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MOLECULAR DOCKING AND TOXICITY STUDIES OF SERIES OF COMPOUNDS FROM DIARYL UREA HITS & SPIRO PIPERIDINE INDOLINYL SERIES AS POTENTIAL P2Y1 RECEPTOR ANTAGONISTS

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ABSTRACT: Scientific investigations revealed that the study of P2Y1 receptors is very much essential in the current scenario because of their potential role in related to various disorders/diseases like thrombosis, cardiovascular problems. P2Y1 receptors belong to G protein-coupled receptors, an important target for ADP induced platelet aggregation. Blockade of P2Y1 receptors leads to the treatment of thrombosis with a potentially improved safe margin. Hence, it is essential to select targeted molecules as P2Y1 receptor antagonists. The present work is to explore P2Y1 receptor antagonists from different series of synthetic compounds by using docking, virtual screening, and toxicity studies. Docking studies were performed and scored to evaluate ligand binding affinities. The present work could be used as a tool to show how different scaffold structures are utilized for the development of suitable P2Y1 receptor antagonists for platelet aggregation activity.

INTRODUCTION: The P2Y1 receptor, which is a G- protein-coupled receptor, became an excellent target for drug design because of its platelet aggregation activity [1]. Activation of the P2Y1 receptor brings about a transient increment in intracellular calcium levels, which leads to a change in platelet shape and rapidly reversible aggregation. Blood platelets play an important role in the pathogenesis of thrombosis and atherosclerosis, platelet aggregation.

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Platelets are associated with many conditions like cardiovascular and cerebrovascular diseases, which lead to death throughout the world. Extensive research on P2Y1 receptors reveals that the cloning of the platelet ADP receptors led to the elucidation of the mechanisms of platelet activation and aggregation induced by ADP [2].

Platelet aggregation induced thrombosis obstructs blood circulation, playing a central role in acute and chronic arterial vascular diseases. The decrease in thrombus formation will be achieved by Anti-platelet drugs; hence more emphasis is given to P2Y1 receptor antagonists, which act as antithrombotic drugs. The P2Y1 receptor protein structure contains a binding site for receptor antagonist MRS2500 within its seven-transmembrane bundles, which also provides

suitable pockets for numerous other ligands to act as nucleotide antagonists of P2Y1 receptors. *In-silico* docking of these compounds into the P2Y1 receptor protein structure within the MRS2500 pocket can identify potential antithrombotic drugs from natural or synthetic source [3].

Both the P2Y1 and P2Y2 receptors form a heteromeric complex with the A1 adenosine receptor in HEK293 cells [4, 5]. Heteromeric association between the Gi-coupled A1 receptor and the Gq-coupled P2Y1 receptor was shown to create a hybrid receptor that responds predominantly to the P2Y1 receptor agonist ADPβS to activate both Gi and Gq.5 Specifically, activation of Gi and inhibition of forskolin-induced CAMP accumulation by the A1- P2Y1 receptor complex displays a hybrid selectivity for P2Y1 and A1 receptor agonists and antagonists, whereas activation of Gq and generation of inositol phosphates occurs only with P2Y1 receptor agonists and not with A1 receptor agonists, 5 suggesting that the cross talks to G proteins for the A1– P2Y1 receptor complex is unidirectional. In contrast, an association of the A1 receptor with the P2Y2 receptor does not affect the ligand selectivity of the heteromeric receptor, although simultaneous stimulation of the A1– P2Y1 receptor complex with A1 and P2Y2 receptor agonists interferes with Gi signaling and enhances Gq signaling [4].

The P2Y1 receptor also is thought to form a heteromeric complex with the P2Y11 and P2Y12 receptor [6, 7,] which for the P2Y11 receptor alters its function. Ecke *et al.,* have shown that co-expression of the P2Y1 and P2Y11 receptors in HEK293 or 1321N1 cells promotes agonist-induced endocytosis of the P2Y11 receptor, which when expressed alone in these cells is unable to undergo agonist-induced endocytosis. The ligand selectivity of the P2Y1–P2Y116 receptor complex, measured by activation of Ca^{2+} signaling, is also different than the agonist potency profile in cells expressing only the P2Y11 receptor.

Current Status and Functions of P2Y1 Receptors in Various Types of Diseases: P2Y1R broadcasts mitogenic signals by activating the EGFR, and the pathway involves PKC, Src, and cell surface metalloproteases. P2Y1R for as little as 15-60 min triggers mitogenesis, mirroring the half-life of extracellular ADP. Apyrase degradation of extracellular nucleotides and drug inhibition of P2Y1R both reduced basal cell proliferation of HeLa and FRT cells. Cell-released nucleotides constitute strong mitogenic stimuli, which act via P2Y1R.

Strikingly, MDCK cells ectopically expressing P2Y1R display a highly proliferative phenotype that depends on EGFR activity associated with an increased level of EGFR, GPCR-mediated regulation of EGFR function and highlight a role of P2Y1R in EGFR-dependent epithelial cell proliferation. P2Y1R could potentially mediate both trophic stimuli of basally released nucleotides and first-line mitogenic stimulation upon tissue damage [8, 9].

TABLE 1: CURRENT STATUS AND FUNCTIONS OF P2Y1 RECEPTORS IN VARIOUS TYPES OF DISEASES

Tissue cell line	Receptor	Signaling Pathway	Functions
Knockout mice/ C57BL/6	P_2Y_1	ADP/Gq—PLCβ, Rac, Rho activation	Platelet aggregation, bone resorption, Leptin secretion, angiogenesis, *etc.*
Mus musculus	P_2Y_1	Purinergic receptor/GPCR	Ubiquitous expression in colon, large intestine, and other tissues
Huh-7 Rat hapatoma	P_2Y_1	Ca^{2+}	Volume-regulatory cell metabolism
PANC-1	P_2Y_1	PLC IP_3/PKC	Pro-proliferative
HCT8/Caco2	P_2Y_1	Ca^{2+}	Pro-proliferative apoptosis-inducing

Due to broad-spectrum and potential range of activities, especially as antithrombotic agents, we felt worthwhile to investigate daryl urea derivatives and spiro piperidine indolinyl series because of the presence of active moiety/pharmacophore urea NH [10]. In this current scenario computational approaches are widely used in the research field. Structure-based methods, such as ligand-protein docking, are efficient and useful tools for novel drug discovery and design. *In-silico* studies reveal about the interactions and mechanisms between the protein target and its suitable ligands [11]. The main objective of the present work is to use an *in-silico* docking approach for the investigation of the potential targets as new P2Y1 receptor antagonists as antithrombotic agents. In this study, we have

collected the information about the synthetic compounds and their experimental values such as IC_{50} values through literature. And also tested their toxicity studies like oral toxicity, carcinogenicity and skin toxicity by using different software which available through online.

Then performing the docking procedure of these total 65 compounds into the pocket structure of receptor P2Y1 R. Analysed results of these high efficient docked compounds, summarized their general characters such as scaffold, and provides information for the innovation of new Anti-platelet targets.

METHODOLOGY:

Computational Studies:

***In-silico* Prediction of Physicochemical Properties:** Physicochemical properties of the titled 65 compounds were calculated using the Qikprop module of schrodinger software [5]. The compounds were first drawn in 2D, prepared using schrodinger's Ligprep module as per standard protocols/all the minimized structures were loaded into Qikprop module and predicted the physicochemical properties.

Molecular Docking: The Dock Score was adopted as the Ligand Fit scoring to rank the drug compounds that docked into the P2Y1R ligand-binding pocket for MRS2500. The Ligand Fit docking procedure consists of the following two steps: (1) identify and select the region of the protein as the active site for docking by cavity detection and (2) dock the candidate ligands to the selected site. The docking cavity was defined using the DS site search module. For all potential drugs, the docking site was derived from the position of the MRS2500, and P2Y1 co-crystallized construction (PDB ID: 4XNW), and the grid resolution was set to 0.5 Å (default). The accessible ligand grid was defined as the minimum distance between a grid point and the protein and was 2.0 Å for hydrogen and 2.5 Å for heavy atoms. This confirmed binding site was used to calculate the nonbonded interactions between all potential compounds and the P2Y1 receptor protein residues. The docking procedure was initiated with the generation of random ligand conformations. The following procedures were performed after a new conformation was generated: The shapes of the potential ligands were compared with the active site, and if the result was acceptable, the docking energy (Dock Score) was computed between the protein and ligand trial conformation. Variable numbers of Monte Carlo steps were used to generate different ligand conformations. Scoring was performed with six scoring functions: Dock Score, Lig Score 1 and 2, Piecewise Linear Potential (PLP) 1 and 2, and Potential of Mean Force (PMF). We assumed that the bioactive orientations ranked by Dock Score and other scoring functions were used to retain each molecule and compute the enrichment factors.

Docking Study: The prepared ligands were subjected to docking against the target enzyme using Glide -ligand docking tool. Docking is done to predict ligand poses and to rank ligands based on predicted affinities to the protein. SP-docking identifies a discrete set of conformations for each ligand and gives the docking score based on a rough metric fit. XP-docking is used for exhaustive sampling to obtain an advanced scoring for higher enrichment.

ADMET Prediction: Absorption, distribution, metabolism, excretion, and toxicity (ADMET) studies is a must for any ligand molecule to be approved as a novel drug molecule. The ADMET properties for the ligand molecules were studied using the QikProp tool in maestro software. In this study, blood-brain barrier (BBB), caco-2 permeability, human Ether-a-go-go-Related Gene (hERG) inhibition, AMES toxicity, number of H-bond donors, number of H-bond acceptors, central nervous system (CNS) permeability, molecular weight, human oral absorption, percentage human oral absorption, and QPlogPo/w properties were predicted. The compounds following the Lipinski rule of 5 were identified as lead compounds.

Other Toxicity Studies:

Protox: Protox is an *in-silico* online prediction tool that is used for evaluating the oral toxicity of the ligand molecules. The prediction method is based on the analysis of the similarity of compounds with known median lethal doses (LD_{50}) values, incorporates the identification of toxic fragments, therefore representing a novel approach in toxicity prediction. The input can be given either in the form of SMILES or PubChem ID or the 2D

structure of the molecules can be sketched in the space provided and then can be subjected to toxicity prediction. This free online tool can be accessed through this link http://tox.charite.de/tox/index.php?site=compound_input.

Carcino-Pred-EL: Carcino-Pred-EL is an online tool available for testing the carcinogenicity of the ligand molecules. It gives results based on three ensemble models Ensemble SVM, Ensemble RF, and Ensemble XGBoost. These models are known to give highly accurate and specific results as compared to other machine-learning systems. This free online tool can be accessed through this link http://ccsipb.lnu.edu.cn/toxicity/CarcinoPred-EL/.

Biodegradability: Biodegradation is an important natural process that occurs in the environment in order to reduce wastage accumulation. It is an important factor to be considered during the manufacturing of novel drugs. Biodegradability test must be done so that harmful, non-biodegradable chemicals or compounds can be filtered and only biodegradable compounds can be used. In this paper biodegradability test is done using the SVM biodegradability predictor. It can be accessed in the following link http://csbg.cnb.csic.es/BiodegPred/. Those compounds collected in the investigational database were evaluated for Lipinski's rule of five before the screening. Poor pharmacokinetics and toxicity are important causes of costly failures during the downstream process of drug development.

Docking Analysis: The virtual screening docking process was performed with the Ligand Fit module. Ligand Fit gives the best poses at the binding site using a stochastic conformational search and the energy of the ligand-protein complex [4]. Compounds from the investigational database were docked to the P2Y1 protein active site.

RESULTS AND DISCUSSION: Screening and structure Analysis **Fig. 1** summarizes the technology roadmap and the screening results after each step. In 1997, Lipinski led to the well known "Rule of Five" (RO5) for selecting drug-like molecules, which demonstrated that orally administered drugs should have good oral bioavailability in order to be effective. According to the "Rule of Five," a drug-like molecule should have no more than one of the following criteria; No more than five hydrogen bond donors, no more than 10 hydrogen bond acceptors, a molecular mass [5]. To ensure this study with reliable and available results: All compounds need to filter by the RO5. From the screening, we obtained 10 hits. The ADMET—Human skin sensitization studies were predicted as well.

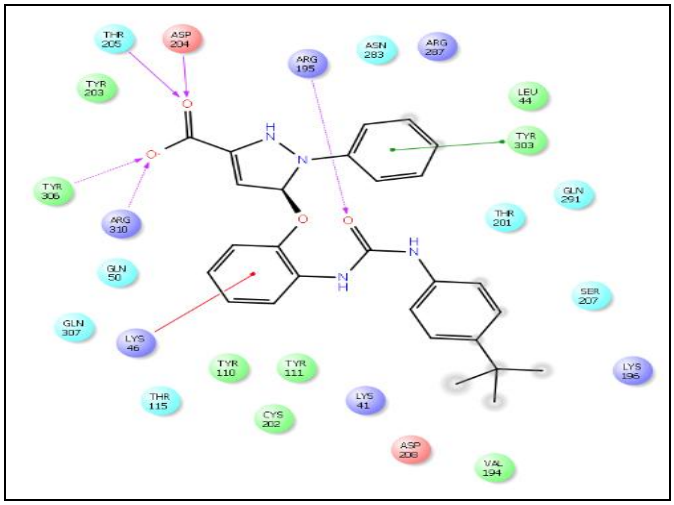

FIG. 1

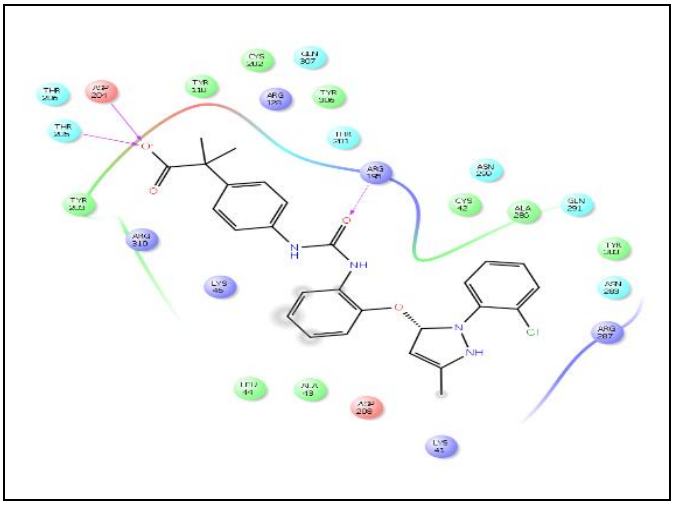

FIG. 2

In the above **Fig. 2,** we see the structural characterization of the select compounds and the assessment of various chemical properties of the compounds based on the simulator analysis. This is an effective means by which we can analyze the potential of the successful hit compounds and assess their pharmacological effects based on a predictive basis with an assurance from the docking studies and the various predictive cross-checks and balances that have been made from the study.

TABLE 1: DOCKING SCORE

Code	Mol. Wt	Glide SP Score
22a1	506.988	-6.812
11a2	512.531	-5.827
11b1	444.532	-5.795
11b5	404.443	-5.664
5a1	504.895	-5.623
46a1	472.543	-5.475
11a6	500.476	-5.415
11a3	538.448	-5.175
13a4	460.962	-5.128
3a	472.348	-5.559

In **Tables 1** and **2,** we see the hit molecules that showed the desired results of our analysis. We checked the following parameters such as glide score, molecular weight, proton donor and acceptor, percentage oral absorption and so on and so forth as indicated in the table. **Table 3** indicates the various toxicities studies' results. Included here are the Protox/LD_{50} data as well as Skin pred/carcinogenicity probability analysis.

TABLE 2: ADME PREDICTION

Code	Mol. Wt	H Donor	H Acceptor	Qplog Po/w	Qplog Herg	Qp Caco	Qplog BB	CNS	Oral: Human Abs
22a1	506.988	4	4.75	5.468	-3.755	48.596	-1.439	-2	1
11a2	512.531	3	2.75	7.174	-5.622	2696.372	-0.047	-1	1
11b1	444.532	3	3.5	5.376	-4.561	3400.395	-0.182	-2	3
11b5	404.443	3	2.75	5.375	-5.735	1874.154	-0.19	-1	1
5a1	504.895	3	2.75	6.433	-5.004	2203.337	0.207	0	1
46a1	472.543	4	4.75	4.982	-3.348	50.993	-1.445	-2	3
11a6	500.476	3	3.5	5.514	-4.058	2418.218	-0.064	-1	3
11a3	538.448	3	2.75	6.396	-4.564	3305.135	0.31	-2	1
13a4	460.962	3	2.75	5.86	-4.594	2570.818	-0.033	0	1
3a	472.348	3	5.25	4.401	-5.25	653.722	-0.427	-1	1

TABLE 3: SKIN TOXICITY PREDICTION RESULTS

Code	LD_{50} mg/kg	Toxic fragments	Skin Pred/Carcinogenicity Probability
22a1	1109	0	55
11a2	260	0	65
11b1	2600	0	60
11b5	1000	0	55
5a1	500	0	53
46a1	1000	0	52
11a6	2700	0	51
11a3	2600	0	54
13a4	2000	0	56
3a	1000	0	51

Sensitivity Studies: Apart from ADMET properties, other toxicity studies such as Protox, carcinogenicity, and biodegradability were also performed for the first ten molecules obtained from docking. Protox is an online tool used for testing of oral toxicity of the ligand molecules. For developing orally active drugs, oral toxicity test is a must in order to identify whether the molecules have any side effects and their level of toxicity. In protox test, the compounds are classified into toxicity classes of range 1 – 6. It also predicts the LD_{50} value in mg/kg. From the results obtained, it can be seen that almost all the compounds belong to toxicity class 4, indicating that the compounds are non-toxic, only hydroxythiobenzanilide 8e belonged to toxicity class 3. The LD_{50} values were seen to vary from 200 mg/kg – 1000 mg/kg, hydroxythiobenzanilide 8e showing the least LD_{50} value of 200 mg/kg. It can also be seen that none of the compounds contains any toxic fragments in the input structure due to which they will not produce any side effects and can be used for developing new orally active drugs against tuberculosis. The results of Protox are shown below in **Table 4**.

TABLE 4: PROTOX RESULTS FOR FIRST TEN COMPOUNDS

Compound	Toxicity class	Toxic fragments	Probability score
11a2	4	0	55
11b1	4	0	65
11b5	4	0	60
5a1	4	0	53
116a	4	0	52
13a4	4	0	56
3a	3	0	51
22a1	4	0	87
11a2	4	0	85
11b1	4	0	81

Carcino-Pred-EL is the free online tool used for the prediction of carcinogenicity of the molecules. The results obtained from all the three ensemble models Ensemble SVM, Ensemble RF, and Ensemble XGBoost were analyzed, and the compounds were shown to be non-carcinogenic and do not possess any cancerous properties and can be used as drugs to combat tuberculosis. The P2Y1 receptor, which is a G- protein-coupled receptor, became an excellent target for drug design because of its platelet aggregation activity. Activation of the

P2Y1 receptor brings about a transient increment in intracellular calcium levels, which leads to a change in platelet shape and rapidly reversible aggregation. Blood platelets play an important role in the pathogenesis of thrombosis and atherosclerosis, Platelet aggregation. Platelets are associated with many conditions like cardiovascular and cerebrovascular diseases, which lead to death throughout the world. In recent years, various *in-silico* based approaches have been developed to manufacture novel drugs to combat thrombosis issue [7]. These approaches have been useful in ligand identification, target identification, and other drug discovery related studies. The development of *in-silico* methods has made the drug discovery process easy in the present decade.

In this paper, molecular docking studies, ADMET studies, oral toxicity, carcinogenicity studies and biodegradability studies have been performed using various *in-silico* tools. Molecular docking and ADMET studies were performed using Schrodinger maestro software; oral toxicity study was performed using Protox web server, carcinogenicity study was done using Carcino-Pred-EL online tool and biodegradability study was done using SVM biodegradability predictor tool. The P2Y1 receptor protein structure contains a binding site for receptor antagonist MRS2500 within its seven trans-membrane bundles, which also provides suitable pockets for numerous other ligands to act as nucleotide antagonists of P2Y1 receptors. *In-silico* docking of these compounds into the P2Y1 receptor protein structure within the MRS2500 pocket can identify potential antithrombotic drugs from natural or synthetic source [7].

In this current scenario, computational approaches are widely used in the research field. Structure-based methods, such as ligand-protein docking, are efficient and useful tools for novel drug discovery and design. *In-silico* studies reveal about the interactions and mechanisms between the protein target and its suitable ligands [12]. Platelet aggregation can be regulated by G protein-coupled P2Y receptor families, particularly P2Y12 and P2Y1. P2Y1 is required for platelet shape change in response to ADP and is also a principal receptor in mediating both physiological and pathological ADP induced platelet aggregation. At higher ADP concentrations, P2Y1-deficient platelets become partially aggregated [13]. *In-vivo*, the bleeding time was increased by the lack of P2Y1 expression, which could protect against collagen- and ADP induced thrombosis. It is sufficient to block ADP-induced platelet aggregation by utilize specific antagonists inhibit the signaling through the P2Y1 receptor, a platelet aggregation inhibitor from ganoderma-lucidum was looked at in previous studies [14]. Molecular docking studies of these receptors were performed using Schrodinger maestro software. Docking was done in order to identify and predict the ability of an individual inhibitor molecule to bind to the active site of the enzyme and based on the docking scores obtained. **Table 3** the molecules were sorted, and the good ones were identified. These molecules were then subjected to ADMET studies to understand the various physicochemical properties of these molecules, such as molecular weight, blood-brain barrier, H-bond acceptors and donors, rotatable bonds, QPlog HERG, QPP CaCo, QPlog Po/w, CNS, human oral absorption and percentage human oral absorption. ADMET studies were done using Schrodinger maestro software. In this study, it can be analyzed whether the molecules follow Lipinski's rule of 5 or not. From the results, it can be seen that the molecules follow Lipinski's rule of 5 and possess drug likeliness, hence it can be safely used for making new drugs.

To identify whether a molecule or drug is toxic, an oral toxicity test is a must. In this paper, Protox web server is used, which is a free online oral toxicity prediction tool used worldwide. Oral toxicity was predicted for the first ten compounds obtained in docking results, and the molecules belonged to class 4 of toxicity. Therefore, these molecules can be considered as orally non-toxic, and hence orally-active medicines can be prepared using these molecules. It is also important to note that before manufacturing drugs, the molecules must not possess any carcinogenic properties, which aids in causing cancer. To avoid such side effects, it is necessary to conduct carcinogenicity tests on the molecules. Here Carcino Pred-EL is the online web server used for this purpose, which is the most commonly used tool. It takes the 2D structure of the ligand molecules as input and gives results based on three models Ensemble SVM, Ensemble RF, and Ensemble XG Boost. As per the results obtained, the molecules did not contain any

carcinogenic properties and are regarded as non-carcinogens. Further, validation needs to be carried out on the results obtained. Finally, the drug molecules should be eco-friendly, *i.e.*, they must degrade easily when discarded and must not cause any harm to the ecosystem or surrounding environment. To determine the biodegradability of the ligand molecules, one must conduct a biodegradability test so that only biodegradable molecules can be used as drug molecules. Many *in-silico* free online tools are available for this purpose. In this paper, for the biodegradability test, SVM biodegradability predictor UM-BBD (University of Minnesota Biocatalysis / Biodegradation Database) is used. Input must be given only in the form of SMILES. Along with classifying molecules as biodegradable and non-biodegradable, this software also gives the reliability score for each ligand molecule.

CONCLUSION: This paper presents work on identifying new molecules and their properties for anti-thrombotic drugs. Molecular docking and toxicity studies were performed on the target and ligand molecules, using various *in-silico* based tools. The results were analyzed in an *in-silico* based approach manner. On observing the analyzed results, it was seen that the ligand molecules are able to block the activity of the platelet aggregation. The molecules are also orally non-toxic, exhibit non-carcinogenicity and are easily biodegradable in nature. Using these molecules, new drugs can be developed. Further experimentations are needed to study the molecular properties of the molecules in detail.

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CONFLICTS OF INTEREST: The authors declare that there is no conflict of interest related to this work.

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