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Research Article

SYNTHESIS AND PRELIMINARY ANTICANCER STUDY OF 5-FLUOROURACIL-PHTHALIMIDE CONJUGATE UTILIZING MOLECULAR HYBRIDIZATION APPROACH

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ABSTRACT

Cancer is still the most challenging disease in the entire world. Molecular hybridization is very interesting approach in design of drug and development depends on the combination of pharmacophoric moieties of two pharmacologically active compounds results in a new hybrid compound with better affinity and efficacy, when compared to the parent drugs. The aim of the present study is to synthesize new 5-fluorouracil derivatives as probable more active anticancer agents than the parent drug. 5-fluoro-4-oxo-1,4-dihydropyrimidin-2-yl2-(1,3-dioxoisoindolin-2-ylamino) acetate [IV] and 2-(2-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-oxoethylamino) isoindoline-1,3-dione [V] have been synthesized utilizing hybridization approach from 5-fluorouracil and phthalimide through amino acetate or 2-oxoethylamino linkers. The structures of the newly synthesized compounds and their intermediates were characterized by FT-IR,^{13}C-NMR ESI-MS spectral analysis. A preliminary cytotoxicity study that evaluated by crystal violet assay using a target breast cancer cell, murine mammary adenocarcinoma cell line indicates that the compounds have considerable anticancer activity relative to the lead one.

Keywords: 5-Fluorouracil, Phthalimide, Molecular hybridization

INTRODUCTION

The molecular hybridization (MH) is a strategy of rational design of new ligands or prototypes based on the recognition of pharmacophoric sub-unities in the molecular structure of two or more known bioactive derivatives which, through the adequate fusion of these sub-unities, lead to the design of new hybrid architectures that maintain pre-selected characteristics of the original templates[1]. The selection of the pharmacophores or chemical moieties is based upon their known bioprofiles, and it is expected that the molecular hybridization might exhibit synergistic or additive pharmacological activities. Hybrid compounds can be constructed by linking pharmacophore subunits directly or through spacer units. The simple association of two distinct active principles can also be considered a hybrid compound [2]. The hybridization process is closely related to the strategy of obtaining a mutual prodrug, with the main difference being that the prodrug action is dependent on it's in vivo cleavage while hybrid compounds can also act like it at their specific receptors or targets[2]. Cancer is a complex disease; it is unlikely that a single mono functional 'targeted' drug will be effective for treating this advanced disease. Combined drugs\active group(s) that impact multiple targets simultaneously are better at controlling complex disease systems, less prone to drug resistance and are the standard of care in cancer treatment. In order to improve the efficiency of using a two-drug cocktail, one approach involves the use of the so-called hybrid drugs[3]. Several compounds were synthesized depending on the molecular hybridization approach such; mitoxantrone- alkylating agent conjugate[4], 5-fluorouracil- propafenone conjugate[5]and Curcumin and Thalidomide[6].

Thalidomide was introduced in the pharmaceutical market in 1956 by the German Pharmaceutical industry Chemie Grunenthal. A drug was withdrawn from the market due to its teratogenic effects [7]. Later several studies proved the anticancer activity of thalidomide and these activities can be attributed to its immunomodulatory action, inhibition of angiogenesis, peptidase inhibition, glucosidase inhibition, cyclooxygenase inhibition, pro-apoptotic action and T-cell co-stimulation [8-10]. Several research groups have now developed thalidomide analogues to improve the pharmacodynamic and pharmacokinetic properties, and thereby reducing the teratogenic effects. The design of new thalidomide analogues devoid of teratogenicity resulted from studies demonstrating that the teratogenic effects are due to the toxicophore glutarimide subunit[11] as shown in figure 1.

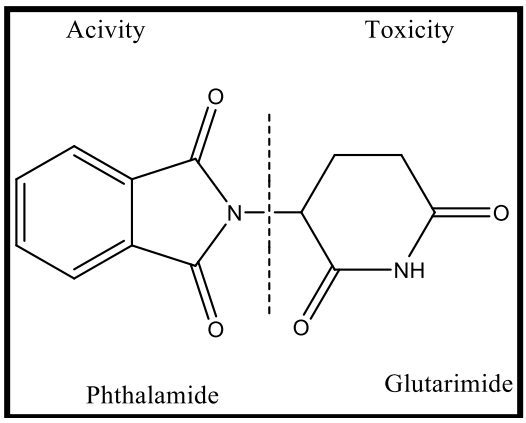


Figure 1: The structure of Phthalamide with glutarimide moiety

The conjugation of phthalimide with other pharmacologically active compounds will lead to improving the pharmacodynamics and pharmacokinetic activity such as anti-asthma activity[12], anti-*Mycobacterium tuberculosis* activity[13], NF-α inhibitor/NO donor

for the treatment of sickle cell disease symptoms[14] and anti-inflammatory activity[15]. In this study, two compounds will be synthesized depending at molecular hybridization approach by conjugation of 5-fluorouracil with phthalimide using 2-amino acetic acid as the spacer.

MATERIAL AND METHODS

All chemicals and solvents were of annular type and generally used as received from the commercial suppliers (Merck, Germany, Reidel-De Haen, Germany, Sigma-Aldrich, Germany and BDH, England) Melting points were determined by capillary method on Bamstead/ Electrothermal 9100 an Electric melting point apparatus (England), FT-IR spectra (KBr) were recorded on Shimadzu FT-R-8400S spectrophotometer, the mass spectra were obtained by using LC-MS systems and a GC-MS (USA) and ^{13}C-NMR spectra measured with Bruker LC-1800 Line NMR using tetramethylsilane as an internal standard. The chemical shifts are expressed in ppm δ scale.

Synthesis of N-aminophthalimide [I]

Phthalic anhydride 5 g (0.033 mol) was dissolved in 100 mL of ethanol. The solution was cooled (ice bath) and stirred at 5 °C. Hydrazine (2 mL 0.033 mol) was added drop wise, and the mixture was stirred for 2hs. ice water (200 ml) was added and the product was filtered, and crystallized from ethanol.
Percent yield (85%), melting point 199-201° C,IR((cm^{-1}): 3462 and 3330 (N-H) of primary amine, 1748 and 1690 (C=O) of cyclic imide, ^{13}C: 128.51-131.41 (Aromatic peaks), 166.83 2(C=O) and ESI-MS for $C_8H_6N_2O_2$ $[M+1]^+$ calculated 163.15; found 163.86.

Synthesis of 2-(1,3-dioxoisoindolin-2-ylamino)acetic acid [II]

A mixture of N- aminophthalimide (compound I) 4.2 g (0.026 mol) , Ethyl bromoacetate 6.52 ml (0.026 mol) and triethylamine 3.6 ml(0.26 mol) in ethanol was refluxed for 3 hr .The solution volume was reduced by vacuum and cooled to 18 °C . Then NaOH (2N, 13 ml, 0.026 mole) was added drop wise, with continuous stirring over a period of 30 mints at 18°C stirring was continued at 18°C for additional 3 hr. The reaction mixture was acidified with HCl (2N, 13 ml, 0.026 mmol), then an excess of cold water was added. The precipitated compound was filtered, dried and re-crystallized from ethanol to give the compound II. Percent yield (79%), melting point 197-198° C, IR((cm^{-1}): 3280 (N-H) of secondary amine, 2500-3100 (OH) of carboxylic acid, 1748 and 1690 (C=O) of cyclic imide, 1705 (C=O) of carboxylic acid, ^{13}C: 43.33 (CH_2) , 128.51-132.77(Aromatic peaks), 167.04 2(C=O) of cyclic imide ,173.52 (C=O) carboxylic acid and the ESI-MS for $C_{10}H_6N_2O_4$ $[M+1]^+$ calculated 220.18; found 221.45.

Synthesis of 2-(1,3-dioxoisoindolin-2-ylamino)acetyl chloride [III]

To a cooled solution of compound [II] 5 g, (0.03 mole) in tetrahydrofuran, thionyl chloride 6 ml was added. The solution was stirred for one hr. at room temperature and then refluxed for one h the excess thionyl chloride was removed in a vacuum, and the resulting solid was used without further purification. Analytical samples were recrystallized from petroleum ether (60-80°C) and dichloromethane CH_2Cl_2. Percent yield 68% melting point 82-83 °C, IR((cm^{-1}): 3250 (N-H) of secondary amine, 1780 (C=O) of acyl chloride, 1730 and 1680 (C=O) of cyclic imide, ^{13}C: 56.49 (CH_2), 123.68-130.06 (Aromatic peaks), 167.35 2(C=O) of cyclic imide, 182.51(C=O) of acyl chloride and the ESI-MS for $C_{10}H_7ClN_2O_3$ $[M+2]^+$ calculated 238.63; found 240.14.

Synthesis of 5-fluoro-4-oxo-1,4-dihydropyrimidin-2-yl 2-(1,3-dioxoisoindolin-2-ylamino)acetate [IV]

Compound [III] (0.03 mole) in 5 ml tetrahydrofuran was added drop wise to the cold solution (0°C) of 5-fluorouracil 3.9 g (0.03 mol) in 5 ml dimethyl formamide with continuous stirring overnight at room temperature. Then cold water was added, and the resulted precipitate was filtered and recrystallized from ethanol give compound [IV]. Percent yield (55%), melting point 270-271 °C, IR((cm^{-1}): 3260 (N-H) of the secondary amine, 3180 (N-H) of the secondary amide, 1730 and 1680 (C=O) of cyclic imide,1700 (C=O) of secondary amide. ^{13}C: 43.32 (CH_2), 125.97-131.90 (Aromatic peaks),121.31 (C=C),124.76(C-F), 158.57, 2(C=O), 167.40, 3(C=O) and the ESI-MS for $C_{14}H_9FN_4O_5$ $[M+1]^+$ calculated 332.24; found 333.15.

Synthesis of 2-(2-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-oxoethylamino)isoindoline-1,3-dione [V]

Compound [III] (0.03 mole) in 5 ml tetrahydrofuran was added drop wise to the cold solution (0°C) of the sodium salt of 5-fluorouracil 4.6 g (0.03 mole) in 5 ml dimethyl formamide with continuous stirring overnight at room temperature. Then cold water was added, and the resulted precipitate was filtered and recrystallized from ethanol give compound [V]. Percent yield (61%), melting point 254-256°C, IR((cm^{-1}): 3230 (N-H) of secondary amine, 3160 (N-H) of secondary amide, 1750 and 1680 (C=O) of cyclic imide,1730 (C=O)of ester, 1705 (C=O)of secondary amide, ^{13}C: 43.33 (CH_2), 143.60 (O-C=N), 127.67--132.77 (Aromatic peaks),121.31 (C=C),136.06(C-F), 167.00 2(C=O), 162.93, (C=O), 173.52 (C=O), and the ESI-MS for $C_{14}H_9FN_4O_5$ $[M+2]^+$ calculated 332.06; found 334.17.

Cytotoxic Activity Study

The preliminary in vitro cytotoxicity study was done at the Iraqi Centre for Cancer and Medical Genetic Research (ICCMGR) using two types of tumor cell lines: primary tumor of a 70 years old Iraqi woman with a histological diagnosis of infiltrating ductal carcinoma (breast cancer cell line AMJ13) , murine mammary adenocarcinoma cell line (AMN3)[16] and one type of normal cell line: rat embryo fibroblast cell line (Ref).[17] They were maintained in growth medium supplemented with 10% fetal calf serum and seeded on micro-titration (96- well plates at a concentration of 1×104 cells/well) and various concentrations of tested compounds (IV and V) were added from (3.125 to 100 µg/ml) prepared by serial two-fold dilutions using maintenance media from stock solution of test sample in triplicate form of each concentration.

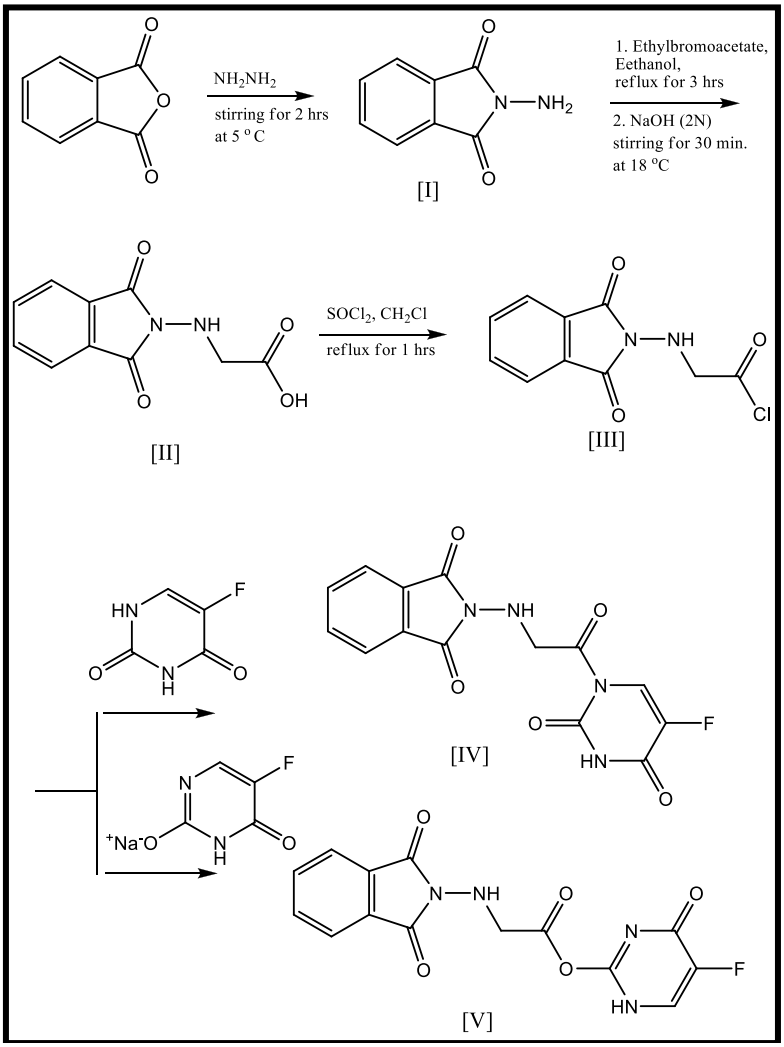
The negative control wells contained only the cells with culture media; then the 96-well cell culture plate incubated at 37°C in an incubator supplemented with 5% CO2 for two different times (48, 72) h. [18] The cytotoxic activity of compounds was evaluated by crystal violet assay, the optical density of each well was measured by using ELISA (Enzyme Linked Immuno Sorbent Assay) reader at a transmitting wave length on 492 nm. The inhibition rate of cell growth (the percentage of cytotoxicity) was calculated as (A-B)/A ×100, where A is the mean optical density of untreated wells (control), and B is the optical density of treated wells. [19]

Data were analyzed by 2-way analysis of variance with ANOVA. The level of significance ($p<0.05$) was used for analysis of the results.

RESULT AND DISCUSSION

Synthesis results

The reaction of phthalic anhydride with hydrazine hydrate resulted in the formation of *N,*aminophthalimide compound [I][20], which was reacted with ethyl bromoacetate then treated with sodium hydroxide in cold condition to form *N,*aminophthalimido acetic acid compound [II][21,22]. Compounds [II] was reacted with thionyl chloride in dry tetrahydrofuran and refluxed for 1 hour to form compound [III][23]) that was reacted with 5-fluorouracil, or sodium salt of 5-fluorouracil leads to the formation of the targeting compounds (IV and V) respectively[23,24]. Structures of these compounds were confirmed, using infrared spectroscopy (IR), ^{13}C-NMR spectroscopy, ESI-MS, and some physicochemical properties, which are listed with each one of these compounds (I-V), and their synthetic procedures were described in schemes (1).



Scheme 1: Synthesis of compounds (IV and V)

Table 1: The effects of different concentrations of compound IV on the growth of AMJ13, AMN3, and Ref cell lines

	48 hours			72 hours		
Conc. µg/ml	AMJ13	AMN3	Ref	AMJ13	AMN3	Ref
3.125	0.5 (1.3)	5.1 (1.4)	3.6(3.6)	3.3 (2.1)	5.4(2.1)	-2.5 (5.1)
6.25	1.7 (0.9)	6.3 (0.9)	6.1(5.3)	0.9 (1.9)	16.3(2.2)	2.7(2.7)
12.5	10.5(2.4)	13.2(2.7)	7.0(3.5)	1.6 (0.6)	21.6(2.6)	-0.3 (1.1)
25	52.8(8.7)	49.8(6.3)	7.0(2.6)	40.1(1.2)	26.1(1.8)	5.2(2.6)
50	55.9(0.6)	53.9(1.8)	0.0(5.8)	50.1(1.0)	30.9(3.1)	-1.6 (5.5)
100	61.7(0.9)	80.3(1.6)	6.4(3.2)	51.2(4.8)	34.4(3.5)	-2.5 (3.2)
Data presented using mean (standard error mean)						

Note: Control= 0% inhibition. Positive results of the % growth inhibition indicate anti-proliferation. Negative results of the % growth inhibition indicate proliferation.

Table 2: The Post-hoc test of each pair of concentrations of compound IV (columns comparison) showing their p values

	48 hours			72 hours		
Conc. µg/ml	AMJ13	AMN3	Ref	AMJ13	AMN3	Ref
3.125 vs. 6.25	NS	NS	NS	NS	NS	NS
6.25 vs. 12.5	NS	NS	NS	NS	NS	NS
12.5 vs. 25	<0.0001	<0.0001	NS	NS	<0.0001	NS
25 vs. 50	NS	NS	NS	NS	NS	NS
50 vs. 100	NS	0.0002	NS	NS	NS	NS
NS: non-significant						

Table 3: The Post-hoc test of each pair of tissue line at a fixed concentration of compound IV (row comparison) showing their p values

	48 hours			72 hours		
Conc. µg/ml	AMJ13 vs. Ref	AMN3 vs. Ref	AMJ13 vs.AMN3	AMJ13 vs. Ref	AMN3 vs. Ref	AMJ13 vs.AMN3
3.125	NS	NS	NS	NS	NS	NS
6.25	NS	NS	NS	NS	NS	NS
12.5	NS	NS	NS	NS	0.004	0.0087
25	<0.0001	<0.0001	NS	<0.0001	0.0061	NS
50	<0.0001	<0.0001	NS	<0.0001	<0.0001	0.0117
100	<0.0001	<0.0001	0.0025	<0.0001	<0.0001	0.0311

Table 4: The effects of different concentrations of compound V on growth of AMJ13, AMN3, and Ref cell lines

	48 hours			72 hours		
Conc. µg/ml	AMJ13	AMN3	Ref	AMJ13	AMN3	Ref
3.125	21.2 (5.1)	4.3 (5.3)	-5.1 (9.2)	30.1(5.5)	3.8 (1.2)	0.0 (4.8)
6.25	17.6 (2.7)	7.4 (2.8)	0.0 (8.9)	27.2 (4.1)	3.6 (1.9)	0.0 (4.8)
12.5	24.1(7.7)	36.7 (5.1)	2.5 (2.6)	22.8 (0.6)	28.3 (4.6)	-2.7 (2.8)
25	45.7 (2.0)	66.8 (2.2)	9.1 (7.1)	45.8 (3.1)	67.7 (3.3)	0.0 (4.8)
50	55.5 (1.5)	62.7 (3.5)	2.7 (2.6)	52.6 (1.0)	65.4 (1.6)	2.7 (2.8)
100	62.1 (3.1)	80.6 (3.7)	10.4(6.8)	63.4 (1.9)	79.3 (3.5)	8.1 (4.8)
Data presented using mean (standard error mean)						

Table 5: The Post-hoc test of each pair of concentrations of compound V (columns comparison) showing their p values

	48 hours			72 hours		
Conc. µg/ml	AMJ13	AMN3	Ref	AMJ13	AMN3	Ref
3.125 vs. 6.25	NS	NS	NS	NS	NS	NS
6.25 vs. 12.5	NS	0.0036	NS	NS	0.0003	NS
12.5 vs. 25	NS	0.0026	NS	0.0006	<0.0001	NS
25 vs. 50	NS	NS	NS	NS	NS	NS
50 vs. 100	NS	NS	NS	NS	NS	NS
NS: non-significant						

Table 6: The Post-hoc test of each pair of tissue line at fixed concentration for compound V (row comparison) showing their p values

	48 hours			72 hours		
Conc. µg/ml	AMJ13 vs. Ref	AMN3 vs. Ref	AMJ13 vs.AMN3	AMJ13 vs. Ref	AMN3 vs. Ref	AMJ13 vs.AMN3
3.125	0.0027	NS	NS	<0.0001	NS	<0.0001
6.25	NS	NS	NS	<0.0001	NS	<0.0001
12.5	0.0152	0.0001	NS	<0.0001	<0.0001	NS
25	<0.0001	<0.0001	0.0172	<0.0001	<0.0001	0.0003
50	<0.0001	<0.0001	NS	<0.0001	<0.0001	0.0377
100	<0.0001	<0.0001	0.0401	<0.0001	<0.0001	0.0092

Cytotoxicity study results

The cytotoxic activities (cell viability assay) of compounds (IV and V) were evaluated by Crystal violet assay.27 A set of six concentrations (3.125, 6.25, 12.5, 25, 50 & 100 µg/ml) was prepared for each product. Two cell lines were studied (AMJ-13 passage no. 50, AMN-3 passage no.117, Ref cell lines passage no. 120) at two times of exposure (48, 72 hours). Data were analyzed by 2-way analysis of variance with ANOVA. The level of significance ($p<0.05$) was used for analysis of the results. The results indicate that significant inhibitory effects appeared in the cancer cell lines (AMJ13 and AMN3) at different concentrations as showed in tables (1 to 6).

CONCLUSION

Two new derivatives of 5-fluorouracil hybridized with phthalimide were synthesized and evaluated for their anticancer activities. The synthesized compounds were characterized and identified by I.R spectra, ^{13}C-NMR study and ESI-MS it was found that all the results showed good agreements with the proposed chemical structures of the synthesized compounds. A preliminary cytotoxicity studies that evaluated by crystal violet assay indicates that the tested compounds have considerable anticancer activity against two cancer cell lines at different concentrations with no significant inhibitory effect of tested compounds on normal cell line.

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