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Research Article

Effect of new synthesized compounds of 2-Thiouracil Sulfonamide Derivatives against colon and liver carcinoma cells "In Vitro Study"

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ABSTRACT

Many studies have been focusedon 2-Thiouracil derivatives as an anti-cancer therapy. The target compounds were prepared to be tested on colon and liver carcinoma cells and compared them with 5-FU. The newly synthesized compounds were showed variable effectiveness against colon cancer; however, the most active compounds were carbothioamides7a and 7c which showed high activity against both types of cell lines. Moreover, the 4a-c, 5a-c, and 6a-c compounds were showed ineffectiveness against liver cancer while other compounds were showed cytotoxic activity more than 5-FU especially 7a, 7c, and 3a, we are recommended that need to study the toxicity effect of these effective compounds and tested them in vivo.

Keywords: synthesized compounds, Thiouracil Sulfonamide, colon, liver carcinoma cells

INTRODUCTION

Colon cancer is one of the most dangerous diseases that caused death worldwide and about more than 250,000 patients have colon cancer [1]. The oldest drug is 5-FU was used as cream or solution for a different type of cancer such as colon, liver, pancreas, and neck due to it have active Pyrimidine moiety [2]. 5-FU resistance remains a majorproblemto use it in the clinical field, therefore many researcher modify the structure of 5-FU to prevent the resistance of drug by cancer cell [3]. From 1957 to 2011, different modifications occurred on thiouracil moiety to produce different compounds that exhibit anticancer activity via inhibiting DNA synthesis [4-7]. Many studies have been reported thiouracil has anticancer [8], antithyroid [9], and antimicrobial (10). Base on these studies, we synthesis anovel thiouracil derivatives to tested it on colonand liver carcinoma cells and compared it with 5-FU as a stander compound.

MATERIAL AND METHODS

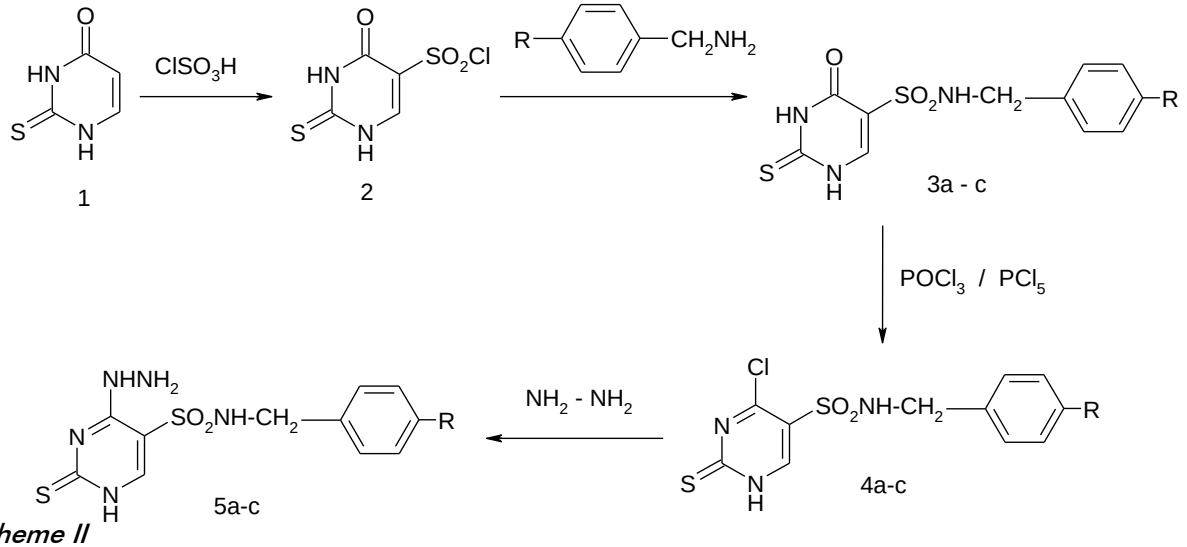
All materials, cells, dyes, and procedures that have been used in this study were prescribed previously [11]. Briefly, Stock cultureswere grown in special media and the cells were plated in microtiter plates at one-two million cells per well. The cells were stained by sulforhodamine B stain, fixed with TCA, and incubated for one hour at 4°C and used tap water to removeTCA. The test compounds were added at different concentrations to the cells, incubated fortwo days at room temperature, fixed, washed, andstained with SRB stain, washed with acetic acid to remove the excess stain, then usedELISA reader to measure the color intensity. Finally, the plot was drawn as surviving against concentration to calculate the IC50.

EXPERIMENTAL

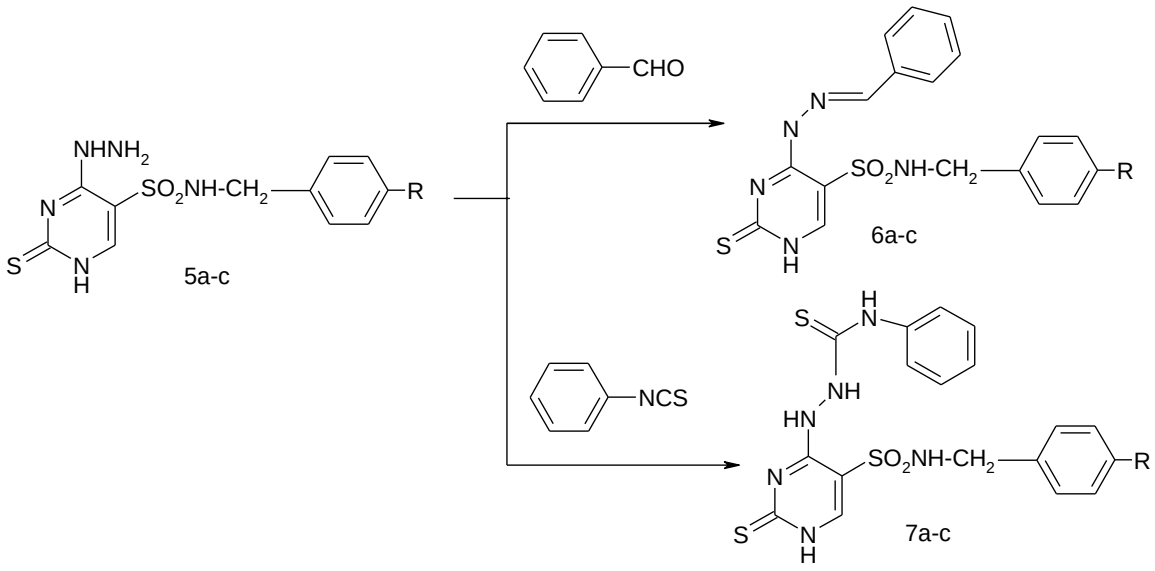
The compounds have been synthesized as prescribed in the literature [11]. Briefly, 2-Thiouracil

was treated with chlorosulfonic acid at 120°C to produce 2-thiouracil-5-sulfonyl chloride. Chlorosulfonation was suppressed when temperature lowered to 30°C, the mixture was poured by using ice and acetic acid. The sulfonyl chloride was reacted withp-fluoro, chloro,or bromobenzyl amine respectively in the presence of pyridine. The final products were treated with POCl3/PCl5 to yielding fluoro Pyrimidine 4a-c. the new compounds (4a-c) were Hydrazinolysed to yield 5a-c, the later when condensed with benzaldehyde, they gave Schiff's bases 6a-c. Moreover, when reacted with phenyl isothiocyanate they yielded 7a-c derivatives.

Scheme I



Scheme II



Statistical analysis

We used mean ±SEM to express the data and One-way ANOVA followed by Tukey's post hoc. We also used $P < 0.05$ to find the difference in IC50 between different compounds. The analysis was done by using the SPSS software update version and the graphs were drawn by GraphPad Prism software v8.0.2.

RESULTS

HT-29 colon carcinoma cells

We found that the newly synthesized compounds have to vary the cytotoxic effect (IC50). There is an insignificant difference ($p>0.05$) between 5-FU, 3a, and 3c (0.59 ± 0.03, 0.59 ± 0.03, and 0.82 ± 0.09 respectively) and they have minimum IC50 as compared with others compounds.There is an insignificant difference ($p>0.05$) between 5b and 7b and both have lowered IC50 as compared with 5a, 5c, 3a-c, 4a-c, and 6a-c. The compounds 6a-6c has maximum IC50 as compared with other new synthesis compounds, see table (1) and figure (1)

Table 1: cytotoxic activity of new synthesized compounds and 5-FU against HT-29 colon carcinoma

Compounds	Mean ± Std. Error	Std. Deviation	95% Confidence Interval for Mean	
			Lower Bound	Upper Bound
3a	2.91 ± 0.01	0.02	2.71	3.10
3b	4.02 ± 0.03	0.05	3.57	4.46
3c	3.45 ± 0.05	0.07	2.81	4.09
4a	4.63 ± 0.08	0.11	3.67	5.58
4b	4.92 ± 0.04	0.05	4.47	5.36
4c	4.60 ± 0.04	0.06	4.02	5.17
5a	4.22 ± 0.03	0.04	3.84	4.60
5b	1.88 ± 0.02	0.03	1.63	2.13
5c	2.39 ± 0.01	0.02	2.19	2.58
6a	5.52 ± 0.03	0.05	5.07	5.96
6b	5.11 ± 0.04	0.06	4.60	5.62
6c	5.44 ± 0.03	0.05	4.99	5.88
7a	0.59 ± 0.03	0.04	0.21	0.97
7b	2.47 ± 0.02	0.03	2.22	2.72
7c	0.82 ± 0.09	0.12	-0.27	1.90
5FU	0.59 ± 0.03	0.04	0.27	0.90

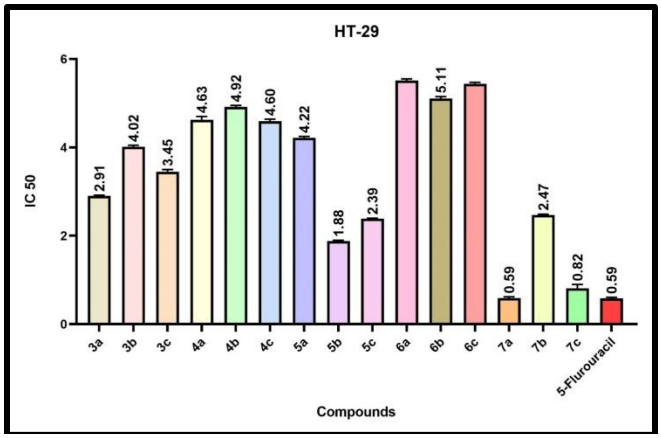


Fig. 1: Cytotoxic activity (IC50) of new synthesized compounds and 5-FU against HT-29 colon carcinoma

HEPG-2 liver carcinoma cells

We found that the compounds 4a-4c, 5a-c, and 6a-c wereineffective against HEPG-2 liver carcinoma cells.All other compounds have lowered IC 50 than 5-FU. There is an insignificant difference ($p>0.05$) between 3a, and 7a while 7c has minimum IC50 as compared with other effective compounds, see table (2) and figure (2)

Compounds	Mean ± Std. Error	Std. Deviation	95% Confidence Interval for Mean	
			Lower Bound	Upper Bound
3a	2.08 ± 0.03	0.04	1.76	2.39
3b	3.61 ± 0.04	0.06	3.03	4.18
3c	3.94 ± 0.06	0.08	3.24	4.63
4a	0.00 ± 0.00	0.00	0.00	0.00
4b	0.00 ± 0.00	0.00	0.00	0.00
4c	0.00 ± 0.00	0.00	0.00	0.00
5a	0.00 ± 0.00	0.00	0.00	0.00
5b	0.00 ± 0.00	0.00	0.00	0.00
5c	0.00 ± 0.00	0.00	0.00	0.00
6a	0.00 ± 0.00	0.00	0.00	0.00
6b	0.00 ± 0.00	0.00	0.00	0.00
6c	0.00 ± 0.00	0.00	0.00	0.00
7a	2.08 ± 0.02	0.03	1.83	2.33
7b	2.97 ± 0.08	0.11	1.95	3.99
7c	1.31 ± 0.03	0.04	0.99	1.62
5FU	5.25 ± 0.25	0.35	2.07	8.43

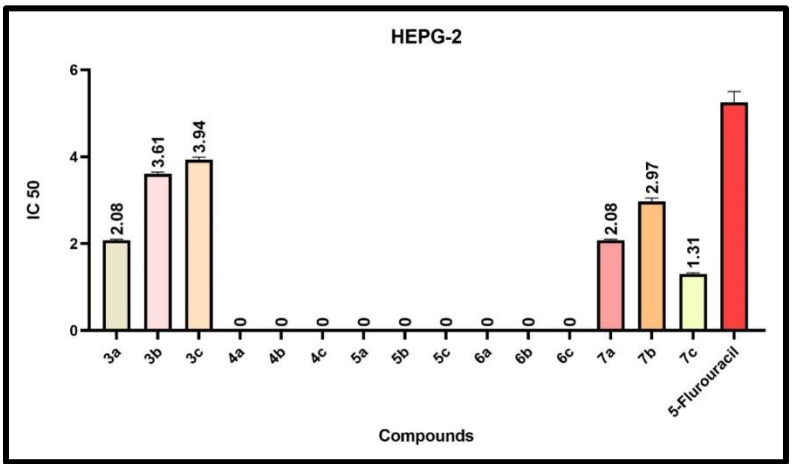


Fig. 2: Cytotoxic activity (IC50) of new synthesized compounds and 5-FU against HEPG-2liver carcinoma

DISCUSSION

Inhibition of cancer cell replication is the most effective mechanism to kill it through targeting their DNA synthesis or repair by using an analog to their basic units, purines, and pyrimidines, to prove an important anticancer drug (2), in our experiment, we synthesis an analog to pyrimidine derivatives to tested them on colon and liver carcinoma cells. Our results were shown that compounds 7a and 7c exhibited the same biological effect against colon carcinoma cells and more effective against liver carcinoma cells than 5-FU. colon carcinoma cell, the compounds 3a-c, 4a-c, 5a, and 6a-c exhibit higher IC50 when tested against colon carcinoma cell that's indicated chlorination at the 4th position may decrease the cytotoxic activity, so they are less effective against this type of cancer, while 5b, 5c, and 7b exhibit moderate activity as compare with 5-FU. liver carcinoma cell, the compound 4a-c, 5a-c, and 6a-c show ineffective against this type of cancer cell while the other compounds exhibit more cytotoxic active than 5-FU. Among them, 7c showedthe lowest IC50 while 7a and 3a exhibit the same cytotoxic activity.

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