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Synthesis of new 1,4-dihydropyrimidine derivatives, Breast cancer anticancer, and In-silico studies

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ABSTRACT

In this research, we synthesized a new pyrimidine Schiff base derivative via a multi-component room-temperature grinding procedure using pyrimidine, a substituted aromatic aldehyde, and the catalyst p-toluene sulfonic acid (p-TSA) under solvent-free conditions. The synthesized compounds are characterized by IR, NMR (13C, 1H), mass spectra, and elemental analysis. Furthermore, molecular docking was performed to assess the binding potential of 1,4-dihydropyrimidine-5-carboxylates (1-3). The 1,4-dihydropyrimidine-5-carboxylate derivative (3) has shown the strongest binding affinity with breast cancer estrogen receptor alpha (ERα) protein. Therefore, (3) could be a potential hit candidate for the management of breast cancer. In silico studies were performed using MOE 2023 (Molecular Operating Environment). Also, the toxicity of the candidates is determined by the Osiris software.

Keywords: pyrimidine, anticancer, Insilico studies.

INTRODUCTION

Cancer Scenario death is one of the most serious health problems all over the world and one of the leading causes of death, so there is an urgent need to develop alternative anticancer drugs with minimal side effects and higher potency[1]. Due to the sharp lack of effective, selectively acting anticancer therapies, the number of deaths continues to rise[2]. Discovering a novel, safer drug for cancer treatment is a major challenge for researchers, chemists, and pharmacists. Nitrogen-containing heterocycles have been attracting attention in drug discovery, and several nitrogen-containing heterocycles have been approved as drugs[3-5]. Pyrimidine is the parent heterocyclic molecule because of its prevalence in nature. Pyrimidine analogues displays a broad range of biological activities for instance, antihistaminic,[10-11] antifungal,[12] antileishmanial,[13] calcium channel blockers,[14] anti-inflammatory[15]analgesic,[16]

antihypertensive,[17] antipyretic,[18] antiviral,[19] antidiabetic,[20] central nervous system (CNS) depressant properties,[21] antiallergic,[22] antibacterial[23] anticonvulsant,[24] herbicidal[25] anticancer,[26] and also act as antioxidants[27].

RESULTS AND DISCUSSION

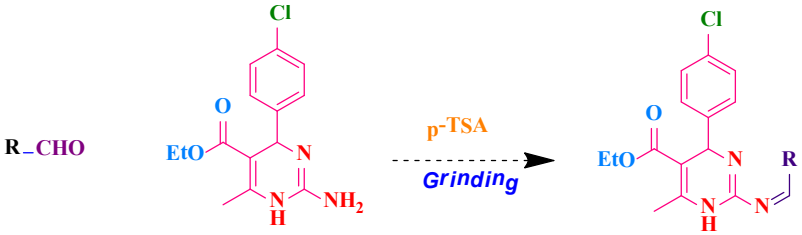
Chemistry

The synthesized compounds were confirmed by analytical methods, including FT-IR, 1H NMR, and 13C NMR. The FT-IR spectra exhibited absorption bands (**1-3**) at 3416-3410, 3352-3332, and 1622-1596 $cm^{-1,}$ indicating OH, NH, and C=N groups. The 1HNMR spectra (**1a–c)** showed chemical shift values at d13.81-13.54,9.48-8.10 and 7.75 - 7.12 ppm, confirming NH in pyrimidine, N=CH in imine, and CH-Ph protons, respectively. The[13]CNMR showed (**1a–1c**) signals at 167.31-167.20,163.77-162.86, 161.47-161.13, and 153.69-153.16ppm, indicating the C=O, N=C, C-NH and N-C-N of carbon atoms. Pyrimidine Schiff base derivatives were affirmed by mass spectroscopy and elemental analysis. The synthesis of pyrimidine Schiff base derivatives is shown in Scheme 1. The synthetic pathway for Pyrimidine-connected Schiff base derivatives is shown in Scheme 2.

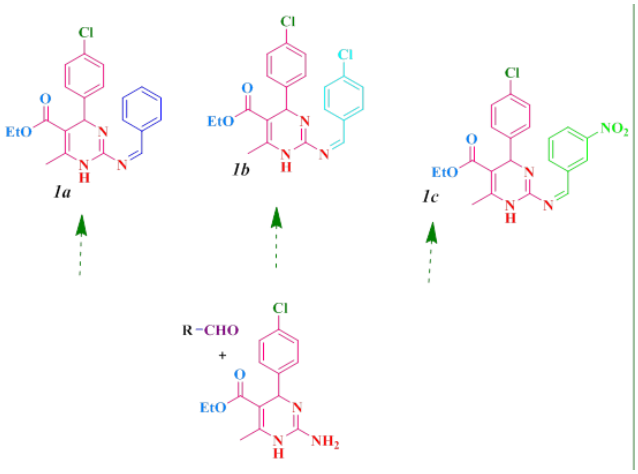
All chemicals were commercially procured and were used without further purification. Melting points were determined under open capillaries and were uncorrected. Purity of synthesized derivatives was assessed by TLC on a silica gel-N plate, with ethyl acetate and n-hexane as developing solvents; spots were visualized in an iodine chamber. The PerkinElmer Spectrum RX FTIR Spectrophotometer was used to record IR spectra. 1H NMR spectrum was recorded on a Bruker Elmer NMR spectrometer 1000 MHz with DMSO-d_6 as solvent using tetramethyl silane (TMS) as an internal standard.

Biology

The novel synthesized compounds were tested for their antitumor activity against the MCF-7 (breast cancer) cell line. All compounds are active, and the target compound 3 is the most cytotoxic, with an IC50 of 9.3 µg/mL compared to the reference cisplatin at 4.03 µg/mL.



Scheme 1: Synthesis of dihydropyrimidine-connected Schiff-based derivatives(**1-3**)



Scheme 2: Synthesis of pyrimidine Schifaf base derivatives(1a-1c).

Table 1: In vitro cytotoxic activity of the newly synthesized thiazoles 1a-c, against the human breast cancer cell line (MCF-7)

Tested compounds	IC^{50} (*μ*g/mL)
1	7.7 ± 1.3
2	8.3 ± 0.9
3	9.3 ± 1.6
Cisplatin	4.03± 0.61

Candidate 3 is recognized as the most active, even more active than the reverberance cis-platin, of IC50 -9.3and 4.03 µg/mL, respectively. This may be due to the presence of the nitro group.

In-silico studies

Molecular docking

Molecular docking is an in silico method for determining molecular interactions between small ligand molecules and macromolecular protein structures. Molecular docking has been successfully applied in many cases to determine the molecular ligand-protein interactions and binding affinities. It is one of the widely used computational methods in drug design and discovery. Therefore, the present study employed molecular docking to assess interactions between a series of 1,4-dihydropyrimidine-5-carboxylate derivatives (1-3) and the breast cancer estrogen receptor alpha (ERα) protein. ERα is a nuclear hormone that promotes cell proliferation in breast cancer. The inhibition of ERα plays a profound role in cell cycle arrest for the management of breast cancer. PDB 7UJW is a transcription protein that was targeted to inhibit Erα. The results showed that compound 1c is the most active, with a docking score of -8.1 kcal/mol.

Osiris Toxicity

It is an AI tool that allows us to predict the toxicity of the prepared derivatives. Molecular docking and Osiris data are presented in Table 2. The OSIRIS Property Explorer lets you draw chemical structures and calculates on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results are valued and color-coded. Properties with high risks of undesired effects, like mutagenicity or poor intestinal absorption, are shown in red. At the same time, a green color indicates drug-conforming behavior.

Methodology

Chemistry

A mixture of p-TSA as a catalyst, dihydro-pyrimidine carboxylate derivative (2.77 g, 0.01mol), and benzaldehyde (0.9 mL,0.01mol) was thoroughly mixed in a mortar by grinding until the completion of the reaction, as indicated by thin-layer chromatography. The initial syrup reaction mixtures solidified within 30 min and were left overnight. The solid was washed with cold water for purification, then dried, and recrystallized from ethanol to give product 1. The synthesis of other compounds 1-3 followed the same procedure.

Ethyl2-(benzylideneamino)-4-(4-chlorophenyl)-6-methyl-1,4-dihydropyrimidine-5-carboxylate (1)

White solid, Yield 76%; mp168°C; IR(KBr) (cm^{-1}); 3349(NH), 3095(Ar-H), 2953(CH_3), 1745(C=O-), 1597 (C=N), 837 (C-Cl); ^{1}HNMR (1000 MHz, DMSO-d6):13.76 (s,1H, NH), 8.17 (s,1H, N=CH), 7.83-7.52 (m,5H, Ar), 7.37-7.17 (m,4H, Ar), 4.20(s,2H, CH_2), 3.53(s,1H, CH), 2.26 (s,3H, CH_3), 1.29 (s, 3H, CH_3); ^{13}CNMR (300MHz, DMSO d6): 167.21, 163.72, 161.33, 153.64, 140.65, 133.76, 131.38, 129.22, 128.84,128.76,102.68,61.79,57. 01,18.44, 14.20; EI-MS:383 (M+,32%); Elemental analysis ($C_{21}H_{20}ClN_3O_2$): Calculated:C,66.05; H,5.28; N, 11.00; Found: C, 66.07; H, 5.30; N, 11.02.

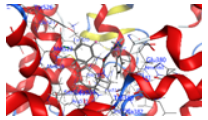
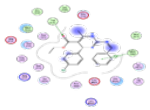
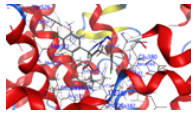
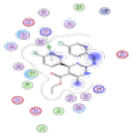
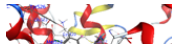
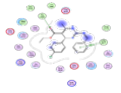
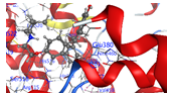
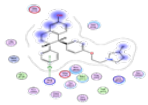
Ethyl2-((4-chlorobenzylidene)amino)-4-(4-chlorophenyl)-6-methyl-1,4-dihydropyrimidine-5-carboxylate (2)

White solid, Yield 80%;mp170°C; IR(KBr) (cm^{-1}); 3350(NH), 3029(Ar-H), 2961(CH_3), 1755(C=O-Ester), 1603 (C=N), 837(C-Cl); ^{1}HNMR(1000 MHz, DMSO-d6):13.78(s,1H, NH), 9.48 (s, 1H, N=CH) 7.84-7.56 (m,4H, Ar), 7.77-7.51(m,4H, Ar), 4.22(s,2H, CH_2), 3.53(s,1H, CH), 2.28(s,3H, CH_3), 1.30(s,3H, CH_3); ^{13}CNMR(300MHz, DMSO-d6):167.31, 163.47, 161.23, 153.16, 140.56, 136.67, 131.83, 131.20, 130.62, 130.42, 128.98, 128.67, 102.16, 61.37, 57.50, 18.54,14.25; EI-MS:416(M+,23%); Elemental analysis ($C_{21}H_{19}Cl_2N_3O_2$): Calculated: C, 60.59; H, 4.60; N, 10.09 %; Found: C,60.61; H, 4.62; N, 10.11%

Ethyl 4-(4-chlorophenyl)-6-methyl-2-((3-nitrobenzylidene)amino)-1,4-dihydropyrimidine-5-carboxylate (3)

White solid, Yield 85%; mp165°C; IR(KBr) (cm^{-1}); 3352 (NH), 3012 (Ar-H), 2942(CH_3), 1741(C=O

Table 2: Molecular docking scores of 1,4-dihydropyrimidine-5-carboxylate derivatives (1a-c), and the interaction between target molecules and PDB ID: 7UJW

Cpd.	3D snap	2D snap	Docking scores kcal/mole	Ligand	Receptor	Interaction	Distance	energy	Toxicity
1			-7.2	O 11 6-ring	NE1 TRP 383 (B) CH3 NME 460 (B)	H-acceptor pi-H	3.18 4.34	-2.2 -0.5	
2			-7.22	6-ring	CE	LYS 520 (C)	4.11	-0.5	
3			-8.1	O 11 6-ring	NE1 TRP 383 (B) CH3 NME 460 (B)	H-acceptor) pi-H	3.18 4.43	-2.2 -0.5	
									
Reference (tamoxifen)			-6.8	6-ring	NH1-ARG 515 (B)	(B) pi-cation	4.42	-2.7	

), 1720 (CO-Ester), 1602(C=N), 1504 (NO_2), 837(C-Cl); ^{1}HNMR(1000MHz, DMSO-d6):13.80(s,1H, NH), 8.21(s,1H, N=CH), 7.86-7.58(m,5H, Ar), 7.83-7.52(m,4H, Ar),4.24 (s,2H, CH_2), 3.53(s,1H, CH), 2.30 (s,3H, CH_3), 1.23 (s,3H, CH_3); ^{13}CNMR(300MHz, DMSO d6):167.20, 163.74, 161.35, 153.66, 148.00, 140.67, 135.38, 134.61, 131.39, 130.49,129.70, 128.79, 126.24, 121.60, 102.61, 61.73, 57.04, 18.47, 14.26; EI-MS: 427(M+,24%); Elemental analysis ($C_{21}H_{19}ClN_4O_4$): Calculated: C,59.09; H, 4.49; N,13.13%; Found: C,59.11; H,4.51; N,13.15%

Biology

Anticancer

Cell Culture

Many human Cell lines were obtained from Egyptian Holding Company for Biological Products & Vaccines (VACSERA), Giza, Egypt, and maintained in the tissue culture unit. The cells were routinely grown in RBMI-1640 medium supplemented with 10% heat-inactivated FBS, 50 units/mL Penicillin, and 50 mg/mL Streptomycin, and maintained in a humidified atmosphere containing 5% CO_2. They were acting as a monolayer culture by serial sub-culturing. The reagents used for cell culture were obtained from Lonza (Basel, Switzerland). The anticancer activity of the compounds under investigation was determined against MCF-7 cells (breast cancer).

Cytotoxicity

Cytotoxicity is determined by Sulforhodamine B (SRB). Cell collections from multiple times-grown cells were performed using 0.25% Trypsin EDTA and seeded into 96-well plates at 1000-2000 cells/well in RBMI-1640-supplemented medium. After 24 h, cells were incubated for 72 h with different concentrations of the synthesized compounds under investigation. After 72 h treatments, the cells were fixed with 10% trichloroacetic acid for 1 h at 4 °C. Wells were stained for 10 min at room temperature with 0.4% SRBC (sulforhodamine B) dissolved in 1% acetic acid. The plates were air-dried for 24 h, and the dye was solubilized in Tris-HCl for 5 min on a shaker at 1600 rpm. OD (optical density) of each well was measured spectrophotometrically at 564 nm using an ELISA microplate reader (ChroMate 4300, FL, USA). IC50 values were calculated using the Boltzmann sigmoidal equation, with nonlinear regression fitting to the concentration-response curve.

Molecular docking

The docking analyses were performed using the Molecular Operating Environment (MOE) software (version 2023). ChemDraw compound preparation, Chem 3d structures, Chem 3D 16 (Molecular Modeling and Analysis; Cambridge Soft Corporation) software, to dock the complexes toward PDB ID: 7UJW. Therefore, the present study employed molecular docking to assess interactions between a series of 1,4-dihydropyrimidine-5-carboxylate derivatives (1-3) and the breast cancer estrogen receptor alpha (ERα) protein. ERα is a nuclear hormone that promotes cell proliferation in breast cancer. The inhibition of ERα plays a profound role in cell cycle arrest for the management of breast cancer.

CONCLUSION

Pyrimidine derivatives are considered of high priority in pharmaceutical organic chemistry. The data obtained from both biological and theoretical analyses indicate that compound 1c is the most active, with an IC50 of 9.3 (referred to as cisplatin), 4.3, and a docking energy of -8.1 kcal/mol, compared to tamoxifen at 6.2 kcal/mol. This leads us to a discovery in organic chemistry.

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