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Synthesis and evaluation of some 1,2,3,4-tetra-hydro pyrimidine derivatives as antitumor agents.

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ABSTRACT
Sixteen [3, 6 (4- substituted aryl)1-(1,2 hydrazino-2-oxo-ethyl)-2oxo-1, 2, 3, 4-tetrahydropyrimidine-5-yl] propionic acid derivatives have been synthesized in a four-step reaction. In the first step benzene or substituted benzene react with glutaric anhydride in presence of aluminum trichloride (Friedel Craft reaction) to obtain 5-(substituted phenyl)-5-oxo pentanoic acid. Second step involves synthesis of [4, 6 (4-substituted aryl)-2-oxo-1, 2, 3, 4- tetra-hydro-pyrimine-5 yl propionic acid by reaction between 5-(substituted phenyl)-5-oxo pentanoic acid, urea and substituted aldehydes (Biginelli reaction).Third step involves reaction of [4, 6 (4-substituted aryl)-2-oxo-1, 2, 3, 4- tetra-hydropyrimine-5 yl propionic acid was dissolved in a solution prepared by reacting Na (0.1mol) with 200ml of absolute ethanol and then solution is refluxed with ethyl chloroacetate to produce. 3-[4-chloro-6-(4-chlorophenyl)-1-(2-ethoxy-2-oxoethyl)-2-oxo-1,2-dihydropyrimidin-5-yl] propanoic acid. In forth step Compound (3) was treated with hydrazine hydrate to form[3, 6 (4- substituted aryl)1-(1,2hydrazino-2-oxoethyl)- 2oxo- 1,2,3, 4tetrahydro pyrimidine -5-yl] propionic acid derivatives. Their structures are confirmed by IR, ^{1}H NMR. TLC of synthesized compounds performed in chloroform: ethanol (3:1) solvent system. All compounds were screened for their antitumor activity by trypan blue assay at. (1 µg /mL, 10 µg/mL, 100 µg /mL, 1000 µg /mL). And their results were compared with standard drug Cyclophosphamide.

Key words: Pyrimidine, Antitumor activity, aryl alkanoic acid.

INTRODUCTION

In medicinal chemistry pyrimidine derivatives have been very well known for their therapeutic applications. [1] The presence of a pyrimidine base in thymine, cytosine and uracil, which are the essential binding blocks of nucleic acids, DNA and RNA is one possible reason for their activity. [2,3,4] The literature indicated that compounds having pyrimidine nucleus possess broad range of biological activities, like 5-fluorouracil as anticancer; [5] idoxuridine and trifluoridine as antiviral; [6] zidovudine and stavudine as antiHIV; [7] trimethoprim, sulphamethiazine and sulphadiazine as antibacterial; [8] sulphadoxin as antimalarial and antibacterial; [9] minoxidil and prazosin as antihypertensive; [10] barbiturates e.g. phenobarbitone as sedative, [11] hypnotics and anticonvulsant; [12] propylthiouracil as antithyroid; [13] thionzylamine as H1antihistamine; [14] and toxoflavin as antibiotics.[15] Pyrimidines derivatives are undertaken with the aim of improving safety profile and reduction of GI side effects by increasing aryl chain length of acid and addition of amide group. [16,17,18]

METHODOLOGY

The chemicals used are benzene, glutaric anhydride, sulphuric acid, aluminium chloride, aluminium hydroxide, methanol, urea, chlorobenzaldehyde, ferrous chloride, ethanol, potassium dichromate, hydrazine hydrate, ethyl chloroacetate were of LR grade and purchased from Sigma Aldrich, Mumbai, India.IR Spectra taken by using Perkin Elmer 65 FT-IR Spectrophotometer using KBr disc.1H NMR Spectra is taken by using Brucker Spectrophotometer (400 MHz) in DMSO from University of Pune Maharashtra, India. All melting points were determined in open capillaries and are uncorrected. Purity of compounds are checked by Thin layer chromatography using prepared silica gel G slides as a stationary phase and chloroform: ethanol (3:1) solvent system as mobile phase. The spots resolved were checked by UV-chamber and iodine chamber.

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Step 1: Synthesis of 5-(substituted phenyl)-5-oxo-pentanoic acid [19]

Placed (0.00225 mol) of substituted benzene and (0.0034 mol) of glutaric anhydride in a 1 liter three-necked flask, Stirred the mixture and added (0.0075 mol) of powdered aluminium chloride all at once. The reaction usually start immediately, HCl is generated, evolved and reaction mixture become hot. If there is no apparent reaction warm gently. Heated in an oil bath to gentle refluxing with continued stirring for a half hour. Allowed to cool, immerse flask in a bath of cold water and slowly added 15 ml of water from a separating funnel. Introduced 5 ml of conc. HCl and separated benzene layer. Transferred the hot mixture to a 60 ml beaker. The 5-(substituted phenyl) -5-oxo-pentanoic acid separated as colourless oil, which soon solidified. Cooled in ice, filtered off acid at the pump and washed with 10 ml of cold water. Dissolved the crude acid in solution of 4g of anhydrous sodium carbonate in 25 ml water by boiling for 10-15 min. filtered the solution, suctioned to remove the small amount of aluminium hydroxide and washed with 2.5 ml portion of hot water. Treated the hot filtrate with 2g of decolourising carbon. Stirred for 5 min and filtered at the pump through a preheated buchner funnel. Transfer the filtrate to 1-liter beaker, cooled to about 50 0C and cautiously acidified with 6-7 ml of conc. HCl. Cooled to 0 0C in a freezing mixture of ice and salt. Filtered, washed thoroughly with cold water, dried for 12 hours upon filter paper and then weighed the compound.

Step–2: Synthesis of [4, 6-(4-substituted aryl)-2-thioxo- 1, 2, 3, 4-tetrahydro-pyrimidin-5-yl]-propanoic acid [20]

An equimolar reaction mixture of 5-(substituted phenyl) -5-oxo- pentanoic acid (0.0022 mol) urea (0.002 mol), substituted aldehyde (0.0022 mol) and K2CO3 (0.0022 mol) in 7 ml ethanol were refluxed in oil bath for 7 hrs. The reaction mixture was cooled and the solid obtained by filtered was dissolved in hot water and filtered. The filtrate was neutralized with acetic acid. The product thus obtained was recrystallized from methanol.

Step-3 : Synthesis of 3-[4-chloro-6-(4-chlorophenyl)-1-(2-ethoxy-2-oxoethyl)-2-oxo-1,2-dihydropyrimidin-5-yl]propanoic acid [21]

The compound 2 (0.1mol) was dissolved in a solution prepared by reacting Na (0.1mol) with 200 ml of absolute ethanol. The solution was refluxed with stirring and ethyl chloroacetate (0.1mol) was added in three portions over a period of 0.5 hr. After heating under reflux for 16 hr, the reaction mixture was filtered while hot to remove precipitated sodium chloride, the solvent was removed on a rotary vaccum evaporator. The crude product was collected and recrystallised from ethanol.

Step-4 : Synthesis of compounds [3, 6 (4- substituted aryl)1-(1,2 hydrazino-2-oxoethyl)-2oxo-1, 2, 3, 4-tetrahydropyrimidine-5-yl] propionic acid derivatives [22]

Mixture of compound 3 (0.01 mole), FeCl3.6H2O (0.02 mole) & 0.01 mole Hydrazine hydrate of was ground by pestle & mortar at room temp. The reaction mixture was digested with water. The resultant solid was filtered, washed with water & the crude material is purified by recrystallization from methanol to afford compound 4.

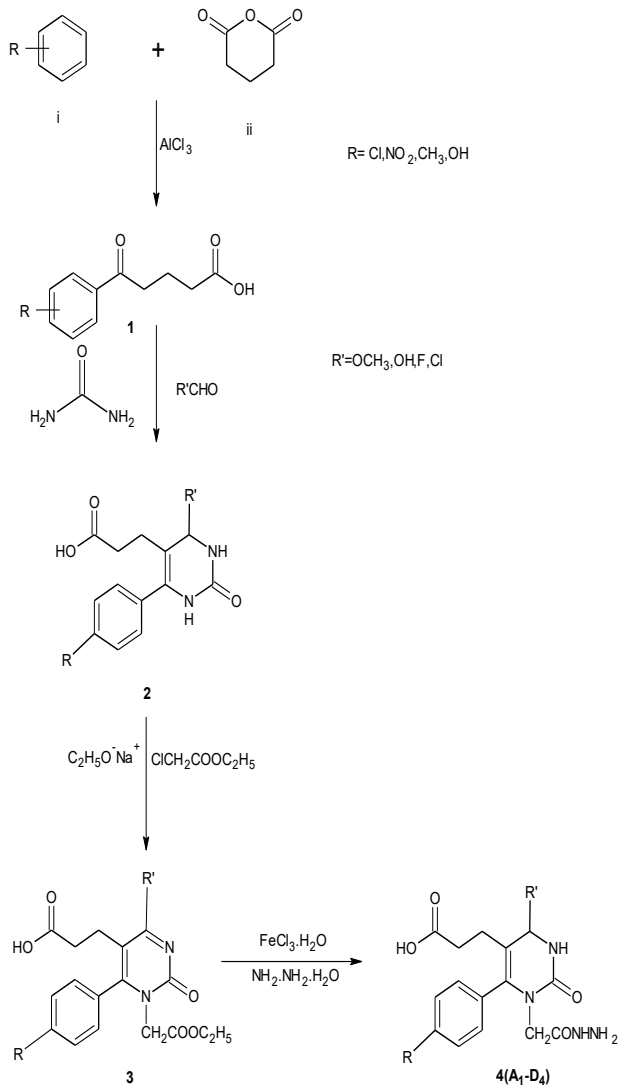
ANTI TUMOR ACTIVITY:

Trypan Blue Assay

Viable Cell Counts Using Trypan Blue

Trypan Blue is a vital dye. The reactivity of trypan blue is based on the fact that the chromophore is negatively charged and does not interact with the cell unless the membrane is damaged. Therefore, all the cells which exclude the dye are viable. HL-60 cell line is taken for antitumor studies

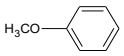
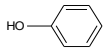
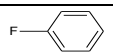
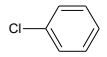
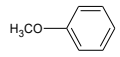
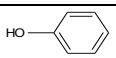
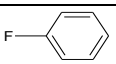
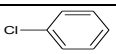
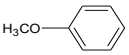
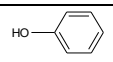
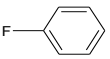
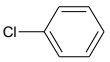
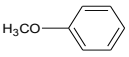
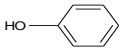
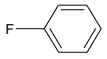
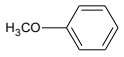
Scheme 1: Synthesis of 1, 2, 3, 4-Tetrahydro-pyrimidine derivatives



Procedure:

Trypan Blue Staining of Cells Place 0.5 ml of a suitable cell suspension (dilute cells in complete medium without serum to an approximate concentration of 1 x 105 to 2 x 105 cells per ml in a screw cap test tube. Add 0.1 ml of 0.4% Trypan Blue Stain. Mix thoroughly. Allow to stand 5 min at 15 to 30°C (room temperature). Fill a hemocytometer as for cell counting. Under a microscope, observe if non-viable are stained and viable cells excluded the stain.

Table 1. Synthesized compounds

Compound	R	R1	Mol. formula	Mol. wt	M.P	% yeild	R.f value (Chloroform: Ethanol)
A1	Cl		$C_{22}H_{23}ClN_4O_5$	458.89	138.5	73.25	0.473
A2	Cl		$C_{21}H_{21}ClN_4O_5$	444.86	134.2	75.23	0.356
A3	Cl		$C_{21}H_{20}FN_4O_4$	446.85	136.9	71.58	0.436
A4	Cl		$C_{21}H_{20}Cl_2N_4O_4$	463.31	142.3	68.22	0.388
B1	OH		$C_{22}H_{24}N_4O_6$	440.44	133.0	76.59	0.412
B2	OH		$C_{21}H_{22}N_4O_6$	426.44	125.8	74.32	0.362
B3	OH		$C_{21}H_{21}FN_4O_5$	428.41	127.4	69.33	0.268
B4	OH		$C_{21}H_{21}ClN_4O_5$	444.86	134.8	75.66	0.387
C1	CH3		$C_{23}H_{26}N_4O_5$	438.36	131.5	81.57	0.425
C2	CH3		$C_{22}H_{24}N_4O_5$	424.44	123.6	69.56	0.389
C3	CH3		$C_{22}H_{23}FN_4O_4$	426.44	125.7	73.66	0.296
C4	CH3		$C_{22}H_{23}ClN_4O_4$	442.89	134.6	78.32	0.432
D1	NO2		$C_{22}H_{23}N_5O_7$	469.44	144.5	68.72	0.459
D2	NO2		$C_{21}H_{21}N_5O_7$	455.22	141.2	76.52	0.342
D3	NO2		$C_{21}H_{21}FN_5O_6$	457.41	142.6	77.25	0.267
D4	NO2		$C_{21}H_{20}ClN_5O_6$	473.86	148.3	68.74	0.496

SPECTRAL DATA

A1-IR (KBr,cm-1) :3430 (O-H)str., 3230 (N-H str.)3068 (Ar-C-H)str,2966 (C-H)str,1697(C=O)str,1650(C=O amide) str,1574 (C=C)str, 1280 (C-O)str.,1109(C-N)str. 667 (C-CI)str.,

1H NMR (CDCl3) :7.2-8 (8H (s) of Ar-H), 6.9 (2 H (s) of pyrimidine), 10.8 (1 H (s) of –COOH), 3.2(3 H (s) of OCH3), 1.42 (2H (t) of CH2), 2.82 (2H (t) of CH2).3.8(1H(S) of –CONH),3.6(2H(S) of –NH2).2.1(2H (s) of CH2).

A2-IR (KBr,cm-1) :3450 (O-H)str., 3280 (N-H str.)3030 (Ar-C-H)str,2940 (CH)str,1720(C=O)str, 1650(C=O amide) str,1550(C=C)str, 1278 (C-O)str.,1115(C-N)str. 662 (C-CI)str.

A3-IR (KBr,cm-1) :3480 (O-H)str., 3250 (N-H str.)3047 (Ar-C-H)str,2957 (CH)str,1715(C=O)str, 1650(C=O amide) str,1558(C=C)str, 1275 (C-O)str.,1120(C-N)str. 662 (C-CI)str. 710(C-F)str.

A4-IR (KBr,cm-1) :3465 (O-H)str., 3278 (N-H str.)3056 (Ar-C-H)str,2950 (CH)str,1715(C=O)str, 1650(C=O amide) str,1556(C=C)str, 1270 (C-O)str.,1110(C-N)str. 662 (C-CI)str.

B1-IR (KBr,cm-1) :3460(O-H)str., 3245 (N-H str.)3030 (Ar-C-H)str,2960 (C-H)str,1715(C=O)str, 1650(C=O amide) str,1574 (C=C)str, 1280 (C-O)str.,1109(C-N)str. 667 (C-CI)str.,

1H NMR (CDCl3) :7.2-8 (8H (s) of Ar-H), 6.9 (3 H (s) of pyrimidine), 10.8 (1 H (s) of –COOH), 3.2(3 H (s) of OCH3), 1.42 (2H (t) of CH2), 2.82 (2H (t) of CH2).3.8(1H(S) of –CONH),3.6(2H(S) of –NH2).3.9(1H(S) of –OH).

B2-IR (KBr,cm-1) :3450 (O-H)str., 3280 (N-H str.)3030 (Ar-C-H)str,2940 (CH)str,1720(C=O)str, 1650(C=O amide) str,1550(C=C)str, 1278 (C-O)str.,1115(C-N)str.

B3-IR (KBr,cm-1) :3476 (O-H)str., 3264 (N-H str.)3047 (Ar-C-H)str,2957 (CH)str,1715(C=O)str, 1650(C=O amide) str,1558(C=C)str, 1275 (C-O)str.,1115(C-N)str, 710(C-F)str.

B4-IR (KBr,cm-1) :3465 (O-H)str., 3278 (N-H str.)3056 (Ar-C-H)str,2950 (CH)str,1715(C=O)str, 1650(C=O amide) str,1556(C=C)str, 1270 (C-O)str.,1110(C-N)str. 660 (C-CI)str.

C1-IR(KBr,cm-1):3430 (O-H)str., 3230 (N-H str.)3068 (Ar-C-H)str,2966 (C-H)str,1697(C=O)str,1650(C=O amide) str,1574 (C=C)str, 1280 (C-O)str.,1109(C-N)str.
1H NMR (CDCl3) :7.2-8 (8H (s) of Ar-H), 6.9 (3 H (s) of pyrimidine), 10.8 (1 H (s) of –COOH), 3.2(3 H (s) of OCH3), 1.42 (2H (t) of CH2), 2.82 (2H (t) of CH2), 3.8(1H(S) of –CONH),3.6(2H(S) of –NH2).
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C4-IR (KBr,cm-1) :3465 (O-H)str., 3278 (N-H str.)3056 (Ar-C-H)str,2950 (CH)str,1715(C=O)str, 1650(C=O amide) str,1556(C=C)str, 1270 (C-O)str.,1110(C-N)str. 660 (C-CI)str.
D1-IR(KBr,cm-1):3430(O-H)str., 3230 (N-H str.)3068 (Ar-C-H)str,2966 (C-H)str,1697(C=O)str,1650(C=O amide) str,1574 (C=C)str,1344(NO2)str, 1280 (C-O)str.,1109(C-N)str.
1H NMR (CDCl3) :7.2-8 (8H (s) of Ar-H), 6.9 (3 H (s) of pyrimidine), 10.8 (1 H (s) of –COOH), 3.2(3 H (s) of OCH3), 1.42 (2H (t) of CH2), 2.82 (2H (t) of CH2),1.9(3H (S)of-CH3),3.8(1H(S) of –CONH),3.6(2H(S) of –NH2).
D2-IR (KBr,cm-1) :3450 (O-H)str., 3280 (N-H str.)3030 (Ar-C-H)str,2940 (CH)str,1720(C=O)str, 1650(C=O amide) str,1550(C=C)str, 1325(NO2)str, 1278 (C-O)str.,1115(C-N)str.
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Table 2:Antitumor activity of [4, 6 (4- substituted aryl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidine- 5-yl] propionic acid derivatives

Sample	Conc. (ug/ml)	Observed Viable Cell	Total cell count	% Viability	Mean ±SEM
Control	-	89	113	78.76	--
A_1	1000	33	117	28.20	28.62 ± 0.4250*
	100	43	103	41.74	45.62 ± 3.8850
	10	48	99	48.48	47.99 ± 0.4850
	1	55	92	59.78	65.52 ± 5.740
A_2	1000	28	119	23.52	23.42 ± 0.0953*
	100	36	108	33.33	32.80 ± 0.5299
	10	47	104	45.19	45.24 ± 0.0432
	1	59	97	60.82	59.79 ± 1.0300
A_3	1000	26	113	24.52	24.42 ± 0.0832*
	100	33	102	34.33	35.80 ± 0.466
	10	56	135	55.12	48.56 ± 0.0657
	1	59	97	60.82	59.79 ± 1.0300
A_4	1000	18	112	16.07	16.44 ± 0.370*
	100	21	126	16.66	17.20 ± 0.540*
	10	27	123	21.95	21.38 ± 0.574*
	1	22	112	19.64	20.18 ± 0.540*
B_1	1000	25	112	22.32	22.97 ± 0.6550*
	100	43	108	39.81	41.33 ± 1.5200
	10	54	96	56.96	56.69 ± 0.2647
	1	60	89	67.41	67.04 ± 0.3746
B_2	1000	45	116	32.56	32.09± 0.4250
	100	47	112	34.45	34.12 ± 2.8850
	10	44	95	42.76	42.65 ± 0.5640
	1	45	82	59.45	58.12 ± 3.687
B_3	1000	33	103	32.03	32.85 ± 0.8149
	100	46	95	48.42	49.21± 0.7900
	10	59	93	63.44	63.82 ± 0.3855
	1	63	85	74.41	71.27 ± 3.1400

B_4	1000	23	108	23.42	23.32 ± 0.0562
	100	34	105	33.32	32.80 ± 0.345
	10	54	137	45.42	44.43± 0.0873
	1	43	98	52.82	51.79 ± 1.0546
C_1	1000	25	110	22.72	23.97 ± 0.5640*
	100	42	105	40.00	40.33 ± 1.5620
	10	58	98	59.18	59.69 ± 0.1345
	1	56	89	62.91	64.04 ± 0.3987
C_2	1000	45	116	32.56	32.09± 0.4250
	100	47	112	34.45	34.12 ± 2.8850
	10	44	95	42.76	42.65 ± 0.5640
	1	45	82	59.45	58.12 ± 3.687
C_3	1000	18	112	16.07	16.44 ± 0.370*
	100	21	126	16.66	17.20 ± 0.540*
	10	27	123	21.95	21.38 ± 0.574*
	1	22	112	19.64	20.18 ± 0.540*
C_4	1000	25	110	22.72	23.97 ± 0.5640*
	100	42	105	40.00	40.33 ± 1.5620
	10	58	98	59.18	59.69 ± 0.1345
	1	56	89	62.91	64.04 ± 0.3987
D_1	1000	18	113	16.54	16.13 ± 0.845*
	100	27	132	20.23	20.43 ± 0.675*
	10	30	139	23.48	24.24 ± 0.459*
	1	48	125	38.58	38.64 ± 0.794*
D_2	1000	23	108	23.42	23.32 ± 0.0562
	100	34	105	33.32	32.80 ± 0.345
	10	54	137	45.42	44.43± 0.0873
	1	43	98	52.82	51.79 ± 1.0546
D_3	1000	25	110	22.72	23.97 ± 0.5640*
	100	42	105	40.00	40.33 ± 1.5620
	10	58	98	59.18	59.69 ± 0.1345
	1	56	89	62.91	64.04 ± 0.3987
D_4	1000	16	110	14.54	14.13 ± 0.845*
	100	25	130	19.23	19.43 ± 0.675*
	10	29	135	21.48	22.24 ± 0.459*
	1	45	123	36.58	36.64 ± 0.794*
Cyclophosphamide	1000	16	102	15.68	16.42 ± 0.324*
	100	19	113	16.81	17. 32± 0.583*
	10	25	120	20.83	21.48 ± 0.276*
	1	21	108	19.44	20.08 ± 0.470*

RESULTS AND DISCUSSION

In scheme all compounds have shown moderate anticancer activity at both the concentration. (100 µg /mL, 1000 µg /mL). Compounds **A_4**, **C_3**, **D_1**, **D_4** have shown excellent anticancer activity at all concentrations (1 µg /mL, 10µg/mL, 100 µg/mL, 1000 µg/mL). Cyclophosphamide was used as standard drug.

Increased antitumor activity possessed by derivatives may be because of presence of tetrahydropyrimidine ring. Cl, F derivatives shows increased antitumor activity.

CONCLUSION

Sixteen [3, 6 (4- substituted aryl)1-(1,2 hydrazino-2-oxoethyl)-2oxo-1, 2, 3, 4-tetrahydropyrimidine-5-yl]

propionic acid derivatives have been synthesized in a four-step reaction. Their structures are confirmed by IR, ^{1}H NMR and TLC. The antitumor activity of all compounds has been recorded on the basis of reference standard Cyclophosphamide. All the compounds showed antitumor activity. The antitumor data shows that use of cloro and fluoro group in product shows increase in activity. The other compounds shows moderate antitumor activity.

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