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Synthesis and anticancer activity evaluation of Novel 6 mercaptopurine derivatives.

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Abstract

A series of five (6- mercaptopurine derivatives) have been synthesized as disulfide, Schiff base, Oxadiazole and amide products and the activity as anticancer was evaluated against three types of cancer lines. The pilot studies indicated that compound 1, 2, 3, 4 and 5 were the active compounds, but only compound (1) reviewed in detail .The reaction progress and products purity were checked by thin layer chromatography. The target chemical structures of compounds and intermediates were proved by their physicochemical properties as melting points, infrared spectroscopy, and elemental microanalysis (CHNS) and proton nuclear magnetic resonance (H1NMR)

Keywords: cancer, 6 -mercaptopurine, disulfide, penicillamine

1. Introduction

Cancer is a complex genetic disease that is caused primarily by environmental factors and genetic factor (1). Anticancer or chemotherapy drugs can denature cancer cells by arresting their growth. Though anticancer drugs affect dividing cancer cells, normal cells are also affected in the course of the event. (2, 3)
Today, more than 100 different drugs have been used for chemotherapy, either alone or in combination with other treatments. (3,4) Chemotherapy of cancer is associated with various adverse effects bone marrow depression, alopecia, drug induced caner, etc. and is often associated with cytotoxicity, gene toxicity to normal cells together with the development of resistance , so its important for the search of Newer and safer anticancer gents.(5)

Purine analogs are widely used against various diseases, particularly cancer. The clinical application of 6- mercaptopurine and Thioguanine in cancer treatment and the development of potent purine based CDK inhibitors, such as Purvalanols, Olomoucine, and Roscovitine, together with other findings based on the purine scaffold, have largely inspired and directed parallel developments in the chemistry and anti-tumor research of related heterocyclic analogs (6), (7),(8) ,(9).

Azomethine group (C=N) containing compounds typically known as Schiff bases have been synthesized by condensation of primary amines with active carbonyl form. Schiff bases from a significant class of compounds in medicinal and pharmaceutical chemistry with several biological applications that induce anticancer activity (10-21).

2. Experimental work

2.1 chemical and solvent

Chemicals used in this work are supplied from HIMEDIA, Fluka and SIGMA companies. All the solvents were of annular grade and used without further purification. Cells lines are supplied from Iraqi center for cancer and genetic research.

2.2 instruments

Melting points were determined by capillary tube method on Banested (UK). The FTIR spectra were recorded on FTIR spectrophotometer, Shimadzu (Japan) at the colleges of pharmacy and Science (Baghdad University).The CHN microanalysis Euro A (Elemental Analyzer), (Italy) and H1NMR performed in the center laboratory of Esfahan University. Thin layer chromatography (TLC) was run on silica gel GF254 (60), Merck (Germany) to check both purity of compounds and their reactions progress. The anticancer study of the synthesized final products was done in Iraqi center for cancer and genetic research

2.3 synthesis

2.3.1 Synthesis of compound1 (22)

This is a sulfhydryl-disulfide exchange reaction performed to produce D-Penicillamine linked to 6 -mercaptopurine

An aqueous solution (20 ml) of D-Penicillamine (10 mmol) and potassium hydroxide (20mmo) was adjusted to pH 7.5.then added to a suspension of 1A (10 mmol) in potassium chloride solution (2M, 10ml) and the

mixture was adjusted to pH 7.5.The mixture was vigorously stirred for 24 hrs. At room temperature. An off white precipitate was formed, collected by filtration the precipitated product was formed, collected and washed with distilled water, crystallized with hot ethanol, dried in an oven at 70 °C. The percent yield, melting point, physical appearance and Rf values are listed in table (A). The FT-IR bands are listed in table (B); CHNS value listed in table (C).HNMR data and spectrum are listed in table D

2.3.2 Synthesis of compound 1A (22)

Hydrogen peroxide (7.5mmol) was added drop wise to a suspension of 6- mercaptopurine (7.5mmol) in absolute ethanol (20 ml) with continuous stirring for 4 hr. at room temperature. A yellow precipitate was formed, collected by filtration, washed excessively with distilled water and crystallized from hot ethanol and the product was dried in an oven at 70 ºC. The percent yield, melting point, physical appearance and R_f values are listed in table (A). The FT-IR is shown in table (B).

2.3.3 Synthesis of compound 2(15)

Compound 2A (10mmol) was dissolved in ethanol (50ml) containing 3-4 drops of acetic acid and refluxed with 4-Dimethylamino-benzaldehyde (10mmol) for 5 h. Evaporate the solvent under vacuum , washed the product thoroughly with distilled water, dried in an oven at 70 °C ,crystallized from ethanol. This afforded compound **2**A, which was dried in an oven at 70°C.The percent yield, melting point, physical appearance and R_f values are listed in table (A). The FT-IR bands are listed in table (B), CHNS value is listed in table (C). HNMR spectrum is listed in table D.

2.3.4 Synthesis of compound 2A (24)

To 6 Mercaptopurine (0.01 mol) dissolved in ethanol, hydrazine hydrate (0.02mol) was added drop wise with stirring and the mixture was then refluxed for (6 h), until disappearance of the H2S gas that was checked by lead acetate paper then the excess solvent was distilled off, the resulting solid was recrystallized from ethanol to give the target product.

The percent yield, melting point, physical appearance and R_f values are listed on table (A). The FT-IR is shown in table (B).

2.3.5 Synthesis of compound 3(25)

Compound 3 B (0.005 mole) was dissolved in potassium hydroxide solution (0.005 mole) to this solution carbon disulfide (0.1 mole) was added with shaking, then refluxed for (40) hrs. (According to lead acetate paper) The solvent was evaporated under reduced pressure and the residue then poured into cold water and acidified with dilute hydrochloride acid. The precipitate was filtered and recrystallized from ethanol.

The percent yield, melting point, physical appearance and R_f values are listed on table (A). The FT-IR bands are listed in in table (B), CHNS value is listed in in table (C). HNMR spectrum is listed in table D

2.3.6 Synthesis of compound 3B (9)

A mixture of compound 3A (0.08 mole) and hydrazine hydrate 99% (0.4 mole) in ethanol (70 ml) was refluxed for 4 hrs. The mixture was concentrated and cooled. The resulted precipitate was filtered and recrystallized from Methanol: Water (50:50). The percent yield, melting point, physical appearance and R_f values are listed on table (A). The FT-IR is shown in table (B).

2.3.7 Synthesis of compound 3A (9)

6- Mercapto Purine (0.05 mole) was dissolved in potassium hydroxide solution (0.05 mole) to this solution ethyl bromo acetate (0.05 mole) was added drop wise, and refluxed for (9) hrs., then excess solvent was evaporated and washed several times with water and 5% sodium bicarbonate solution. Recrystallized from ethanol. The percent yield, melting point, physical appearance and R_f values are listed on table (A). The FT-IR bands are listed in in table (B).

2.3.8 Synthesis of compound 4(15)

Compound 3B (10mmol) was dissolved in ethanol (75ml) containing 3-4 drops of acetic acid and refluxed with 1-Naphthylaldehyde (10mmol) for 6 h. Cool the mixture and precipitate was collected by filtration , washed thoroughly with distilled water, dried in an oven at 70 °C ,crystallized from n-hexane. This afforded compound 4, which was dried in an oven at 70°C. The percent yield, melting point, physical appearance and R_f values are listed on table (A). The FT-IR bands are listed in in table (B), CHNS value is listed in in table (C). HNMR spectrum is listed in table D

2.3.9 Synthesis of compound5 (22)

To a stirred solution of compound 3B (10 mmol) in (5 ml) N, Dimethyl formamide (DMF). A solution of compound 5B (5 mmol) in 8 ml DMF was added to the reaction mixture .The mixture was then cooled to (15C), DCC (10 mmol) and HOSU (10 mmol) was added with stirring, the stirrer was continued for (120 hrs.) at (0 C) and for (72 hrs.) at ambient temperature (20 C). Ethyl acetate (50 ml) was added to the reaction mixture and then filtered to get rid of the precipitated N,N-dicyclohexylurea (DCU). The filtrate was evaporated to dryness under vacuum, and the residue was re-dissolved in ethyl acetate (50 ml), the excess

DCU which was still adhesive on the residue was precipitated out and filtered. The clear filtrate was washed twice with (10 ml) HCl (0.1 N) solution, once with (10 ml) D.W, and with (10 ml) NaCO3 5% using the separator funnel. The ethyl acetate layer was dried using anhydrous magnesium sulfate, and then evaporated to dryness. The percent yield, melting point, physical appearance and R_f values are listed on table (A). The FT-IR bands are listed in in table (B), CHNS value is listed in in table (C). HNMR spectrum is listed in table D

2.3.10 Synthesis of compound5B (22)

Compound 5A (0.05 mole) was dissolved in minimum volume of mixture of dioxane / water (5:1) then sodium hydroxide (0.075) was added on period of 30 min., then stirring at room temp for 4 hr., equivalent amount of HCl was added, and as crushed ice was added, as precipitate appear, filtrated and Recrystallized from methanol. The percent yield, melting point, physical appearance and Rf values are listed on table (A). The FT-IR bands are listed in table (B).

2.3.11 Synthesis of compound5A (26)

2- Mercapto Benzothiazole (0.05 mole) was dissolved in potassium hydroxide solution (0.05 mole) to this solution ethyl bromo acetate (0.05 mole) was added drop wise and refluxed for (6) hrs., then excess solvent was evaporated and washed several times with water and 5% sodium bicarbonate solution Recrystallized from ethanol. The percent yield, melting point, physical appearance and R_f values are listed on table (A). The FT-IR bands are listed in in table (B)

2.4 Cytotoxicity against Cancer Cell Lines

Compounds from 1- 5 were tested for their cytotoxic activity by pilot study, and Compounds 1, reviewed in detail and show significance cytotoxic activity, Compounds 1 (20–1 µg/mL) was tested for its cytotoxic activity against 3 human cancer cell lines: HeLa (cervical), AMN3 (adenocarcinoma), RD (Rhabdomyosarcoma), all cell lines were maintained in RPMI medium supplemented with 10% fetal bovine serum, compound 1 was dissolved with DMF until reaching a concentration of 1 mg/mL. The final concentration of DMF in the culture medium was kept constant, below 0.1% (v/v). A compound 1 was incubated with the tested cells as separately for 24hours. The negative control received the same amount of DMF, The cell viability was determined by reduction of the yellow dye 3-(4,5-dimethyl-2-thiazol)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) to a blue formazan product as described by Mosmann (26), result is listed in table(E)

3. Results and Discussion

The present investigation involves the synthesis of new series compounds of D Penicillamine and 6-mercaptopurine moieties as shown in schemes, the pathway of synthesis of 6- mercaptopurine derivatives that have a characteristic imine and Oxadiazole, amide and disulfide moeities. Compound 1 represents mutual prodrug as disulfide derivatives.

Schiff bases were prepared by condensation of 6-mercaptopurine derivatives with suitable aldehyde using acetic acid as catalyst that will increase the nucleophilicty of the amine group, and the reaction was followed by IR and showed the appearance of a characteristic absorption bands for (C=N) and (N-H), and disappearance of the band for Primary amine group as shown in table (B).

Compounds were prepared and their chemical structures were proved by spectral and elemental analyses and H1NMR. The cytotoxicity activity of these compounds was screened against three cells lines using MTT assay method.

Compound 1 has good, broad spectrum anticancer activity against all tested cell lines. Compounds 1 obtained by sulfhydryl-disulfide exchange reaction applied on D-penicillamine to be reacted with compound 1A as an aqueous solution at pH 7.5 This reaction involves a nucleophilic attack (S_N2) of the thiolate anion of penicillamine to compound 1A disulfide as the electrophile.

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Table (A), the percent yield, melting point, physical appearance and Rf values of synthesized compounds

Compound no.	Color	Yield %	Melting point	Rf value
1	yellow powder	40	303-306	0.43
1A	Yellow powder	50	214-217	0.90
2	yellow crystal	55	255-258	0.89
2A	Golden powder	65	225-227	0.21
3	Yellow crystal	40	232-234	0.85
3B	Off white crystal	60	254-255	0.11
3A	White powder	70	119-122	0.45
4	Off white powder	48	285-187	0.95
5	Yellow powder	85	202-204	0.93
5B	White crystal	70	148-151	0.70
5A	Yellow crystal	80	74-77	0.90

Solvent system: Methanol chloroform (3:7)

Table (B) The FT IR spectral data of synthesized compounds

Compound No.	Characteristic peaks cm-1
1	* 3481 - 3435 Characteristic stretching vibration of primary amine group * 3412 Characteristic stretching vibration of secondary amine group * 3091 Characteristic peaks for unsaturated C-H stretching groups of aromatic ring * 2939, 2901 Characteristic peaks for Asymmetric and symmetric saturated C-H methyl * 1720 Characteristic peak for carbonyl stretching vibration carboxylic acid * 1656 Characteristic peak stretching vibration for imine groups
1A	*3313 Characteristic one peak for secondary amine group of purine ring. *3033 Characteristic peak for unsaturated C-H groups *1681 Characteristic peaks for imine group (purine ring).
2	*3317 Characteristic peaks for N-H stretching vibration of secondary amines(for NHN=) *3197 Characteristic peaks for N-H stretching vibration of secondary amines (Purine). *3010 Characteristic peaks for unsaturated C-H. *1674 and 1618 Characteristic peak for imine groups (imidazole ring and Schiff) *2960 and 2889 Characteristic peaks for asymmetrical and symmetrical saturated C-H
2A	*3455 and 3398 Characteristic two peaks for primary amine groups. *3249 Characteristic one peak for secondary amine groups. *1629 Characteristic peak for imine groups
3	*3429 Characteristic one peak for secondary amine groups. *3093 Characteristic peak for unsaturated C-H methyl *2966 and 2812 Characteristic peaks for asymmetrical and symmetrical saturated C-H *2565 Characteristic peak for thiol group. *1670 and 1618 Characteristic peaks for imine groups
3B	*3321 and 3288 Characteristic two peaks for primary amine groups. *3190 Characteristic one peak for secondary amine groups. *3099 Characteristic peak for unsaturated C-H group *1672 Characteristic peaks for amide groups *1616 Characteristic peaks for imine group
3A	*3288 Characteristic one peak for secondary amine groups. *3055 Characteristic peak for unsaturated C-H group. *2945 and 2794 Characteristic peaks for asymmetrical and symmetrical saturated C-H *1728 Characteristic peaks for ester groups *1662 Characteristic peaks for imine group.
4	*3188 Characteristic one peak for secondary amine groups. *3076 Characteristic peak for unsaturated C-H group. *2962 and 2818 Characteristic peaks for asymmetrical and symmetrical *saturated C-H methyl groups *1693, 16255 Characteristic peaks for imine groups. (imidazole ring and Schiff) *1595 and 1568 Characteristic peaks for aromatic ring
5	*3045 Characteristic peak for unsaturated C-H group. *2958 and 2883 Characteristic peaks for asymmetrical and symmetrical saturated C-H *1648 Characteristic peaks for amide groups *1693, 16255 Characteristic peaks for imine groups. (imidazole ring and Schiff) *1595 and 1568 Characteristic peaks for aromatic ring
5B	*3072 Characteristic peak for unsaturated C-H group. *2854 and 2789 Characteristic peaks for asymmetrical and symmetrical saturated C-H *1710 Characteristic peaks for carboxylic acid groups *1581 and 1560 Characteristic peaks for aromatic ring
5A	*3072 Characteristic peak for unsaturated C-H group. *1730 Characteristic peaks for ester groups

Table(C), CHNS micro elemental analysis of final compounds

Cpd	Molecular formula	C% calculate / found	H% calculate / found	N% calculate / found	S% calculate / found
1	**C10H13N5O2S2**	**40.12/ 40.18**	**4.38/ 4.36**	**23.39 /23.66**	**21.42/21.45**
2	**C14H15N7**	**59.77 / 59.13**	**5.37 / 5.31**	**34.85/ 35.15**	**-------**
3	**C10H8N4OS2**	**45.44/ 45.18**	**3.05/ 3.03**	**21.20/21.35**	**24.26/ 24.57**
4	**C18H14N6OS**	**59.65/59.02**	**3.89/3.81**	**23.19/23.97**	**8.85/8.71**
5	**C16H13N7O2S3**	**44.53/45.55**	**3.04/3.01**	**22.72/22.31**	**22.29/22.45**

Table (D), HNMR data for synthesized compounds, solvent / (DMSO), BRUKER400 MHZ

CPD No.	δ PPM	Groups	No. of H	Interpretation
1	13.7	-NH-Purine	1	Singlet, 1H
	8.2	Purine ring	1	Singlet, 1H
	8.4	Purine ring	1	Singlet, 1H
	3.4	NH2-CH-	1	Singlet, 1H
	2.5	NH2-	1	Singlet, 1H
	1.03	CH3-	6	Singlet, 6H
2	2.88	CH3-N	6	Singlet, 6H
	3.4	-NH-	1	Singlet, 1H
	6.74-8.5	• Aromatic • Purine • benzylidene	7	Multiplet, 7H(overlap)
	11.9	-NH- Purine	1	Singlet, 1H
3	14.5	-NH- • Purine	1	Singlet, 1H
	8.7-6.5	• Aromatic • Oxadiazole	4	Multiplet, 4H(overlap)
	4.8	-CH2-S-	2	Singlet, 2H
	3.4	SH-	1	Singlet, 1H
4	13.2	-NH-	1	Singlet, 1H
	7.5-8.5	• Aromatic-H • Purine • benzylidene	10	Multiplet, 10H(overlap)
	9.11	Purine-C=H-	1	Singlet, 1H
	3.4	-CH2-S-	2	Singlet, 2H
5	10.45	-NH-	1	Singlet, 1H
	8.45-8.65	-NH-NH-	2	Doublet , Doublet,2H
	7.3-7.9	• Aromatic-H • Purine	6	Multiplet, 6H(overlap)
	4.4 3.5	-CH2-S-Benzothiazole -CH2-S Purine	2 2	Singlet, 2H Singlet, 2H

Table E: Growth inhibition (%) of different cancer cell lines after 24 hr incubation with different concentrations of compound 1 (µg/ml)

Cell type	Growth inhibition (%)				
	1 µg	5 µg	10 µg	15 µg	20 µg
HeLa	46 ± 3.1^{a}	$49\pm4.9^{a,b}$	$52\pm4.8^{b,c}$	$57\pm3.7^{c,d}$	62 ± 4.4^{d}
RD	44 ± 2.9^{a}	$50\pm4.4^{a,b}$	$55\pm5.7^{b,c}$	$57\pm5.9^{c,d}$	63 ± 4.7^{d}
AMN3	46 ± 6.9^{a}	59 ± 4.7^{b}	$68\pm5.1^{c,d}$	$72\pm8.0^{d,e}$	77 ± 5.9^{e}

Values are expressed as mean±SD of 10 measurements; values with non-identical superscripts (a,b,c,d,e) within the same cell line are significantly different (P<0.05); Hela:, RD, AMN3

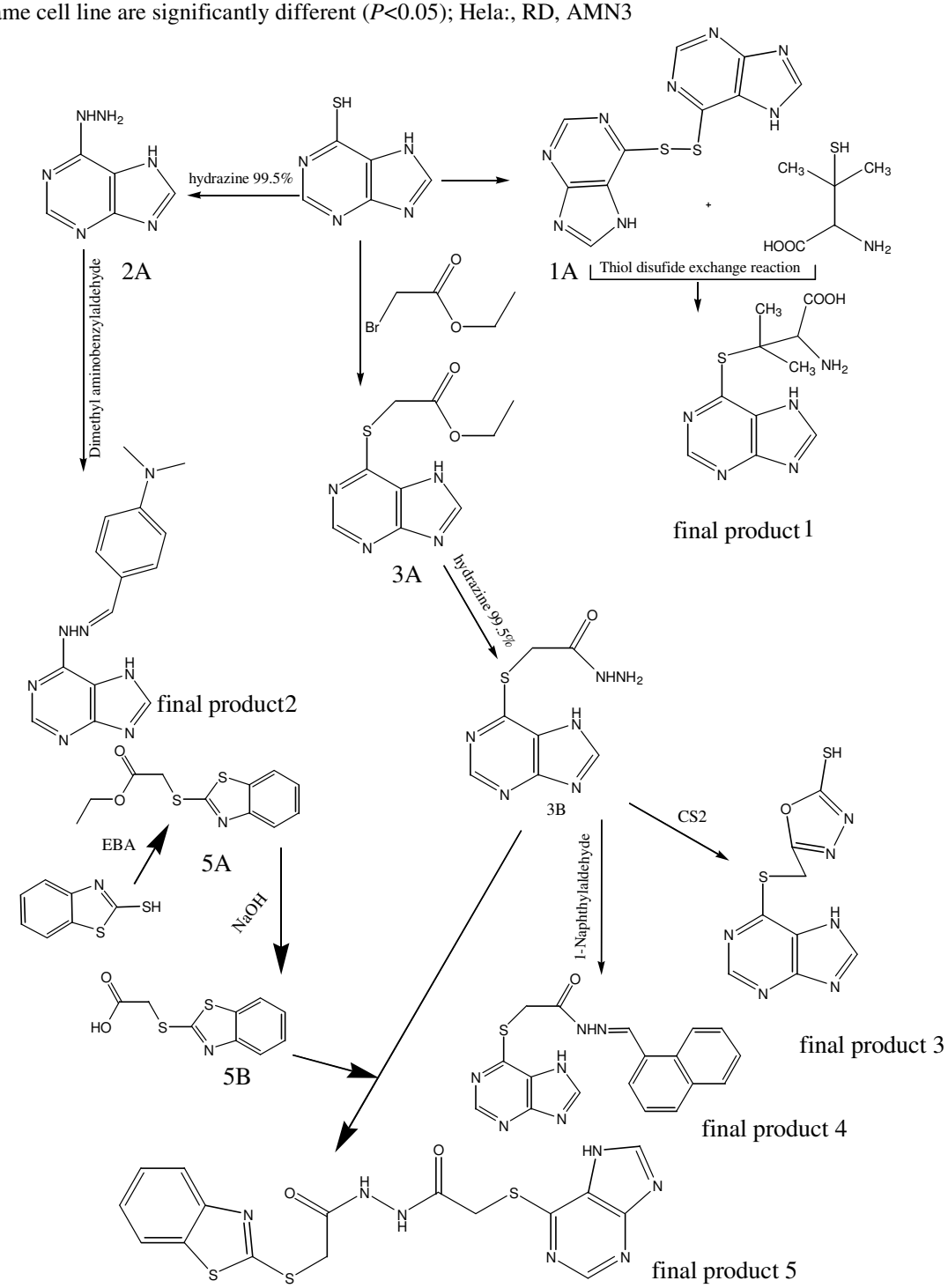

Figure 1, scheme for synthesis of targets compounds

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