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SYNTHESIS AND IN-VITRO CYTOTOXIC ACTIVITY OF SOME NOVEL 4-(2H- CHROMEN-3-YL)-6- PHENYL PYRIMIDIN-2-AMINE AND (2Z)-2- {(4-(2H-CHROMEN-3-YL)-6-PHENYL PYRIMIDIN-2-YL) IMINO}-3-THIAZOLIDIN-4-ONES

E.Kalyan Rao[1*], A.Mahendar[1] and K.Praveen Kumar[2]

Mahatma Gandhi University[1], Nalgonda, Andhra Pradesh, India.
Department of Pharmaceutical Chemistry[2], Vaagdevi Pharmacy College, Bollikunta, Warangal, Andhra Pradesh - 506002, India.

ABSTRACT

A series of novel 4-(2H- chromen-3-y1)-6- phenyl pyrimidin-2-amine IIIa-h and (2Z)-2- {(4-(2H-chromen-3-y1)-6-phenyl pyrimidin-2-y1)imino}-,3-thiazolidin-4-one Va-h analogs is described. Reaction of 3[(E)-3-Aryl-propen-2-enoyl]-2H-chromen-2-ones II with guanidine hydrochloride in presence of potassium hydroxide and ethanol yielded 4-(2H-chromen-3-y1)-6-phenyl pyrimidin-2-amineIII. Subsequent reaction of III with chloro acetyl chloride in tri ethyl amine gave 2-chloro-N-(4-(2H- chromen-3-y1)-6-phenyl pyrimidin-2-y1) acetamide IVa-h which upon treatment with ammonium isothiocyanate in ethanol furnished (2Z)-2- {(4-(2H-chromen-3-yl)-6-phenyl pyrimidin-2-yl) imino }-1,3 –thiazolidin-4-ones.All the title compounds III(a-h) and V(a-h) were screened for Invitro Cytotoxic activity using A-549 lung cancer cell lines and HT-29 colon cancer cell lines by MTT method. The structures of newly synthesized compounds were established on the basis of elemental analysis,IR and ^{1}H NMR spectral data.

Keywordst:-Cytotoxic activity,Thiazolidinones,Pyrimidines,cisplatin.

INTRODUCTION

Thiazolidinone nucleus is a ubiquitous structural unit of many biologically active alkaloids and pharmaceutical agents. Hence the importance of this Thiazolidinone nucleus in biological system has stimulated interest in designing and constructing new heterocyclic systems using a molecular modification approach, Thiazolidinone derivatives have been found to be associated with diverse pharmacological activities such as anti-inflammatory(Taranalli *et al.*, 2009), antitubercular (Parekh *et al.*,2004),antifungal (Hui-Ling *et al.*,2000), anticonvulsant (Raqab *et al.*, 1997), antimicrobial activites (Altintas *et al.*, 2009), Thiazolidinone herbicides are the potent inhibitors of glucose incorporation into cell wall (Sharples *et al.*,1998),. They have also proved to be calcium antagonists with both calcium overload inhibitors and antioxidant activity (Kota *et al.*, 1999), (Mei-Hsui *et al.*,2004).

In addition,it was was reported that pyrimidines exhibit various biological activites (Kappe *et al.*,1997), (Sondhi *et al.*,2005), (Rovnyak *et al.*,1992). Pyrimidines are associated with various therapeutic activites like anitumour (Silvana *et al.*,2000), anti-HIV (Sterzycki *et*

Corresponding Author

E.Kalyan Rao
E:Mail:kalyanenugala@gmail.com

al.,1990), anti-inflammatory (Tozkoporam *et al*.,1990), antitubercular (Virsodia *et al*.,2008), antineoplastic (Lin *et al*.,1983). Similarly coumarin unit constitute an easily accessible nucleus that is present in a number of natural and pharmacological compound and display a wide range of organic reactivites and could be used as effective means of preparing new molecular scaffolds(Borges *et al*.,2005), (Laurin *et al*.,1999).

A literature survey revealed that when one biodynamic heterocylic system was coupled with another, a molecule with enhanced biological activity (Clark *et al*.,1983), was produced. Inspired by the biological profile of Thiazolidinone, pyrimidine, coumarin and in continuation of our research on biologically active heterocycles it was thought worthwhile to synthesize new heterocyclic compounds containing thiazolidinone, pyrimidine, coumarin in one molecular frame work.

MATERIALS AND METHODS

Synthetic methods for the preparation of thiazolidinones **V (a-h)** and pyrimidine **III (a-h)** are summarized in **scheme-1**. Chalcones were synthesized by the reaction of 2-acetyl chromen-2-one and various substituted aromatic and heterocyclic aldehydes in presence of piperidine in absolute alcohol led to the formation of 3 [(E)-3-Aryl-propen-2- enoyl]-2H-chromen-2-ones. Pyrimidine derivatives were obtained in good yield by reaction of chalcones **II(a-h)** in presence of aqueous KOH and ethanol. Compounds **III(a-h)** on reaction with chloroacetyl chloride in the presence of tri ethyl amine in dry benzene furnished 2- Chloro-*N*- [4-(2H-chromen-3-y1)-6-phenyl pyrimidin-2-y1) acetamide **IV(a-h)**. Compounds **IV(a-h)** on cyclocondensation with ammonium thiocyanate in refluxing ethanol afforded (2Z)-2-{[4-(2H-chromen-3-y1)-6-phenyl pyrimidine-2-y1) imino)-1,3-thaizolidin-4-ones **V(a-h).** All the melting points were determined on a cintex melting point apparatus and are uncorrected. Analytical TLC was performed on Merck precoated 60. F_{254} silica gel plates. Visualization was done by exposing to Iodine vapor. IR spectra (KBr pellet) were recorded on Perkin-Elmer BX series FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a varian Gemini 300 MH_Z spectrometer. Chemical shift values are given in ppm (δ) with tetramethyl silane as internal standard. Elemental (C,H and N) analyses were carried out on a carlo-Erba 106 and perkin-Elmer 240 analyzers.

Preparation of 3[(E)-3- Aryl-Propen-2-enoyl]-2H-Chromen-2-ones II(a-h):

A mixture of 2- Acetyl chromen-2-one (0.01) **(I)** and appropriate aldehyde (0.0l mol) was refluxed in ethanol(20ml) in the presence of piperidine (1ml) for one hour. 3-cinnamoyl coumarin separated as solid while refluxing is in progress. The reaction mixture was cooled and the product on recrystallization from ethanol gave lemon yellow crystals.

Preparation of 4-(2H-chromen-3-yl)-6-Phenyl pyrimidin-2- amine III(a-h):

3[(E)-3- Aryl-Propen-2-enoyl)-2H-chromen-2-one **II(a-h)** (0.01 mol) was condensed with guanidine HCl (0.01mol) in absolute ethanol (20ml) at reflux temperature for 4h. The solvent was evaporated in vacuum and crushed ice was added to the residue while mixing thoroughly. Where upon a bright yellow solid separated out. This solid was filtered under vaccum, dried and purified by column chromatography to give pure pale yellow solid.

Preparation of 2-chloro-*N*-[4-(2H-Chromen-3-yl)-6-phenyl pyrimidin-2-yl) acetamide IV(a-h):

4-(2H-Chromen-3-yl)-6- phenyl pyrimidin-2-amine **III(a-h)** (0.01mol), chloro acetyl chloride (0.01mol) and tri ethyl amine (0.5ml) were taken in dry benzene. The contents were refluxed with stirring for 4-6 h. The precipitated tri ethyl-amine hydrochloride was removed by filtration. The gummy product obtained after the removal of solvent at ambient temperature was titrated with methanol. Recrystallization of the product was effected form aqueous methanol.

Preparation of (2Z)-2-{[4-(2H-chromen-3-y1)-6- phenyl pyrimidin-2-yl] imino}-1,3-Thaizolidin-4-ones V(a-h):

2-chloro-*N*-(4-(2H- chromen-3-4)-6-phenyl pyrimidine-2-yl) acetamide **IV(a-h)** (0.01mol) and NH_4SCN (0.02mol) were taken in ethanol and refluxed on a water bath for 4-6 hr. After completion of the reaction (monitored with TLC). The reaction mixture was concentrated by rotary evaporator and the residue was washed thoroughly with cold water and it was purified by recrystallization from ethanol

Pharmacology

Sixteen compounds of 4-(2H- chromen-3-y1)-6-phenyl pyrimidin-2-amine **III(a-h)** and (2Z)-2- {(4-(2H-chromen-3-y1)-6-phenyl pyrimidin-2-y1) imino}-,3-thiazolidi-4-one **V(a-h)** analogs is synthesized. The antitumor activity of these compounds was examined against two different human tumor cell lines i.e. HT-29 (Colon cancer) and A549 (Lung cancer). Among16 compounds, only five exhibited good cytotoxic activity.

Biological Assays

The new molecules containing **III(a-h)** and **V(a-h)**were screened for cytotoxicity (MTT assay) Antiproliferative study by Microculture tetrazolium **(MTT)** assay **(**sridhar *et al* 2011)(Mashelkar *et al* 2005**):** Both HT-29 (Colon cancer), A549 (Lung cancer) cell lines, obtained from National Center for Cell Science) (NCCS) Pune, India. were grown as adherent cells in DMEM media supplemented with 10% fetal bovine serum, 100 µg/ml penicillin, 200 µg/ml streptomycin, 2mM L-glutamine, and culture was maintained in a humidified atmosphere with 5% CO_2 at 37°C for 72 hr. The cytotoxicity was determined by the micro culture tetrazolium (MTT) assay**,** based on the metabolic ability of mitochondrial dehydrogenase enzyme to reduce 3-(4, 5-dimethylthiazol-2, 5-diphenyl) tetrazolium bromide (MTT) to water insoluble formazan crystals, which gives direct correlation of viable cells. The required dilutions were made with sterile water to get required concentrations from stock solution of 10 mg/ml in DMSO. HT-29 (Colon cancer), A549 (Lung cancer) cell line were seeded at a density of 1 x 104 cells (cell number was determined by Trypan blue exclusion dye method) per each well in 100 µl of DMEM supplemented with 10% FBS.12 hrs after seeding, above media was replaced with fresh DMEM supplemented with 10% FBS then 10µl sample from above stock solutions were added to each well in triplicates which gives final concentration of 200, 100, 50, 10 µg/well. The above cells were incubated for 48 hrs at 37°C with 5% CO_2. After 48 hrs incubation the above media was replaced with 100 µl of fresh DMEM without FBS and to this 10 µl of MTT (5mg dissolved in 1 ml of PBS) was added and incubated for 3 hrs at 37°C with 5% CO2. After 3 hrs incubation, the above media was removed with multi channel pipette, and then 200 µl of DMSO was added to each well and then incubated at 37°C for 15 min. Finally, the plate was read at 570 nm using spectrophotometer (Spectra Max, Molecular devices). In all experiments, cisplatin (IC_{50} 25 µM) was used as the positive control. The results are expressed as the average of triplicate assays.

Calculations:

$$\% \text{ Cytotoxicity} = \frac{(T_{dead} - C_{dead})}{T_{total}} \times 100$$

Where,

T dead is the number of dead cells in the test

C dead is that in the control group

T total is the total number of dead and live cells in the test compound.

Table 1. Physical Data of the Prepared Compounds III(a-h) and V(a-h)

S.NO	Ar	Mol.Formula	M.P(°c)	Yeild%	(%calc.)			(%found)		
					C	H	N	C	H	N
IIIa	Phenyl	$C_{19}H_{13}N_3O_2$	215-217	65	72.37	4.16	13.33	72.31	3.98	12.94
IIIb	4-chloro phenyl	$C_{19}H_{12}N_3ClO_2$	230-232	60	65.24	3.46	12.01	65.19	3.42	11.92
IIIc	4-methoxy phenyl	$C_{20}H_{15}N_3O_3$	195-193	72	69.56	4.38	12.17	69.48	4.32	12.15
IIId	4-methyl phenyl	$C_{20}H_{15}N_3O_2$	173-175	67	72.94	4.59	12.76	72.89	4.52	12.72
IIIe	2-chloro phenyl	$C_{19}H_{12}N_3ClO_2$	180-182	82	65.24	3.46	12.01	65.29	3.39	12.04
IIIf	2-methoxy phenyl	$C_{20}H_{15}N_3O_3$	165-167	79	69.56	4.38	12.17	69.59	4.31	12.09
IIIg	2-pyrrolyl	$C_{17}H_{12}N_4O_2$	247-249	82	67.10	3.97	18.41	67.08	3.91	18.35
IIIh	2-thienyl	$C_{17}H_{11}N_3O_2S$	197-199	70	63.54	3.45	13.08	63.49	3.41	13.04
Va	Phenyl	$C_{22}H_{14}N_4O_3S$	125-126	67	63.76	3.40	13.52	63.71	3.31	13.41
Vb	4-chloro phenyl	$C_{22}H_{13}N_4ClO_3S$	107-109	79	58.87	2.92	12.48	58.83	2.89	12.32
Vc	4-methoxy phenyl	$C_{23}H_{16}N_4O_4S$	288-289	75	62.15	3.63	12.61	62.11	3.59	12.59
Vd	4-methyl phenyl	$C_{23}H_{16}N_4O_3S$	112-114	81	64.47	3.76	13.08	64.41	3.64	13.04
Ve	2-chloro phenyl	$C_{22}H_{13}N_4ClO_3S$	127-128	81	58.87	2.92	12.48	58.81	2.86	12.41
Vf	2-methoxy phenyl	$C_{13}H_{16}N_4O_4S$	192-194	72	62.15	3.63	12.61	62.08	3.57	12.54
Vg	2-pyrrolyl	$C_{20}H_{13}N_5O_3S$	214-217	74	59.55	3.25	1736	59.52	3.19	17.26
Vh	2-thienyl	$C_{20}H_{12}N_4O_3S_2$	204-206	68	57.17	2.88	13.32	57.09	2.82	13.29

Table 2: Spectral Data of the Prepared Compounds

S.NO	IR Spectral data	^{1}H NMR Spectral data chemical shift (δ) in ppm
IIIa	3370(NH_2), 1645(C=N), 1510(C=C) ,1730(C=O)	5.3(2H,s,-NH_2), 7.35(1H,s,Pyrimidine-H) 6.1(1H,s, Coumarin-H), 7.1-7.8(m,9H-Ar-H)
IIIb	3365(NH_2), 1635(C=N), 1500(C=C) ,1725(C=O)	5.25(2H,s,-NH_2), 6.83(1H,s,Pyrimidine-H), 6.21(1H,s, Coumarin-H), 7.0-7.6(m,8H-Ar-H)
IIIc	3420(NH_2), 1589(C=N), 1490(C=C) ,1710(C=O) 1220(C-O-C)	5.11(2H,s,-NH_2), 7.32(1H,s,Pyrimidine-H), 7.72(1H,s, Coumarin-H), 3.82(s,3H,OCH_3) , 7.2-7.8(m,8H-Ar-H)
IIId	3335(NH_2), 1590(C=N), 1485(C=C) ,1718(C=O)	5.22(2H,s,-NH_2), 7.40(1H,s,Pyrimidine-H), 7.22(s, Coumarin-H), 2.45(s,3H,CH_3), 7.1-7.7(m,8H-Ar-H)
IIIe	3362(NH_2), 1630(C=N), 1485(C=C) ,1732(C=O)	5.18(2H,s,-NH_2), 6.72(1H,s,Pyrimidine-H), 6.18(1H,s, Coumarin-H), 7.1-7.8(m,8H-Ar-H)
IIIf	3430(NH_2), 1585(C=N), 1480(C=C) ,1705(C=O) 1210(C-O-C)	5.18(2H,s,-NH_2), 7.14(1H,s,Pyrimidine-H), 7.68(1H,s, Coumarin-H), 3.79(s,3H,OCH_3) , 7.2-7.9(m,8H-Ar-H)
IIIg	3410(NH_2), 1575(C=N), 1470(C=C) ,1710(C=O)	5.24(2H,s,-NH_2), 7.22(1H,s,Pyrimidine-H), 7.58(s, Coumarin-H), 7.02-7.11(4H,m,Ar-H),9.9(s,1H,Pyrrole,NH), 6.81-7.01(m,3H,Pyrrole-H)
IIIh	3407(NH_2), 1565(C=N), 1415(C=C) ,1712(C=O)	5.28(2H,s,-NH_2), 7.18(1H,s,Pyrimidine-H), 7.58(s, Coumarin-H), 6.82-7.02(4H,m,Ar-H),9.9(s,1H,Pyrrole,NH), 6.71-6.81(m,3H,Thiophen-H)
IVa	1692(C=O),3320(-NH-) 1470(C=C),1620(C=N)	9.92(bs,1H,NH),4.21(s,2H,CH2) , 6.84(1H,s,Coumarin-H),7.21(1H,s,Pyrimidin-H), 7.31-7.94(m,9H,Ar-H)
IVb	1675(C=O),3290(-NH-) 1420(C=C),1610(C=N)	9.84(bs,1H,NH),4.24(s,2H,CH2), 6.90(1H,s,Coumarin-H),7.49(1H,s,Pyrimidin-H), 7.52-7.94(m,8H,Ar-H)
IVc	1679(C=O),3295(-NH-) 1415(C=C),1625(C=N)	9.34(bs,1H,NH),4.14(s,2H,CH2), 6.82(1H,s,Coumarin-H) 3.84(s,3H,OCH3),7.14(1H,s,Pyrimidin-H),7.20-7.60(m,8H,Ar-H),
IVd	1681(C=O),3326(-NH-) 1419(C=C),1618(C=N)	9.20(bS,1H,NH),4.23(S,2H,CH2),6.74(1H,S,Coumarin-H),7.01(1H,Pyrimidin-H), 2.32(S,3H,CH3) 7.15-7.55(m,8H,Ar-H),
IVe	1682(C=O),3310(-NH-) 1430(C=C),1624(C=N)	9.52(bs,1H,NH),4.41(s,2H,CH2), 6.80(1H,s,Coumarin-H),7.31(1H,s,Pyrimidin-H), 7.42-7.89(m,8H,Ar-H)
IVf	1672(C=O),3280(-NH-) 1440(C=C),1630(C=N)	9.23(bs,1H,NH),4.22(s,2H,CH2),6.71(1H,s,Coumarin-H), ,7.08(1H,s,Pyrimidin-H),7.28-7.68(m,8H,Ar-H),3.92(s,3H,OCH3)
IVg	1672(C=O),3210(-NH-) 1450(C=C),1632(C=N)	9.41(bs,1H,NH),4.39(s,2H,CH2), 6.89(1H,s,Coumarin-H),7.21(1H,s,Pyrimidin-H), 7.34-7.62(4H,m,Ar-H),8.82(s,1H,Pyrrole-H),6.61-7.14(m,3H,Pyrrole-H)
IVh	1674(C=O),3250(-NH-) 1410(C=C),1680(C=N)	9.38(bs,1H,NH),4.24(s,2H,CH2),6.62(1H,s,Coumarin-H),7.01(1H,s,Pyrimidin-H),7.28-7.79(m,4H,Ar-H),6.94-7.14(m,3H,Ar-H)
Va	1660(C=O),3190(-NH-) 1380(C=C),1610(C=N)	8.61(bs,1H,NH),4.02(s,2H,CH_2),6.22(1H,s,Coumarin-H), 7.06(1H,s,Pyrimidine-H),7.28-7.66(m,9H,Ar-H)
Vb	1674(C=O),3250(-NH-) 1410(C=C),1630(C=N)	9.24(bs,1H,NH),4.18(s,2H,CH_2),6.31(1H,s,Coumarin-H), 6.89(1H,s,Pyrimidine-H),7.14-7.55(m,8H,Ar-H)

Vc	1685(C=O),3281(-NH-) 1420(C=C),1618(C=N)	8.98(bs,1H,NH),4.09(s,2H,CH_2),6.74(1H,s,Coumarin-H), 7.06(1H,s,Pyrimidine-H), 7.12-7.55(m,8H,Ar-H),3.71(S,3H,OCH_3)
Vd	1690(C=O),3210(-NH-) 1435(C=C),1629(C=N)	8.84(bs,1H,NH),4.17(s,2H,CH_2),6.67(1H,s,Coumarin-H), 6.92(1H,s,Pyrimidine-H), 2.81(s,3H,CH_3), 7.22-7.82(m,8H,Ar-H),
Ve	1694(C=O),3419(-NH-) 1412(C=C),1630(C=N)	8.79(bs,1H,NH),4.32(s,2H,CH_2),6.69(1H,s,Coumarin-H), 7.45(1H,s,Pyrimidine-H),7.55-7.89(m,8H,Ar-H)
Vf	1634(C=O),3220(-NH-) 1418(C=C),1645(C=N)	9.04(bs,1H,NH),4.42(s,2H,CH_2),6.89(1H,s,Coumarin-H), 7.18(1H,s,Pyrimidine-H),7.34-7.92(m,8H,Ar-H)
Vg	1610(C=O),3280(-NH-) 1424(C=C),1650(C=N)	8.74(bs,1H,NH),4.09(s,2H,CH_2),6.63(1H,s,Coumarin-H), 7.06(1H,s,Pyrimidine-H),7.04-7.45(m,4H,Ar-H),7.92(s,1H,Pyrrole-H),6.22-6.87(m,3H,Pyrrole-H)
Vh	1640(C=O),3240(-NH-) 1420(C=C),1690(C=N)	9.02(bs,1H,NH),4.14(s,2H,CH_2),6.41(1H,s,Coumarin-H), 6.82(1H,s,Pyrimidine-H),7.10-7.44(m,4H,Ar-H),6.32-6.94(m,3H,Ar-H)

Table 3. Cytotoxic activity of 4-(2H-chromen-3-yl)-6-Phenyl pyrimidin-2- amine III(a-h)

S.no	compound	substituent	A549 Lung cancer cell lines IC50 values (µM)	HT-29 Colon cancer cell lines IC50 values (µM)
1	IIIa	C6H5	202.0	220.00
2	III b	4-ClC6H4	38.82	45.73
3	IIIc	4-CH3OC6H4	180.00	170.00
4	IIId	4-CH3C6H4	152.70	172.20
5	IIIe	2-ClC6H4	75.02	65.70
6	IIIf	2-CH3OC6H4	120.00	149.50
7	IIIg	PYROLYLIL	100.12	128.40
8	IIIh	THIENYL	110.11	126.00
9	Cisplatin		25	25

Table 4. Cytotoxic activity of (2Z)-2-{[4-(2H-chromen-3-y1)-6- phenyl pyrimidin-2-yl] imino}-1, 3-Thaizolidin-4-ones V(a-h).

S.NO	Compound	Substituent	A549 Lung cancer cell lines IC50 values (µM)	A549 Lung cancer cell lines IC50 values (µM)
1	Va	C6H5	210.50	230.00
2	Vb	4-ClC6H4	40.92	47.83
3	Vc	4-CH3OC6H4	199.00	210.00
4	Vd	4-CH3C6H4	168.12	172.20
5	Ve	2-ClC6H4	68.70	52.12
6	Vf	2-CH3OC6H4	128.00	156.29
7	Vg	Pyrolyl	108.00	148.24
8	Vh	Thienyl	112.00	123.00
9	cisplatin		25	25

RESULTS AND DISCUSSION

Biological assay

All the compounds **(III, V)** were evaluated for cytotoxicity properties on human lung and liver carcinoma cell lines with cisplastin as a standard. Inhibition of cell-proliferation was measured by MTT assay. The IC_{50} values are coated in tables.

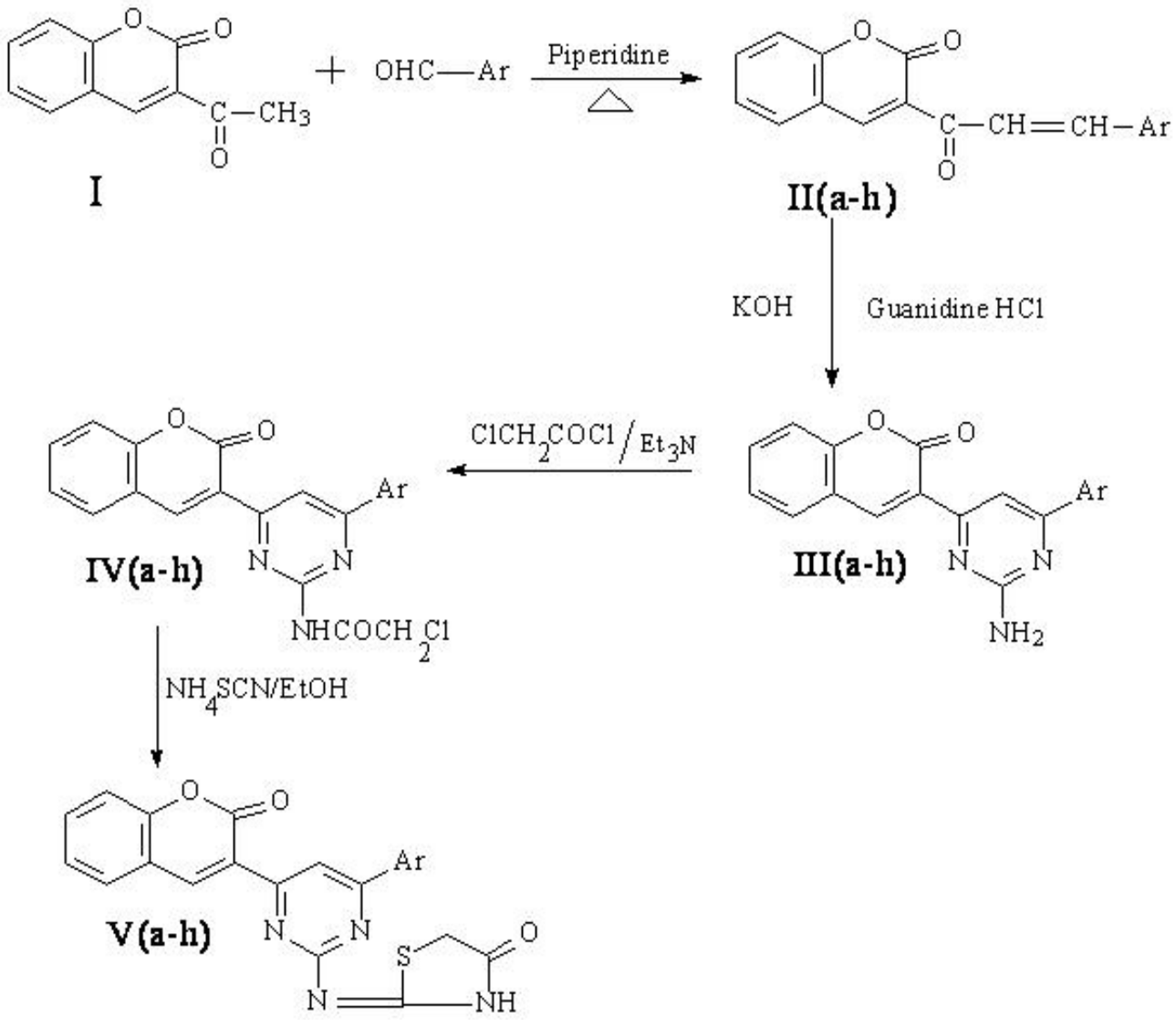
MTT (Micro culture Tetrazolium Assay)

The cytotoxic activity of 4-(2H- chromen-3-y1)-6- phenyl pyrimidin-2-amine **III(a-h)** and (2Z)-2- {(4-(2H-chromen-3-y1)-6-phenyl pyrimidin-2-y1)-imino}-,3-thiazolidi-4-one **V(a-h)** analogs is presented in **Table 3&4.** Almost all the compounds exhibited good activity against A-549 and HT-29 cell lines. Among the test

compounds, compound **IIIb,Vb** (Ar=4-Cl-) showed comparatively good cytotoxic activity with an IC_{50} values as 38.82,45.73&40.92,47.83 µM against A-549 (lung cancer) and HT-29 (colon cancer) cell lines respectively. The title compounds 4-(2H- chromen-3-y1)-6- phenyl pyrimidin-2-amine and (2Z)-2-{(4-(2H-chromen-3-y1)-6-phenyl pyrimidin-2-y1) imino},3-thiazolidin-4-ones were synthesized in good yields **(scheme-1).** Some of the compounds have significant cytotoxic effects against the cell lines A549 Lung cancer cell lines IC50 values (µM) , A549 Lung cancer cell lines IC_{50} values (µM)

Out of all the compounds, **IIIb & Vb** containing Chloro substitution on para position of pyrimidine and thiazolidinone nucleus showed maximum activity, closely followed by **IIIe &Ve** Containing chloro substitution on ortho position. These compounds also need to be tested on other cancer cell lines in order to predict their activity and therapeutic usefulness.

SCHEME-1



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