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Research Article

SYNTHESIS, *IN SILICO* DOCKING AND ADMET STUDIES OF ARYLACETIC ACID DERIVATIVES AS PROSTAGLANDIN ENDOPEROXIDE H SYNTHASE-2 INHIBITORS

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ABSTRACT

Objectives: To study the inhibition of prostaglandin endoperoxide H synthase-2 (PHSH-2) for arylacetic acid derivatives.

Methods: This study was performed to evaluate the anti-inflammatory activity of the synthesized arylacetic acid derivatives through molecular docking via Discovery Studio 4.0 and Schrodinger Software. ADMET study was conducted to find the assessment on genotoxicology.

Results: The synthesized arylacetic acid derivatives were confirmed by nuclear magnetic resonance, liquid chromatography-mass spectrometry, and purity by high-performance liquid chromatography. The synthetic pathway is economical, industrial scalability and is achieved with high yield and purity. The *in silico* studies identified the active pocket and compared with the standard drug.

Conclusion: Results from this work conclude that the arylacetic acid derivatives have very good inhibition and very low binding energy toward the active pocket, hence can be considered as good inhibitors of PHSH-2 on comparison with iodosuprofen. The compounds qualified Lipinski rule of five and the ADMET results were non-mutagenic and non-carcinogenic.

Keywords: Arylacetic acid, 1 phenyl glycidyl ether protein, ADMET, *In silico* docking, Anti-inflammatory.

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INTRODUCTION

Prostaglandins are lipids, present in human and animals which act as potential mediators in acute pain, inflammation, and hyperpyrexia. These lipids are synthesized not on a specific site but throughout the body. The remedial action of nonsteroidal anti-inflammatory drugs (NSAIDs) is exercised through the inhibition of prostaglandin G/H synthase (PGHS), which is expressed as two isoenzymes, termed PGHS-1 and PGHS-2 [1]. Most of the NSAIDs are non-selective to the target and causes side effects such as gastric irritation and ulceration. Finding a potential inhibitor for the inflammation is more challenging and promising in the field of drug discovery. Small molecular inhibitors with computational etiquette have been flourishing in diagnosing disease and curative intervention in earlier research [2-5]. With this inspiration, *in silico* docking studies have been deployed for recognition of PGHS-2 inhibitors. The small molecular drugs were synthesized and virtually screened for biological activities [6]. Some of the drugs which were used effectively in inhibiting the enzymes responsible for inflammation are represented in Fig. 1. On intense study of these drugs, we tried to synthesize analogous functional moiety of library molecules so that they may be useful in prediction of activity.

The main objective of this study is to provide a best industrial route in an economical method with high pure and high yield. These molecules are virtually screened for biological activity. In order to synthesize the library molecules containing acetic acid groups, various methods have been tried and implemented. To add to its credential, these compounds can be used in synthesis of many chiral drugs as resolving agent and chiral auxillary. To date, synthesized arylacetic acid derivatives were not screened for ADMET prediction, hence, we attempt to predict the biological activity and toxicology via docking method.

METHODS

Proton (^{1}H- nuclear magnetic resonance [NMR]) and carbon-13 (^{13}C-NMR) magnetic resonance spectra were recorded at 300 MHz and 75 MHz, respectively, in acetone-d 6 at 25°C. Chemical shift values are reported in ppm with tetramethylsilane as an internal reference. J values are given in Hz. The mass spectra were done using GC-MS (SHIMADZU GC-MS QP 2010 -CI mode) or liquid chromatography-mass spectrometry (LC-MS) 6010 (electrospray ionization [ESI] mode). The starting materials were purchased from Sigma-Aldrich.

Synthesis of arylacetic acid derivatives

In a multi-neck flask, under nitrogen atmosphere, sodium hydroxide (~1.6-1.8 mol eq) was dissolved in dimethylformamide (DMF) and stirred for 10 minutes at 10-20°C. The appropriate aryl cyanide (0.75-0.85 mol eq) was slowly added to the flask for about 30 minutes and stirred at 20°C for 2-3 hrs. Alkyl bromide such as EtBr, iPrBr, and N BuBr (~0.95-1.2 mol eq) was dissolved in 100 ml DMF solvent and added slowly to the reaction mixture for 30 minutes by maintaining the temperature at below 15°C for 5-8 hrs. After completion of reaction, the mixture was quenched in water (100 ml) and tBME (200 ml), the layers were separated and the solvent was removed using vacuum distillation. The concentrated alkyl substituted aryl cyanide was used to next step without further purification.

The concentrated alkyl substituted aryl cyanide (0.5-0.6 mol eq) was dissolved in propylene glycol (100 ml) and added potassium hydroxide flakes in lot quantities (exothermic reaction) for 1 hr at below 10°C. The reaction mixture was heated to 130-140°C and maintained at the same temperature for 7-10 hrs. The reaction mixture was quenched in water-tBME, the layers were separated and subjected to pH adjustment using conc. HCl (pH=1.0-2.0). Then, purified using dichloromethane and concentrated under vacuum. The purity of the product was done using high-performance liquid chromatography (HPLC), and the yield of the obtained arylacetic acid was 80-85% with purity 99% as solid.

Compound 5: Following the general method described above, isopropyl bromide and benzyl cyanide reacted to give the product as colorless solid with HPLC purity 99.0% and yield: 75 g; 1 proton (H-NMR) ($CDCl_3$)

δ_H 0.70 (d, 3H), 1.08 (d, 3H), 2.33 (m, 1H), 3.14 (m, 1H), 7.29 (m, 5H), 10.99 (bs, 1H); 13C NMR (CDCl3) δ_C 20.10, 21.46, 31.55, 60.09, 127.46, 129.54, 128.59, 137.72, and 180.59; GC-MS (CI; MeOH): M/z 133(100), [M+H] at m/z 179(2), M^+ At m/z 193 (4); LC-MS (ESI): M/z 196.

All other compounds were analyzed by HPLC and the characterization using LC-MS in ESI mode were tabulated in Table 1.

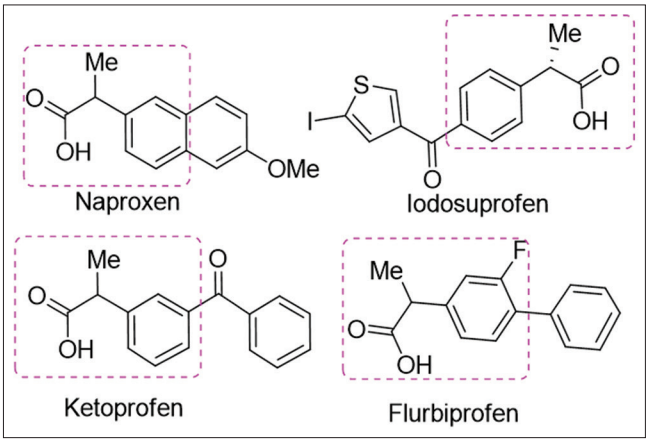


Fig. 1: Functional group similarity of prostaglandin G/H synthase-2

Chromatographic conditions

Instrument: Shimadzu 2010A with UV detector or equivalent.
Column: Zorbax SB C18, 150 mm × 4.6 mm, 3.5 µ or equivalent.
Flow rate: 1.0 ml/minute.
Detection: UV at 300 nm.
Column temperature: 25°C.
Sample compartment temperature: 25°C.
Injection volume: 10 µl.
Runtime: 10 minutes.

RESULTS

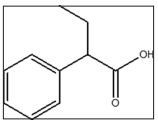
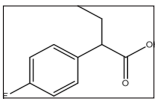
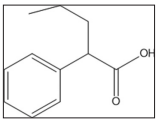
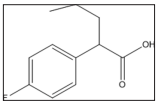
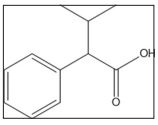
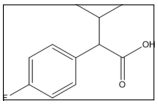
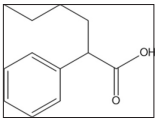
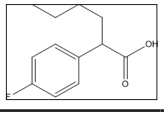
The general method for preparing arylacetic acids is outlined in scheme 1.

While comparing the previous research [7] on the synthesis of arylacetic acid derivatives involve lengthy route with low pure compounds, whereas the route of synthesis suggested in this study can be utilized in industrial scale with economic pathway and achieved with high pure and high yields. The synthesized arylacetic acid derivatives can be resolved further to give chiral arylacetic acids which have extraordinary use in the field of pharmaceutical chemistry and in drug synthesis.

Molecular docking studies

The three dimensional structure of the protein was retrieved from the RCSB with protein data bank (PDB) Id-1 phenyl glycidyl ether (PGE) with X-ray diffraction resolution of 3.5 Å5 [5,6]. The preparation of retrieved protein was executed using the prepare protein wizard of

Table 1: Experimental data of synthesized compounds

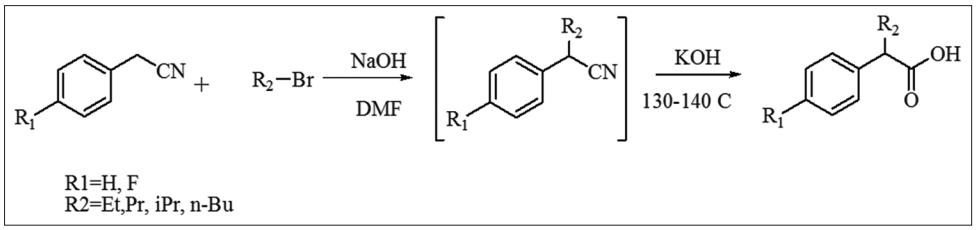
Compound No	Compound name	Structure	Time	Yield* (%)	ESI: m/z
1	2-phenylbutanoic acid		9 hrs	75	163.2
2	(4-fluorophenyl)butanoic acid		8 hrs	78	195.9
3	2-phenylpentanoic acid		8 hrs	69	177.0
4	4-fluorophenyl-3-methylbutanoic acid		10 hrs	72	195.7
5	3-methyl-2-phenylbutanoic acid		7 hrs	75	177.2
6	2-(4-fluorophenyl)-3-methyl-butanoic acid		8 hrs	86	195.1
7	2-phenylhexanoic acid		9 hrs	80	191.5
8	2-(-4-fluorophenyl)-hexanoic acid		7 hrs	74	209.1

*Batch size: 100 g scale, ESI: Electrospray ionization

Table 2: Docking result for synthesized compounds and comparison with 1PGE cocrystal

Compound	Discovery studio	Schrodinger			
		Rigid		Flexible	
	Lib dock score	Docking score	Glide energy	Docking score	Glide energy
1PGE-cocrystal				−5.30	−34.88
Compound 1	90.13	−9.17	−27.47	−6.34	−27.09
Compound 2	87.37	−7.23	−23.53	−5.39	−25.42
Compound 3	93.43	−9.37	−28.06	−5.05	−30.77
Compound 4	93.21	−7.28	−28.83	−4.97	−27.65
Compound 5	86.71	−7.42	−27.57	−8.32	−31.73
Compound 6	86.23	−7.46	−29.71	−5.66	−29.51
Compound 7	95.03	−8.04	−26.84	−4.22	−32.95
Compound 8	88.36	−7.28	−28.83	−5.39	−25.42

PGE: Phenyl glycidyl ether



Scheme 1: Preparation of arylacetic acid derivatives

accelrys Discovery Studio 4.0 by applying CHARMm force field. Initially, all the internal ligands, water molecules, ions and metal elements were removed and inserted the missing atoms before minimization of target protein. Glide parameters were defined in a similar way as that of accelrys.

In this study, the inhibitory activity of compounds 1-8 was investigated using molecular docking studies which were performed in two different commercial software like Discovery Studio and Schrodinger. The protein PDB structure of 1PGE is in complex with the 8 ligands through hydrogen bonding and hydrophobic interactions.

DISCUSSION

To determine the molecular binding interaction of the 8 ligands, they were docked into the active binding site of PGE protein and the docking results are listed in Table 2. The PDB sum active site analysis discloses the hydrogen bonding of ligand with His388A, His386A, Arg120, Ser516A, His90A, Tyr355A, Ser530A, Glu520A and Tyr385A of the receptors having the bond distance~2.8 A. The best results were analyzed based on the docking score, non-bonded interactions and Glide energy. The binding energy, i.e., glide energy was calculated based on optimized potential for liquid simulations-all atom force field. On comparing, these synthesized ligands with that of cocrystal (iodosuprofen) in the 1PGE, the hydrogen bonding was similar and their binding energies were tabulated in Table 2. The interacting amino acids of 1PGE with iodosuprofen were Tyr 355, Arg120, Ser 530 and are shown in Fig. 2.

Significance of Arg120 residue

The molecular docking of the proposed active site of PGHS shows the –COOH group of compounds 5 and 2 located in a favorable position for interacting with the guanidinium group of Arg120 (Fig. 3). These data provide biochemical evidence of the importance of the Arg120 residue [8] in PGHS-1 for interaction with arachidonic acid and NSAIDs containing a free carboxylic acid moiety [9-12].

Based on the results obtained from docking and ADMET studies, the best compounds determined are compounds 7, 3, and 8 (Fig. 4) and almost all compounds have been predicted to have good inhibition (Fig. 5).

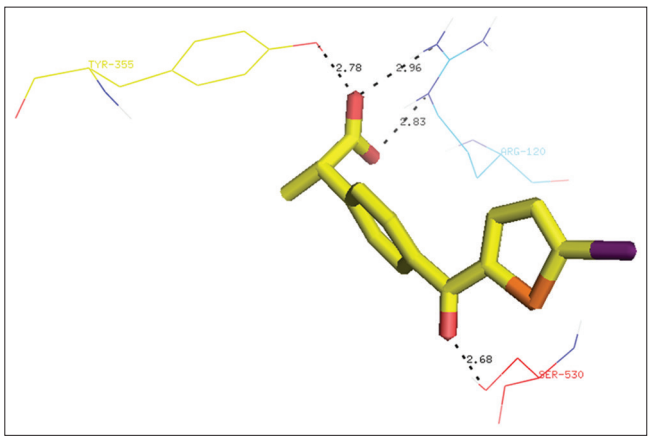


Fig. 2: Prostaglandin H2 synthase-1 complexed with co-crystal P (2'-iodo-5'-thenoyl)-hydrotropic acid (iodosuprofen)

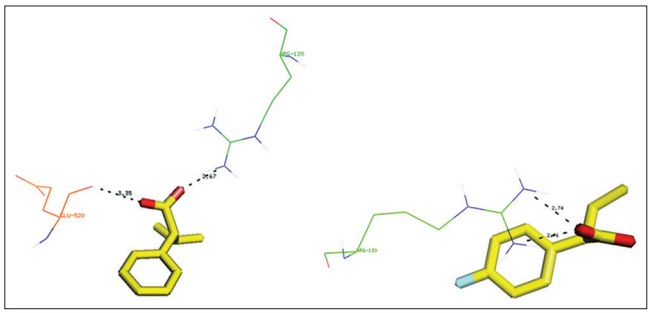


Fig. 3: Arg120 interaction with compounds 2 and 5

The results indicated that the synthesized arylacetic acid derivatives have a predicted inhibiting activity almost similar to standard drug (Table 2). Hence, they may have anti-inflammatory activity.

ADMET study

The pharmacokinetic study [14] of the compounds 1-8 were predicted by Discovery Studio 4.0. ADMET 2D-graph was plotted against AlogP98

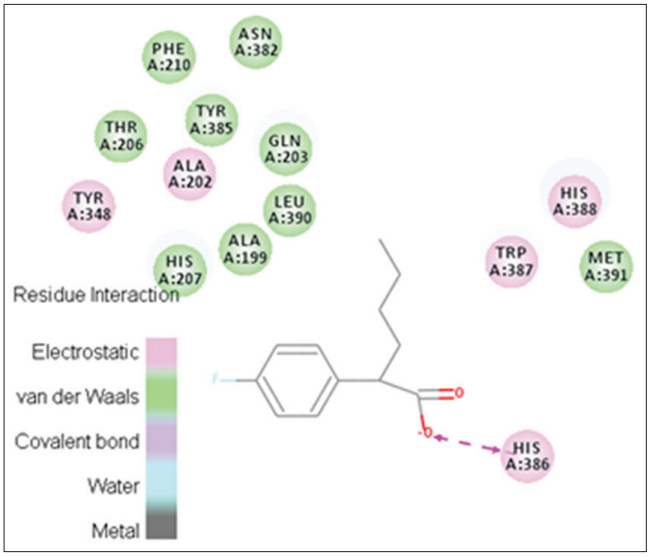


Fig. 4: Overall interactions of 1 phenyl glycidyl ether with compound 8-2D-diagram

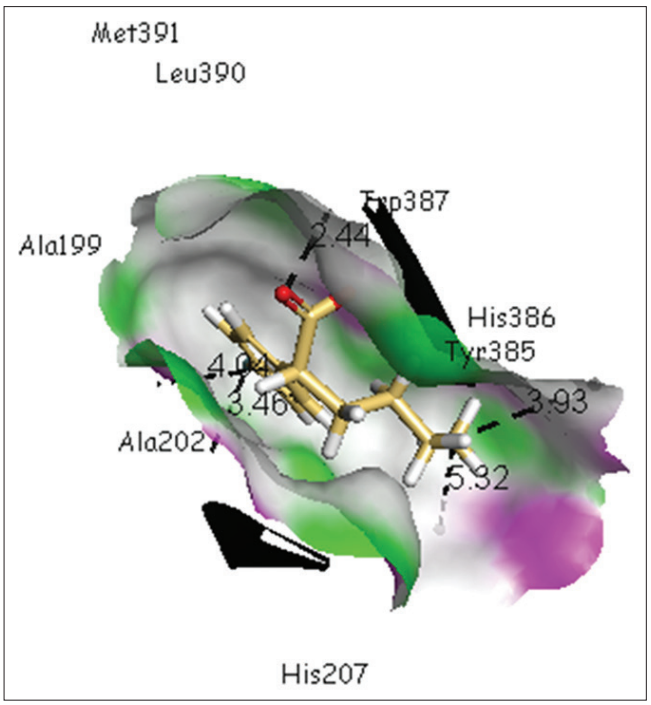


Fig. 5: Hydrogen bonding interaction between receptor and compound 8

versus polar surface area (Fig. 6). The absorption model corresponding to blood-brain barrier and human intestinal absorption is indicated with 95% and 98% confidence limit ellipses. The compounds found to have good absorption level and they are well within the limit. The ADMET aqueous solubility predicted at 25°C found to have good and optimal levels (Table 3). The hepatotoxic level for all the compounds was predicted to be 0 based on ADMET. The mutagenicity and carcinogenicity prediction found to be 0.

CONCLUSION

Eight derivatives of arylacetic acids were synthesized in very reasonable yields. ADMET results showed that the synthesized compounds were non-mutagenic and non-carcinogenic and they meet the criteria of Lipinski rule of five [13]. Based on molecular docking studies, very

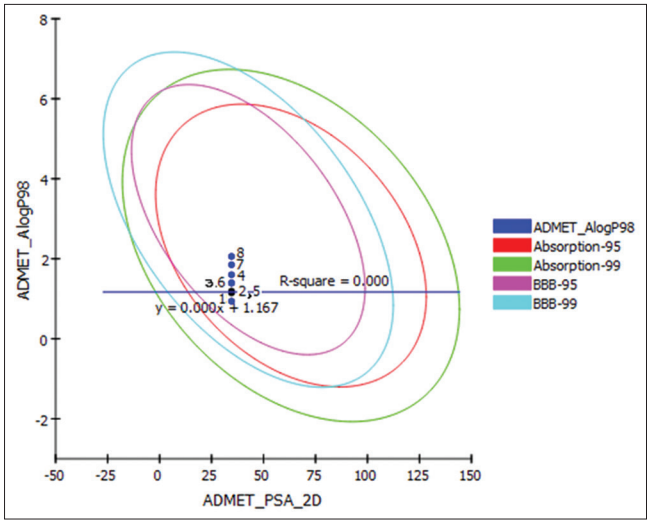


Fig. 6: ADMET 2D-graph of compounds 1-8: AlogP98 versus polar surface area

Table 3: ADMET prediction

Compound	CYP2D6	ADMET _AlogP98	ADMET Solubility level	ADMET _PSA_2D
1	−2.63678	0.939	4	34.601
2	−1.08336	1.144	4	34.601
3	−2.37804	1.395	3	34.601
4	0.03815	1.601	3	34.601
5	−2.81111	1.191	4	34.601
6	−1.49353	1.396	3	34.601
7	−1.23456	1.851	3	34.601
8	1.41748	2.057	3	34.601

low binding energy and very good inhibition toward the active pocket, hence they can be considered as good inhibitors of prostaglandin endoperoxide H synthase-2 on comparison with the standard drug iodosuprofen. Hence, the synthesized compounds may have anti-inflammatory activity.

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