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COMPUTATIONAL APPROACH FOR THE SYNTHESIS OF SUBSTITUTED PYRIMIDINE DERIVATIVES AS POTENTIAL NUTRITIONAL NOVEL INHIBITORS

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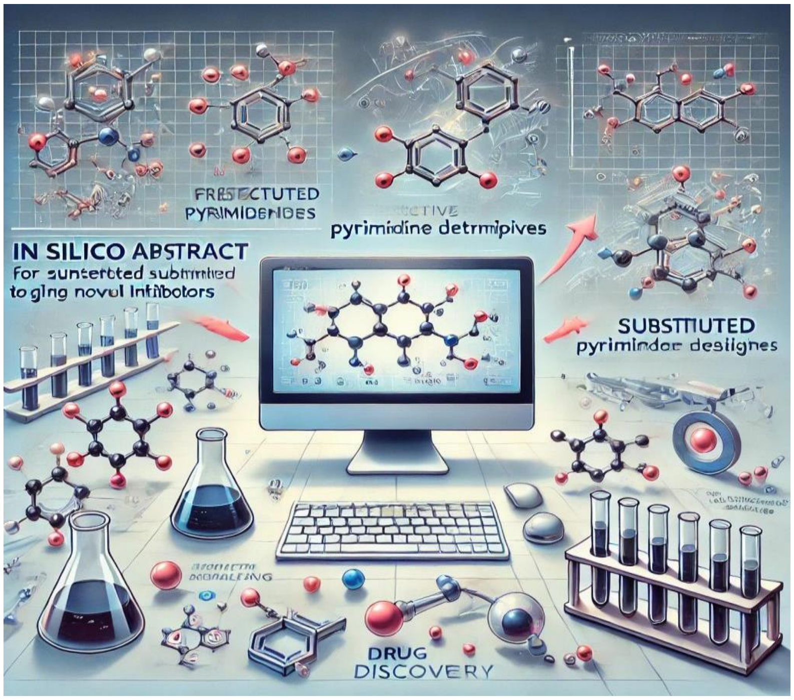
Abstract:

In silico approach explores the innovative utilization of in silico methodologies in the synthesis of substituted Pyrimidine derivatives, aiming to design novel inhibitors. The computational approach involves predictive modeling of synthetic routes, retrosynthetic analysis, and property-based filtering. By synergizing computational insights with experimental validation, this approach holds promise for expediting inhibitor discovery. The article discusses challenges, opportunities, and the transformative potential of in silico synthesis in reshaping modern drug design.

Keywords: silico synthesis, substituted Pyrimidine derivatives, inhibitor design, predictive modeling, retrosynthetic analysis, drug discovery.

Graphical Abstract:



1. Introduction:

A series of structure based drug design hypotheses and focused screening efforts led to the identification of tetrahydropyrrolo-diazepenones with striking potency against ERK2 kinase. The role of fluorination in mitigating microsomal clearance was systematically explored. Ultimately, it was found that fluorination of a cyclopentanol substructure provided significant improvement in both potency and human metabolic stability [1].

The extracellular signal-regulated kinase (ERK) is a component of the mitogen-activated protein kinase cascade. These data indicate that ERK2 plays an essential role in mesoderm differentiation during embryonic development. Extracellular signal-regulated kinase-1 and -2 (ERK1/2) proteins regulate a variety of cellular functions, including cell proliferation and differentiation, by interacting with and phosphorylating substrate proteins [2].

In these studies, we provide a quantitative analysis of ERK2 interactions with substrates using surface Plasmon resonance to measure real time protein-protein interactions. These studies provide a quantitative evaluation of specific docking domains involved in mediating interactions between ERK2 and protein substrates and define the contributions of these interactions to phosphate transfer [3].

Molecular docking technique is used in the present study for the comparison of binding affinity and selectivity of parent scaffolds and their integrated complex against ERK-2 Kinase. Where insilico integrated set up made for parent scaffolds and their varied substituted complex with ERK2. During this insilico process following preliminary Settings prepared for the docking run platform [4].

2. Targeting

2. 1. Targeting the ERK2 Kinase.

The mitogen activated protein (MAP) kinase family of enzymes regulates most biological processes including cell growth, proliferation, differentiation, inflammatory responses, and programmed cell death. Changes in MAP kinase activity have been implicated in the patho-physiology of cancer, inflammatory diseases, and neuro- degenerative disorders [5]. The three main members of MAP kinases include the extracellular signal-regulated kinases (2)(ERK), the c-Jun N-terminal kinases (JNK), and p38 MAP kinases. Currently, there is much interest in understanding the role of MAP kinases in disease as these proteins may be promising targets of new chemotherapy and anti-inflammatory agents.

The extracellular signal-regulated kinase (ERK) signalling pathway plays a crucial role in almost all cell functions and therefore requires exquisite control of its spatiotemporal activity. Depending on the cell type and stimulus, ERK activity will mediate different antiproliferative events, such as apoptosis, autophagy and senescence in vitro and in vivo. ERK activity can promote either intrinsic or extrinsic apoptotic pathways by induction of mitochondrial cytochrome c release or caspase-8 activation, permanent cell cycle arrest or autophagic vacuolization [6].

The role of the ERK signalling pathway in cancer is thought to be most prominent in tumours in which mutations in the receptor tyrosine kinases RAS, BRAF, CRAF, MEK1 or MEK2 drive growth factor-independent ERK1 and ERK2 activation and thence inappropriate cell proliferation and survival. New drugs that inhibit RAF or MEK1 and MEK2 have recently been approved or are currently undergoing late-stage clinical evaluation [7].

The selected enzyme structure was prepared in such a way that it has no ambiguities in the form of missing atoms or amino acids. All the hetero atoms (i. e. non- receptor atoms such as water, ions, etc.) were removed. To perform docking, protein grid design using the grid design tools available with Autodock. Docking was performed using both genetic (GA) and non-genetic (Non-GA) algorithm techniques. The genetic algorithm is the newly adopted conformational search techniques and provides very accurate and quality results in very short duration of simulation time. The controlled parameter and settings, which were used for docking. Extracellular regulated kinases (ERKs) 1 and 2 are closely related serine-threonine protein kinases. They are components of the RAS-ERK pathway, a critical signal transduction pathway that is activated in response to growth factor binding. ERK lies downstream from the small GTPase RAS and the protein kinases RAF and MEK in this pathway (8). This pathway is activated in many tumors due to activating mutations of the KRAS, NRAS, and BRAF genes. This observation provided strong rationale for targeting the RAS-ERK pathway BRAF and MEK inhibitors have demonstrated clinical activity in patients with BRAF-mutant melanoma [9].

The aim of the present study is to understand the inhibition possibilities and interaction details between (name of compound zenthindione) classes of compounds using molecular modeling techniques. Also utilizing the structure based drug design techniques, evaluate the possible conformations of small molecules and their binding energies with Crystal structure having PDF reference number 5BVF. Also to rank the best three molecules are evaluated on the basis of binding energy, cluster size and possibilities of hydrogen bond.

2.2 Preparation of receptor enzyme

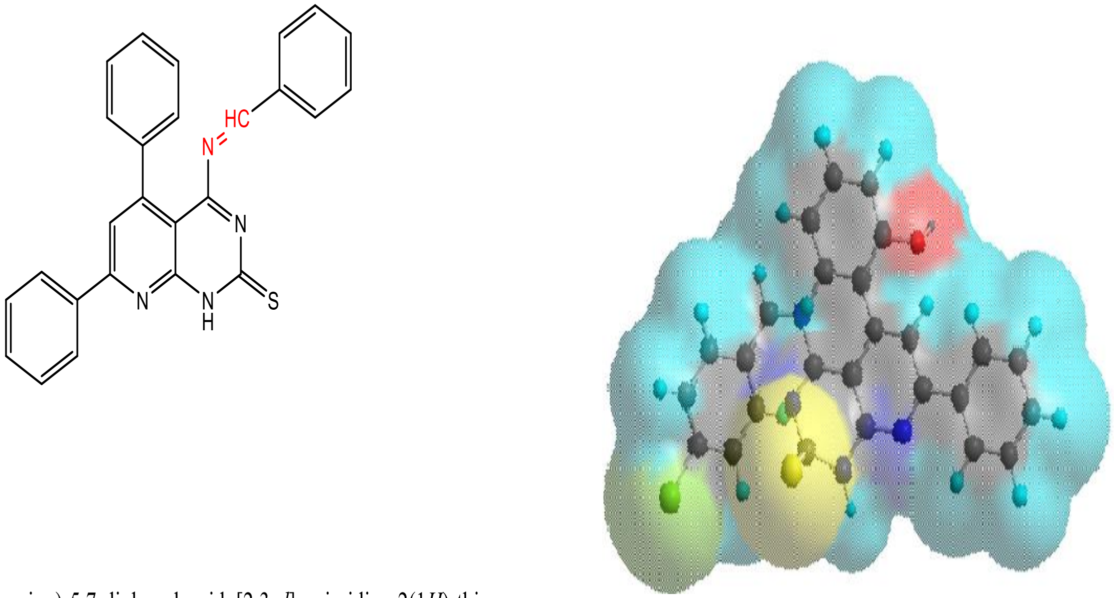
The selected enzyme whose crystal structures are available online has PDB reference 5BVF. The structure was downloaded from online protein data bank [8, 9]. The selected 3D structure of enzyme was having natural inhibitor **2-[(1S)-1-(3-chlorophenyl)-2-hydroxyethyl]-8-(2-{[(1S,3R)hydroxycyclopentyl]amino}pyrimidin-4-yl)-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepin-1-one.** The 3-D structure of enzyme is generally not complete. It needs the exhaustive checking for the missing bonds and atoms. Using the computer based Autodock tools these anomalies were removed and corrected for 5BVF. This is done only in binding site, as it is the place under investigation for the interactions with ligand. The solvation process was performed followed by preparation of enzyme grid for docking process using Auto Dock [10].

2.3 Selection of binding site

To understand the inhibition possibilities, the designed small molecule should be placed in the selected active site of the enzyme. The place is also called as Motif. The motif is the active site consisting of enzyme folding where the drug actually interacts with the amino acids of enzyme. Figure 1 depicts the selected active site and also list amino acids involves in active sites whereas figure 2 shows the 2-D and 3-D structure of natural inhibitor in enzyme.

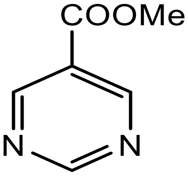
3. Validating the docking model by known drugs

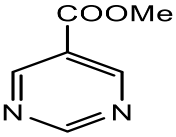
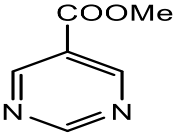
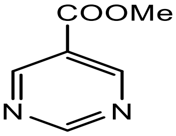
Before docking the prepared set of molecules the model needs validation and hence, the known drugs tetrahydropyrrolo-diazepenones were docked with the selected enzyme. The docking results for these known drugs are depicted in **table 1**. The known drugs interact with enzyme and successfully docked. The reported binding energies are negative and the ligand-enzyme complexes are stable. The results of known drugs are validating the docking methodology as the drugs are already interacting with selected binding site in vitro. The higher negative value of free energy is also supporting the validity of docking methodology. Though docking procedure does have ± 1.0 kcal mol-precision, still the results are supporting our model to be used for the unknown molecules.

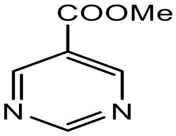


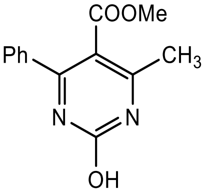
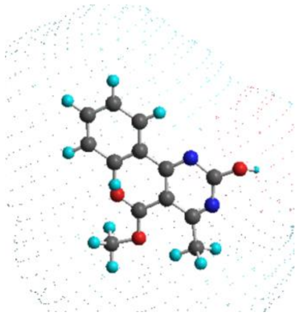
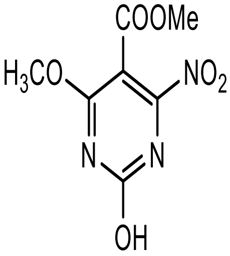
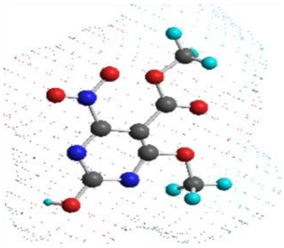
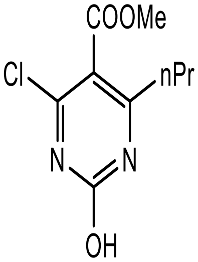
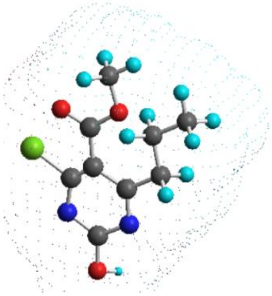
4-(benzylideneamino)-5,7-diphenylpyrido[2,3-*d*]pyrimidine-2(1*H*)-thione

Fig. 1 : Molecular docking of tetrahydropyrrolo-diazepenones were docked with the selected enzyme

Basic Target Molecule

Methyl pyrimidine-5-carboxylate Table:.1

Sr No.	Substituted pyrimidine compounds	R1	R2	R3
A.		-Ph	$-CH_3$	-OH
2		$-COCH_3$	$-NO_2$	-OH
3		-Cl	-n-Propyl	-OH

4		-C_2H_5	-F	-OH
Table:2 Newly Designed Substituted pyrimidine based compounds				

2-D Structure	3-D Structure
1.  methyl 2-hydroxy-4-methyl-6-phenylpyrimidine-5-carboxylate	
2.  methyl 2-hydroxy-4-methoxy-6-nitropyrimidine-5-carboxylate	
3.  methyl 4-chloro-2-hydroxy-6-propylpyrimidine-5-carboxylate	

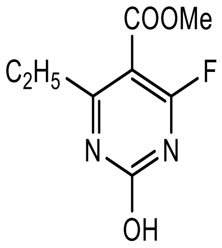
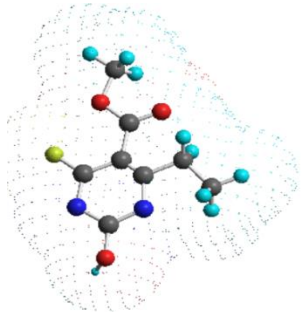
4	 methyl 4-ethyl-6-fluoro-2-hydroxypyrimidine-5-carboxylate	

Table 3:Design and prapartion substituted pyrimidine compounds

4. Conclusion:

Targeted cancer therapy takes advantage of distinguishing between cancerous and normal cells, which leads to the significant improvements in effectiveness of cancer treatments and minimizing side effects. For this purpose, this approach inhibits specific enzyme or protein in cancer cells. Here we reported Compounds **3a, 3b** and **4d**inhibited the potential lead compounds identified through this work will be useful in the further optimization of drug candidates against antimicrobial activities and potential lead compound for the development of new anticancer agents. The SAR studies of the discussed molecules offered a greater understanding of the pattern of substituents on their basic skeleton and appropriate substitutions accountable for its effectiveness. In addition, we have explored their structure activity relationships, as well as a binding mode through molecular docking studies.

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