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Molecular modeling, docking and ADMET studies towards development of novel Disopyramide analogs for potential inhibition of human voltage gated sodium channel proteins

Khunza Meraj[1], Manoj Kumar Mahto[2, 6]*, N Blessy Christina[3], Nidhi Desai[4], Sajad Shahbazi[5] & Matcha Bhaskar[6]

[1]Department of Biotechnology, CMR College of Engineering & Technology, Hyderabad, AP, India; [2]Department of Biotechnology, Acharya Nagarjuna University, Guntur, AP, India; [3]Department of Human Genetics, Andhra University, Vishakhapatnam, AP, India; [4]Department of Biotechnology, PESIT, Bangalore University, Bangalore, Karnataka, India; [5]Department of Biotechnology, Kakatiya University, Warangal, AP, India; [6]Division of Animal Biotechnology, Department of Zoology, Sri Venkateswara University, Tirupati, AP, India; Manoj Kumar Mahto – Email: manoj4bi@gmail.com; Phone: +91-9885928832; *Corresponding author

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Abstract:
The sodium "channelopathies" are the first among the ion channel diseases identified and have attracted widespread clinical and scientific interests. Human voltage gated sodium channels are sites of action of several antiarrhythmic drugs, local anesthetics and related antiepileptic drugs. The present study aims to optimize the activity of Disopyramide, by modification in its structures which may improve the drug action by reducing its side effects. Herein, we have selected Human voltage-gated sodium channel protein type 5 as a potent molecular target. Nearly eighty analogs of Disopyramide are designed and optimized. Thirty are selected for energy minimization using Discovery studio and the LigPrep 2.5. Prior to docking, the active sites of all the proteins are identified. The processing, optimization and minimization of all the proteins is done in Protein preparation wizard. The docking study is performed using the GLIDE. Finally top five ranked lead molecules with better dock scores are identified as having strong binding affinity to 2KAV protein than Disopyramide based on XP G scores. These five leads are further docked with other similar voltage gated sodium channel proteins (PDB IDs: 2KBI, 4DCK, 2L53 and 4DJC) and the best scoring analog with each protein is identified. Drug likeliness and comparative bioactivity analysis for all the analogs is done using QikProp 3.4. Results have shown that the top five lead molecules would have the potential to act as better drugs as compared to Disopyramide and would be of interest as promising starting point for designing compounds against various Sodium channelopathies.

Keywords: Disopyramide, Human voltage-gated sodium channel proteins, Schrödinger 2011, QikProp 3.4, Docking, GLIDE, ADME, XP G Scores.

Background:
In silico approaches include homology modeling, Docking, quantitative structure activity relationships, virtual ligand screening, similarity and pharmacophore searching, data mining, and data analysis tools are becoming increasingly important in new drug design and have been frequently used in the discovery and optimization of novel molecules with enhanced affinity and specificity for the selected therapeutic targets **[1-4].** Today there is a considerable increment in the application of *in silico* molecular modeling and docking studies

to predict potential inhibitors (drugs) for the treatment of several diseases **[5].** Further computational prediction of pharmacokinetic parameters like Absorption, Distribution, Metabolism and Excretion (ADME) & toxicity studies have become increasingly important in drug selection and promotion process and are promising tools for early screening of potential drug candidates **[6]**. Despite numerous studies carried out on the pharmacologic therapy of various sodium channel opathies and other related diseases, the application of Computer Aided Drug Design (CADD) and Quantitative Structure-activity Relationship (QSAR) study on the design and development of new drugs for these diseases is scarce. The sodium channelopathies include a variety of inherited human disorders affecting heart rhythms, skeletal muscle contraction and nervous system **[7].**

The human voltage gated sodium channel proteins play a fundamental role in the propagation of action potential in electrically excited cells **[8].** They are assumed to be the site of action for many types of drugs, such as local anesthetics, anticonvulsants, and anti-arrhythmic. These drugs elicit their effects by interfering with the rapid influx of sodium ions, which is responsible for the generation of action potential in excited cells.

Disopyramide and its mode of action

Systematic (IUPAC) name: 4-[bis (propan-2-yl) amino]-2-phenyl-2-(pyridin-2-yl) butanamide. Formula: $C_{21}H_{29}N_3O$. Disopyramide is a type I anti-arrhythmic drug that has been in wide use for several contractility. Disopyramide is a myocardial depressant which can depress contractility**.**Disopyramide does not reverse or attenuate cardiac hypertrophy in patients with Hypertrophic cardiomyopathy (HCM) but the beneficial effects of Disopyramide are largely attributable to its negative inotropic effects. It is a potential alternative drug regimen for treatment of obstructive HCM **[9, 10].** It slows down conduction, increases refractory periods and decreases cardiac automaticity **[11].** Therefore it is highly effective in HCM patients with significant left ventricular outflow tract (LVOT) obstruction. Data from previous studies show that approximately two third of the patients with LVOT gradient can be managed with Disopyramide in combination with beta-blockers **[12].** It may have a superior effect on exercise tolerance compared with beta-blockers. However they are, best used in combination because Disopyramide alone tends to accelerate atrio-ventricular node (AV) node conduction and increase the potential risk from supra-ventricular arrhythmias.

Many cardiac anti-arrhythmic drugs and local anesthetics have the ability to block sodium channels in axonal and cardiac sarcolemmal membranes **[13].** Disopyramide is similar in action to Quinidine without the adrenergic effects. It has the ability to block sodium channels in axonal and cardiac sarcolemmal membrane **[14].** It targets sodium channels to lengthen their action potential. It depresses the increase in sodium permeability of the cardiac myocyte during Phase 0 of the cardiac action potential, in turn decreasing the inward sodium current.

Undesired effects of Disopyramide

The most significant side effects of Disopyramide are its anti-cholinergic effects. Studies have shown that long term therapy of this drug is associated with a low rate of serum enzyme elevations and is a rare cause of acute liver injury. Main side effects are Ventricular tachycardia, ventricular fibrillation, QT interval prolongation, myocardial depression, hypotension, AV block; anti-muscarinic effects including dry mouth, blurred vision, urinary retention, gastrointestinal irritation. Contraindications of disopyramide include second and third degree heart block and sinus node dysfunction (unless pacemaker fitted) cardiogenic shock severe uncompensated heart failure **[15, 16].** Main drug interactions comprise increased risk of ventricular arrhythmias with amiodarone, anti-arrhythmics, torsadogenic agents, diuretics (due to hypokalemia) increased plasma concentration with macrolides decreased plasma concentration with rifampicin; increased myocardial depression with anti-arrhythmics and beta-blockers.

In this study, we designed eighty possible structural analogues of Disopyramide by changing 'R' (= $CH_2CH_3CH_3$) functional group as shown in the **(Figure 1)** and thirty analogs were checked for their binding affinities with the target site. All the thirty analogues showed better affinity and interaction with the Human voltage-gated sodium channel (HVGSC) protein type 5 subunit alpha (PDB ID: 2KAV) but five of the 30 analogs showed highest affinity with the target 2KAV comparatively to Disopyramide drug. These results have been confirmed by the G Scores obtained from Grid – based Ligand Docking with Energetics (GLIDE) of Schrödinger 2011 **[17, 18].** These five inhibitors with highest dock scores are probable potent drugs which can be considered for further invitro studies. Further these top five analogs are docked with other HVGSC proteins with PDB IDs: 2KBI, 4DCK, 4DJC & 2L53 and also the predicted ADME and toxicity studies of these analogues were evaluated.

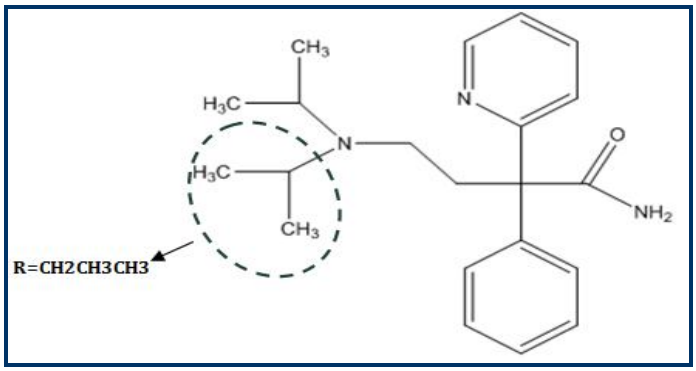

Figure 1: Structure of Disopyramide depicting the 'R' position

Methodology:

Preparation of ligands

The chemical structure of Disopyramide molecule was retrieved from drug bank database into two-dimensional MDL/SDF format. Further 30 Disopyramide analogues were drawn in Osiris property explorer and checked for drug likeliness whether it followed Lipinski rule or not by modification of the 'R' position of Disopyramide drug (as shown in **Figure 1**). These analogs are further designed and geometrically optimized with the help of Hyperchem 8.0 software using the Bio+Charmm force field, RMS gradient of 0.01 kcal/(mol-Angstrom), maximum cycles upto 2000, in vacuum and Polak-Ribiere algorithm as parameters. The molecules were then loaded into Discovery Studio 2.5 for structure refinement such

as energy minimization for 2000 steps with CHARMm force field.

The energetically minimized analogs **Table 1 (see supplementary material)** are obtained in .mol2 format from Discovery studios 2.5 and are used as input structures for processing in LigPrep 2.5 which is run from maestro9.2. The LigPrep 2.5 process consists of a series of steps that perform conversions, apply corrections to the structures, generate variations on the structures, eliminate unwanted structures and optimize the structures.

LigPrep protocol of Schrodinger 2011 generated all 30 as valid ligand conformations using Epik 2.0 in the pH range of 7±2. The LigPrep produces a single, low-energy, 3D structure with correct chiralities for each successfully processed input structure. It also produce a number of structures from each input structure with various ionization states, tautomers, stereochemistries, and ring conformations, and eliminate molecules using various criteria including molecular weight or specified numbers and types of functional groups present. The resulting structures are saved in either SD or Maestro format.

Protein Preparation

Prior to docking, it is important to identify the binding site in the target protein, information for which is available many times through the structures of the complexes of the protein with its substrate. Possible pockets in the set of sodium channel protein structures were first identified by detecting binding sites in all the proteins and then by identifying unique pockets that could serve as feasible targets for inhibitors.

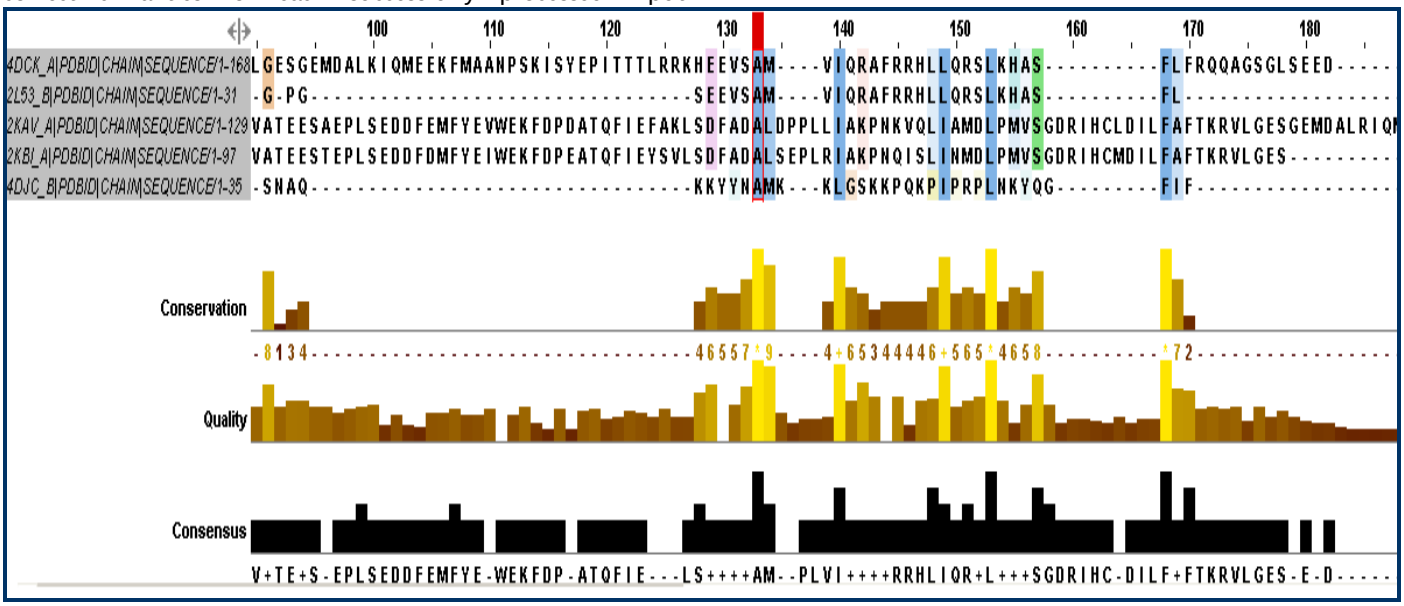

Figure 2: Clustal 2.1 multiple sequence alignment using jalview editor. Multiple sequence alignment of 2KAV with 4DJC, 2KBI, 4DCK and 2L53 sequences showed five highly conserved regions and the one highlighted region in red denotes the conserved active site residues.

Multiple Sequence alignment and Active site prediction

The binding pockets of proteins 2KBI, 4DCK, 2KAV, 2L53 and 4DJC were identified using the Computer Atlas of Topography of Proteins (CASTp), a program for identifying and characterizing protein active sites, binding sites and functional residues located on protein surface.

The protein sequences of human voltage gated sodium channel protein type 5 were obtained from PDB in FASTA format. To identity the conserved residues in all the 5 proteins, they were subjected to the Clustal W. The multiple sequence alignment of **2KBI chain A, 4DCK chain A, 2KAV chain A, 2L53 chain B and 4DJC chain B** sequences showed five conserved residues as shown below in **(Figure 2).**

The PDB structure files of the proteins are imported. The processing, optimization and minimization of these proteins is carried out in the protein preparation wizard of the Schrodinger 2011 by applying the OPLS_2005 force field. The conserved residue **Alanine** is found to be the active site amino acid in all the five proteins and is specified in the receptor grid generation **Table 2 (see supplementary material).**

Docking

Docking refers to the optimal positioning of a ligand molecule with respect to the binding site of a target structure. GLIDE offers the full spectrum of speed and accuracy from high-throughput virtual screening of several compounds to extremely accurate binding mode predictions, providing consistently high enrichment at every level.

A site of 20x20x20 A° around the centric of pocket residues were exploited to check docking interaction with Disopyramide analogs. All the 30 analogs were subjected to docking in GLIDE of Maestro 9.2 with the protein with 2KAV. All 30 ligands docked with negative XP G Score and the compounds were ranked by the interaction energy. Overall, the Vander Waals energy contributed most to the interaction energy, but the electrostatic energy showed the greatest variation and was therefore the major factor for the ranking of molecules. Top five lead molecules were obtained after docking of 30 Disopyramide analogs with 2KAV which had comparatively higher binding efficiency than Disopyramide drug **Table 3 (see supplementary material).**

The XP form of G Score is more physically accurate. The XP protocol includes ligand flexibility by docking multiple conformers in a rigid receptor, and the resulting complexes were ranked by XP G Scores.

These five top ranked compounds were selected for Glide XP docking with the other four similar proteins with PDB IDs: 2KBI, 4DCK, 2L53 & 4DJC. The docking results for these five leads are tabulated in the following **Table 4 (see supplementary material).**

ADME & Toxicity studies

Most of drug candidates fail in clinical trials due to poor ADME properties. Thus, an important aspect of drug discovery is to avoid compounds not having drug likeliness and good ADME property. So to streamline the virtual screening, drug likeliness and ADME properties of all the thirty compounds were predicted using QikProp, version 3.4 of Schrodinger 2011 **[19].** Lipinski filter and reactive filter were applied before virtual screening to avoid false positive lead molecule using OSIRIS Property explorer. Lipinski filter rejected ligands not following Lipinski rule of five and reactive filter rejected ligands with reactive functional groups.

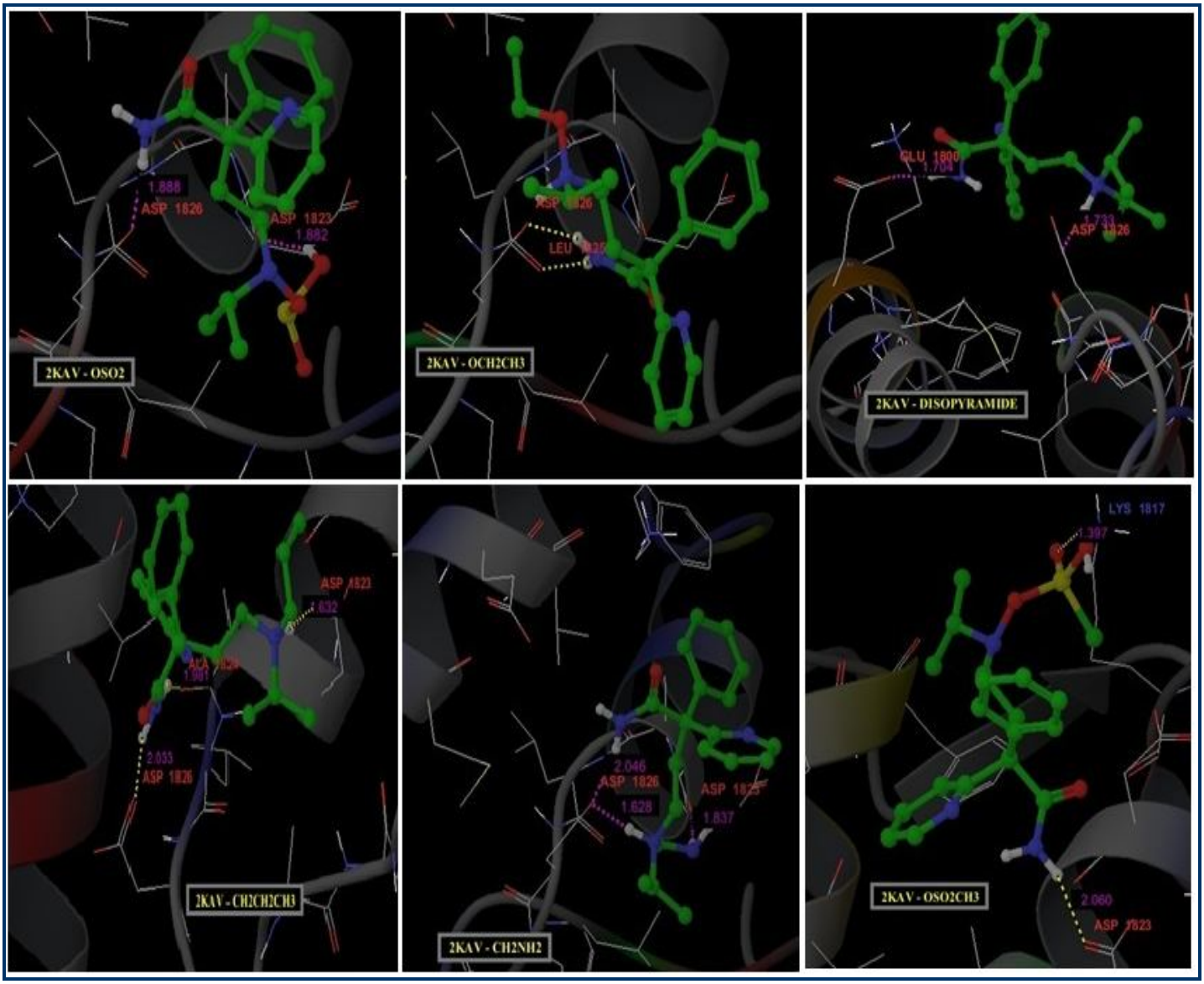

Figure 3: Docking maps of five lead compounds & Disopyramide showing hydrogen bonds with 2KAV protein residues.

Results and Discussion:

All the thirty designed disopyramide analogs with chemical substitutions at the R' (= CH2CH3CH3) position were found to have zero violation towards Lipinski rule. In the present study, five lead molecules with CH_2NH_2, OCH_2CH_3, OSO_2, $CH_2CH_2CH_3$, and OSO2CH3 substitutionswere showing higher XP G Scores of **-3.6, -3.2, -2.87, -2.76 & -2.74** respectively than Disopyramide (G Score = **-2.63)** as a result of docking of 30 analogs and Disopyramide with 2KAV protein. These five leads along with Disopyramide when further docked with 2KBI, 4DCK, 2L53 & 4DJC have shown better dock scores compared to Disopyramide. Hence these are expected to bind strongly onto voltage gated sodium channels binding pockets and the docking interaction of all the five leads with protein 2KAV shown in the **(Figure 3).**

Drug likeliness, log P, log S, molecular weight and toxicity risks may be used to judge the compound's overall potential to

qualify a ligand as potential drug candidate. All thirty ligands have appropriate logP (octanol/water) value for biological efficacy. Each of them had zero Lipinski violation and satisfying pharmacological properties of 95% available drugs with high to medium predicted oral absorption availability. Molecular weight of each ligand falls within the range of 297-404 Daltons. The ligands are having no toxic functional groups. Log S values of these ligands are within the acceptable range of 95% of existing drugs. The overall pharmacological properties (Table VA & VB) of these ligands justify that the molecules are biologically active without any toxic functional groups. Hydrophobic compounds have relatively poor solubility, high log P, and high serum protein binding, but good cell permeability; whereas the opposite is true for hydrophilic compounds. This dichotomy was responsible for the classic lead optimization struggle of solubility versus permeability. Poor oral availability and permeability may lead to drug failure. The five lead molecules reported in the present study are well within the hydrophobic and hydrophilic extremes at the same time percentage of oral availability is also high. The five lead compounds have better pharmacological properties and can be considered as potential lead molecules for invitro drug discovery targeting HVGSC protein.

Conclusion:

A thorough study was carried out over thirty computationally designed Disopyramide analogs using various software programs with the goal of identifying potential lead molecules that bind to the human voltage-gated sodium channel protein(VGSC) type 5 relying on computational docking and pharmacological properties prediction with GLIDE of Schrodinger 2011 and QikProp 3.4 respectively. The comparatively higher XP G Scores of five analogs compared to Disopyramide when docked with 2KAV protein at the conserved active site residue suggest these novel leads would potentially bind more strongly to the pockets of VGSC proteins. Further, the five leads are docked with 2KBI, 4DCK, 2L53, and 4DJC proteins to predict their binding efficiencies with other similar sodium channel proteins apart from 2KAV. All proteins except 2KBI showed high XP G Scores for the analogs compared to Disopyramide. Also, these five novel lead molecules have better pharmacological properties compared to Disopyramide. Thus, it is hoped that these five Disopyramide analogs identified in this study if synthesized and tested in animal models would hold promising results for new drug discovery.

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Supplementary material:

Table 1: Thirty Disopyramide analogs with substitutions at 'R' position and their energies calculated by ligprep 2.5 run from maestro of schrodinger 2011

S. No	Ligand	Potential Energy-OPLS-2005	S. No	Ligand	Potential Energy-OPLS-2005
1	Br	104.2940	16	I	99.8832
2	$CH_2CH_2CH_3$	123.8643	17	NC	109.5581
3	$CH_2CH_2OCH_3$	130.8421	18	$NHCOCH_3$	100.4750
4	CH_2CH_2OH	127.5840	19	$O(CH_2)_3CH_3$	96.91685
5	CH_2CH_3	126.8252	20	$OCH_2(C_6H_5)$	129.5305
6	SCH_2CH_3	131.812	21	$OCH_2CH_2CH_3$	95.6623
7	CH_2NH_2	130.2494	22	$OCH_2CH_2OCH_3$	98.0414
8	CH_3	120.8010	23	OCH_2CH_3	103.2310
9	Cl	125.7437	24	OCH_2C0NH_2	111.009
10	$CO(CH_2)_2CH_3$	160.9634	25	OCH_3	120.68
11	CO	138.4588	26	OH	81.8115
12	$COCH_2CH_3$	165.5926	27	OSO_2	109.4914
13	$COCH_3$	159.6694	28	OSO_2CH_3	99.9659
14	SO_2	115.3763	29	SCH_3	118.0760
15	H	99.59754	30	SH	106.1195
Disopyramide154.4078					

Table 2: The conserved active site residue subjected for grid generation and docking

Protein	Chain	Residue number
2KAV	A	ALA 1824
2KBI	A	ALA 1820
4DCK	A	ALA 1905
2L53	B	ALA 1905
4DJC	B	ALA 1497

Table 3: G scores from the glide XP docking run of Disopyramide analogs with 2KAV

Ligand	*GScore	LipophilicEvdW	HBond	Electro	LowMW	Penalties	PhobicPenal	RotPenal	Activity
CH_2NH_2	-3.6	-0.9	-1.9	-1.45	-0.41	0	0.69	0.38	-3.6
OCH_2CH_3	-3.2	-0.56	-2.39	-1.33	-0.36	0.02	1.01	0.42	-3.2
OSO_2	-2.87	-0.97	-1.29	-1.11	-0.24	0.01	0.33	0.41	-2.87
$CH_2CH_2CH_3$	-2.76	-0.76	-1.8	-1.17	-0.37	0	0.91	0.42	-2.76
OSO_2CH_3	-2.74	-0.86	-1.27	-1.3	-0.19	0.02	0.48	0.38	-2.74
Disopyramide	-2.63	-0.52	-1.25	-1.33	-0.37	0.11	0.37	0.35	-2.63
$NHCOCH_3$	-2.56	-0.98	-1	-0.85	-0.32	0.01	0.19	0.39	-2.56
$CH_2CH_2OCH_3$	-2.49	-0.8	-2.01	-1.12	-0.31	0.14	1.15	0.45	-2.49
CH_2CH_2OH	-2.45	-0.57	-1.94	-1.65	-0.36	1.01	0.57	0.49	-2.45
CH_3	-2.24	-0.64	-1.03	-0.78	-0.46	0.01	0.26	0.41	-2.24
NC	-2.22	-0.93	-1	-0.53	-0.41	0	0.27	0.38	-2.22
H	-2.22	-0.8	-1.56	-1.08	-0.5	0	1.28	0.44	-2.22
$COCH_2CH_3$	-2.21	-1.06	-0.93	-0.59	-0.32	0	0.3	0.39	-2.21
OCH_2C0NH_2	-2.07	-1.45	-0.68	-0.72	-0.27	0.03	0.59	0.42	-2.07
SO_2	-2.03	-1.1	-0.96	-0.43	-0.3	0.01	0.37	0.38	-2.03
CO	-1.82	-0.86	-0.82	-0.6	-0.42	0.01	0.5	0.38	-1.82
CH_2CH_3	-1.79	-0.59	-1.88	-1.09	-0.41	0.03	1.78	0.38	-1.79
$OCH_2CH_2OCH_3$	-1.67	-0.95	-0.75	-0.5	-0.26	0.11	0.19	0.48	-1.67
$CO(CH_2)_2CH_3$	-1.64	-1.15	-0.7	-0.35	-0.28	0.02	0.43	0.43	-1.64
$COCH_3$	-1.58	-0.77	-0.99	-0.75	-0.37	0	0.94	0.35	-1.58
$OCH_2(C_6H_5)$	-1.56	-0.97	-0.7	-0.47	-0.15	0	0.38	0.36	-1.56
Cl	-1.43	-0.83	-0.7	-0.37	-0.39	0.04	0.46	0.37	-1.43
OCH_3	-1.36	-0.81	-0.7	-0.37	-0.41	0.03	0.52	0.38	-1.36
$OCH_2CH_2CH_3$	-1.33	-0.88	-0.45	-0.5	-0.32	0.01	0.35	0.45	-1.33
SCH_3	-1.28	-0.79	-0.35	-0.32	-0.36	0.04	0.16	0.34	-1.28
OH	-1.28	-1	-0.7	-0.53	-0.46	0	1.01	0.41	-1.28
$O(CH_2)_3CH_3$	-1.26	-0.91	-0.76	-0.51	-0.27	0	0.7	0.48	-1.26
I	-1.18	-0.74	-0.79	-0.5	-0.09	0.17	0.53	0.24	-1.18
SH	-1.08	-1.13	-0.28	-0.24	-0.4	0.04	0.57	0.37	-1.08
Br	-1.02	-0.57	-1	-0.59	-0.25	0.05	1.04	0.29	-1.02
F	-0.87	-1.22	0	-0.15	-0.45	0.02	0.52	0.4	-0.87

*Total G Score = sum of all XP terms; for all the above ligands PhobEn = PhobEnHB = PhobEnPairHB = Sitemap = PiCat = ClBr = HBPenal = 0

Table 4: G scores of the top 5 analogs including Disopyramide docked with similar sodium channel proteins

Ligand	2KBI	4DCK	2L53	4DJC
CH_2NH_2	-2.18	-3.98	-1.53	1.23
OCH_2CH_3	-2.77	-3.46	-1.47	-0.73
OSO_2	-2.73	-3.24	-2.22	-2.52
$CH_2CH_2CH_3$	-2.62	-3.15	-2.58	-0.51
OSO_2CH_3	-2.39	**-5.45**	**-2.72**	**-3.65**
Disopyramide	**-3.00**	-3.26	-1.99	-1.43

Table 5 (A): QIKPROP 3.4 predictions of ADMET for the 32 compounds in the study

Molecule	#stars	CNS	mol_MW	dipole	SASA	volume	DonorHB	accptHB	QPlogPoct
Br	0	0	376.295	6.098	564.891	1046.93	2	5	17.239
$CH_2CH_2CH_3$	0	1	339.48	6.749	630.88	1172.61	2	5.5	18.553
$CH_2CH_2OCH_3$	0	1	355.479	6.366	584.967	1144.028	2	7.2	18.747
CH_2CH_2OH	0	-1	341.452	5.853	598.756	1118.957	3	7.2	20.064
CH_2CH_3	0	1	325.453	6.745	621.726	1132.854	2	5.5	18.254
CH_2NH_2	1	0	326.441	5.155	551.659	1062.806	4	6.5	20.45
CH_3	0	1	311.426	6.738	587.145	1069.581	2	5.5	17.733
Cl	0	0	331.844	6.377	563.237	1041.552	2	5	17.185
$CO(CH_2)_2CH_3$	0	-1	367.49	5.758	650.394	1249.776	2	6.5	19.994
CO	0	-2	325.41	1.875	594.233	1083.494	2	6.5	18.204
$COCH_2CH_3$	0	-1	353.463	1.33	600.086	1150.862	2	6.5	18.72
$COCH_3$	0	-1	339.436	6.859	610.305	1124.969	2	6.5	19.159
Disopyramide	0	1	339.48	6.109	629.794	1166.294	2	5.5	18.651
H	0	0	297.399	4.144	548.055	1001.161	3	5	17.606
I	0	0	423.296	6.306	569.434	1055.978	2	5	17.424
NC	0	0	326.441	6.51	604.49	1106.553	3	6	19.677
$NHCOCH_3$	0	-1	354.451	6.426	629.907	1178.954	3	7.5	21.57
$O(CH_2)_3CH_3$	0	-1	369.506	4.007	614.466	1203.52	2	6.7	18.736
$OCH_2(C_6H_5)$	0	-1	403.523	4.579	687.929	1314.642	2	6.7	21.378
$OCH_2CH_2CH_3$	0	-1	355.479	4.554	628.41	1203.681	2	6.7	19.167
$OCH_2CH_2OCH_3$	0	-1	371.478	3.16	629.464	1205.485	2	8.4	19.652
OCH_2CH_3	0	-1	341.452	4.619	627.686	1163.713	2	6.7	18.798
OCH_2C0NH_2	0	-2	370.45	8.695	582.669	1121.424	4	9.2	23.239
OCH_3	0	-1	327.425	4.403	608.103	1108.691	2	6.7	18.301
OH	0	-1	313.399	4.985	552.989	1023.641	3	6.7	18.784
OSO_2	0	-2	377.457	6.953	601.081	1114.996	3	9.5	21.557
OSO_2CH_3	1	-2	393.5	5.271	613.62	1166.836	3	8.5	21.552
SCH_2CH_3	0	0	357.513	4.326	622.396	1171.084	2	5.5	18.305
SCH_3	0	0	343.486	4.155	601.698	1117.156	2	5.5	17.877
SH	0	-1	329.459	6.137	587.515	1068.391	2.8	5.5	18.793
SO_2	0	-2	361.458	7.609	600.727	1106.26	3	8	21.044

Table 5 (B): QIKPROP3.4 predictions of ADMET for Disopyramide analogs in the study

Molecule	QPlog Poct	QPlo gPw	QPlog Po/w	QPlo gS	QPlo gBB	QPlog Kp	IP	EA	HO A	PSA	Rule Of Three
Br	17.239	12.063	2.96	-2.808	-0.435	-1.331	9.325	0.328	3	57.844	0
$CH_2CH_2CH_3$	18.553	12.518	2.669	-1.944	-0.365	-3.313	9.213	0.284	3	60.342	0
CH_2CH_2OCH	18.747	13.623	1.983	-0.522	-0.317	-3.293	9.248	0.194	3	65.647	0
CH_2CH_2OH	20.064	15.696	1.32	-0.713	-0.856	-4.218	9.337	0.283	2	82.198	0
CH_2CH_3	18.254	12.723	2.566	-1.962	-0.32	-3.399	9.21	0.29	3	60.54	0
CH_2NH_2	20.45	16.047	0.809	0.88	-0.023	-5.793	9.07	0.16	2	78.577	1
CH_3	17.733	12.922	2.211	-1.54	-0.241	-3.493	9.242	0.299	3	61.132	0
Cl	17.185	12.06	2.905	-2.757	-0.45	-1.327	9.329	-0.012	3	57.713	0
$CO(CH_2)_2CH_3$	19.994	14.589	2.682	-2.676	-0.847	-1.559	9.271	0.286	3	72.323	0
CO	18.204	16.858	1.384	-1.451	-1.151	-2.46	9.526	0.391	3	90.768	0
$COCH_2CH_3$	18.72	15.848	1.981	-1.583	-0.897	-1.937	9.45	0.408	3	81.726	0

$COCH_3$	19.159	15.684	1.836	-2.157	-0.888	-1.93	9.348	0.101	3	82.372	0
Disopyramide	18.651	12.559	2.644	-2.186	-0.173	-3.066	8.778	0.53	3	56.007	0
H	17.606	13.607	1.679	-0.969	-0.229	-3.596	8.675	0.287	3	65.598	0
I	17.424	12.07	3.042	-2.915	-0.419	-1.326	9.076	0.959	3	59.118	0
NC	19.677	14.768	1.429	-0.202	-0.013	-5.684	8.856	0.301	2	71.877	0
$NHCOCH_3$	21.57	16.191	2.292	-2.783	-0.926	-1.785	9.361	0.362	3	94.154	0
$O(CH_2)_3CH_3$	18.736	12.854	2.98	-2.26	-0.875	-1.334	9.305	0.141	3	64.839	0
$OCH_2(C_6H_5)$	21.378	14.529	3.935	-3.641	-0.802	-0.544	9.319	0.356	3	69.056	0
$OCH_2CH_2CH_3$	19.167	13.298	3.085	-2.682	-0.768	-1.094	9.354	0.284	3	64.718	0
O(CH2)2CH3	19.652	14.645	2.419	-2.031	-0.83	-1.053	9.396	0.348	3	74.625	0
OCH_2CH_3	18.798	13.518	2.783	-2.833	-0.75	-1.214	9.346	0.282	3	65.864	0
OCH2CONH2	23.239	22.203	0.348	0.127	-1.286	-2.405	9.346	0.39	2	114.324	0
OCH_3	18.301	13.737	2.485	-2.683	-0.709	-1.32	9.355	0.278	3	66.753	0
OH	18.784	15.183	1.697	-1.749	-0.824	-1.756	9.326	0.039	3	80.682	0
OSO_2	21.557	20.29	1.614	-0.334	-1.202	-2.104	9.352	0.734	1	99.022	1
OSO_2CH_3	21.52	16.95	1.773	-2.112	-1.051	-1.982	7.301	0.509	3	93.802	0
SCH_2CH_3	18.305	12.227	3.332	-3.201	-0.648	-1.184	8.726	0.361	3	58.532	0
SCH_3	17.877	12.462	2.938	-3.054	-0.573	-1.269	8.738	0.349	3	58.74	0
SH	18.793	13.865	2.746	-2.777	-0.566	-1.323	8.931	0.289	3	61.219	0
SO_2	21.044	19.348	1.945	-0.722	-1.331	-2.493	8.964	0.659	1	101.305	1