.1-11.7 (3H, 4NH exchangeable with D_2O).	3135 (NH, b), 3020 (CH, aromatic), 2960 (CH, aliphatic) 1720 (CO of acetyl group), 1680 (CO of thiouracil), 1320, 1175 (SO_2), 1115 (C=S of thiouracil).	404 M^+ (2.4%), 358 (1%), 318 (3%), 282 (1%), 255 (100%), 224 (6.3%), 175 (3.5%), 191 (37%), 163 (1%), 64 (64.17%).
3c	7.2 (2H, s, NH_2 exchange able with D_2O), 7.5, 7.7 (4H, d, aromatic), 8.2 (1H, s, thiouracil), 11.2-11.6 (NH exchangeable with D_2O).	3200 (NH, b), 3093 (CH aromatic), 1660 (CO of thiouracil), 1320, 1175 (SO_2), 1270 (C=S of thiouracil).	440 (M).
3d	7.2 (2H, d, aromatic), 7 (1H, t, heterocyclic), 7.7 (2H, d, aromatic), 8.2 (2H, hetero-cyclic), 8.4 (1H, s, thiouracil 11-11.6 (2 NH exchange-able with D_2O).	3180 (NH, b), 2960 (CH aliphatic), 1660 (CO of thio-uracil), 1320, 1165 (SO_2), 1270 (C=S of thiouracil).	435 M^+ (0.1%), 254 (0.2%), 211 (2%), 185 (100%), 158 (1.8%), 65 (7%)
3e	2.1 (6H, s, 2 CH_3), 7.1 (1H, s, -C=CH), 7.1, 7.4 (4H, dd, aromatic), 8.1 (1H, s, thiouracil), 11-11.5 (4H, 4NH exchangeable with D_2O).	3360 (NH_2), 3200 (NH,b), 1650 (CO of thiouracil), 1320, 1140 (SO_2), 1270 (C=S of thiouracil).	404 M^+ (02%), 254 (12%), 218 (21%), 192 (7.6%), 172 (27%), 156 (32%), 144 (86.7%), 93 (25 %), 73 (46.5%), 64(100%).

Table II. Continued

Comp No.	1H-NMR (DMSO-d6) ppm	IR (KBr) Cm-1	Mass Fragments %
5a	2.1, 2.3 (6H, s, CH_3), 6.8 (2 H, d, aromatic), 7.2 (2H, d, aromatic), 8.2 (1H, s, thiouracil), 11-11.4 (3 NH, s, exchangeable with D2O).	3106, 3010 (NH), 1660 (CO of thio-uracil), 1140, 1320 (SO_2), 1270 (C=S of thiouracil).	413 (M^{+1})
5b	1.3 (3H, t, CH_3), 1.5 (2H, q, CH_2), 1.6 (3H, s, CH_3), 7.2-7.4 (4H, dd, aromatic), 10, 11-11.5 (4H, 4NH exchangeable with D_2O).	3224, 3041 (NH), 1680 C=O of uracil), 1178, 1321 (SO_2), 1270 (C=S of thio-uracil).	424M^{-2} (14.5%), 422 (14.5%), 382 (21%), 353 (35%), 300 (9.8%), 231 (24%), 223 (12.1%), 191 (26%), 180 (15.6%), 158 (100%), 99 (35.8%), 55 (61%), 53 (49%).
5c	1.5 (3H, s, CH_3), 7.2-7.4 (5H, m, aromatic), 7.5 (4H, d, aromatic), 8.4 (1H, s, thiouracil), 10, 11.1, 11.3 (3H, s, NH exchangeable with D_2O).	3219, 3067 (NH), 1724 (C=O of aromatic), 1648 (C=O of turacil), 1176, 1314, (SO_2),1217 (C=S of thiouracil).	502 (M)
5d	1.5 (3H, s, CH_3), 1.6 (10H, t of cyclo hexane), 7.2-7.5 (4H, dd, aromatic), 10, 11-11.5 (4H, 4NH exchangeable with D_2O).	3220, 3070 (NH), 1724 (C=O of aromatic), 1660 (C=O of thiouracil), 1176, 1312 (SO_2), 1270 (C=S of thio-uracil).	510 (M^{+1})
5e	1.3 (3H, s, CH_3), 7, 2 (4H, d, aromatic), 7.5 (4H, d, aromatic), 8.4 (1H, s, thiouracil), 10, 11.1, 11.3 (3H, s, NH exchangeable with D_2O).	3221, 3040 (NH), 1724 (C=O of aromatic), 1680 (C=O of thiouracil), 1176, 1318 (SO_2), 1270 (C=S of thio-uracil), 50.6 (C-Cl).	481 (M^{+1})
6	2.4 (2H, s, CH_2), 7.2, 7.4 (4H, d, aromatic), 11.6 (NH exchange-able with D^2O).	3166, 3058 (NH), 1770 C=O of aromatic), 1674 (C=O of thiouracil), 1270 (C=S of thiouracil), 1140, 1320 (SO_2).	404M+ (0.1%), 382 (2%), 255 (14%), 254 (100%), 82 (12.54%), 64 (5%).
7a	6.9-7.7 (4H, dd, aromatic), 7.7 (1H, thiazol), 7.8 (1H, s, -N=CH), 8.3 (1H, s, thiouracil), 11-116 (4H, s, 4NH exchangeable with D_2O).	3842, 3622 (NH), 2600 (SH), 1750 (C=O of thiouracil), 1320, 1140 (SO_2).	485 (M^{+1})
7b	2.6 (1H, s, CH=C-), 2.8 (1H, s, CH=N-), 3.7 (3H, s, OCH_3), 6.9-7.6 (4H, d, aromatic), 7.8 (4H, d, aromatic), 8.1 (1H, s, of thiouracil), 11.2, 11.6 (2 NH exchangeable with D_2O).	3750, 3443 (NH), 2600 (SH), 1714 (C=O of thiouracil), 1219 C-O-C, 1302, 1168 (SO_2).	515 (M^{+1})
7c	2.6 (1H, s, CH=C), 2.8 (1H, s, CH=N) 3.6 (3H, s, OCH_3), 7.2-7.8 (7H, m, aromatic), 8.3 (1H, s, of thiouracil), 9 (1H, s, OH), 11.1, 11.4 (2 NH exchangeable with D_2O).	3752 (NH), 3903 (OH), 2600 (SH), 1711 (C=O of thio-uracil), 1274, 1136 (SO_2).	530 (5%), 469 (.2%), 362 (.5%), 298 (21%), 265 (10%), 264 (71%), 151 (12%), 59 (4%).
7d	6.8-7.7 (4H, dd, aromatic), 7.1-7.3 (3H, m, thiophene), 7.7 (1H, s, thiazol), 7.8 (1H, s, N=CH), 8.3 (1H, s, thiouracil), 11-11.6 (4H, s, 4NH exchangeable with D_2O).	3839, 3752 (NH), 2600 (SH), 1715 (C=O of thiouracil), 1321, 1185 (SO_2).	493 M+ 2 (1.66%), 278 (3%), 256 (43%), 191 (18%), 97 (10%), 83 (16%).
7e	1.9 (3H, s, CH3), 6.9-7.8 (4H, dd, aromatic), 7.2-7.3 (2H, d, furan), 7.7 (1H, s, thiazol), 7.8 (1H, s, -N=CH), 8.3 (1H, s, thiouracil), 11-11.7 (4H, s, 4NH exchangeable with D_2O).	3023 (NH), 2600 (SH), 1732 (C=O of thiouracil), 1381, 1174 (SO_2), 1214 (C-O of furyl).	488 (M)
7f	2.4 (1H, s, CH=C), 2.6 (2H, s, CH=CH), 2.8 (1H, s, CH=N), 3.6 (3H, s, OCH_3), 7.2-7.8 (4H, d, aromatic), 8.3 (1H, s, of thio - uracil), 9 (1H, s, OH) 11.1, 11.4 (2 NH exchangeable with D_2O).	3440 (NH), 2600 (SH), 1730 (C=O of thiouracil), 1315,1140 (SO_2).	514 (M)
8a	6.5, 7 (2H, d, chalcone), 7.5, 7.6, 8, 6.1 (9H, m, aromatic), 8.2 (1H, s, thiouracil), 11.6 (1H, s, NH exchangeable with D_2O).	3752 (NH), 1671 (C=O of thiouracil), 1604 (C=C of chalcone), 1321, 1171 (SO_2),1270 (C=S of thiouracil).	413 (M)
8b	6.6-7.1 (2H, dd, chalcone), 7.5, 7.7, 8 (8H, m, aromatic), 8.2 (1H, s, thiouracil), 11-11.9 (4H, s, 3NH, OH exchangeable with D_2O).	3158 (NH), 1694, C=O of thiouracil), 1671 (C=O), 1607 (C=C), 1320, 1141 (SO_2), 1270 (C=S of thiouracil).	430 (M^{+2})

Table II. Continued

Comp No	1H-NMR (DMSO-d6) ppm	IR (KBr) Cm-1	Mass Fragments %
8c	3.9 (3H, s, CH3), 6.7-7.2 (2H, dd, chalcon), 7.6, 7.7, 8.1 (8H, m, aromatic), 8.2 (1H, s, thiouracil), 11.1-11.8 (3H, s, 3NH exchangeable with D_2O).	3154 (NH), 1692 C=O of thiouracil), 1650 (C=O), 1605 (C=C of chalcone), 1338, 1173 (SO_2), 1270 (C=S of thiouracil).	443 (M^{+2})
8d	3.9 (3H, s, OCH_3), 6.5, 7 (2H, d, chalcone), 7.5, 7.6, 8, 6.1 (8H, d, aromatic), 8.2 (1H, s, thiouracil), 11.6 (1H, s, NH exchangeable with D_2O).	3068 (NH), 1695, C=O of thiuuracil), 1630 (C=O), 1601 (C=C of chalcone), 1325, 1176 (SO_2), 1270 (C=S of thiouracil).	443 (M^{+2})
8e	2.3, 2.5 (6H, s, 2 CH_3), 7.2 (4H, d, aromatic), 7.3 (1H, dd, chalcone), 7.6 (4H, d, aromatic), 8.2 (1H, s, of thiouracil), 11.4 (1H, s, NH exchangeable with D_2O).	3451 (NH), 1662 (C=O of thiouracil), 1642 (C=O), 1600 (C=C of chalcone), 1371, 1164 (SO_2), 1270 (C=S of thio uracil).	456 (M)
8f	7.1-7.3 (3H, m, thiophene), 6.7-7.2 (2 H, dd, chalcone), 7.3-7.4 (4H, dd, aromatic), 8.2 (1H, s, thiouracil), 11 11.6 (3H, s, 3NH exchangeable with D_2O).	3493 (NH), 1688 (C=O of thiouracil), 1607 (C=C of chalcone), 1325, 1170 (SO_2), 1270 (C=S of thiouracil).	417 (M)
8g	3.9 (3H, s, OCH_3), 6.5,7 (2H, d, chalcone), 7.5, 7.6 (4H, d, aromatic), 8.1 (2H, s, -CH=CH-), 8.2 (1H, s, thiouracil), 11.6 (1H, s, NH exchangeable with D_2O).	3160 (NH), 1720 (C=O of thiouracil), 1610 (C=C of chalcone), 1320, 1175 (SO_2), 1270 (C=S of thiouracil).	419 (M)
9a	3.8 (3H, s, OCH3), 7.2 (4H, d, aromatic), 7.6-8.1 (4H, d, aromatic), 8.3 (1H, s, of thiouracil), 11.5 (1H, s, NH exchangeable with D_2O).	3415 (NH), 2214 (CN), 1618 (C=O of thiouracil), 1585 (C=O of pyridone), 1262 (C-O), 1364, 1124 (SO_2),1270 (C=S of thiouracil).	507 (M)
9b	7.1-7.2 (4H, m, aromatic), 7.2-7.3 (4H, dd, aromatic), 8.3 (1H, s, pyridone), 8.4 (1H, s, thiouracil), 11 11.9 (4H, s, 3NH, OH exchangeable with D_2O).	3415 (NH), 2218 (CN), 1618 (C=O of thiouracil), 1585 (C=O of pyridone), 1262 (C-O), 1364, 1124 (SO_2),1270 (C=S of thiouracil)	495 (M^{+2}) (1.57%), 282 (0.2%), 200 (100%).
9c	7.2, 7.3 (2H, d, CH=CH of chalcone), 7.6 (1H, s, CH=C of pyridine), 7.7 (5H, m, aromatic), 7.6-8.3 (4H, d, aromatic), 7.5-11.5 NH exchangeable D_2O)	3413 (NH), 2218 (CN), 1615 (C=O of thiouracil), 1585 (C=O of pyridone), 1262 (C-O), 1364, 1124 (SO_2), 1270 (C=S of thiouracil).	504 (M^{+2})
9d	3.5 (3H, s, OCH_3), 7.2 (4H, d, aromatic), 7.4 (1H, s, C=CH), 7.5-7.7 (4H, m, aromatic), 8.3 (1H, s, of thiouracil), 11.5 (1H, s, NH exchange able with D_2O).	3425 (NH), 2220 (CN), 1615 (C=O of thiouracil), 1585 (C=O of pyridone), 1364, 1124 (SO_2), 1270 (C=S of thiouracil).	508 (M^{+1})
10a	2.5 (3H, s, CH_3), 7.2 (2H, d, CH=CH), 7.3 (1H, s, C=CH), 7.5-7.7 (4H, m, aromatic), 8.3 (1H, s, of thiouracil), 11.5 (1H, s, NH exchangeable with D_2O).	3051 (NH), 2208 (CN), 1673 (C=O of thiouracil), 1321, 1117 (SO_2), 1270 (C=S of thiouracil).	482 (M^{+1}) (1.37%), 445 (14%), 414 (2.25%), 192 (15.5%), 144 (50.2%), 64 (100 %).
10b	7.2 (2H, m, thiophen), 7.1-7.4 (4H, dd, aromatic), 7.7 (1H, s, pyridine), 8.2 (1H, s, thiouracil), 9.11-11.5 (5H, s, 3NH, NH_2 exchangeable with D_2O).	3090 (NH), 2214 (CN), 1663 (C=O of thiouracil), 1322, 1174 (SO_2), 1270 (C=S of thiouracil).	482 (M)
10c	5.2 (2H, s, NH_2), 7, 7.2 (4H, d , aromatic), 7.4 (1H, s, C=CH), 7.5-7.7 (5H, m, aromatic), 8.3 (1H, s, of thiouracil), 11.5 (1H, s, NH exchangeable with D_2O).	3062 (NH), 2198 (CN), 1660 (C=O of thiouracil), 1322, 1117 (SO_2), 1270 (C=S of thiouracl).	476 (M)
10d	7.1-7.2 (3H, m, aromatic), 3.9 (3H, s, OCH3), 7.3-7.5 (4H, dd, aromatic), 7.7 (1H, s, pyridine), 9, 10, 11-11.5 (5H, s, 3NH, NH2, OH exchangeable with D2O)	3062 (NH), 2206 (CN), 1671 (C=O of thiouracil), 1608, 1321, 1216 (SO_2), 1270 (C=S of thiouracil).	523 (M^{+1})
10e	2.3, 2.5 (6H, s, CH_3), 5.4 (2H, s, NH_2) 7.1, 7.3 (4H, d, aromatic), 7.5 (1H, s, C=CH), 7.4-7.7 (4H, d, aromatic), 8.3 (1H, s, of thiouracil), 11.5 (1H, s, NH exchangeable with D_2O).	3140 (NH), 2206 (CN), 1680, C=O of thiouracil), 1600, 1321, 1140 (SO_2), 1270 (C=S of thiouracil).	519 (M)

Table III. Antimicrobial test of the synthesized compounds with comparison to the standard antimicrobial agents measured by disc diffusion method by a 10 mm disc and broth dilution methods

		Disc Diffusion test and Broth dilution test													
		E. coli		*S. aureus*		*P. aeruginosa*		*S. pyogenes*		*B. subtilis*		*M. phlei*		*C. albicans*	
		A* mm	B** µg/ml	A* mm	B** µg/ml	A* mm	B** µg/ml	A* mm	B** µg/ml	A* mm	B** µg/ml	A* mm	B** µg/ml	A* mm	B** µg/ml
The tested compounds	2 a	18	20	10	-----	20	18	10	-----	10	-----	10	-----	10	-----
	2 b	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----
	2 c	11	13	15	21	11	19	12	10	11	18	10	-----	10	-----
	2 d	15	1.6	12	1.9	12	18	15	9.0	13	11	10	-----	10	-----
	2 e	12	15	12	18	11	10	13	18	12	11	10	-----	10	-----
	2 f	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----
	2 g	11	13	15	21	11	19	12	10	11	18	10	-----	10	-----
	2 h	18	21	12	13	11	10	18	10	11	11	10	-----	10	-----
	2 j	10	-----	10	-----	10	----	10	-----	10	-----	10	-----	10	-----
	3 a	18	21	12	13	11	10	18	10	11	11	10	-----	10	-----
	3 b	15	24	14	22	18	10	15	11	12	15	11	31	10	-----
	3 d	10	------	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----
	3 e	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----
	5 a	14	10	12	20	14	10	11	15	11	12	10	-----	10	-----
	5 b	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----
	5 c	12	12	15	10	10	12	15	18	12	11	10	-----	10	-----
	6	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----
	7 a	18	16	12	15	12	12	12	16	10	23	10	-----	10	-----
	7 c	12	12	14	12	18	12	11	15	10	-----	10	-----	10	-----
	7 d	13	10	12	10	15	18	11	24	15	15	10	-----	10	-----
	7 e	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----
	8 d	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----
	8 f	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----
	9 a	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----
	9 b	12	15	10	------	17	10	10	------	10	------	10	------	10	------
	9 d	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----
	10 d	12	15	10	------	17	------	10	------	10	------	10	------	10	------
	1j	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----	10	-----
	1+	20	16	31	12	25	12	12	19	18	10	10	-----	10	-----
	2+	22	10	30	17	15	15	18	12	12	05	10	-----	10	-----
	3+	15	12	16	18	19	10	15	06	15	12	10	-----	10	-----
	4+	15	5.0	12	22	19	38	12	24	12	22	10	-----	10	-----
	5+	34	0.7	21	8.0	20	19	25	34	22	12	10	-----	10	-----

*= Zone Inhibition in mm.

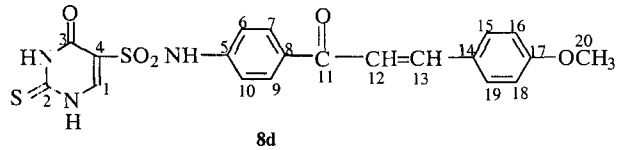
**=MIC after 24 hr in µg/ml and after 48 hr for *C. albicans* ----=not tested.

+=1: Guandine; 2: thiouracil; 3: thiourea; 4: sulfacetamide; 5: sulfanilamide; 6: Sulfadimidine.

RESULTS AND DISCUSSION

In view of the above findings it was considered of interest to undertake the synthesis of new 5-substituted-2-thiouracil containing phenyl, uracilyl, sulphonamido, thiosemicarbazones, thiazoles, chalcones, pyridone and aminopyridines hopping that these compounds might possess certain anti metabolic function against living microorganisms.

Synthesis of the desired compounds was achieved by allowing 2-thiouracil-5-sulphonyl chloride **1** to react with a series of aromatic and/or heterocyclic amines namely aniline, p-toluedene, p-bromoaniline, m-fluoro-aniline, 5-chloro-2-methyl-aniline, 2-methyl-5-nitro-aniline, 2,4-dichloro-aniline, p-chloroaniline, 3,5-dichloro-aniline and 5-amino-uracil in absolute ethanol containing pyridine as acid scavenger giving compounds **2a-j**. The same compound 1 was allowed to react with a series of sulphonamides namely sulphanilamide, sulphaguanidine, sulphacetamide, sulphadiazine and sulphadimidine in ethanol containing pyridine as acid scavenger giving compounds **3a-e**. Also



8d

compound 1 was reacted with p-aminoacetophenone in ethanol containing pyridine giving 2-thiouracil-5-sulphonamide-p-acetophenone **4**. which in turn condensed with a series of alkyl thiosemicarbazides namely methyl, ethyl, benzoyl, p-chlorophenyl and cyclohexyl thiosemicarbazides in absolute ethanol to give the corresponding thiosemicarbazones **5a-e** respectively.

2-Thiouracil-5-sulphonamide (p-bromoacetylphenyl) **6** was prepared by bromination of 4 in acetic acid. Condensation of 4 with certain aldehyde hydrazones namely benzaldehyde, p-methoxy benzaldehyde, 3-hydroxy-4-methoxy benzaldehyde, 2-thiophenaldehyde and 5-methyl-2-furanaldehyde thiosemi -carbazones gave the corresponding hydrazinothiazolyl-2-thiouracil-5-sulphonamide (p-phenyl) derivatives **7a-f.** The hydrazones **7a-f** were also prepared by the reaction of **6** with the hydrochloride of acetyl thiosemicarbazide then the product was treated with the same aldehydes.

Claisen-Schimidt condensation of **4** with various aromatic or heterocyclic aldehydes namely benzaldehyde, salicylaldehyde, m-methoxy anisaldehyde, p-methoxy anisaldehyde, P-N,N-dimethylaminobenzaldehyde, 5-methyl-2-furaldehyde and 2-thiophenaldehyde in presence of 10% sodium hydroxide solution afforded the corresponding 2-thiouracil-5-sulphonamide (p-cinnamoyl) derivatives **8a-g** respectively.

The ^{13}C NMR of compound 8d showed signals at 160 ppm (C3) corresponding to C=O of thio uracil, at 185.948 ppm (C2) corresponding to C=S of thio uracil, at 112.778 ppm (C4), at 153.949 ppm (C1), at 141.475 ppm (C5), at 116.034, 122.715, 116.084, 122.715 ppm corresponding to (C6), (C7), (C10), (C9) respectively.

A signal appears at 125.356 corresponding to (C8), at 185.998 corresponding to (C11), at 113.048, 116.048 to (C12) and (C13), at 153.945 ppm to (C17), at 121.313, 129.335, 131.232, 136.623 and 141.4 ppm corresponding to (C14), (15), (C16), (C18), and (C19) respectively. A signal appears at 55.295 ppm corresponding to (C20).

Compound **4** was reacted with ethyl cyano acetate and/or malononitrile in presence of ammonium acetate anhydrous and series of aromatic and heterocyclic aldehyde namely anisaldehyde, salicylaldehyde, cinnamaldehyde, m-methoxy anisaldehyde, 5-methyl-2-furanaldehyde, 2-thiophenaldehyde,benzaldehyde, 3-hydro xy4-methoxy benzaldehyde and N,N-dimethyl aminobenzaldehyde in absolute ethanol to give the corresponding 3-cyno-pyridin-2-one or 3-cyano-2-amino pyridine derivatives **9a-d** and **10a-e** respectively. All the newly compounds were confirmed by the corrected physical and analytical data.

Interpretation of microbiological study of the prepared compounds

This work is an attempt to screen the antibacterial action of some novel 2-thiouracil derivatives substituted at 5-position due to its antimetabolite effect (inhibition of nucleic acid synthesis).

Interpretation of Results

Substitution in the phenyl group may affect the activity as follow:

Series 2

i- The presence of halogen gave active compounds, this could be accepted if we know for example that *Staphylooccoccus* sp. Could be grawen on milk agar broth containing 10% NaCl which can be used as a selective medium for isolation of Staph. Sp from other bacteria thus these halogenated compounds could penetrate the cell wall of bacteria easily.

ii- The presence of methyl group gave inactive compounds because they could not penetrate the cell wall of bacteria.

iii- When the phenyl group is free, an active compounds was obtained.

iv- Replacement of phenyl group by heterocyclic ring abolish the activity because the heterocyclic ring is less aromatic than benzene ring at the receptor sites of the cell membrane of bacteria.

Series 3

i- R-group should be smaller group thus increasing the molecular weight of R group gives inactive compounds especially if R is a heterocyclic ring, this is due to decreasing the solubility of the compound and this affects its penetration power into the cell wall of bacteria. I.e. give very bulky molecule which cannot fit the receptor sites of the enzymes of bacteria, if R=NH_2 or R=-$COCH_3$, active compounds were obtained, this is due to the ability of C=O and NH_2 groups to form hydrogen bonding with the receptor sites of the cell wall of bacteria and this increase the penetration power of these compounds.

ii- In known sulphonamides the presence of free NH_2 is essential for the activity (unless broken in vivo) in these compounds there is no free NH_2 group thus the antibacterial action of these compounds is due to the presence of the thiouracil moity and not sulphonamide group.

iii- If R=-$COCH_3$, this gave a compound showing a weak bactencidal activity against M. phlei, all tested

compounds including standard compounds are inactive against this bacteria, this because ability of -C=O group to form hydrogen bonding with the receptor sites of the cell wall and also the synergestic action of sulphonamide and thiouracil in the same molecule in this compounds.

Series 5

i- If R=CH3 or C_6H_5-CO, an active compounds were obtained.

ii- If R= CH_2CH_3,, inactive compound was obtained, thus R should not be very bulky to retain the activity, the carbonyl group could form hydrogen bonding with the receptor sites of the cell wall bacteria.

Series 7

In this series a thiazole ring is introduced to retain the antimicrobial activity

i- If R=phenyl, -3-hydroxy,4-methoxyphenyl or 2-thienyl group active compounds were obtained.

ii- If R=2-furyl-5-methyl group an inactive compound was obtained. i.e The introduction of thiazol ring maintain the activity except in one case where R=2-furyl-5-methyl, when R=2-thienyl group the activity was retained, this is because the thiophen ring is more stable than furan ring while in case of furan the ring could be reduced by bacteria into tetrahydrofuran (inactive).

Series 8

This substitution gave inactive compounds.

Series 9

i- It is active only against E-coli and p-aerouginosa i.e it is of limited and weak activity.

ii- Replacement of NH_2 group by C=O group (i.e amino pyridine is replaced by pyridone) gave inactive compounds tis because the ability of NH_2 group to form hydrogen bonding with the receptor sites in enzymes of bacteria is higher than C=O group. Also tautomerism will decrease the activity.

Interpretation of antiviral study of the prepared compounds

The effects of the incorporation of 2-thiouracil into RNA have been studied chiefly with respect to enzyme induction and reproduction of RNA viruses Peter Lang, (1975). Tobacco virus was one of the first biological systems in which the inhibitory action of 2-thiouracil Commoner *et al.* (1952) and its incorporation into RNA were shown to occur together. The inhibition shows some similarity with that of the DNA viruses by 5-bromo and 5-iodouracil in that non infection particles are produced Francki R.I.B,virology, 10,374 (1960).

All compounds showed related antiviral activity and this may be due to the break down of all compounds into R-SO_3H or R-SO_2NH_2 where R=2-thiouracil by the virus. Both R-SO_3H and R-SO_2NH_2 may inhibit orotidine-5'-phosphate pyrophosphate of the virus Holmes W.L, J. Biol. Chem. 223,677 (1956).

Conclusion :

Any substitution in the sulphonamido groub of 2-thiouracil-5-sulphonamide may retain the antiviral activity.

RESULTS

The preliminary antiviral activity revealed that all compounds confirmed moderate activity compared to standard free nucleus of 2-thiouracil and guanidine which showed 32% and 4 % reduction in plaques respectively, on the other hand all tested compounds showed % reduction from 63 to 75.

The percent reduction in plaques count seem to be related to the amount of thiouracil ring in each compound because the test was carried out using mg not m mol.

Interpretation of Results of some new synthesis of 5-substituted-2-thiouracil on the viability of tumour cell *in vitro*

Thiouracils act as antineoplastic agents they interfere with the synthesis of DNA by blocking the conversion of deoxyuridyl acid to thymidylic acid by the cellular enzyme thymidylate. synthetase, they also interfere with RNA synthesis. DNA and RNA are essential for cell division and their deprivation by the action of thiouracils lead to death of cells Peter Lang. (1975).

From the experiments we obtained four active compounds **5a**, **9a, 2f and 7b**.

Compound **5a** is active due to presence of thiouracil nucleus and thiourea part while the activity of compound **9a** is owing to the thiouracil nucleus and pyridone nucleus. Compound **2f** is active due to presence of thiouracil nucleus and the benzene nucleus with NO_2 group and **7b** is active because of the presence of thiouracil nucleus beside the presence of thiazole ring.

Table IV. Effect of some 5-substituted-2-thiouracils 2a, 2f, 3e, 5a, 7b, 7c, 8f, 9a and 10a on the viability of Tumour cells in Vitro

Tested compounds	Dose µg/ml		
	100	50	20
2a	----	----	----
2f	100	60	30
3e	----	----	----
5a	70	70	70
7b	100	40	20
7c	----	----	----
8f	----	----	----
9a	80	60	30
10a	----	----	----

General comment on the biology of 2-thiouracil-5-substituted

Substitution at the 5-position of 2-thiouracil gives active compounds as antibacterial, antiviral, and antineoplastic agents more investigation must be carried out.

REFERENCES

Abdel-Hamid, A. Z. and Fathalla, O. A. Effect of some new uracil derivatives on ehrlish ascites carcinoma cells. *Egypt. J. Pharm. Sci.*, 34, 67-80 (1993).

Affi A. Contribution to the chemical carcinogenesis in Xenopus. "Ph.D. Thesis, UCL, Louvainha Neuve, Belgium, 90-91 (1986).

Bauer, A. W., Kirby, W. M. M., Sherris, J. C. and Turck, M. Antibiotic susceptibility testing by a standardized single disc method. *Amer. J. Clin. Pathol.*, 45, 493-496 (1966).

Beri A., Ross, L., Goodn, K. and Bakr, B. Potentionl anticancer agents (XL), synthesis of the B-anomer ef 9-(D-arabinofuranosyl) adinene. *J. A. Chem. Soc.*, 82, 4585 (1960).

Delia, T., Scovill, J., Munslow, W. and Burchalter. 1B-D-Arabinofuranosyl cytosine and its derivatives and their biological activity. *J. Med. Chem.*, 19, 344 (1976).

Ebeid, M. Y., Kamel, M. M., Nofal, Z. M., Gadalla, K. Z. and Abdou, W. A. M. Sythesis of some new-p-cinnamoylamino pyrimidines and other related products of possible Anti-Schistosomal activity. *Egypt. J. Pharm. Sci.*, 32, 381-387 (1991).

Essawy, S. and Wasfy, A. Convenient synthesis of heterocyclic compounds Bearing a succinimido moity. *Egypt. J. Chem.*, 37, 283-293 (1994).

Fathalla, O. A. Synthesis of some 1,3-dimethyluracil-5-sulphonamide-p-derivatives with expected biological activity. Bulleten of Faculty of Science, Al-Azhar University, 3, No2 (Dec) 713-726 (1992).

Fathalla, O. A. Synthesis of New Pyrazolo [1,5-a] Pyrimidine Derivatives Using 5-Aminouracil and Ketene Dithio Acital With expected Biological Activity. *Arch. Pharm. Res.*, 22, 571- 574 (1999).

Fathalla, O. A., Gad, H. S. M. and Maghraby, A. S. Synthesis of some new uracil-5-sulphonamide-p-phenyl derivatives and their effect on *biomphalaria alexandrina* snail's nucleoproteins. *Arch. Pharm. Res.*, 23, 128-138 (2000).

Giner Sorolla, Alfredo and Mediek. L. Synthesis and properties of 5-mercapto methyluracil and related derivatives. *J. Med. Chem.*, 9, 79 (1966).

Hamers, R. and Hamers, C. Synthesis by E-coli of a B-galadosidase- like protein under the influnce of thiouracil. *Biochem. et Biophys. Acta* 33, 269-271 (1956).

Lang, P. Antimetabolites of Nucliec acid metabolism, New York (1975).

Mamesi, E. A. and Marciane, A. Action of thiouracil on the development of Lactobacillus species. *Boll. Soc. Ital. Biol. sper.*, 37, 228-231 (1961).

Maniates, T., Fritsch, E. F. and J. Sambrook CSH. Molecular cloning, Alaboratory Manual, 55-75 (1989).

Moravek, J., Parkanyi, C. and Skoda, J. Antimicrobial effect of some pyrimidine analoges and related compounds. *J. Gut*, 3154-3162 (1980).

Nakamura, M. and Jonsson, S. The effect of antimetabolites on the growth of Entamoebahistolyica. *Archives of Biochemistry and Biophysics*, 66, 183-189 (1957).

Sarkar, B. R. and Pathak, B. Synthesis of 4,4'-bithiazoles and 4-(2-thia-zolyl)aminoquinolines and their antiamobic activity. *J. Ind. Chem. Soc.*, LXI, 151-153 (1984).

Wyrzykiewicz-E, Bartkowiak, G. and Kedzia, B. Synthesis of anti-microbial properties of S-Substituted derivatives of 2-thiouracil. Farmaco, Poland., 48 (Jul), 979-988 (1993).