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IN SILICO DESIGN, BASE CATALYSED SYNTHESIS OF 2-CHLORO-5-FLUORO (4, 5-DIPYRIMIDINE) 2-AMINE

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ABSTRACT

Tuberculosis remains the second leading cause of death from an infectious disease globally, despite the incessant efforts to control it. Research and development into new TB medicine is imperative for effective TB control, however new strategies for the rational use of existing drug such as finding the binding affinity between drug and target by molecular docking could also significantly enhance this process. The base catalyzed study of synthesis of 2-chloro-5-flouro-(4,5-Bipyrimidine)2'-amine to improve the yields and economically viable industrialization process from its biological active pyrimidine derivative of 5-fluorouracil.In this study, the designed compounds were docked with receptors such as protease, Reverse Transcriptase and Vascular Endothelial Growth Factor by using Mcule Docking. Among these Reverse Transcriptase shows good binding affinity with compound on the basis of docking score.

Keywords: Chlorination, Animation of 5-flouro uracil, Base catalyzed synthesis, Molecular docking etc.

INTRODUCTION

Fluoropyrimidines were first described in 1957 as anticancer agents that also exhibited profound inhibitory effects on the growth and viability of various microorganisms [1]. The pyrimidine analog 5-fluorouracil (5-FU) and its derivatives demonstrate clinical efficacy in a wide variety of cancers [2]. Although 5-FU is arguably the most successful drug approved to date for the treatment of cancer, its use as an antibacterial agent has not been extensively explored. In our Current proposed work we have tried to establish a base Catalyzed Chlorination process for the synthesis of fluoropyrimidine derivative's [3-5].

MATERIAL AND METHOD

Tools and Materials Used: - In our proposed study we used, biological database like PDB (protein data bank) and software like ACD chem. Sketch and molecule docking software mcule.

PDB is database contains structural data of biological macromolecules, established in Brookhaven national laboratories (BNL) in 1971. It is a database which contains three-dimentional structural information or data of various biological molecules such as nucleic acid, protein, etc. the data of such biological molecules is obtained by NMR Spectroscopy, X-ray Crystallography or by Cryo-electron microscopy. ACD/chem. sketch is the chemically intelligent drawing software from ACD/labs developed to help chemist quickly and easily draw schematic diagrams, molecules, reactions, and calculate their chemical properties such as molecular weight, molecular formula, logP values and to generate the IUPAC name. ACD chem. sketch can convert "SMILES" notations to structure and vice versa. Docking is a process which predicts preferred orientation of one molecule to another when they bind to each other to form a stable complex. Docking allows us to predict the strongest binders based on various scoring functions. It explores ways in which two molecules, such as drugs and an enzyme or receptor fit together and docks to each other. By binding with a receptor, molecule can inhibits its function, and thus act as drug. We have used mcule docking software which is integrated drug discovery platform enable scientist to identify, optimize and order hits and leads. It is combination of services providing us a

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cost effective and fast way to identify new drug candidate.Melting points were determined routinely in open capillary tube. The completion of reaction was routinely monitored by TLC on percoated silica gel-G plates. IR spectra were recorded on Shimadzu-8400 FT-IR spectrometer in Ker (in cm-1).

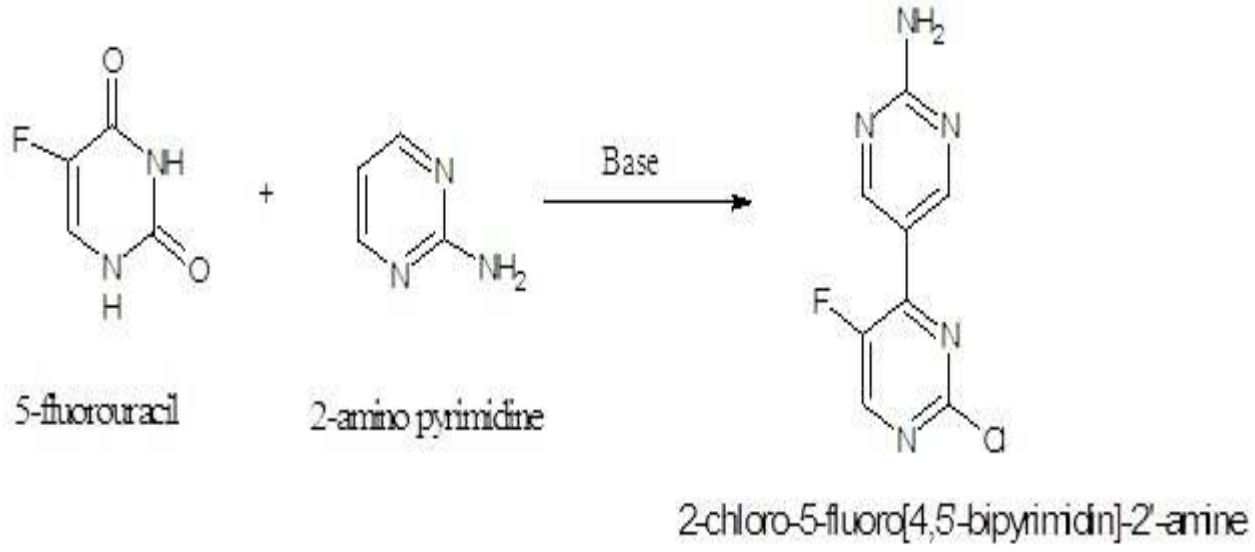
GENERAL PROCEDURE

Step 1: (Preparation of 2, 4-Dichloro-5-flouro Pyrimidine.)

1. To a clean and dry round bottom flask added 116.51gms of Phosphorous oxy chloride (POCl3) and base (0.5ml) at room temperature.
2. After that stirred it for 10min and 25gm of 5-fluorouracil was added portion wise and sir for 20 min at room temperature (control the exothermic reaction by adding little ice outside the flask which contain water at room temperature).
3. Then slowly rose the temperature 90 -110 deg C for 14 hrs.
4. If TLC complies then cool the reaction mass to room temperature and Pour it into ice cold water (100ml) under vigorous stirring.
5. The pH of reaction mixture was adjusted to pH-8, and the resulting mixture was stirred for 15 minutes.
6. The obtained light brown colored solid was filtered, Washed with (2x10ml) water and dried well to report the yield.

Step 2: (preparation of 2-chloro-4-Amino-5- flouro Pyrimidine.)

1. The Pure stage-1 compound 1 was taken in a clean RBF & 47.5gm of 2-amino pyrimidine was added at Room Temperature, slowly rise the temperature to 60^{o}C and was maintain for 1 hrs.
2. If TLC complies Cool to room temperature. Filter the obtained Solid material, Washed with water (2x20ml) and dried at 70-80^{O}C for half hour, report the Yield.



DOCKING STUDY: DOCKING POSE

Fig 1. Docking pose of VEGF

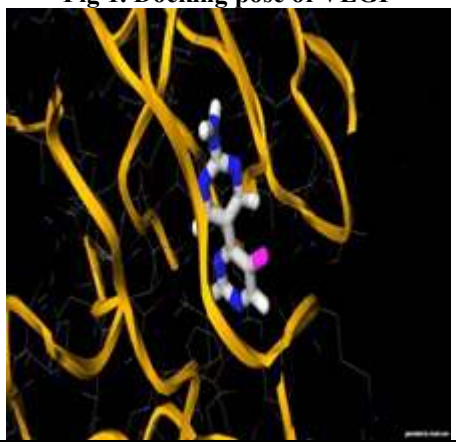


Fig 2. Docking pose of Protease

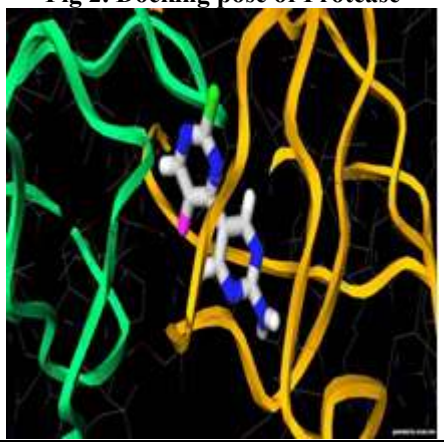


Fig 3. Docking pose of Reverse Transcriptase

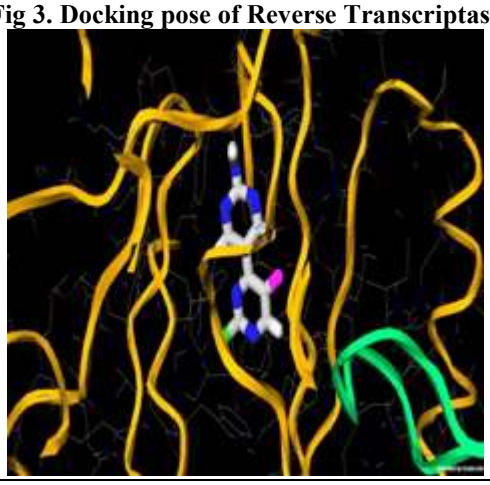


Fig 5 IR Spectra

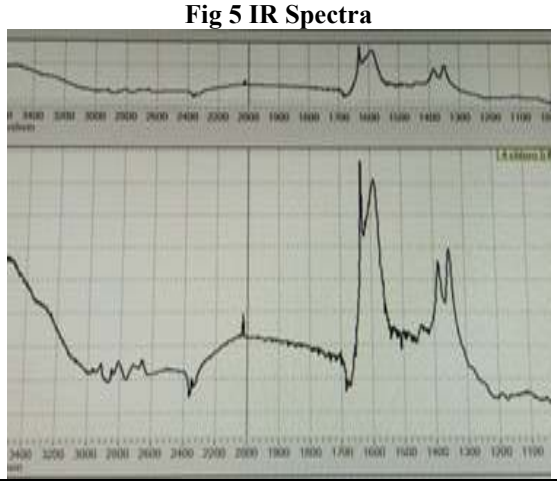


Table 1. Docking score of targets

Docking pose	Docking score of VEGF	Docking score of Protease	Docking score of Reverse Transcriptase
#1	-6.1	-6.2	-8.0
#2	-6.1	-6.1	-7.8
#3	-5.6	-6.0	-7.7
#4	-5.6	-5.9	-7.4

Table 2. Drug likeliness

Parameter	Result
Compound Code	1C
Base	DMSO
LogP	0.87
LogS	-3.07(inLog(moles/L)) 189.44 (in mg/L)
TPSA	55.89 A²
Drug Likeliness Score	-0.62

Table 3. Experimental results with various parameter

Compound Code	Base	Temp In °C	% yeild	Rxn.time In Hours	Mol Weight	Melting Point In °C	Rf Value	Colour
1C	DMSO	95-100	63.63%	5	224.01	114-116	0.56	Brown
2C	diethylamine	95-100	Product not obtained	5	224.01	-	-	-
3C	N,N-dimethyl amine	95-100	Product not obtained	5	224.01	-	-	-
4C	Diphenylamin e	95-100	Product not obtained	5	224.01	-	-	-

RESULT AND DISSCUSSION

We have tried to synthesis a of 2-chloro-5-flouro-(4,5-Bipyrimidine)2'-amine by using various base such as DMSO, diethylamine, N,N-dimethyl amine, Diphenylamine etc. In this study, the designed compounds were docked with receptors such as protease, Reverse Transcriptase and Vascular Endothelial Growth Factor by using Mcule Docking. The docking pose and docking

Score obtained from Mcule docking are as shown in fig 1, 2 & 3 and table 1 respectively. Drug like properties, LogP, LogS& TPSA properties are predicted from molsoft L.L.C. as shown in table 2. The IR spectra was obtained from and the spectra shows presence functional group such as C-H stretch at 2900cm^{-1}, C=C stretch at 1675cm^{-1}, C=N stretch at 2250cm^{-1}, C-H bend at 1350cm^{-1} etc. but the spectra does not show presence of

N-H bond, shown in as in fig 5 .The other physicochemical Obtained, Observed experimental results are mentioned as shown as in the table 3.

CONCLUSION

From the above results, we can say that the target **Reverse Transcriptase** show good ligand-protein interactions than the other targets and give better docking score than other target. Hence it may be a lead for our Anti-tubercular drug to patient coinfected with HIV research. Experimentally the yields was observed in case of DMSO base only and not with other bases.

The IR study the obtained IR spectra does not show peaks for nitrogen i.e. IR studies for obtained compound do not support the chemical structure of the compound. Hence finally we conclude that, this method of base catalyzed synthesis is not suitable for synthesis of proposed compound.

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Nil.

CONFLICT OF INTEREST

None.

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