

Novel pyrimidine derivatives: Synthesis, Molecular Docking Studies, and structure activity relationship

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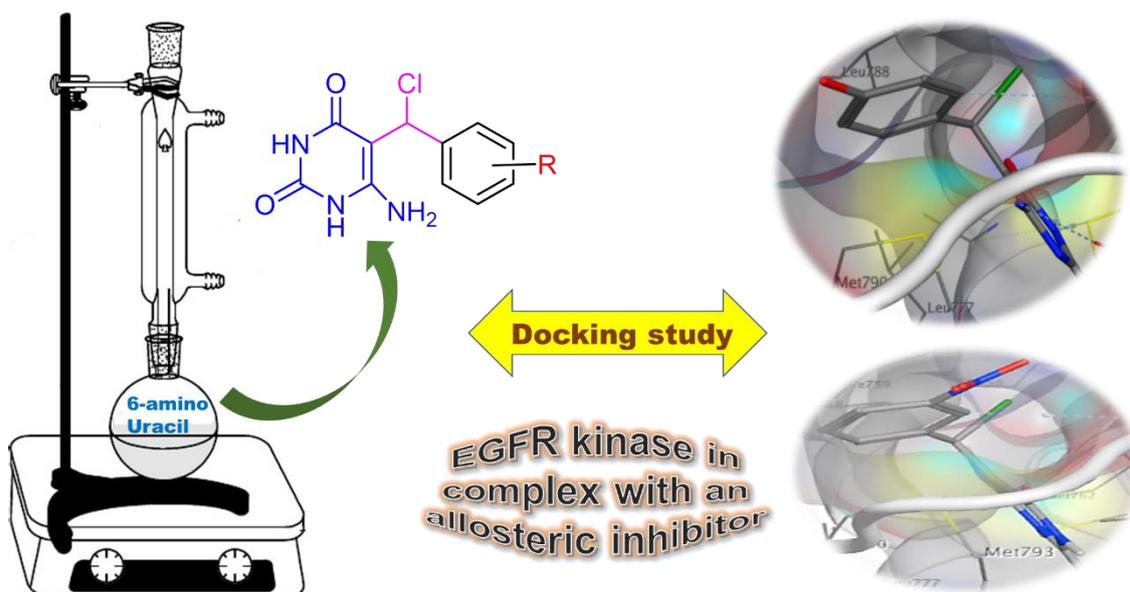
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ABSTRACT : Novel 5-substituted uracil has been synthesized as part of a research. The interaction of 6-amino uracil (1) and aromatic aldehydes 2a, b in conc. hydrochloric acid gives the Novel 5-substituted uracils 3a, b in good yields. The usage of IR, ¹H- NMR, ¹³C- NMR, and mass spectra to examine the composites' structural details. The computational Chemistry program MOE (2015) was use to investigate molecular docking, using reference substance with studying their SAR. The database's examination of molecular docking to investigate the proposed a style of action (PDB code : 7JXQ, resolution : 1.83). Although epidermal growth factor receptor small molecule therapy to lung cancer. EGFR allosteric inhibitor that binds to an alternative site on EGFR were developed to treat cancers with mutations in the EGFR that cause resistance to existing ATP-competitive EGFR.

KEYWORDS : 6-aminouracil ; Molecular docking ; and EGFR.

GRAPHICAL ABSTRACT

I. INTRODUCCION



Because uracil may be helpful structures in the field of drug development, their discovery has sparked the eye of medicinal chemists [1, 2]. Antitumor and antiviral the two most common types of discussed uracil-related activities, together with bactericidal, and herbicidal effects [3]. Bioactive compounds of uracil's substituted at

Fifth place stands one of the most biologically active derivatives of uracil's [4] has antiviral [5], anticancer, cytotoxic [6], antimycobacterial [7], anti-inflammatory [8], and antitumor [9, 10] activities. Several compounds containing the uracil moiety showed promise against a wide spectrum of microorganisms.

Undoubtedly, heterocyclic molecules, especially those with nitrogen, oxygen, and Sulphur atoms, have important biological functions [11, 12]. Pyrimidines are interesting heterocyclic systems with a range of biological and therapeutic effects [13-16]. Their compounds have been found to exhibit a variety of pharmacological properties, including anticancer properties [17] antiviral [18] and antifungal [19]. Also, applications of pyrimidine derivatives are extended to agriculture as a pesticide [20], and plant growth regulators [21]. Pyrimidines' 6-position function shown significant anti-HIV-1 efficacy [22, 23] with the presence of anti-rubella virus [24, 25]. A Several anticancer medications produced from pyrimidine derivatives are currently being used in care medicine, with some of these treatments successfully treating a number of neoplastic disorders like leukemia and testicular cancer.

Presented here is the synthesis of novel 5-substituted uracil having various aryl group. The goal of the current study is to find an easy and efficient way to synthesize system set to begin with 6-aminouracil (1), it is thought of as the adaptable first component of a basic synthon leading to the desired result, containing an uracil nucleus in its structure system. In the present work, A number of novel 5-substituted uracil were created using novel processing techniques. The compounds were identified using mass, ¹H-NMR, IR, and ¹³C-NMR spectra.

We also performed research using molecular docking for the synthesized medicines that can predict a receptor's characteristic three-dimensional shape binding mode(s) with a protein [26-28]. Main factor for lung cancer is cancer-related deaths cell. Lung cancer is common among American men and women, both accounting for 85% of all lung [29, 30] with non-small cancer. One of the most frequent modified oncogenic drivers in NSCLC is EGFR. A transmembrane protein called EGFR is a member of the ERBB family of tyrosine kinase (TK) receptors, which also includes the three other members ERBB2, ERBB3, and ERBB4. Computational Studies using molecular docking (MOE 2015) were applied to the novel compounds, while researching their SAR (structure activity relationship).

II. EXPERIMENTAL

Materials and methods

High-quality materials were employed to complete this project. Sigma-Aldrich provided all of the chemicals (Taufkirchen, Germany). All solvents were provided by the El-Nasr Pharmaceutical Chemicals Company in Egypt (analytical reagent grade). The melting points were tested using a Cole-Parmer Uncorrected digital Electrothermal IA 9100 Series equipment is located at Beacon Road in Stone, Staffordshire, ST15 OSA, UK. Analyses of C, H, and N were performed using a PerkinElmer CHN 2400. The IR spectra (KBr disks). For generating Bruker 400, 100 MHz NMR Spectrometer, ¹H and ¹³C-NMR spectra was utilized, DMSO-*d*₆ served as the solvent, and chemical changes were displayed in (ppm) in the Main Laboratory of Zagazig university, Egypt. Thin-layer chromatography (TLC) sheets covered with UV fluorescent silica gel used to monitor the reactions, which were observed employing different solvents as mobile phases and a UV laser. Chloroform, methanol (9:1), and ethyl acetate, toluene (1:1) were used as eluent solvents. Molecular docking studies were applied by using MOE software (2015).

synthesis

6-Aminouracil

(1):

Compound 1 was commercially available, Aldrich Chemical Company Inc. and also prepared in our lab. by heating under reflux, the ethyl cyanoacetate and urea in sodium ethoxide and abs. ethanol as a reported method [31, 32]. In 2013, Sunil S. Chavan *et. al.* report the creative, one-pot synthesis of cyanoacetylureas by generation of ureas and their cyclization to 6-aminouracils in the presence of the recyclable solvent and catalyst, 1,1,3,3-tetramethylguanidine lactate [TMG][Lac] [33, 34].

General procedure for 3a, b:

6-Aminouracil (1) (0.2g, 1.78mmol) was added, and then aromatic aldehydes 2a, b (1.78mmol) was dissolved in hot, concentrated HCl (30ml). For 14 hours, the mixture was refluxed. The resulting precipitate solid was then cooled to RT, was filtered, thoroughly washed with HCl, and oven-dried after collection. The separated solid was recrystallized by methanol to produce compounds 3a, b.

6-amino-5-[chloro(3-nitrophenyl)methyl]pyrimidine-2,4(1H,3H)-dione (3a):

Yellow crystal. Yield: 43.4%, m.p.:240-242°C. IR (v, cm⁻¹): 3229 (broad band NH₂), 3061 (CH aromatic), 2923, 2853 (CH aliphatic), 1697 (C=O), 1573, 1407 (NO₂). ¹H-NMR (DMSO-*d*₆, 400 MHz): δ = 5.45 (s, 1H, CH), 7.83 (s, 4H, Ar-H), 7.87-7.93 (s, 2H, NH₂ exchangeable by D₂O), 11.33 (s, 2H, 2NH exchangeable by D₂O), ¹³C-NMR (DMSO-*d*₆, 100 MHz): δ = 43.89 (C₁), 88.64(C₅ of pyrimidine), 123.02, 132.65, 134.43, 165.61 (C₆ of pyrimidine), 169.34 (2C=O).); MS: m/z (intensity %): 298.14 (10) [M²⁺], 296.38 (60) [M⁺], 280.72 (28) [M⁺-H₂N],

243.59 (5) $[M^+ - H_2ClN]$, 158.89 (23) $[M^+ - C_2H_4ClN_3O_2]$, 118.62 (100) $[M^+ - C_5H_7ClN_3O_2]$; Anal. Calcd. for $C_{11}H_9ClN_4O_4$ (296.67): C, 44.54; H, 3.06; N, 18.89; Found; C,44.56; H, 3.08; N, 18.90.

6-amino-5-[chloro(4-hydroxyphenyl)methyl]pyrimidine-2,4(1H,3H)-dione (3b):

White crystal. Yield: 43%, m.p.:304-306°C. IR (ν , cm^{-1}): 3654 (OH), 3456, 3200 (broad band for NH_2), 3061 (CH aromatic), 2854 (CH aliphatic), 1710 (C=O). 1H -NMR (DMSO- d_6 , 400 MHz): δ = 5.76 (s, 1H, CH), 7.62 (s, 2H, NH_2 exchangeable by D_2O), 7.83 (s, 4H, Ar-H), 7.88 (s, 1H, OH), 11.33 (s, 2H, 2NH exchangeable by D_2O), ^{13}C -NMR (DMSO- d_6 , 100 MHz): δ = 49.06 (C_{Cl}), 55.33(C_5 of pyrimidine), 123.40, 132.65, 133.04, 134.80, 150.50 (C_6 of pyrimidine), 165.11, 169.73 (2C=O).); MS: m/z (intensity %): 269.52 (22) $[M^2]$, 267.61 (28) $[M^+]$, 230.26 (10) $[M^+ - Cl]$, 202.48 (2) $[M^+ - CClO]$, 160.62 (100) $[M^+ - C_2HCINO_2]$, 118.62 (100) $[M^+ - C_5H_7ClN_3O_2]$; Anal. Calcd. for $C_{11}H_{10}ClN_3O_3$ (267.67): C, 49.36; H, 3.77; N, 15.70; Found; C,49.40; H, 3.78; N, 15.75.

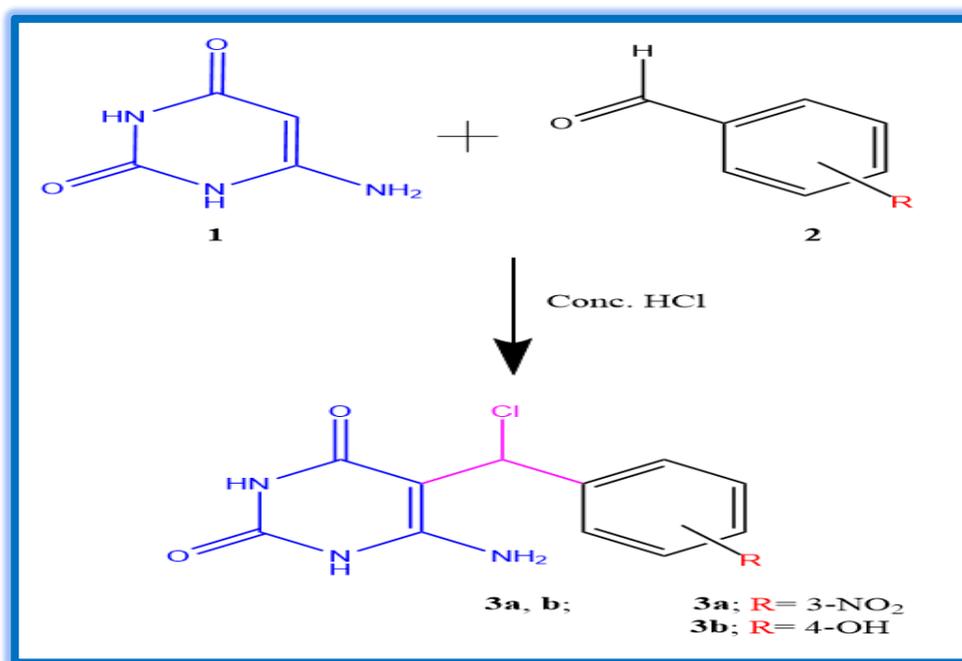
Docking study:

The computational methodologies for the most bioactive chemicals that would be docked utilizing Molecular Operating Environment software were developed using Chemdraw 12.0. (2015). The data were evaluated using the London DG force and force field energy. The data were evaluated using the London DG force and force field energy. All MMFF 94 (Merck molecular force field 94) was used to complete the minimizations until a root mean square deviation (RMSD) gradient of $0.1 \text{ kcal mol}^{-1} \text{ \AA}^{-1}$ was reached [35] and partial charges were estimated automatically. The dock function (S, Kcal/mol) of the MOE programme was used to assess the ligand's binding ability. The enzyme's X-ray crystal structure in PDB format came from the Protein Data Bank (PDB ID): 7JXQ, resolution: 1.83). In order to prepare the enzyme for docking studies, water was removed, hydrogen bonds were added, potential was fixed, false atoms were created from the resulting alpha spheres [36], and the ligand interaction with the amino acids in the active site was then examined. The most significant decrease in the the active ligand yields the best docking Score [36, 37].

III. Results and Discussion

Chemistry

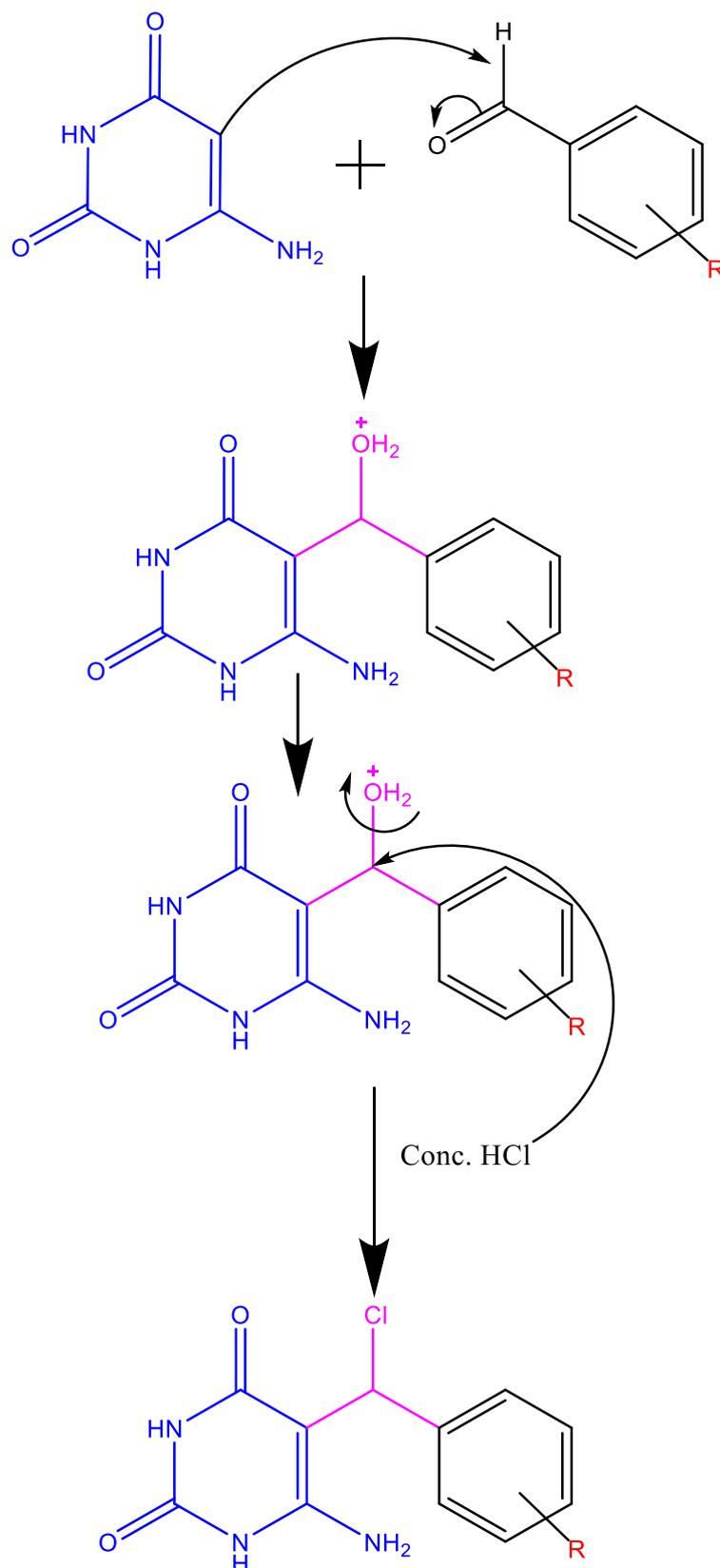
In the course of our study, we obtained the novel 5-substituted uracil **3a, b** in good yields, based on the reflux circumstances, 6-amino uracil (**1**) combined with one equal of aromatic aldehydes **2a, b** produced **3a, b** (Scheme 1).



SCHEME (1) The synthesis of novel 5-substituted uracil **3a, b**.

The Infrared spectra of **3a** exhibited Peak at 3061 cm^{-1} was associated with the CH aromatic. The NO_2 group in aromatic aldehyde moiety have the signal has peaks at 1573 and 1407 cm^{-1} , respectively. while the 1H -NMR signal decided to show at 5.45 ppm for the CH_{Cl} that was found to be at 43.89 ppm in ^{13}C -NMR spectra. The structural peak was seen on the MS (M/Z) at (296.38), while the base signal was visible at (118.62).

The Infrared spectra of **3b** showed a peak at 3654 cm^{-1} that matched the OH group in the aromatic aldehyde moiety. Peak at 3061 cm^{-1} was associated with the CH aromatic, while the $^1\text{H-NMR}$ signal decided to show at 5.76 ppm for the CH_α that was found to be at 49.06 ppm in $^{13}\text{C-NMR}$ spectra. The structural peak was seen on the MS (M/Z) at (267.61), while the base signal was visible at (160.62).



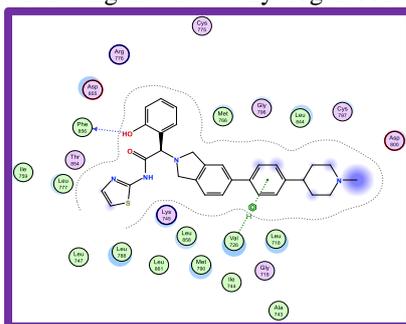
SCHEME (2) The proposed mechanism underlying the creation of novel 5-substituted uracil 3a, b.
Computational Chemistry

Molecular docking study:

The newly developed and synthesized therapeutic targets, in the database's study using molecular docking to determine the potential mechanism of action (PDB code: 7JXQ). The name of this enzyme is EGFR kinase in complex with an allosteric inhibitor according to site of protein data bank. A transmembrane protein called EGFR is a member of the ERBB family of tyrosine kinase (TK) receptors, which also includes the three other members ERBB2, ERBB3, and ERBB4. Allosteric EGFR inhibitors that bind to a different site on EGFR were developed to treat cancers with EGFR mutations that mediate resistance to existing ATP-competitive EGFR. The goal of this research was to gain a better knowledge of how the chemicals created to attach to the enzyme's protein-allosteric site. Re-docking of the co-crystallized ligand using the active site and the same number of criteria in order to validate the results of the present docking experiment at the active site. The root mean square deviation and energy score for the best-docked position were both 1.4415 and -8.9263 Kcal/mol, respectively, supporting the docking study performed with MOE software. Reference ligand created hydrogen bond with Phe856 (**figure 1**).

Figure (1). 2D receptor ligand

Compound **3b** suggested binding score of -7.1471. Compound **3a** has an kcal/mol, as indicated in **table (1)**.



interactions of reference

mode has a kcal/mol energy value of -6.7890

Table (1). The binding scores, RMSD values, distance and receptor interactions of the novel compounds **3a, b** compared to the reference ligand that is docked.

Comp.	Score (Kcal/mol)	RMSD	Residues that interact		
			Receptor interactions	Distance (Å)	E (Kcal/mol)
3a	-6.7890	1.9799	Asp855/ <i>H</i> -donor Met766/ <i>H</i> -donor Lys745/ <i>H</i> -acceptor	3.37 3.41 3.01	-1.3 -3.0 -5.0
3b	-7.1471	1.7906	Thr854/ <i>H</i> -donor Met766/ <i>H</i> -donor	2.90 3.27	-1.2 -3.1
Reference ligand	-8.9263	1.4415	Phe856/ <i>H</i> -donor	3.26	-1.6

Comp.

2D receptor interactions

3D receptor interactions

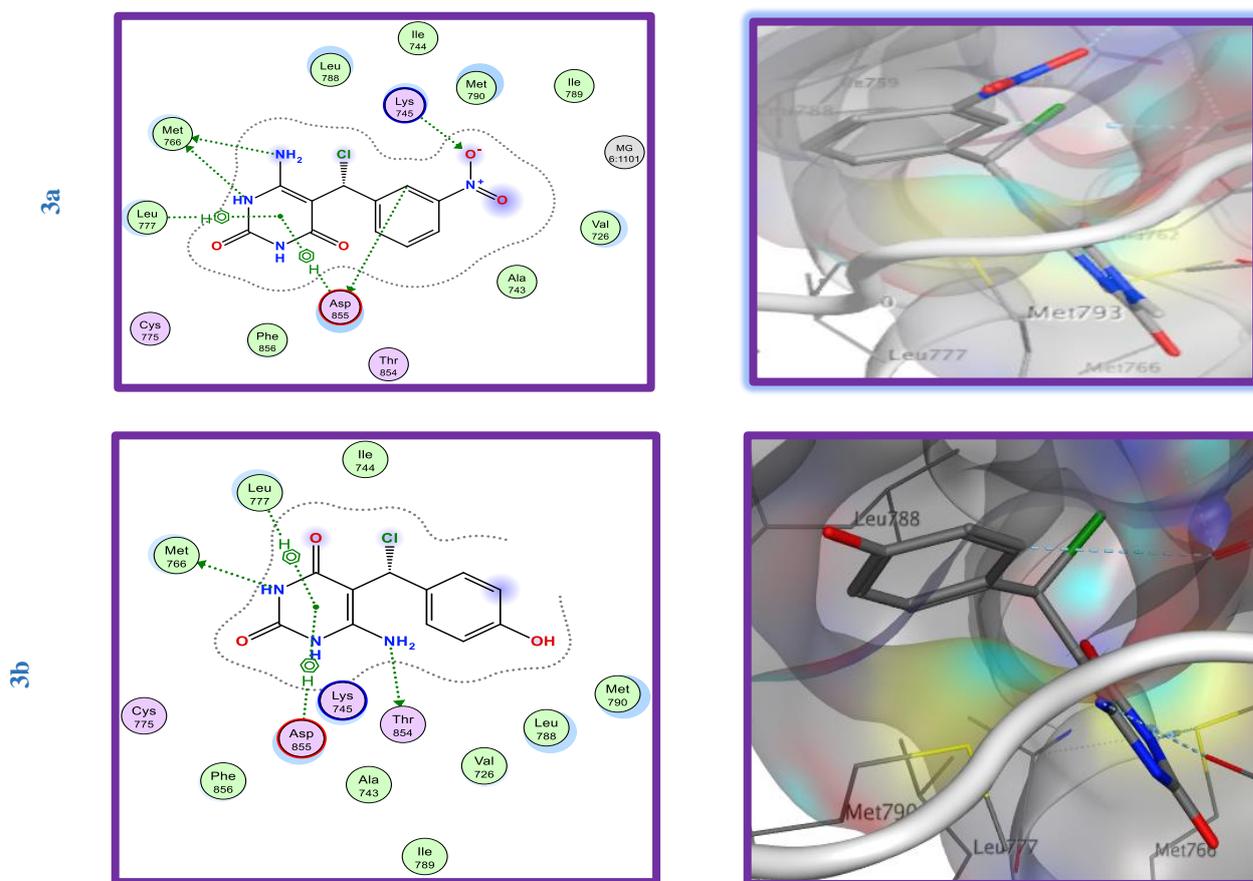
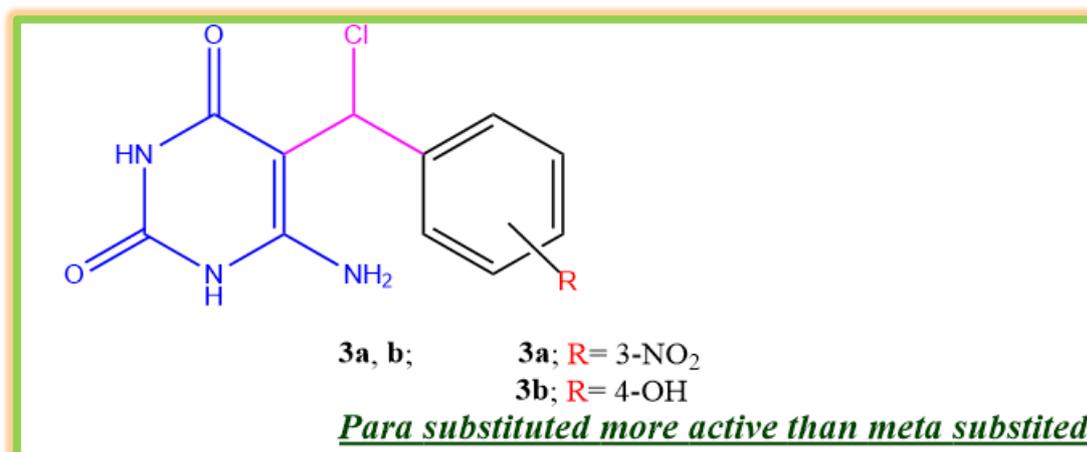


Figure (2). Interactions between the 2D and 3D receptors of synthesized compounds

Structure activity relationship (SAR):

the para substitution of phenyl moiety **3b** was found to have a significant impact on the inhibition of the receptor. As illustrated in (figure 2), orientation of compound **3b** (para hydroxy substituent) in pocket expiated the ideal formation than compound **3a** (steric substituent).; thus, compound **3b** shows more activity than meta substituted compound **3a**.

VI. CONCLUSION



The synthesis used in this paper is novel 5-substituted uracils. The authors also created a tentative molecular docking research that was successful for the produced molecules **3a**, **b** with EGFR enzyme (PDB ID: 7JXQ). Compound **3b** more active than compound **3a** according to docking and SAR studies.

DECLARATIONS

Conceptualization contributions from B.F.A., S.A.K.; and W.S.M.; Software, B.F.A.; Validation, B.F.A.; Formal analysis, B.F.A.; Investigation, B.F.A.; Resources, B.F.A. and W.S.M.; Data curation, B.F.A.; Writing—original draft, B.F.A. and S.A.K.; Writing—review & editing, B.F.A., and S.A.K.; Visualization, B.F.A. and S.A.K.; Supervision, S.A.K. and W.S.M.; The manuscript's published form was approved by all authors after they had read it.

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CONFLICT OF INTEREST

According to the authors, there are no conflicts of interest.

V. REFERENCE

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