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SYNTHESIS AND INSILICO EVALUATION OF 4,6-DIPHENYL PYRIMIDINE-2(1H)-THIONE DERIVATIVES

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Abstract:

*A Series of Bioactive compounds, 4,6-diphenyl pyrimidine-2(1H)-thione**(1a)**, 4-(4-cholophenyl)-6-phenylpyrimidine-(1H)-thione**(1b)**,4-(4-aminophenyl)-6-phenyl pyrimidine-2(1H)-thione**(1c)**, 4-(4-nitrophenyl)-6-phenyl pyrimidine -2(1H)-thione**(1d)**, 4-(4-methoxyphenyl)-6-phenylpyrimidine-2(1H)-thione**(1e)**, were Synthesized according to the Literature methods. The Synthesized compounds were characterized by NMR, IR & Mass Spectroscopy.*

Keywords: *4,6-diphenyl pyridine-3(2H)-one, chalcones, aldehydes, thiourea.*

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INTRODUCTION:

Synthetic derivatives demonstrate an essential role in modern medicines such as quinazoline alkaloids, which Exhibit hypnotic activity [1]. Many simple fused pyrimidines such as purines and pteridine are biologically active. Some Have bronchodilator potential and act as antagonist of the human A2A adenosine receptor and constitute some Valuable naturally occurring substances such as nucleic acids.[2] Similarly, the presence of a pyrimidine base in cytosine, Uracil, and thymine (building blocks of DNA and RNA) is one of the possible reasons for their activities. Some Pteridine derivatives are also used as antileukemic drugs [3]. moreover, a pyrimidine ring is also found in isoalloxazine Vitamin B2 flucytosine (used as a nucleoside antifungal agent for the treatment of systemic severe infections), Thiamine, riboflavin(6,7-dimethyl-9(D-1-ribityl), and folic acid [4]. A few pyrimidine derivatives also show Potassium-conserving diuretic and anti-malarial activity [5]. The biological significance of the pyrimidine derivatives has led us to the synthesis of substituted pyrimidine. As pyrimidine is a basic nucleus in DNA & RNA, it has been found to be associated with diverse biological Activates[6].

MATERIALS AND METHODS:

Melting points were determined in open glass capillaries using Gallen Kamp (MFB- 600) melting point apparatus and were uncorrected. IR spectra (KBr discs) Bruker analysers were confirmed by Shimadzu FTIR Spectrophotometer using KBr pellets technique, Model No.8400S (Japan). 1H and 13C NMR spectra were recorded on Bruker 400 MHz NMR spectrometer (Switzerland) using DMSO as solvent. T.L.C. was run on silica gel G plates using ethyl acetate: n-hexane (7:3) as developing solvent to assess the progress of reaction and purity of the compounds. All other chemicals used in the present study were of analytical grade.

Drugs and chemicals:

Benzaldehyde-(FINAR.B.NO.60107022LU),Chlorobenzaldehyde(PALLAV.B.NO.PC/388-L/17-L), Nitrobenzaldehyde (PALLAV.B.NO.PC/2186/16-L), Acetophenone (FINAR.B.NO.50560212BP), Ethanol (CCS.B.NO.110605), KOH(www.researchlab.in.1245190918), Thiourea (universallaboratories. B. NO. C123811169), Ethyl acetate (AVRA), Silica gel-G- (RESEARCH-LAB FINE CHEM industries-B.NO. l317310113), Anisaldehyde (ULTRAPURE-LABCHEMINDUSTRIES.B. NO.AA/277/21), Aminobenzaldehyde (SIGMA-ALDRICH, Co., 3050Sprucest.,), n-Hexane (PHARMACO-AAPER.B.NO. WO115400).

Chemical synthesis:

Step-1: Synthesis of substituted chalcone derivatives:

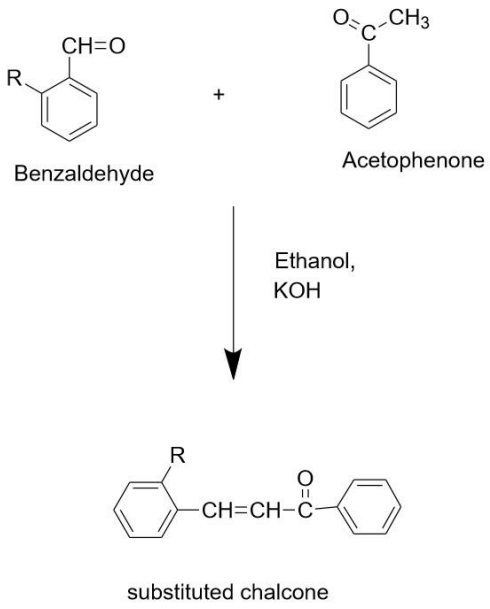
Equimoles of different benzaldehydes and acetophenones were taken into mortar, and pulverized by pestle at room temperature by employing the friction method. Then the mixture was moist with few drops of ethanol and KOH. The progress of the reaction was checked by TLC, and all the reactions were found to be completed in times of 10-12 min. The product was recrystallized from ethanol. The purity was confirmed by thin-layer chromatography and melting point.

Step-2: Synthesis of Pyrimidine compounds:

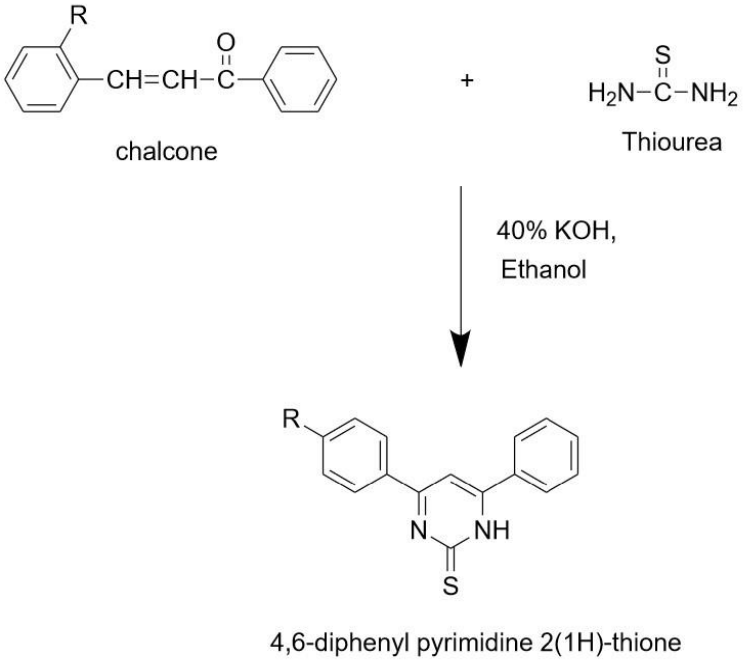
Equimoles of substituted chalcone derivatives and thiourea were taken into mortar, and pulverized by pestle at room temperature by employing the friction method at room temperature using ethanol, KOH. The mixture was neutralized and transferred to ice cold water, precipitate was filtered, dried and recrystallized from ethanol. The purity and progress of reaction was confirmed by thin layer chromatography.

SCHEME:

Step-1:



Step-2:



Where R: Cl, NH_2, NO_2, OCH_3

TABLE 1: PHYSICAL DATA

Code	Compound	M.F	M.W	%yield	C%	H%	O%	N%	Cl%	S%
1a	4,6-diphenyl pyrimidine-2(1H)-thione	$C_{16}H_{12}N_2S$	264.34	72%	72.70	4.58	_	10.60	_	12.13
1b	4-(4-chloro phenyl)-6-phenyl pyrimidine-2(1H)-thione	$C_{16}H_{11}ClN_2S$	298.07	74%	64.32	3.71	_	9.38	11.87	10.73
1c	4-(4-amino phenyl)-6-phenyl pyrimidine-2(1H)-thione	$C_{16}H_{13}N_3S$	279.36	75%	68.79	4.69	_	15.04	_	11.48
1d	4-(4-nitro phenyl)-6-phenyl pyrimidine-2(1H)-thione	$C_{16}H_{11}N_3O_{2S}$	309.34	78%	62.12	3.58	10.34	13.58	_	10.37
1c	4-(4-Methoxy phenyl)-6-phenyl pyrimidine2(1H)-thione	$C_{17}H_{14}N_2O_S$	294.37	78%	69.36	4.79	5.44	9.52	_	10.89

Compound [1a]: Synthesis of 4,6-diphenyl 2(1H)-thione: Yield-72%; **IR Data:** FTIR (γ max, C m-1) 1650 (-C=C), 2050 (=C-H stretch), 1500 (=C-H bend), 1590 (-C=N), 3000 (- C- NH),1150 (C-N-), 1250 (C=S), 2500 (C-SH). **^{1}HNMR:** (500MHZ, CDC13), ð 6.6, 6.8, 7.0, 7.1, 7.2, 7.21, 7.38, 7.45, 7.7, 8.1, 8.2 (Ar-H). **^{13}CNMR:** (500MHZ, CDC13), ð 120.3, 120.7, 121.1, 122.3, 130.5, 130.9, 135.6, 141.4, 145.8, 146.6, (C-H), ð 152.34 (C=N), ð 190.6(C=S).
Compound [1b]: Synthesis of 4-(-4chlorophenyl)-6-phenylpyrimidine-2(1H)-thione: Yield- 74%, **IR Data:** FTIR (γ max, C m-1) 1640(-C=C), 2842(= C-H stretch), 1510(=C-H bend), 1145 (-C-N), 2990(- C-NH),2510(SH),1255(C=S),710(-C-CL),1600(C=N). **^{1}HNMR:** (500MHZ, CDC13), ð 6.1, 6.5, 7.4, 7.5, 7.9, 8.05, 8.1, 8.19, 8.26, 8.34, (Ar-H)**. ^{13}CNMR:** (500MHZ, CDC13), ð 120.1, 120.9, 121.3, 122.5, 123.3, 134.4, 136.9, 141.2, 145.6, 145.7 (C-H), ð 153.24 (C=N), ð 55.9 (C=Cl), ð190.1 (C=S).
Compound [1c]: Synthesis of 4-(-4aminophenyl)-6-phenylpyrimidine-2(1H)-thione: Yield- 75%, **IR Data :** FTIR (γ max, C m-1) 1660(-C=C stretch), 2855(= C-H stretch), 1505 (=C-H bend), 1155 (-C-N), 3010 (- C-NH).1260(C=S),2505(C-SH),3010(C-NH).3300(C-NH2).**^{1}HNMR :** (500MHZ, CDC13), ð 6.12, 6.24, 6.7,7.31, 7.42, 7.41, 7.53, 7.59, 7.6, 7.89, (Ar-H). **^{13}CNMR:** (500MHZ, CDC13), ð 120.0, 123.1, 123.5, 133.5, 135.5, 145.3, 145.7, 148.0, 149.5, 150.0 (C-H), ð 151.34 (C=N), ð 1901.0 (C=S), ð 129.08 (C-NH2).

Compound [1d]: Synthesis of 4-(-4nitrophenyl)-6-phenylpyrimidine-2(1H)-thione: Yield- 78%, **IR Data:** FTIR (γ max, C m-1) 1655(-C=C stretch), 2860 (= C-H stretch), 1515 (=C-H bend), 1610 (-C=N), 3005 (- C-NH).1268(C=S),2525(C-SH),3005(C-NH),1470(C-NO2). **^{1}HNMR:** (500MHZ, CDC13), ð 6.31, 6.35, 6.7, 6.81, 6.85, 7.12, 7.4, 7.54, 7.85, 7.91, (Ar-H)**. ^{13}CNMR:** (500MHZ, CDC13), ð 128.9, 130.1, 132.2, 135.5, 135.6, 136.2, 136.9, 137.1, 145.5, 146.4 (C-H), ð 154.34 (C=N), ð 190.3 (C=S), ð 146.1 (C-NO2).
Compound [1e]: Synthesis of 4-(-4methoxyphenyl)-6-phenylpyrimidine-2(1H)-thione: Yield- 78%, **IR Data:** FTIR (γ max, C m-1) 1645(-C=C stretch), 2865(= C-H stretch), 1525 (=C-H bend), 1142 (C-N), 3015 (- C-NH).1258(C=S), 2515(C-SH),3015(C-NH),1605 (C=N). **^{1}HNMR** (500MHZ, CDC13), ð 6.4, 6.45, 6.78, 6.9, 7.01, 7.57, 7.89, 8.02, 8.23, 8.34, (Ar-H)**. ^{13}CNMR:** (500MHZ, CDC13), ð 121.5, 123.6, 125.01, 130.4, 135.5, 145.5, 146.6, 147.1,148.5, 150.0 (C-H), ð 151.34 (C=N), ð 79.9 (C-OCH3), ð 190.9 (C=S).

In silico evaluation for drug-likeness and toxicity predictions [7-8]

Currently, in this work three cheminformatics programmes were used to evaluate the drug likeness of compounds, toxicity predictions, to assess the inhibition of the derivatives against 5 subtypes of cytochrome P450. Open-source program OSIRIS Property Explorer was used to predict the fragment-based drug-likeness of title compounds and comparing them with Fluconazole and tetracycline, to assess the occurrence frequency of each fragment in the individual structure. The program estimated the risks of side effects, such as mutagenic, tumorigenic, irritant and reproductive effects, as well as drug-relevant properties including cLogP, LogS (solubility), MW and drug-likeness. Molinspiration cheminformatics used for calculation of important molecular properties like logP, Polar surface area, Number of hydrogen bond donors, Number of hydrogen bond acceptors, Number of rotatable bonds, Volume, Number of violations from rule of five. It was also used to predict bioactive scores for the most important drug targets like GPCR ligand, Kinase inhibitors, Ion channel modulators, nuclear receptors, Protease inhibitors, Enzyme inhibitors.

Table-3: OSIRIS Calculations:

Compound	Toxicity Risks				Molecular Properties Calculation				
	MUT	TUMO	IRRI	REP	M.W	CLP	logS	DL	DS
1a					264	3.45	-4.33	2.2	0.7
1b					298	4.05	-5.06	3.03	0.6
1c					279	2.77	-4.4	1.66	0.7
1d					293.0	3.22	-4.84	-0.31	0.2
1e					294	3.38	-4.34	1.77	0.68

MUT: Mutagenic; **TUMO:** Tumorigenic; **IRRI:** Irritant; **REP:** Reproductive Effective; **CLP:** CLogP; **Log s:** Solubility mol/lit; **DL:** Drug-Likeness; **DS:** Drug-Score. **MW:** Molecular weight

Table.4: Molinspiration Drug Likeness Properties

Compound code	Compound IUPAC Names	Log P	Polar Surface Area	H-Bond Acceptors	H-Bond Donor	Volume
1a	4,6-diphenyl pyrimidine-2(1H)-thione	3.56	28.68	2	1	235.55
1b	4-(4-chlorophenyl)-6-phenyl pyrimidine-2(1H)-thione	4.24	28.68	2	1	249.09
1c	4-(4-aminophenyl)-6-phenyl pyrimidine-2(1H)-thione	2.64	54.71	3	3	246.84
1d	4-(4-nitrophenyl)-6-phenyl pyrimidine-2(1H)-thione	3.52	74.51	5	1	258.88
1e	4-(4-methoxyphenyl)-6-phenyl pyrimidine-2(1H)-thione	3.62	37.92	3	1	261.10

Table.5: Molinspiration BIOACTIVE SCORES

Compound	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1a	-0.35	-0.39	-0.34	-0.42	-0.55	-0.29
1b	-0.29	-0.38	-0.30	-0.38	-0.53	-0.30
1c	-0.24	-0.31	-0.15	-0.44	-0.38	-0.16
1d	-0.39	-0.41	-0.37	-0.38	-0.53	-0.37
1e	-0.13	-0.26	-0.16	-0.15	-0.16	-0.10

The Online Chemical Modelling Environment (OCHEM) a unique and a web-based platform which supports all the steps required to create a predictive model: one such model developed was cytochrome P450 with 5 subtypes the compounds were evaluated to assess their Inhibition on the subtypes of cytochrome P450

Table .6: O– CHEM (Online Chemical Modelling Environment):

Co mpound	Aqueous solubility	LogIGC50	AMES	CYP3A4	CYP2D6	CYP2C19	CYP2C9	CYP1A2
1a	5.4	0.19	Inactive	+	-	+	+	+
1b	4.6	0.66	Inactive	+	+	+	+	+
1c	3.7	0.31	Active	+	+	+	-	+
1d	4.2	0.7	Active	+	+	+	+	+
1e	5.6	1.1	Inactive	+	+	+	+	+

+ Inhibitor, - Non inhibitor, AQ-aqueous, IGC 50-Environmental toxicity

RESULTS AND DISCUSSION:

The derivatives synthesised were evaluated by three online software's- OSIRIS, MOLINSPIRATION, OCHEM. OSIRIS results predicts that the compound **1a,2a** have high drug score 0.7 and compound 2b have low drug score 0.2toxicity predictions inferred that 2b compound shows mutagenic and tumorigenic and remaining compounds are safe. From the OCHEM results, all the synthesised compounds were found to inhibit the subtype CYP3A4, CYP2C19, CYP1A2 of cytochrome P450. Molinspiration results inferred that all the derivatives satisfy Lipinski rule of five so as to behave as a drug and found to have kinase and enzyme inhibition properties.

CONCLUSION:

In conclusion, we have developed a simple, benign and expeditious synthesis of biologically significant pyridine derivatives with good yields under mortar and pestle grinding method and fully characterized the products by IR. 'H NMR, Mass spectral and Elemental analysis. The Synthesis of pyridine derivatives by mortar and pestle grinding method (yield 70%-78%). By Molinspiration software we found that compounds are having better bioactive score against enzyme inhibition and protease inhibition. All the synthesised compounds were found to inhibit the subtype CYP1A2, CYP2D6, CYP2C19, CYPC9 of cytochrome P450 in O-Chem software.

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