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SYNTHESIS AND INSILICO EVALUATION OF 4, 6- DIPHENYL PYRIDINE-3 (2H) -ONEDERIVATIVES

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ABSTRACT

A Series of Bioactive compounds, 4,6-diphenyl pyridine-3(2H)-one(1a), 6-(4-cholo phenyl)-4-phenylpyridne-3(2H)-one(1b), 6-(4-amino phenyl)-4-phenyl pyridine-3(2H)-one(2a), 6-(4-nitro phenyl)-4-phenyl pyridine -3(2H)-one(2b), 6-(4-methoxy phenyl)-4-phenylpyridine-3(2H)-one(3a), were Synthesized according to the Literature methods. The Synthesized compounds were characterized by NMR, IR & Mass Spectroscopy.

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INTRODUCTION

Pyridine is a heterocyclic organic compound with the chemical formula C5H5N. It is structurally related to benzene where the one CH group in aromatic six membered ring is replaced nitrogen atom. Pyridine was industrially produced by extraction from coal tar [1]. It was found in natural sources such as alkaloids (nicotine), vitamins (niacin and pyridoxine) and coenzymes [2].

Pyridine is water miscible, flammable and colourless to yellow liquid. Its boiling point was 115.5c and melting point -41.6c. pyridine bears an unpleasant/foul smell and some hazardous properties. Cyclic pyridine is planar with a sp2 hybridized N atom and five C atoms and has a delocalized Pi-molecular orbital that fulfils the Huckel criteria {(4n+2) π electrons} and thus confirms its aromaticity. Structurally, pyridine is isoelectronic with benzene and exhibits unusual isotopic polymorphism properties [3]. The biological activities and physical properties of pyridine analogues can be improved by introducing various function groups into the pyridine scaffold. For example, vitaminB3, also known as nicotinic acid and with multiple biological activities, contains the carboxylic acid moiety at the C-3 position of the pyridine [4-6]. Pyridine is not abundant in nature, except for the leaves and roots of belladonna (Atropa belladonna) [7] and in marshmallow (Althaea officinalis) [8].

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(FINAR.B.NO.60107022LU),Acetophenone(FINAR.B.NO.50560212BP), Ethanol(CCS.B.NO.110605), Ethyl acetate (AVRA), KOH (www. researchlab.in.12451909181), Silica gel-G- (RESEARCH LAB FINECHEM INDUSTRIESB.NO.1317310113), Anisaldehyde (ULTRA PURE LAB CHEM INDUSTRIES.B. NO.AA/277/21), Glycine(FISHER SCIENTIFIC Prod.NO.24755), Aminobenzaldehyde (SIGMA-ALDRICH, Co.,3050Spruest), n-Hexane(PHARMACO - AAPER.B.NO.WO115400).

Chemical synthesis

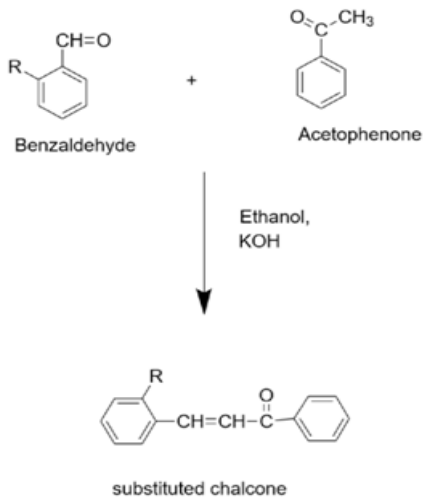
Step-1: Synthesis of substituted chalcone derivatives:

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.

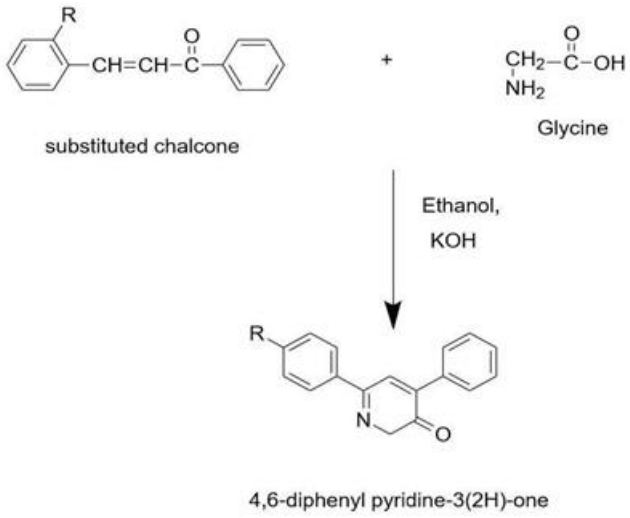
Step-2: Synthesis of Pyridine compounds:

Equimoles of substituted chalcone derivatives and glycine 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, NO_2, NH_2, OCH_3

TABLE 1: PHYSICAL DATA.

Code	Compound	M.F	M.W	%yield	C%	H%	O%	N%	Cl%	S%
1a	4,6-diphenyl pyridine-3 (2H)-one	$C_{17}H_{13}NO$	247.29	72%	82.57	5.30	6.47	5.66	–	–
1b	6-(4-chloro phenyl)-4-phenyl pyridine-3(2H)-one	$C_{17}H_{12}ClNO$	281.73	75%	72.47	4.29	5.68	4.97	12.58	–
1c	6-(4-amino phenyl)-4-phenyl pyridine-3(2H)-one	$C_{17}H_{14}N_2O$	262.31	77%	77.84	5.38	6.10	10.68	–	–
1d	6-(4-nitro phenyl)-4-phenyl pyridine-3(2H)-one	$C_{17}H_{12}N_2O_3$	292.29	77%	69.86	4.14	16.42	9.58	–	–
1c	6-(4-Methoxy phenyl)-4-phenylpyridine3 (2H)-one	$C_{18}H_{15}NO_2$	277.32	78%	77.96	5.45	11.54	5.05	–	–

Compound [1a] :4,6-Diphenyl pyridine-3(2H)-one: Yield-72%; **IR Data:** 2820 (C–H stretching), 1400(C–H bend), 1625(C=N), 1690(C=O), 1630(C=C) **^{1}HNMR:** (500MHZ, CDC13), δ 6.65, 7.14, 7.26, 7.34, 7.39, 7.57, 7.63, 7.71, 8.04, 8.10, 8.43 (Ar-H), δ 1.4 (R-CH_2).**^{13}CNMR:** (500MHZ, CDC13), δ 128.85, 127.54, 130.77, 130.02, 121.20, 116.02, 145.17, 121.27, 128.89, 135.89, 143.83(C-H), δ 46.97 (C-CH_2), δ153.34 (C=N), δ 210(C=O)

Compound [1b]:6-(4-chlorophenyl)-4-phenyl pyridine-3(2H)-one-: Yield- 75%, **IR Data:** 670 (-C–Cl), 2800 (= C-H stretch), 1420 (=CH bend), 1615 (-C=N), 1700(C=O). **^{1}HNMR:** (500MHZ, CDC13), δ 7.40, 7.42, 7.51, 7.63, 7.72, 7.77, 7.98, 8.04, 8.25, 8.34. (Ar-H), δ 1.3(C-CH2), δ 3.23 (C-Cl)**. ^{13}CNMR:** (500MHZ, CDC13), δ 128.85, 127.54, 130.77, 130.02, 120.74, 116.02, 145.17, 121.27, 128.89, 131.78 (C-H), δ56.87 (C-Cl), δ154.34 (C=N), δ 213(C=O).

Compound [1c]: 6-(4-aminophenyl)-4-phenyl pyridine-3(2H)-one: Yield- 77%, **IR Data:** 3250(=C–NH2), 2815(=CH stretching), 1410(=CH bend), 1620(C=N), 1640(C=C). **^{1}HNMR:** (500MHZ, CDC13), δ 7.40, 7.42, 7.51, 7.63, 7.65, 7.77, 7.89, 8.02, 8.32, 8.43 (Ar-H), δ 1.32(C-CH2), δ 7.63 (C-NH2).**^{13}CNMR:** (500MHZ,CDC13), δ 128.85, 127.54, 130.77, 130.02, 120.74, 116.02, 145.17, 121.27, 128.89, 132.34 (C-H), δ129.06 (C-NH_2), δ155.34 (C=N), δ 215(C=O).

Compound [1d]: 6-(4-nitrophenyl)-4-phenyl pyridine-3(2H)-one: Yield- 77%, **IR Data :** 2810(=CH stretching), 1405(C–H bond), 1680(C=O), 1615(C=C), 1490(C–NO2), 1610(C=N). **^{1}HNMR:** (500MHZ, CDC13), ð 7.40, 7.42, 7.51, 7.63, 7.77, 7.87, 7.93, 8.02, 8.32, 8.47 (Ar-H), ð 1.47(C-CH2), ð 7.63 (C-NH_2). **^{13}CNMR:** (500MHZ, CDC13), ð 127.85, 125.54, 133.77, 134.02, 125.74, 118.02, 146.17, 124.27, 129.89, 134.45 (C-H), ð147.30 (C-NO_2), ð152.34 (C=N), ð 217(C=O).

Compound[1e]: 6-(4-methoxyphenyl)-4-phenyl pyridine: Yield- 78%,**IR Data:** 1620(C=C), 1695(C=O), 1630(C=N), 1415(C–H bend), 2805(C–H stretching`), 2800(C– CH3).**^{1}HNMR:** (500MHZ, CDC13), ð 6.60, 6.82, 7.01, 7.53, 7.65, 7.78, 7.89, 8.05, 8.25, 8.43 (Ar-H), ð 1.24 (C-CH2).**^{13}CNMR:** (500MHZ, CDC13), ð 122.85, 124.54, 129.77, 130.02, 127.74, 114.02, 146.17, 128.27,138.89, 148.78 (C-H), ð76.89 (C-OCH3), ð157.34 (C=N), ð 220(C=O).

In silico evaluation for drug-likeness and toxicity predictions[9-10]

Currently, in this work three chem. informatics programmes were used to evaluate the drug likeness of compounds, toxicity predictions, to assess the inhibition of the derivatives against 5 subtypes of cyto chrome 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					247	2.61	-3.39	4.64	0.81
1b					281	3.2	-4.13	5.24	0.61
1c					262	1.94	-3.47	4.0	0.86
1d					276	2.38	-3.9	2.7	0.29
1e					277	2.54	-3.41	4.04	0.84

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: Mol inspiration Drug Likeness Properties.

Compound code	Compound IUPAC Names	Log P	Polar Surface Area	H-Bond Acceptors	H-Bond Donor	Volume
1a	4,6-diphenyl pyridine-3(2H)-one	2.73	29.43	2	2	231.07
1b	6-(4-chlorophenyl)-4-phenyl pyridine-3(2H)-one	3.41	29.43	2	2	244.61
1c	6-(4-aminophenyl)-4-phenyl pyridine-3(2H)-one	1.81	55.46	3	2	242.36
1d	6-(4-nitrophenyl)-4-phenyl pyridine-3(2H)-one	2.69	75.26	5	3	254.41
1e	6-(4-methoxyphenyl)-4-phenyl pyridine-3(2H)-one	2.79	38.67	3	0	256.62

Table.5: Molinspiration BIOACTIVE SCORES.

Compound	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1a	-0.26	-0.00	-0.57	-0.17	-0.19	-0.02
1b	-0.20	-0.01	-0.52	-0.14	-0.19	-0.05
1c	-0.15	-0.06	-0.37	-0.19	-0.04	-0.09
1d	-0.31	-0.07	-0.56	-0.15	-0.22	-0.14
1e	-0.21	-0.10	-0.49	-0.09	-0.16	-0.67

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):

Compound	Aqueous solubility	LogIGC50	AMES	CYP3A4	CYP2D6	CYP2C19	CYP2C9	CYP1A2
1a	3.9	1.2	Inactive	-	-	+	+	+
1b	4.6	1.4	Inactive	-	-	+	+	+
1c	3.9	0.79	Active	+	+	+	+	+
1d	4.4	1.6	Inactive	-	-	+	+	+
1e	4.2	1.3	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 2a have high drug score 0.86 and compound 2b have low drug score 0.29. toxicity predictions inferred that 1b compound shows tumorigenic action and 2b shows mutagenic and tumorigenic action and 1a, 2a and 3a compounds are safe. From the OCHEM results, all the synthesised compounds were found to inhibit the subtype CYP1A2, CYP2D6, CYP2C19, CYPC9 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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