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FULL PAPER

Synthesis, *in silico* ADMET, docking, antioxidant, antibacterial and antifungal evaluations of some pyrimidine derivatives

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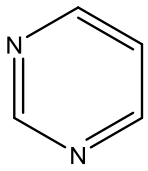
1,2,3,4-Tetrahydro-pyrimidine-5-carbonitrile derivatives were synthesized (compounds 1a-d) by the Biginelli reaction of substituted aromatic aldehydes, cyano-ethyl acetate, and urea/thiourea in absolute ethanol. In the next step, acid compounds (2a-d) were formed via the hydrolysis of nitrile group using sulfuric acid (70%), and condensed with the appropriated amino phenol to give the corresponding N-Aryl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide derivatives (3a-d). FTIR, ^{1}H-NMR, and ^{13}C-NMR were used to verify the structures of the discovered compounds. All of these novel compounds yielded spectroscopic evidence consistent with their suggested structures. Compounds having strong anti-fungal action against *Candida neoformans* (ATCC 208881, H99 Type strain) and *Candida albicans* (ATCC 90028, CLSI reference) were found by the Communities for Antimicrobial Drug Development in Australia.

KEYWORDS

DHPM derivatives; biginelli reaction; antimicrobial; antioxidant; molecular docking.

Introduction

Bacteria and other microbial pathogens are the primary cause of life-threatening infectious illnesses. Bacterial pathogens have evolved a number of strategies to counteract the inhibitory and bactericidal effects of antimicrobial drugs [1]. So, it is critical to conserve effective antimicrobials as long as feasible while still continuing to use them in the service of animal and human health [2]. Antibacterial medications have become less effective, if not completely ineffective, as a result of resistance evolution. Several ways for combating antibiotic resistance have recently been proposed. One of the suggested methods for reaching this goal involves combining other molecules with ineffective medicines, and it appears to restore the appropriate antibacterial activity [3]. A six-membered heterocyclic ring containing two nitrogen atoms is called pyrimidine (m-diazine) (Figure 1).



Pyrimidine (m-diazine)

FIGURE 1

Heterocyclic systems are crucial to pharmacological and biological processes. Because of their extensive spectrum of pharmacological and biological properties, such as their anti-inflammatory, antihypertensive, anticancer, antioxidant, and antibacterial capabilities [4,5], DHPM derivatives are one of the most significant

members of the heterocyclic compounds. DHPMs derivatives also play a significant part in drug development and pharmaceutical research, just like the anticancer drug 5-fluorouracil, the antimalarial drug pyrimethamine, and the hypertension drug Complera. They are all composed of pyrimidine rings. Italian Pietro Biginelli published the first description of the DHPM synthesis process in 1893. This reaction involved the condensation of benzaldehyde with a -keto ester molecule, urea, or thiourea in a single pot containing three components. Long-term and difficult conditions are needed for this reaction [6].

The aim of this work is to design, synthesize, and dock new tetrahydropyrimidine derivatives having antimicrobial activity.

Experimental

Materials and methods

All of the compounds were analytical grade and readily available in the commercially. Without further filtration or drying, all reagents and solvents were employed. Using an electrothermal melting point equipment, in an open capillary, all melting points were found and adjusted. To assess the purity of the product and track the progress of reactions, ascending thin layer chromatography was used on Merck's Kieslgel GF_{254} (type 60). Compounds were revealed by reactivity through irradiation with UV light or with iodine vapor. Chromatograms were eluted by using the following solvent systems A- Ethyl acetate/n-Hexane (3:7) [7]; B- Chloroform: Ethanol (85:15). Infrared spectra were recorded by using FTIR spectrophotometer from the Shimadzu (Japan). Spectra of ^{1}H-NMR were recorded on an Agilent technologies Varian 500 (USA) (500 MHz for proton) instrument with $DMSO_{d6}$ solvent and TMS as an internal reference. ^{13}C-NMR was recorded by an Agilent technology Varian 125 (USA).

Chemistry

General procedure of preparation 1,2,3,4-tetrahydropyrimidine-5-carbonitrile derivatives [1a-h]

A mixture of various substituted aromatic aldehydes (0.03 mol.), cyano-ethyl acetate (0.03 mol.), and urea/thiourea (0.03 mol.) in absolute ethanol (25 mL) containing (0.01 mol.) of K_2CO_3 were refluxed for 8-12 h. under temperature between 80-100 °C. The compound's potassium salt that precipitated throughout the reaction was poured into the water and acidified by diluted acetic acid. The precipitate was filtered and gently washed in water before being dried and recrystallized by ethanol [8].

General procedure of preparation 1,2,3,4-tetrahydropyrimidine-5-carboxylic acid derivatives [2a-2h]

Compounds [1a-h] (0.01 mol.) were dissolved in 70 percent sulfuric acid (15 mL), then heated by reflux for three hours. The reaction mixture was allowed to cool before being put onto ice and neutralized by NH_4OH. To obtain the desired acid derivatives, the precipitate was filtered out, left to dry, and recrystallized by ethanol [9].

6-(4-Chlorophenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (Compound 2a): Yield: 52%; m.p.=217-218 °C. R_f(A)= 0.73; (B)= 0.33; IR cm^{-1}: 3178 (NH stretching vibration), 1651 (C=O stretching vibration), 1535 (C=C aromatic stretching vibration), 1222 (C–O stretching vibration), 3100-3400 (O–H broad stretching vibration), 833 (C–Cl stretching vibration).

6-(4-Hydroxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (Compound 2b): Yield: 48%; m.p.=205-207 °C. R_f(A)=0.62; (B)=0.29; IR cm^{-1}: 3224 (N-H stretching vibration), 1678 (C=O stretching vibration), 1512 (C=C aromatic stretching vibration), 1222 (C–O stretching vibration), 3000-3400 (O–H broad stretching vibration).

6-(4-Chlorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (Compound 2d): Yield: 57%; m.p. = 224-226°C. R_f(A)= 0.73; (B)= 0.36; IR cm^{-1}: 3186 (N-H stretching vibration), 1689 (C=O stretching vibration), 1562 (C=C aromatic stretching vibration), 2900-3350 (O–H broad stretching vibration).

6-(4-Formylphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (compound 2f): Yield: 51%; m.p. = 215-218 °C. R_f(A)= 0.73; (B)= 0.37; IR cm^{-1}: 3271 (N-H stretching vibration), 1681 (C=O stretching vibration), 1516 (C=C aromatic stretching vibration), 1168 (C–O stretching vibration), 2900-3400 (O–H broad stretching vibration).

General procedure of preparation N-Aryl-1,2,3,4-tetra-hydropyrimidine-5-carboxamide derivatives [3a-3d]

The carboxylic acid compounds [1a-h] (0.01 mol.) were dissolved in 50 mL of DCM, then TEA (0.012 mol.) was added to form a clear solution. The solution was cooled in an ice bath to -5 °C, after that ethyl chloroformate (0.012 mol.) was added slowly with continuous stirring and left for 25-30 minutes on the magnetic stirrer. The heat of the mixture was kept below 0 °C. The p-amino phenol (0.01 mol.) was dissolved in 10 mL of DCM and added gradually to the cold mixture with continuous stirring. The mixture was left for one hour in the ice bath and keeps it with continuous stirring for 20 hours. Then, it was refluxed for three hr. The product mixture was put into a separator funnel and washed with 5% sodium bicarbonate three times, 5% HCl solution three times, and finally washed with H_2O three times. The layer that was organic was then dried by $MgSO_4$, then by using a rotary evaporator, the crude precipitated product was collected and washed with petroleum ether 40-60%, n-hexing and the finally pure product was obtained by recrystallization from ethanol [10].

6-(4-Chlorophenyl)-N-(4-hydroxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 3a): Yield 59%; m.p. =174-176 °C. R_f(A)=0.42; (B)= 0.61; IR cm^{-1}: 3340 (OH stretching of phenol), 3236 (NH stretching of amide), 3109 (NH stretching of DHPM ring), 2978 (C–H stretching), 1701 (C=O stretching), 1523 (C=C aromatic stretching). ^{1}H-NMR (500 MHz, DMSO-d6): 12.72 (s, 1H, NH, N3 pyrimidine ring), 11.42 (s, 1H, NH amide), 11.23 (s, 1H, NH, N1 pyrimidine ring), 9.33 (s, 1H, OH phenolic ring), 7.74 (dd, 2H) (C3&C5 aryl ring), 7.29 (dd, 2H) (C2&C6 aryl ring), 7.42 (dd, 2H) (C2&C6 phenolic ring), 6.96 (dd,2H) (C3&C5 phenolic ring). ^{13}C NMR (100 MHz, DMSO-d6): 175.77, 166.06, 163.18, 152.06, 150.07, 135.54, 135.27, 131.79, 130.67, 130.30, 128.54, 121.93, 114.64.

N,6-bis(4-hydroxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 3b): Yield 63%; m.p.=169-172 °C. R_f(A)=0.27; (B)=0.56; IR cm^{-1}: 3400 (OH stretching of phenol), 3194 (NH stretching of DHPM ring), 2951 (C–H stretching), 1697 (C=O stretching), 1516 (C=C aromatic stretching). ^{1}H-NMR (500 MHz, DMSO-d6): 11.03 (s, 1H, NH, N3 pyrimidine ring), 10.9 (s, 1H, NH amide), 9.6 (s, 1H, OH phenolic ring), 9.51 (s, 1H, OH phenolic ring), 7.79 (dd, 2H) (C3&C5 aryl ring), 7.08 (dd, 2H) (C2&C6 aryl ring), 6.99 (dd, 2H) (C2&C6 phenolic ring), 6.71 (dd,2H) (C3&C5 phenolic ring). ^{13}C-NMR (100 MHz, DMSO-d6): 165.45, 164.91, 160.29, 154.53, 152.20, 151.86, 132.18, 131.27, 129.51, 125.07, 115.34, 115, 98.88.

6-(4-Chlorophenyl)-N-(4-hydroxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 3c): Yield 49%; m.p. =164-166 °C. R_f(A)=0.51; (B)=0.77; IR cm^{-1}: 3224 (NH stretching of amide), 3116 (NH stretching of DHPM ring), 2978 (C–H stretching), 1697 (C=O stretching), 1516 (C=C aromatic stretching), 2900-3100 (O–H broad stretching). ^{1}H-NMR (500 MHz, DMSO-d6): 8.52(s, 1H, NH, N3 pyrimidine ring), 8.68 (s, 1H, NH amide), 8.49 (s, 1H, NH, N1

pyrimidine ring), 7.39 (dd, 2H) (C3&C5 aryl ring), 7.29 (dd, 2H) (C2&C6 aryl ring), 7.36 (dd, 2H) (C2&C6 phenolic ring), 6.68 (dd,2H) (C3&C5 phenolic ring). ^{13}C-NMR (100 MHz, DMSO-d6): 165.39, 163.07, 153.59, 152.22, 150.86, 132.71, 130.60, 128.58, 128.36, 122.64, 115.23, 110.04.

6-(4-Formylphenyl)-N-(4-hydroxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 3d): Yield 40%; m.p. = 147-152 °C. R_f(A)= 0.38; (B)= 0.62; IR cm^{-1}: 3475 (OH stretching of phenol), 3367 (NH stretching of DHPM ring), 3039 (C–H stretching), 1647 (C=O stretching), 1523 (C=C aromatic stretching). ^{1}H-NMR (500 MHz, DMSO-d6): 11.36 (s, 1H, NH, N3 pyrimidine ring), 11.09 (s, 1H, NH amide), 11.33 (s, 1H, NH, N1 pyrimidine ring), 9.73 (s, 1H, OH phenolic ring), 7.66 (dd, 2H) (C3&C5 aryl ring), 7.55 (dd, 2H) (C2&C6 aryl ring), 7.37 (dd, 2H) (C2&C6 phenolic ring), 6.88 (dd,2H) (C3&C5 phenolic ring). ^{13}C-NMR (100 MHz, DMSO-d6): 176.76, 163.46, 163.06, 155.11, 152.93, 150.43, 134.43, 130.82, 128.77, 122.91, 116.92, 116.86, 97.41.

Results and discussion

Predication of ADME parameters of the final products

The physicochemical parameters of the synthetic pyrimidine derivatives (3a-3d) were calculated using sever www.Swissedme.com as shown in Table 1 [11].

TABLE 1 ADME parameters calculation of compounds (3a-d)

Comp. No.	MF	MW	RB	H.B$_d$	H.B.$_a$	TPSA (A^2)	log*P*	log*S*
3a	$C_{17}H_{12}ClN_3O_3S$	373.8	4	4	3	130.03	2.90	-4.66
3b	$C_{17}H_{13}N_3O_5$	339.3	4	5	5	135.28	1.24	-3.43
3c	$C_{17}H_{12}ClN_3O_4$	357.7	4	4	4	115.05	2.96	-4.02
3d	$C_{18}H_{13}N_2O_5$	350.3	5	3	5	120.09	1.77	-3.38

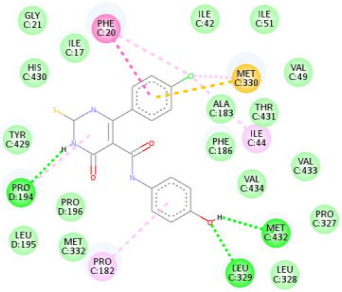
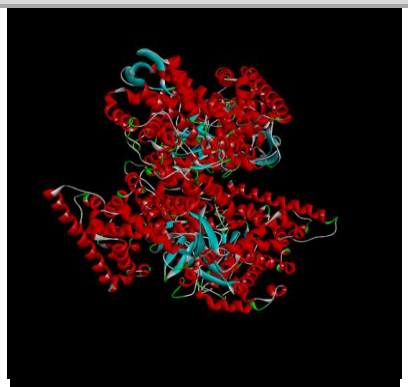
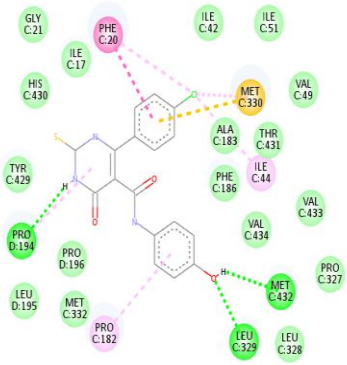
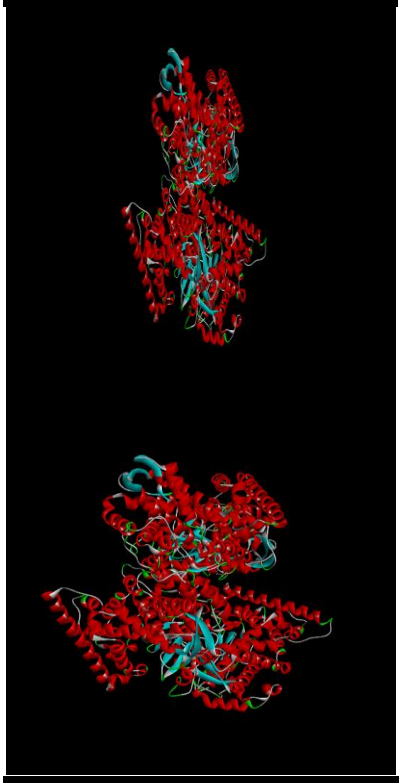
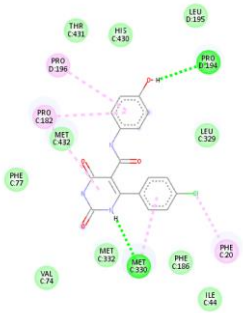
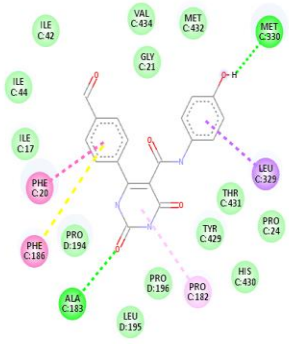
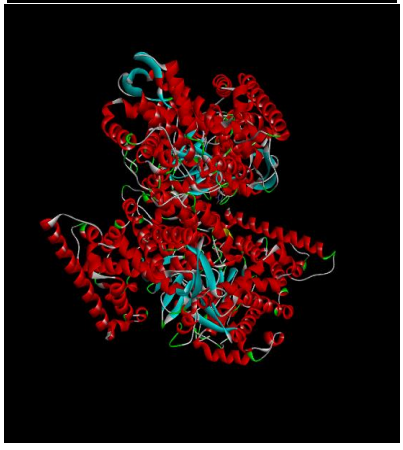
MF: Molecular formula: MW: Molecular weight: RB: Rotatory bond: H.B$_d$: Hydrogen bond donor: H.B.$_a$: Hydrogen bond acceptor: TPSA: Topological polar surface area: log*P*: predicated logarithm Octanol/Water coefficient: log*s*: Predicated aqueous solubility.

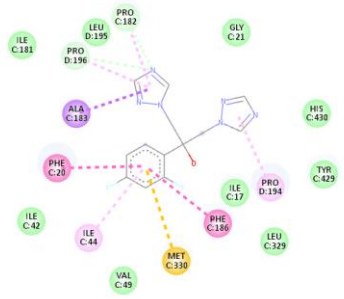
Molecular docking of the final products

The modes of binding of the most compounds that is active (3a, 3b, and 3d) to active sites of the lanosterol-14-alpha demethylase enzyme, which was taken with the reference drug Fluconazole for antifungal activity assay, were discovered using *in-silico* procedure a structure-based retrieved from the Data Bank of Protein server, (http://www.pdb.org). The 2-D and 3-D structures of the compounds and the scores of the binding are fixed in Table 2 [12].

To examine the impact of symmetry correction in docking RMSD calculation relative to the native score≤2.0 Å, one would anticipate the RMSD (the root mean square deviation) value should be low; these values do not reflect the correct corresponding of the atomic mapping derived from the synthetic tetrhydropyrimidine derivatives (ligand) bonding 3D structures. The hydrogen bond formed between (OH) and Met (330), and the N-H of the pyrimidine ring with Pro. The Vander Waals forces with different amino acids were Val, Ala, Leu, Gly.

TABLE 2 Docking studying of the synthetic compounds (3a-3d) with lanosterol 14-α-demethylase (*Candidia Albicans*)

Comp. No.	2-D	3-D	Score Kcal/mole
3a			-9.3
3b			-9.2
3c			-8.2
3d			-8.9

Ref			-7.8

Reference: Fluconazole (antifungal agent)

Antioxidant evaluation

Preparation of the samples

A (0.02 g) of each sample (3a, 3b, 3c and 3d) was dissolved in 5 drops DMSO, then dissolved in 1mL of distilling water at room temperature with shaking [13].

Radical scavenging effect of the phenolic pyrimidine derivatives in DPPH radical

The activity of free radical scavenging of each sample was measured according to Lee, *et al.* (2004) as follows: Known volumes (50, 100, 150 µL) of each sample were added individually to test tubes, which were then completed to a known volume (1.0 mL) by D.W. (1.0 mL) of 2,2-diphenyl-1-picrylhydrazyl (DPPH) solution (0.2 mM in ethanol) was added to each tube then mixed well and incubated at room temperature for 30 min [14]. The same process was used to prepare the control (ascorbic acid). Ascorbic acid solution (0.03% w/v) was used as a positive control. All the samples were run in triplicates. At 517 nm, the solution's absorbance (A) was determined by using T60 PG Instruments visible spectrophotometer [UK]. The inhibition free radical of DPPH in present (I%) was calculated from the following equation. I%=[(Ac-As)/Ac].100 as shown in Table 3, where I represents the inhibition DPPH, the sample absorbance value of is A_S, while the control reaction absorbance value is A_C [15].

TABLE 3 Scavenging activity of (aqueous samples) and Ascorbic acid against DPPH radical

Aq. sample (OPEs)	Conc. (ppm)	% of scavenging activity
Aqueous sample 3a	500	50.1
	1000	76.9
	1500	80.5
Aqueous sample 3b	500	23.23
	1000	28.61
	1500	32.92
Aqueous sample 3c	250	28.15
	500	36.76
	750	54.0
Aqueous sample 3d	500	36.92
	1000	46.30
	1500	51.23
Ascorbic acid (standard)	7.5	92.6
	15	92.9
	23	95.5

CO-ADD antimicrobial assay

Communities for Antimicrobial Drug Development plus discovery conducted antimicrobial research to test the prepared compounds, which was financed by The University of Queensland as well as the Welcome Trust University. The antibacterial test employing traditional broth microdilution methods was done about 32 mg/mL against many common fungi and bacteria listed in the main part [16-20]. A hit confirmation for dangerous substances was triggered, and the toxic effects were assessed via a dose–response study against a certain microorganism species strain [21]. In this investigation, no animals were utilized. The American Type Culture Collection included cell lines (fungus, bacteria plus mammals). Human blood was collected and used in haemolysis analysis. This was authorized by Human Research Committee of The University of Queensland. Number of approvals was 2014000031. Antimicrobial testing procedure followed the Communities for Antimicrobial Drug Development plus Discovery, Australia, as follows:

CO-ADD antibacterial assay

Every bacterium, E. coli, K. pneumoniae, A. baumannii, S. aureus, and P. aeruginosa, were cultured in Cation-adjusted Mueller Hint. broth overnight around 36-37 °C. Each colony was diluted 4x10 times in freshly prepared media then incubated at 36-37 °C over 3 to 1.5 hrs. The resulting mid-log phase cultures were diluted (OD600 CFU/mL) and fed to each well of the plates, containing compound, yielding a density of a cell of 50 x10^4 CFU/mL and final volume of 5x10 microliter. All of the plates covered then incubated for18 hours have passed with no stirring.

TABLE 4 Minimum Inhibitory Concentration (MIC) of compounds (3a-d) against bacteria

Comp No.	Sa ATCC 43300	Ec ATCC 25922	Kp ATCC 700603	Ab ATCC 19606	Pa ATCC 27853
3a	>32.0	>32.0	>32.0	>32.0	>32.0
3b	>32.0	>32.0	>32.0	>32.0	**Partial Active**
3c	>32.0	>32.0	>32.0	>32.0	>32.0
3d	>32.0	>32.0	>32.0	>32.0	>32.0
Vancomycin.HCl	**100**	-	-	-	-
Colistin sulfate	-	**100**	**100**	**100**	**100**

(Minimum inhibition concentration) in (µg/mL) of tested compounds (3a-3d).

CO-ADD antifungal assay

Fungi strain *C. albicans* and H99 strain kind of *C. neoformans* were cultivated on three days over thirty C on YPD agar (Yeast Extract-Peptone Dextrose type). 5 colonies were utilized to create a yeast solution with (10-50) 10^5 CFU/mL (as tested using OD530). After diluting the solution, it was applied to each well which containing compounds, yielding a final cell density of 0.25x10^4 CFU/mL and a up to volume of fifty liter, where plates were closed with a cover and incubated for 1.5 day around 35 °C with no agitation [22].

TABLE 5 Minimum Inhibitory Concentration (MIC) of compounds (3a-3d) against fungi

Comp. No.	Ca ATCC 90028	Cn H99; ATCC 208821	Activity
3a	54.1	>32.0	Inactive
3b	**66.2**	>32.0	**Partial Active**
3c	**70.3**	>32.0	**Partial Active**
3d	**96.0**	>32.0	**Active**
Fluconazole	**100**	**100**	

CO-ADD cytotoxicity assay

HEK293 cells were individually measured by numbering using Neubauer hemocytometer before even being plated at 6000 cells/well density in a finished volume of 50 microliter in 384 wells-plates contained compounds. Growth medium was DMEM supplemented with 10 percentage FBS. Then, the chemicals were applied to the cells during twenty hours around 36-37 °C in 0.5x10% CO_2 [23,24].

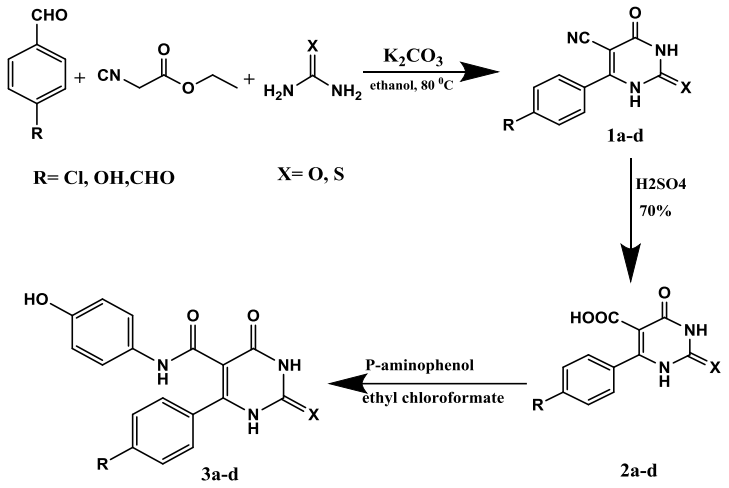
TABLE 6 Cell line Human embryonic Kidney (HEK-293) (Homo Sapien)

Comp. No.	Hm ATCC CRL-1573	Activity
3a	**96.8**	**Partial cytotoxic**
3b	30.10	Inactive
3c	-	Inactive
3d	20.50	Inactive
Tamoxifen PKC inhibitor	**100**	

Discussion

In this study, we synthesized a new series of tetrahydropyrimidine derivatives in three steps using Biginelli reaction (Scheme 1).

The new compounds (3a-3d) structures were confirmed by FTIR, ^{1}H&^{13}C-NMR Spectroscopy. The characteristic bands were 3475-3350 cm^{-1} for phenolic OH group, 3360-3194 cm^{-1} for NH, 3100-2990 cm^{-1} for aromatic C-H.



SCHEME 1 Synthesis way for1,2,3,4- tetrahydro pyrimidine derivatives products (3a-3d)

The ^{1}H-NMR(in DMSO-d6, δ (ppm) spectra data of compounds (3a-3d) give an idea that the four final products showed similar chemical shifts: The chemical shift 11.36-11.40 ppm for phenolic OH, the chemical shift of the heterocyclic tetrahydropyrimidine ring the imide (NHCO) and imido (CONHCO)groups at 11.13-11.36 ppm, while the amide side chain 11.09 ppm. The chemical shift of the aromatic protons 6.7-6.8 (dd, 4H) due to the para substitution in phenolic ring, 6.9-8.2 (dd, 4H) for aryl ring, except the compound 3d the peak at 9.73 for (S,1H) for aldehyde. ^{13}C-NMR spectra carbon of (C=O) groups appeared at 176 ppm for aldehyde, while the side chain carbonyl amide (CO-NH) was assigned at 163-165 ppm. The carbonyl group in the pyrimidine ring was assigned at 150-160 ppm due to the cyclic ring. Within aromatic area, the peaks have been seen in the estimated regions. For the aromatic ring of the phenol, the carbon atoms were assigned at 155 ppm for C-OH at para-position, and the NH-C= within the range of 128-132 ppm. Other positions were low chemical shifts.

The carbonyl group in the pyrimidine ring was assigned at 150-160 ppm due to the cyclic ring. In the aromatic region, the peaks were seen at the estimated areas. As for the aromatic ring of the phenol, the carbon atoms were assigned at 155 ppm for C-OH at para-position, and the NH-C= within the range 128-132 ppm. Other positions were low chemical shifts [25].

The ADME predications properties of the final products (3a-3d) were carried out by the Swissadme. All predicated compounds followed the rule of five (Lipinski Rule). These properties are essential and important of new drug design, and used in optimization of a biological activity as shown in Table 1. The four synthetic pyrimidine derivatives are highly GI absorption and can enhance the pharmacokinetic parameters.

In addition to the *in vitro* analysis, studies of docking were carried out in order to achieve greater binding between the ligand (final synthetic molecules) and the lemosteol-14-alpha-methylase from *candida albicans,* using Fluconazole as a reference. The (2-D and 3-D) interacting mode of compounds happened (3a-3d) at the active site of the enzyme lanosterol-14-alpha-demethylase. The score of the docking order (Kcal/mole) was as follows: 3a>3b>3d>3c as shown in Table 2 [26-28].

The antioxidant activity by DPPH radical scavenging activity was evaluated. The four samples of 3a, 3b, 3c and 3d exhibited moderate antioxidant activity equivalent to that of the reference substance. Ascorbic acid showed 92% scavenging activity as a positive control (Table 3, Figure 2).

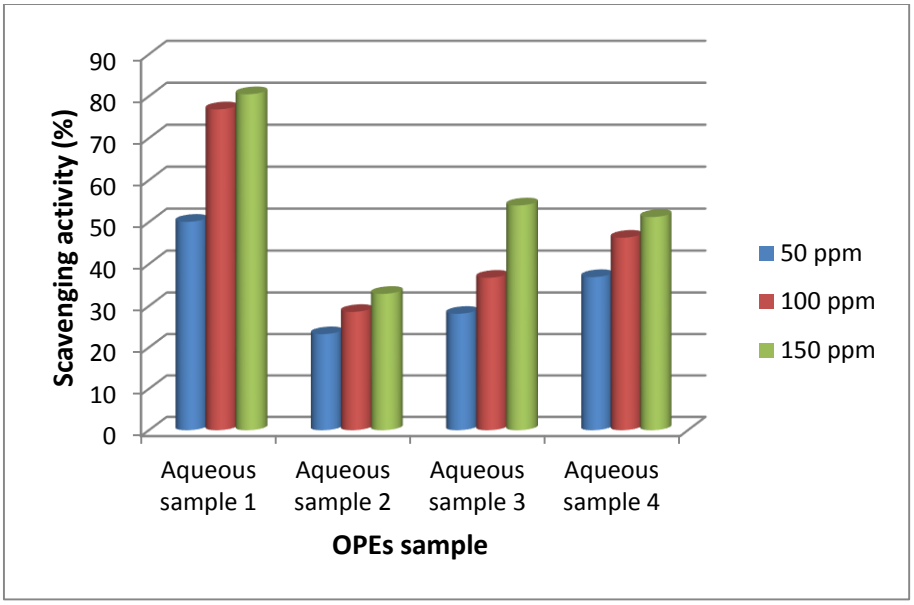


FIGURE 2 Comparison between four compounds antioxidant activity

The antioxidant mechanism of actions involved either transfer of a single electron or hydrogen atom transfer. The (OH) group of the phenolic compounds can protect the free radical.

Antimicrobial activities were conducted using MIC assay (Table 4). The MIC methods were described by CO-ADD protocol. The four synthetic compounds were preliminary screened against 5 types of the pathogenic bacteria and 2 types of fungi. The absence of bacterial growth on the nutrients' agar streaked from the lowest clear MIC values validated the MIC values as a consequence. On other side, the compound 3d revealed significant inhibition for the tested *Candida albicans* (Table 5). Compared with the reference medications, the title compounds displayed poor or no inhibitory efficacy against the tested microorganisms. Finally, the cytotoxicity HEK93 (Homo sapien) showed strong inhibition towards the test compound 3a (Table 6).

The compounds 3a, 3b and 3d, owing to their simple synthesis and relevant bioactivity as antioxidants, antifungals, and cytotoxic agents, provided a promising structure for future therapeutic development. Because of toxicity, low efficacy rates, and drug resistance, antifungal medications may be limited. Some of these traditional therapies are being given new formulations to improve absorption and efficacy.

Conclusion

The conclusion of the research is that the theoretical studies are identical to the experimental study of the biological activity; the three compounds (3a, 3b, & 3d) are active compounds, except for compound 3c is inactive.

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Conflict of Interest

There are no conflicts of interests.

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References

[1] M.F. Varela, J. Stephen, M. Lekshmi, M. Ojha, N. Wenzel, L.M. Sanford, A.J. Hernandez, A. Parvathi, S.H. Kumar, *Antibiotics*., **2021**, *10*, 593. [Crossref], [Google Scholar], [Publisher]
[2] G. Cheng, M. Dai, S. Ahmed, H. Hao, X. Wang, Z. Yuan, *Front. Microbiol*., **2016**, *7*, 470. [Crossref], [Google Scholar], [Publisher]
[3] R. Rana, R. Sharma, A. Kumar, *Infect. Disord. Drug Targets*, **2018**. [Crossref], [Google Scholar], [Publisher]
[4] Y.L.N. Murthy, R.M.R. Saviri, A.R. Parimi, S. Nareesh, *Org. Commun*., **2013**, *6*, 47-54. [Google Scholar], [Pdf]
[5] A. Adhikari, B. Kalluraya, K.V. Sujith, Gouthamchandra, R. Mahmood, *Saudi Pharm J*., **2012**, *20*, 75–79. [Crossref], [Google Scholar], [Publisher]
[6] A. El-Malah, Z. Mahmoud, H.H. Salem, A.M. Abdou, M.M.H. Soliman, R.A. Hassan, *Green Chem. Lett. Rev*., **2021**, *14*, 221–233. [Crossref], [Google Scholar], [Publisher]
[7] B. Padmashali, B.N. Chidananda, B. Govindappa, S.M. Basavaraj, S. Chandrashekharappa, K.N. Venugopala, *J. Appl. Pharm. Sci*., **2019**, *9*, 133-140. [Crossref], [Google Scholar], [Pdf]
[8] C.K. Jadhav, A.S. Nipate, A.V. Chate, *ACS Omega*., **2019**, *4*, 22313−22324. [Crossref], [Google Scholar], [Publisher]
[9] S.K. Ramadan, E.A.E. El-Helw, H.A. Sallam, *De Gruyter Heterocycl*., **2019**, *25*, 107-115. [Crossref], [Google Scholar], [Publisher]
[10] T.T. Bui, D. Quang Ngo, V. Loc Tran, *Vietnam journal of science, technology and engineering*, **2020**, *62*, 34-37. [Crossref], [Google Scholar], [Publisher]
[11] A. Daina, O. Michielin, V. Zoete, *J. Chem. Inf. Model.*, **2014**, *54*, 3284. [Crossref], [Google Scholar], [Publisher]
[12] M. Madhavaram, V. Nampally, S. Gangadhari, M.K. Palnati, P. Tigulla, *Journal of Receptors and Signal Transduction*, **2019**, *39*, 312–320. [Crossref], [Google Scholar], [Publisher]
[13] I.L. Gonc¸alves, L. Rockenbach, G. Goethel, E. Sauer, L.P. Kagami, G.M. das Neves, T. Munhoz, F. Figueiro´, S.C. Garcia, A.M. Oliveira Batasttini, V.L. Eifler-Lima, *Future Med. Chem*., **2020**, *12*, 20. [Crossref], [Google Scholar], [Publisher]
[14] K. Venkatesan, V.S.V. Satyanarayana, A. Sivakumar, *Bull. Chem. Soc. Ethiop*., **2016**, *30*, 119-128. [Crossref], [Google Scholar], [Publisher]
[15] Z. Akar, M. Küçük, H. Doğanb, *J. Enzyme Inhib. Med. Chem.*, **2017**. [Crossref], [Google Scholar], [Publisher]
[16] A. Frei, J. Zuegg, A.G. Elliott, M. Baker, S. Braese, C.Brown, F. Chen, C.G. Dowson, G. Dujardin, N. Jung, A.P. King, A.M. Mansour, M. Massi, J. Moat, H.A. Mohamed, A.K. Renfrew, P.J. Rutledge, P.J. Sadler, M.H. Todd, C.E. Willans, J.J. Wilson, M.A. Cooper, M.A.T. Blaskovich, *Chem. Sci*., **2020**, *11*, 2627. [Crossref], [Google Scholar], [Publisher]
[17] S.O. Mirabootalebi, G.H. Akbari, R.M. Babaheydari, *J. Appl. Organomet. Chem.*, 2021, *1*, 76-85. [crossref], [Google Scholar], [Publisher], [Download Pdf]
[18] S. Alghamdi, M. Asif, *J. Appl. Organomet. Chem.*, 2021, 1(3), 116-124. [crossref], [Google Scholar], [Publisher], [PDF Download]
[19] M.V. Gaikwad, *J. Appl. Organomet. Chem.*, 2021, *1*, 59-65. [crossref], [Google Scholar], [Publisher], [Download Pdf]
[20] S.B Biradar, D.V. Narte, R.P. Kale, K.I. Momin, M.S. Sudewad, K.C. Tayade, D.G. Palke, *J. Appl. Organomet. Chem.*, 2021, *1*, 41-47. [crossref], [Google Scholar], [publisher] , [Download Pdf]
[21] R. Ochoa, *Elsevier*, **2018**. [Crossref], [Google Scholar], [Publisher]
[22] R.M. Jebir, Y.F. Mustafa, *J. Med. Chem. Sci*., **2022**, 5, 831-847. [Crossref], [Pdf], [Publisher]
[23] M.A.T. Blaskovich, J. Zuegg, A.G. Elliott, M.A. Cooper, *ACS Infect. Dis.*, **2015**, *1*, 285–287. [Crossref], [Google Scholar], [Publisher]
[24] M.M. Cadelis, S.A. Li, M.L. Bourguet-Kondracki, M. Blanchet, H. Douafer, J.M.

Brunel, B.R. Copp, *Chem Med Chem.*, **2020**. [Crossref], [Google Scholar], [Publisher]

[25] G. Venkatesh, Y.S. Mary, P. Vennila, Y. Shyma Mary, M. Govindaraju. *J. Appl. Organomet. Chem.*, 2021, *1*(3), 148-158. [crossref], [Google Scholar], [Publisher], [PDF Download]

[26] A. Stana, D.C. Vodnar, R. Tamaian, A. Pîrnău, L. Vlase, I. Ionuț, O. Oniga, B. Tiperciuc, *Int. J. Mol. Sci.*, **2017**, *18*, 177. [Crossref], [Google Scholar], [Publisher]

[27] A.A. Sagatova, M.V. Keniya, R.K. Wilson, B.C. Monk, J.D.A. Tyndall, *Antimicrob agents chemother.*, **2015**, *59*, 4982–4989. [Crossref], [Google Scholar], [Publisher]

[28] Y. Davoudabadi Farahani, V. Safarifard. *J. Appl. Organomet. Chem.*, **2022**, 2(4), 180-194. [Crossref], [Google Scholar], [Publisher], [PDF Download]

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