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MOLECULAR DOCKING AND SYNTHESIS OF 5- ACETYL PYRIMIDINE 2, 4, 6 TRIONE BASED CHALCONES

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ABSTRACT

In an attempt to find a novel, potent, selective and less toxic anti inflammatory agents, a series of sixteen 5- acetyl pyrimidine 2, 4, 6 trione based chalcones were designed and evaluated. Docking studies were performed using patch dock software server against the COX-2 receptor (5PP1). Patchdock was used to study the protein ligand interactions. Physicochemical properties, solubility, pharmacokinetics, drug likeness and bioactivity scores of designed compounds were evaluated by using molinspiration software and Swiss ADME software. According to patch dock results the compound M2 showed that highest affinity to COX-2 (5PP1) receptor with an ACE value of –238.55. M16 showed that lowest affinity with an ACE value 13.92. Lower the ACE values higher will be the activity. The most active compounds among the designed compounds were synthesized and characterized by spectral analysis.

KEYWORDS: 5-acetyl pyrimidine 2, 4, 6 trione based chalcones, Patch Dock, molinspiration software, Swiss ADME software, anti inflammatory activity.

INTRODUCTION

Pyrimidine is an important aromatic heterocyclic organic compound. It is the six membered ring with two nitrogen atoms at positions 1 and 3 of the ring. Pyrimidine containing compounds shows widespread therapeutic applications because pyrimidine base in thymine, cytosine, uracil are the essential building blocks of nucleic acids DNA AND RNA. The literature survey indicated that compounds containing pyrimidine nucleus showed wide range of pharmacological activities like anti inflammatory, anti bacterial, anti cancer, anti malarial, anti hypertensive, anti viral, anti convulsant, neuroprotective, anti microbial, herbicidal, anti tubercular, and hypolipidemic effects.

MATERIALS AND METHODS

Molinspiration: molinspiration is a free online software. It was used to calculate the physicochemical properties of compounds like Log P, M.WT, TPSA, no of hydrogen bond donors and acceptors, no of rotational bonds. And also it is used to calculate the bioactivity scores of compounds. Molinspiration cheminformatics web page was opened and then clicked on calculation of molecular properties and prediction of bioactivity on left side of web page. After that molecular property calculator was opened and the structures were drawn by using symbols around the box. Physicochemical properties and bioactivity scores were calculated by clicking on calculate properties and predict bioactivity.

Molecular docking studies: The protein-ligand interactions were performed by utilizing a web based docking tool called PatchDock. The input is two molecules in PDB format one is ligand PDB, another one is receptor PDB. These two PDB molecules are uploaded in Patch Dock server. Docking results were obtained through the e-mail which has datails about docking score and ACE value. Based on ACE score compounds were evaluated.

Swiss ADME: Swiss ADME is a free online software. It was used to predict the ADME parameters, pharmacokinetic properties, drug likeness nature, medicinal chemistry of compounds. Swiss ADME server was opened and the structures were drawn after that they coverted into smiles, finally clicked on run button, results were obtained.

Method of synthesis

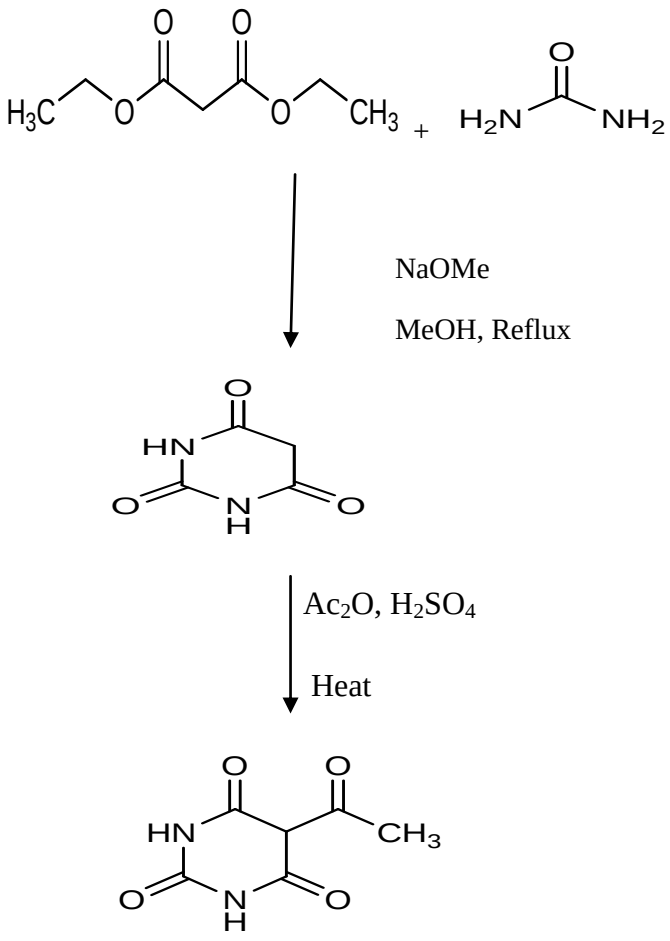
Synthesis of pyrimidine 2, 4, 6-(1H, 3H, 5H) trione: Diethylmalonate (20 gm, 0.5 mol), urea (7.5 gm, 0.5 mol), anhydrous sodium methoxide (2.875 gm, 0.5 gm atom in 62.5 ml in anhydrous methanol) and 62.5 ml methanol were taken in a flat bottom flask and refluxed for 7 hrs on waterbath at 65^0C. A white solid separates. To the reaction mixture 125 ml of hot (50^oC) water was added and then acidified with hydrochloric acid. After the completion of the reaction, the resulting solution was filtered and cooled in an ice bath overnight. The white solid product was formed and it was separated out by filtration and washed with 50 ml of cold water. The product was dried in an oven at 105-110^{o}C for 3-4 hrs to give the compound (10.4 gm, 65%), as a white powder.[87]

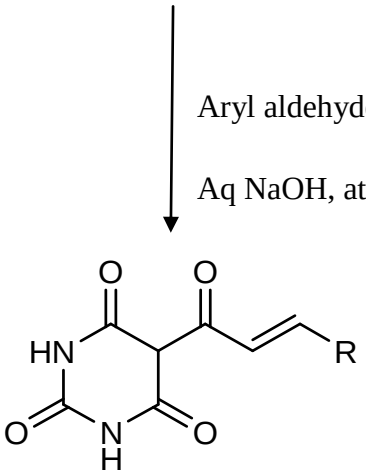
Synthesis of 5-acetyl pyrimidine 2, 4, 6-(1H, 3H, 5H) trione : Pyrimidine 2, 4, 6-(1H, 3H, 5H) trione (6.4 gm, 0.05 mol) and acetic anhydride (150 ml) were taken in round bottom flask and to this few drops of H_2SO_4 acid was added and refluxed for 1 hr. The reaction

mixture in the beginning was a suspension however after around 10 min of refluxing, it changes to orange colour and turns into a solution. The reaction mixture was concentrated in to half of its original volume and cooled at about 10^{o}C. The solid product was separated out by filtration and washed with hot water then acetone. The product was dried at 80^{o}C for 30 min to give compound (7.8 gm), 92% yield, as a yellow powder.[88]

General procedure for synthesis of chalcones: To a stirred solution of 5-acetyl pyrimidine 2, 4, 6 trione (1.148 mmol) in 40% aqueous sodium hydroxide solution, equimolar quantity of the appropriate aryl aldehyde (for e.g., benzaldehyde 0.121 gm, 1.148 mmol) was added. The reaction mixture was stirred at room temperature for about 12 hrs. The reaction was monitored by TLC using chloroform-methanol and hexane-ethyl acetate (4:1 v/v) mixture. After the completion of the reaction, final compound was separated out from water at 6-7 P^{H}. Further purification of separated final compound was done by recrystallization in methanol. Similarly, other compounds were synthesized.[87, 88]

Scheme of synthesis





RESULTS AND DISCUSSION

Molecular descriptors and drug likeness

Physicochemical parameters of the compounds were predicted and tabulated in Table 3. The predicted values revealed that all the 16 designed compounds obeyed Lipinski rule of five with 0 violations by possessing ≤ 5 hydrogen bond donors (OH and NH groups), ≤ 10 hydrogen bond acceptors (notably N and O), ≤ 15 rotatable bonds (rotb) and ≤ 5 log P values. LogP(partition coefficient) is an important parameter which measures molecular hydrophobicity. Hydrophilic/lipophilic nature of drug molecule affects drug absorption, bioavailability, drug-receptor interactions, metabolism of molecules and their toxicity. Log P values of designed chalcone derivatives were found to be in the range of -0.78 to 1.94. Low molecular weight drug molecules (<500) can easily transported, diffused and absorbed as compared to heavy molecules. Molecular weight values for derivatives were found to be in the range of 248.19 to 364.36.

Total polar surface area (TPSA) is related to the hydrogen bonding potential of a molecule and it is a good predictor of drug transport properties like intestinal absorption, bioavailability, blood brain barrier penetration etc. TPSA of all derivatives was found in the range of 92.34 to 131.03, which lies within the standard value 160 A^{o}.

Number of rotatable bonds measures molecular flexibility and it is a good descriptor of oral bioavailability of drugs. All designed compounds were found to be flexible. All the designed compounds obeyed Lipinski rule of 5 hence orally active.

Table 1: Calculation of physicochemical properties for newly designed analogues.

Compound	miLogP	TPSA	MW	Non	Nohnh	Nvio	Nrotb	Vol
M1	0.14	92.34	258.23	6	2	0	3	218.19
M2	0.58	92.34	304.33	6	2	0	4	252.88
M3	1.94	92.34	334.33	6	2	0	4	289.59
M4	1.79	101.57	364.36	7	2	0	6	315.38
M5	0.12	92.34	272.26	6	2	0	4	234.99
M6	0.42	108.13	297.27	7	3	0	3	247.16
M7	1.33	92.34	308.29	6	2	0	3	262.18
M8	-0.52	121.80	304.26	8	3	0	4	251.75
M9	-0.50	131.03	334.28	9	3	0	5	277.29
M10	0.66	92.34	284.27	6	2	0	4	245.60
M11	-0.78	105.48	248.19	7	2	0	3	199.75
M12	0.24	95.58	301.30	7	2	0	4	264.09
M13	1.07	95.58	361.79	7	2	0	4	300.87
M14	1.45	92.34	300.31	6	2	0	5	268.35
M15	1.85	92.34	314.34	6	2	0	4	284.37
M16	0.31	92.34	276.22	6	2	0	3	223.12
Celecoxib	3.61	77.99	381.38	5	2	0	4	298.65

Log p- partition coefficient, TPSA- Topological polar surface area, MW- Molecular weight Non- No of hydrogen bond acceptors, Nohnh- No of hydrogen bond donars, nvio- No of violations, Nrotb- No of rotatable bonds, Vol- volume.

Bioactivity score prediction

The bioactivity scores of the compounds were predicted for the targets like GPCR ligand, kinase inhibitor, protease inhibitor, ion channel inhibitor, nuclear receptor ligand, enzyme inhibitor activities. As a general rule, higher bioactivity score indicates that the compound/ derivative is biologically more active. If the bioactivity score of the compound is >0, then it is biologically more active. If the compounds bioactivity score values in between -0.50 to 0.00 are expected to be moderately active and if score is < -0.50, it is presumed to be inactive.[14] The results of the present study revealed that designed compounds are biological active molecules, and they will produce the biological activity by interacting with GPCR ligands, nuclear receptor ligands, and protease inhibitor and other enzymes.

Table 2: Calculation of bioactivity score for newly designed analogues.

Compound	GPCR Ligand	Ion channel inhibitor	Kinase Inhibitor	Nuclear Receptor Ligand	Protease inhibitor	Enzyme inhibitor
M1	-0.37	-0.32	-0.59	-0.54	-0.11	-0.08
M2	-0.36	-0.40	-0.59	-0.42	-0.02	-0.10
M3	-0.14	-0.21	-0.27	-0.22	0.11	-0.00
M4	-0.15	-0.23	-0.33	-0.19	0.11	-0.03
M5	-0.13	-0.13	-0.45	-0.26	0.06	0.12
M6	-0.02	-0.23	-0.21	-0.42	0.05	0.15
M7	-0.16	-0.26	-0.34	-0.28	0.09	-0.01
M8	-0.25	-0.34	-0.42	-0.31	-0.08	-0.05
M9	-0.24	-0.31	-0.35	-0.30	-0.02	-0.02
M10	-0.16	-0.20	-0.39	-0.25	0.07	0.07
M11	-0.71	-0.80	-1.01	-0.87	-0.54	-0.35
M12	-0.23	-0.32	-0.38	-0.35	-0.02	-0.08
M13	-0.17	-0.26	-0.43	-0.32	-0.00	-0.17
M14	-0.14	-0.24	-0.47	-0.22	0.10	-0.01
M15	-0.16	-0.20	-0.38	-0.20	0.04	-0.04
M16	-0.30	-0.32	-0.48	-0.43	-0.09	-0.08
Celecoxib	-0.06	-0.27	0.01	-0.28	-0.06	0.17

Protease inhibitor

Compounds M3, M4, M5, M6, M7, M10, M14, M15, were found to be highly bioactive (>0) towards protease inhibitor. The compounds M1, M2, M8, M9, M16 showed scores in between -0.5 to 0.0 hence they found to be moderately active. Compound M11 showed the value -0.54 which is less than <-0.5, Hence it was found to be inactive.

GPCR ligand

Bioactivity score for GPCR ligand was found to be in the range of -0.5 to 0.0 for all tested compounds except M11. M6 compound showed highest score -0.02 among all the derivatives. The compound M11 showed -0.71 which is less than -0.5 hence it was found to be inactive.

Ion channel receptor

Compound M11 showed the value -0.80 which is less than -0.50 hence inactive. Remaining compounds (M1-M10, M12-M16) were found to be moderately active because they showed values in the range of -0.5 to 0.0. Among all the designed compounds M5 showed the highest score -0.13.

Kinase inhibitor

Compounds M1, M2, M11 were found to be inactive (<-0.5). Remaining compounds (M3-M10, M12-M16) were found to be moderately active because they showed bioactivity score in the range of -0.5 to 0.0. The highest score -0.21 showed by the compound M6.

Nuclear receptor ligand

Compounds M1, M11 were found to be inactive (<-0.5). Remaining compounds (M2-M10, M12–M16) were found to be moderately active because they showed bioactivity score in the range of -0.5 to 0.0. The highest score -0.19 showed by the compound M4.

Enzyme inhibitor

Compounds M5, M6, M10 were found to be highly bioactive (>0) towards protease inhibitor. M1, M2, M3, M4, M7, M8, M9, M11, M12, M13, M14, M15, M16 compounds showed the bioactivity score values in the range of -0.5 to 0.0 hence moderately active. Among all the compounds M6 showed highest score 0.15.

Swiss ADME Results

ADME properties of the designed compounds were calculated and tabulated in table 5. Log s scale: insoluble< -10 < poorly< -6 < moderately < -4 < soluble < -2 < very <0 < highly soluble.

Table 3: Swiss ADME data of the newly designed analogues.

COMPOUND	M.R	GI absn	BBB permeation	Log k_p (skin permeation)	Log s (ESOL)	Bioavailability score
M1	73.08	High	No	-7.26 cm/s	-2.02	0.55
M2	84.80	High	No	-7.17 cm/s	-2.55	0.55
M3	98.51	High	No	-6.56 cm/s	-3.58	0.55
M4	104.06	High	No	-6.86 cm/s	-3.51	0.55
M5	77.09	High	No	-7.13 cm/s	-2.22	0.55
M6	84.93	High	No	-7.40 cm/s	-2.42	0.55
M7	90.58	High	No	-6.68 cm/s	-3.21	0.55
M8	81.59	High	No	-7.74 cm/s	-2.03	0.55
M9	88.08	High	No	-8.01 cm/s	-2.06	0.55
M10	82.22	High	No	-6.95 cm/s	-2.51	0.55
M11	65.34	High	No	-7.83 cm/s	-1.37	0.55
M12	87.28	High	No	-7.43 cm/s	-2.28	0.55
M13	102.73	High	No	-7.01 cm/s	-3.33	0.55
M14	87.66	High	No	-6.56 cm/s	-2.97	0.55
M15	92.35	High	No	-6.41 cm/s	-3.32	0.55
M16	73.63	High	No	-7.30 cm/s	-2.19	0.55
Celecoxib	89.96	High	No	-6.21 cm/s	-4.57	0.55

M.R- molar refractivity, GI absn- Gastro intestinal absorption, BBB permeation- Blood brain barrier permeation, Log s (ESOL)- Estimated water solubility.

All newly designed analogues have high GI absorption, no BBB permeation, and good bioavailability score.

The compounds M1,M2,M3,M4,M5,M6,M7,M8,M9,M10,M12,M13,M14,M15,M16 showed Log s (ESOL) values in the range of -2 to -4 hence all these compounds were found to be soluble. In all the above compounds, M11 compound showed -1.37 value which lies in the range of -2 to 0, hence it was found to be very soluble. The standard drug Celecoxib, its Log s value was found to be -4.57, indicating that it was moderately soluble.

Patch dock results

Molecular docking studies were performed for sixteen newly designed compounds and standard drug Celecoxib using Patch Dock. Cyclooxygenase-2 (Pdb code:5PP1) was taken as target protein to study the binding interactions of the test set with in the active site. Patch Dock results were tabulated in Table 6. The ACE score mentioned in the table 6 gives an idea about the binding energy of the ligand with the receptor. Lower the ACE values higher will be the activity.

Table 4: Docking results of receptor COX-2 (Pdb Id: 5PP1) with 5-acetyl pyrimidine 2, 4, 6 trione based chalcones analogues using Patch Dock.

COMPOUND	RECEPTOR COX-2 PDB ID	PATCHDOCK SCORE	ACE
M1	5PP1	3514	-42.54
M2	5pp1	3682	-238.55
M3	5PP1	4414	-34.12
M4	5PP1	4606	-40.05
M5	5PP1	3608	-16.45
M6	5PP1	3682	-28.50
M7	5PP1	3874	-55.04
M8	5PP1	3628	-42.49
M9	5PP1	3886	-33.10
M10	5PP1	3656	-24.20
M11	5PP1	3220	-56.89
M12	5PP1	3948	11.21
M13	5PP1	4198	-37.07
M14	5PP1	3998	-5.85
M15	5PP1	3882	-41.16
M16	5PP1	3490	13.92
Celecoxib	5PP1	4410	-31.03

The calculated ACE scores of compounds were compared with standard anti inflammatory drug Celecoxib and the compounds M1, M2, M3, M4, M7, M8, M9, M11, M13, M15 were found to be more potent than standard Celecoxib because they showed lower ACE values than Celecoxib. Remaining compounds M5, M6, M10, M12, M14, M16 were found to be less potent than standard because they showed higher ACE values than Celecoxib.

Among all the designed compounds M2 had highest affinity to 5PP1 (COX-2) with an ACE value of -238.55 Kcal/Mol, so it was found to be highly bioactive compared to all other designed compounds and M11, M7 had next highest affinity to 5PP1 (COX-2) with an ACE values of -56.89 Kcal/Mol, -55.04 Kcal/Mol respectively.

Spectral data

The compounds M2, M7, M11 were synthesized and characterized by spectral analysis. The I.R spectra of compounds showed a characteristic bands between 1600 cm^{-1} and 1680 cm^{-1} confirming the presence of (C=C) groups. I.R spectrum of compounds showed a characteristic bands between 1694 cm^{-1} and 1716 cm^{-1} confirming the presence of C=O groups. I.R spectrum of compounds showed a characteristic bands around 3436 cm^{-1} confirming the presence of -NH- groups. The ^{1}H NMR spectra revealed signals 3.50 ppm appears as signals for DMSO solvent. The ^{1}H NMR data of compounds revealed signals between 4.19 and 4.25 ppm for CH of pyrimidine ring. The ^{1}H NMR data of compounds revealed signals between 10.61 and 11.84 ppm for NH of pyrimidine ring. The ^{1}H NMR data of compounds revealed signals between 7.01 and 8.14 ppm for aromatic protons of phenyl ring.

SUMMARY AND CONCLUSION

By using molecular docking studies, all the designed compounds were screened for anti-inflammatory activity, the derivative with para thiomethyl benzaldehyde showed maximum activity among the designed compounds. And also the designed compounds were screened for the drug likeness properties and bioactive score, from which maximum number of compounds designed were found to be worthwhile. 5- Acetyl pyrimidine 2, 4, 6 trione based chalcones were synthesized by Claisen Schimdt reaction between a benzaldehyde and an acetophenone in the presence of NaOH as a catalyst and ethanol as a solvent. In this study the most active three chalcones derivatives were synthesized using various aryl aldehydes as 4-thiomethyl benzaldehyde, furfuraldehyde, naphthaldehyde and characterized by spectral analysis.

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