Design, Molecular Simulation, DFT and ADME Prediction of Some New Schiff Base Diols; Potential standalone or adjuvantAgainst Cortisone Reductase Deficiency2

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ABSTRACT:

Ten new Schiff base diols derived from isovanillin and syringaldehyde were virtually designed using in-silico tools. Analysis of absorption, distribution, metabolism, and excretion (ADME) properties using SWISS ADME tool evidenced the drug likeness of the Schiff base diols.The designed compounds showed no violation to Lipinski"s „rule of five" except for molecular weights of few compounds. The physicochemical properties showed that all designed Schiff base diols have good oral absorption and adequate skin permeability. Geometry optimizations of the diols were done using Density Functional Theory (DFT) calculations using the Gaussian 09W software package. Further DFT calculations were used to investigate HOMO, LUMO, Mulliken charges, and theoretical modes of vibrations of the Schiff base diols. HOMO and LUMO studies showed that among the ten Schiff base diols, compound 5 is the most stable(ΔE= 0.178) and compound 9 is the most reactive with lowest energy gap(ΔE= 0.035). Molecular docking was used to predict the binding ability of the Schiff base diols with cortisone reductase deficiency 2 (CORTRD2). The compounds 3,5, and 7 exhibited strong interactions with (PDB CODE: P28845) receptor via hydrophobic interaction and hydrogen bonding.

KEY WORDS: In-silico, Lipinski, Physicochemical properties, Geometry optimization, DFT, Mulliken Charges, CORTRD2.

INTRODUCTION

Vanillin based Schiff bases have been synthesized by many researchers andreported for their good antimicrobial activities. Isovanillin, an isomer of vanillinwhichcanbe extractedfromaromaticroots [1]possessesantispasmodic [2]andantidiarrheal

[3]activities.TheyhavebeenrarelyexploredasSchiffbasesaswellas compounds.Since,isovanillincontainstworeactivesitessuchascarbonyl and hydroxyl, it can be used to synthesize Schiff base diol compoundsusing compounds containing amine and hydroxyl groups such as aminophenol asshown in **Fig1**. Similarly a series of Schiff base diol compounds of isovanillin can be synthesized usingdifferent substituted aminophenols.

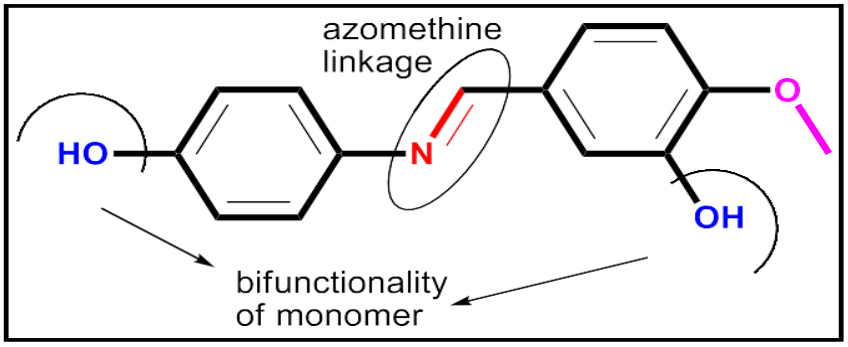


Fig1.Structure of isovanillin based Schiffbasediolcompound

Syringaldehydeisanaturally occurring uniquearomaticaldehydewhichpossesses excellent antimicrobial activity[4]. It contains aldehyde and hydroxyl groupsandcanbeextractedfromnaturalpolymer.Inthispresentstudy, syringaldehydewastakenacompoundtosynthesizeSchiff base diolcompoundswithaminophenols as shown in **Fig 2**. SimilarlyaseriesofSchiffbasediolcompoundofsyringaldehyde wassynthesizedusingdifferent substituted aminophenols.

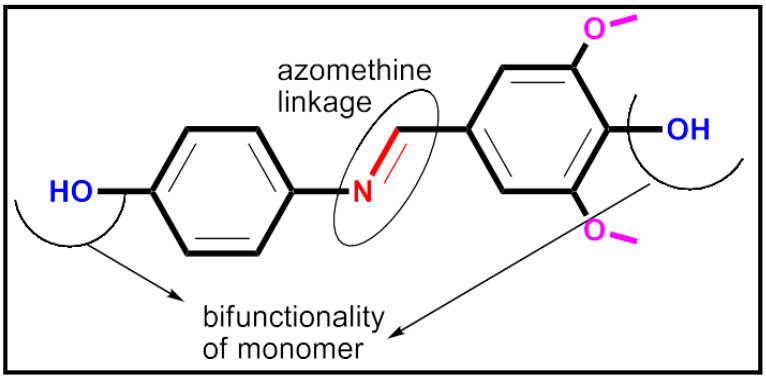


Fig 2.StructureofsyringaldehydebasedSchiffbasediolcompound

Experimental methods:

Pharmacokinetics Analysis

The drug-likeness of the compounds (1–10) was determined by Lipinski's „rule of five" which predicts the solubility and permeability by demonstrating molecular weight, number of hydrogen bond donors, number of hydrogen bond acceptors, Log P, and molar refractivity of the complexes. According to Lipinski's „rule of five" the molecules will have good absorption or permeability across the cell membrane when there are five or less H-bond donors, ten or less H-bond acceptors, molecular weight less than 500, high lipophilicity (Log P < 5), and polar surface area up to 140 (TPSA ≤ 140). The Lipinski's "rule of five" was predicted using online software, supercomputing facility for bioinformatics, and computational biology (http://www.scfbio-iitd.res.in/software/ drugdesign/lipinski.jsp) provided by the Indian Institute of Technology, Delhi. Other pharmacokinetics properties of compounds (1– 10) such as gastrointestinal (GI) absorption, water solubility (Log $molL^{-1}$), blood–brain barrier (BBB) permeant, skin permeation (Log Kp), lipophilicity (Log Po/w), and Pgp substrate were estimated using Swiss ADME tool of the Swiss Institute of Bioinformatics (http://www. swissadme.ch/) .

Computational methodology

The computational results were acquired using Guass-View 5.0 molecular visualization program [5] and Guassian 09 W program packages.[6] The density functional theory (DFT) predictions were carried out using the basic set with B3LYP[7,8] With 6 – 31G (d,p) and rb3lyp/lanl2mb.[9] The geometry optimizations were followed by frequency calculations to prove the stability of the compounds. The depiction of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) and density calculations were also performed using Gauss view program.

Molecular docking studies

To evaluate the binding affinity of the compounds with Cortisone reductase deficiency 2(CORTRD2), the docking studies were carried out for all the compounds using Auto Dock Tool (ADT) version 1.5.6 and Auto Dock Tool version 4.2.5.1 docking program . The Schiff base diol compounds were docked into the active sites of the CORTRD2. The CORTRD2 protein was downloaded in pdb format from the Protein Data Bank (https://www.rcsb.org./pdb). All the heteroatoms and water molecules were deleted followed by the addition of polar hydrogen atoms and Kollman charges to the receptor molecule.

Results and Discussions:

Physicochemical Properties:

The results from **Table 1** show that most of the compounds own molecular weights below 500 Daltons and thus obey one of the criteria of Lipinski rule of five except a few compounds whose molecular weights are above 500 Daltons. The compounds 7, 8, and 10 have 10 rotational bonds and rest of the compounds possess less than 10 rotatable bonds and hence, satisfy the norms for oral bioavailability. The PSA is calculated using the fragmental technique called topological polar surface area (TPSA), considering sulfur and phosphorus as polar atoms [10]. This was proved to be a useful descriptor in many models and rules to quickly estimate some ADME properties, especially with regards to biological barrier crossing such as absorption and brain access[11]. It is evident from **Table 1** that TPSA values range from 62.05 Å2 to 144.62 $Å^2$,where the compound 8 is found to be more polar with TPSA 144.62 Å2 and compound 1 has the lowest TPSA value of 62.05 $Å^2$.

Solubility is significant for absorption and subsequent bioavailability of a drug *in vivo* and is a critical component in lead generation and optimization. Higher solubility increases absorption and the poor solubility limits absorption of the drug in the gastrointestinal tract [12]. Thus a reduction in log P increases the compound‟s solubility [13]. Table 1 suggests that the compounds 3,7, and 8 are poorly soluble and compound 2 is moderately soluble and compounds 1,4,5,6, and 10 are more soluble with log S between -1 and 5.6 and thus could make good oral absorbtion.

Table 1. Physicochemical Properties

COMPOUND	MW	Number of Rotatable bonds	TPSA	ESOL Class
1	243.26	3	62.05	Soluble
2	516.56	8	126.16	Moderately soluble
3	468.5	8	92.87	Poorly soluble
4	328.36	7	83.64	Soluble
5	342.39	8	83.64	Soluble
6	273.28	4	71.28	Soluble
7	528.55	10	111.33	Poorly soluble
8	576.62	10	144.62	Poorly soluble
9	388.41	9	102.1	Soluble

10	402.44	10	102.1	Soluble

Pharmacokinetic Properties

The synthesized compounds 1,4,5,6,9, and 10 were observed to have a high intestinal absorption whereas the compounds 2,3,7, and 8 which have low GI absorption and high TPSA, and the compounds with high GI absorption could permeate quite easily across the intestinal lining of the cell membrane. Distribution of drugs into the central nervous system (CNS) plays an important role in drug discovery as CNS lies behind the blood--brain barrier (BBB). Drugs need to pass over the blood brain barrier to reach their target. It is observed from the Table 2 that all the compounds have no BBB penetration and hence do not affect the CNS, except compounds 1 and 6 which will affect the CNS. P-glycoprotein (P- gp) plays a key role in keeping non-essential molecules out of the brain and thus have partial permeability [14,15].The Table shows that all the compounds are substrates of P- gp except 3 and 7 which are not substrates of P-gp.

Table 2.Permeability effect of the compounds

COMP-OUNDS	GI absorption	BBB permeant	Ilogp	Pgp substrate	log Kp (cm/s)	CYP1A2 inhibitor	CYP2D6 inhibitor
1	High	Yes	2.3	No	-6.04	Yes	No
2	Low	No	3.94	No	-6.22	No	No
3	Low	No	4.18	Yes	-5.41	No	Yes
4	High	No	3.28	No	-6.88	No	No
5	High	No	3.05	No	-6.71	No	Yes
6	High	Yes	2.43	No	-6.92	Yes	No
7	Low	No	4.98	Yes	-5.81	No	No
8	Low	No	4.54	No	-6.63	No	No
9	High	No	3.23	No	-7.29	No	No
10	High	No	3.86	No	-7.12	No	Yes

The isoenzyme cytochrome P 450 is not worthy in drug elimination through metabolic biotransformation [16]. Hinderance of these isoenzymes is clearly one prime cause of pharmacokinetics-related drug-drug interactions [17,18].The data from the Table show that most of the compounds are metabolized by CYP1A2 and CYP2D6. From the log K_p values it is seen that compound 3 has the least negative value and thus it is more skin permeant. Compound 9 has more negative log $k_p$valueand hence least is its skin permeant.

Fig 3.Probability

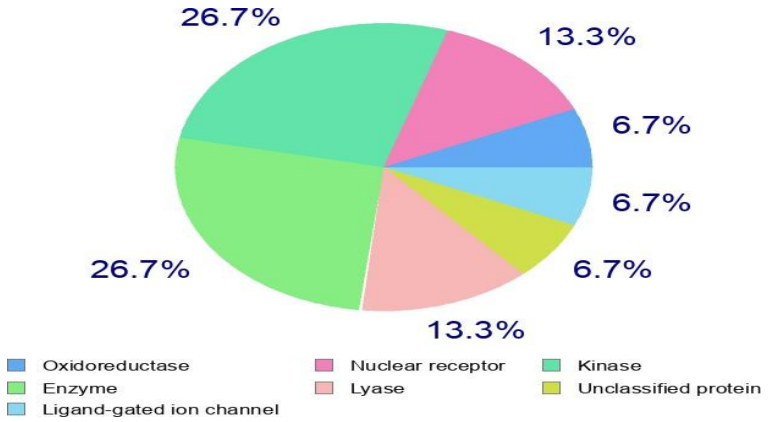


Table 4. Target Prediction Report:

Protein	Count	% composition
Oxidoreductase	6	8.45
Enzyme	15	21.13
Ligand-gated ion channel	1	1.41
Nuclear receptor	5	7.04
Lyase	3	4.23
Unclassified protein	3	4.23

Skin Permeable Model:

The skin permeation detection totally rely on TPSA. More polar the molecule , less is the skin permeant. Hence, compound 8 having TPSA value 144.62 Å2 is found to be less skin permeant and compound 1 with TPSA 62.05 Å2 is considered as more skin permeant.(**Table 1**)

Drug Likeness and Medicinal Chemistry:

Lipophilicity is a criterion which is more important in drug likeness that contributes to ADMET characteristics of a drug, to encounter an effect on their metabolism and pharmacokinetics. The synthesized compounds possesslog p values ≤ 5, except compound 7 and hence, they forecast to have good oral absorbtion and good permeability. The lower the permeability lower is the lipophilicity. The lower the log p value increases the compound stability.

Drug likeness qualitatively evaluates the chance for a molecule to become an oral drug with respect to bioavailability. The designed compounds showed no violation to lipinski"s „rule of five" except for molecular weights of few compounds. Compound 8 has one violation with respect to Veber (TPSA >140) and few compounds have one to two violation with Egan (TPSA > 131.6).The Abbot bioavailability score is a rule- based score completely rely on total charge, TPSA, and violation to Lipinski rule explains four classes of compounds with probabilities 11%,17%,56%,85%.The data from Table 4 show that the compounds have the bioavailability score (BAS) of 55% and thus they are found to be good oral drugs.

Medicinal Chemistry

Medicinal chemistry gives assistance to chemists in drug discovery process. PAINS (for pan assay interference compounds or promiscuous compounds) are molecules which contain substructures which show false response with biologically potent output regardless of the protein target [19]. Brenka structural alert warns about putatively toxic, metabolically unstable, chemically reactive fragments with poor pharmacokinetic properties present in the structure[20]. Lead- likeness is similar to drug-likeness, which aids the medicinal chemist to focus on the physicochemical boundaries to identify the appropriate molecule for initiating lead optimization. The data from the Table 4 show that the compounds 4 and 6 have zero violation and compounds 1 and 5 have one violation and others have two to three violations according to lead-likeness. The synthetic accessibility (SA) score is rescaled between 1 (easy synthesis) and 10 (very difficult synthesis). The SA scores for all the candidates in the library were found to be less than 4 and hence, it is easy to synthesize them.

Table 3.Druglikeness and medicinal chemistry

COMPOUND	LIPOPHILICITY					DRUGLIKENESS				MEDICINAL CHEMISTRY			
	iLOGP	XLOGP	WLOGP	MLOGP	Cons logP	NO OF VIOLATIONS			BAS	#ALERTS		Lead likeness	SA
						L	V	E		PAINS	Brenk		
1	2.3	2.45	2.86	1.67	2.43	**0**	**0**	0	0.55	0	1	1	2.29
2	3.94	4.55	6.53	2.81	4.65	1	0	1	0.55	0	1	3	3.52
3	4.18	5.28	6.41	2.92	4.98	0	0	1	0.55	0	1	3	3.46
4	3.28	2	2.65	0.94	2.6	0	0	0	0.55	0	1	0	2.73
5	3.05	2.36	3.04	1.17	2.83	0	0	0	0.55	0	1	1	2.81
6	2.43	1.47	2.87	1.37	2.21	0	0	0	0.55	0	1	0	2.54
7	4.98	5.23	6.43	2.28	5.04	1	0	1	0.55	0	1	3	3.86
8	4.54	4.49	6.55	2.19	4.67	1	1	2	0.55	0	1	3	3.9
9	3.23	1.94	2.67	0.35	2.5	0	0	0	0.55	0	1	2	3.15
10	3.86	2.3	3.06	0.57	2.9	0	0	0	0.55	0	1	2	3.23

SA- Synthetic AccessibilityCons.LogP - Consensus LogP, L- Lipinski, V- Veber, E- Egan,BAS- Bioavailability Score.

Boiled Egg Representation:

The BOILED-Egg is an exclusive and accurate method to evaluate the passive gastrointestinal absorption (HIA) and brain penetration (BBB) with respect to WLOGP-versus-TPSA[21]. The white yolk of the egg is of high probability of passive absorption by the gastrointestinal tract, and the yellow region(yolk) is of high probability of brain penetration. The

compounds 4,5,9, and 10 lie in white region, compounds 1 and 6 are predicted as brain-penetrant (in the yolk) and not subject to active efflux (red dot), and 2,3,7 and 8 is out of range of the plot. All the compounds are non-substrates of P-gp which is indicated by red dots, except 3 and 7 which are effluxed by P-gp are coloured blue.(**Fig 4**)

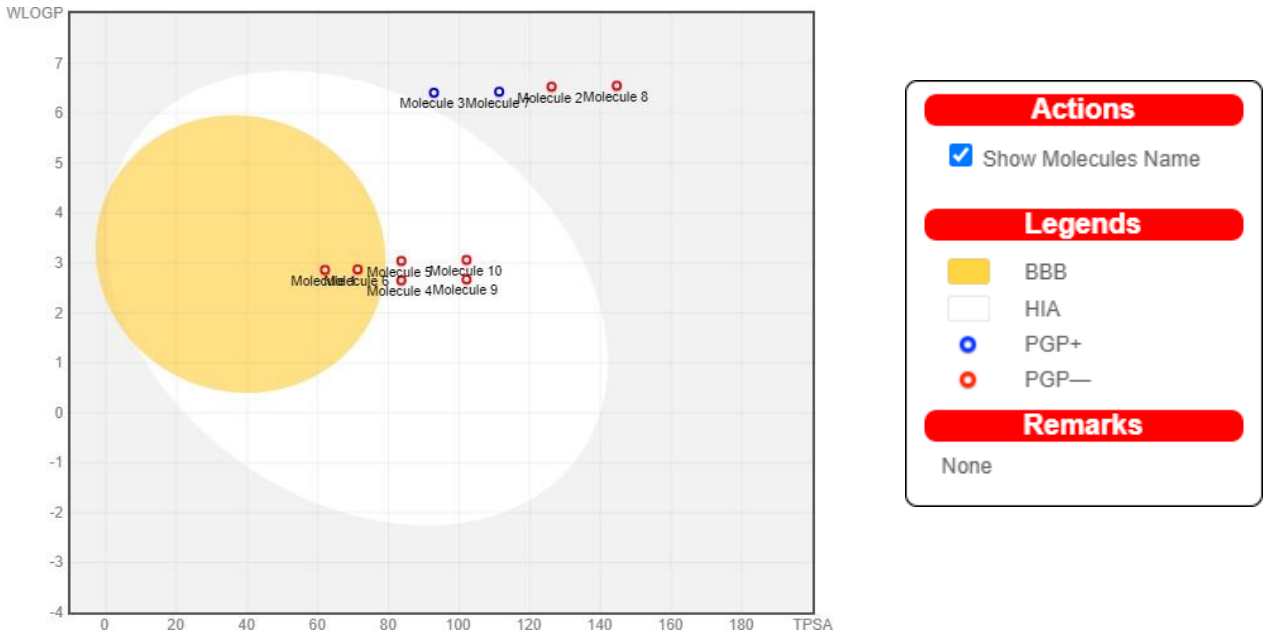
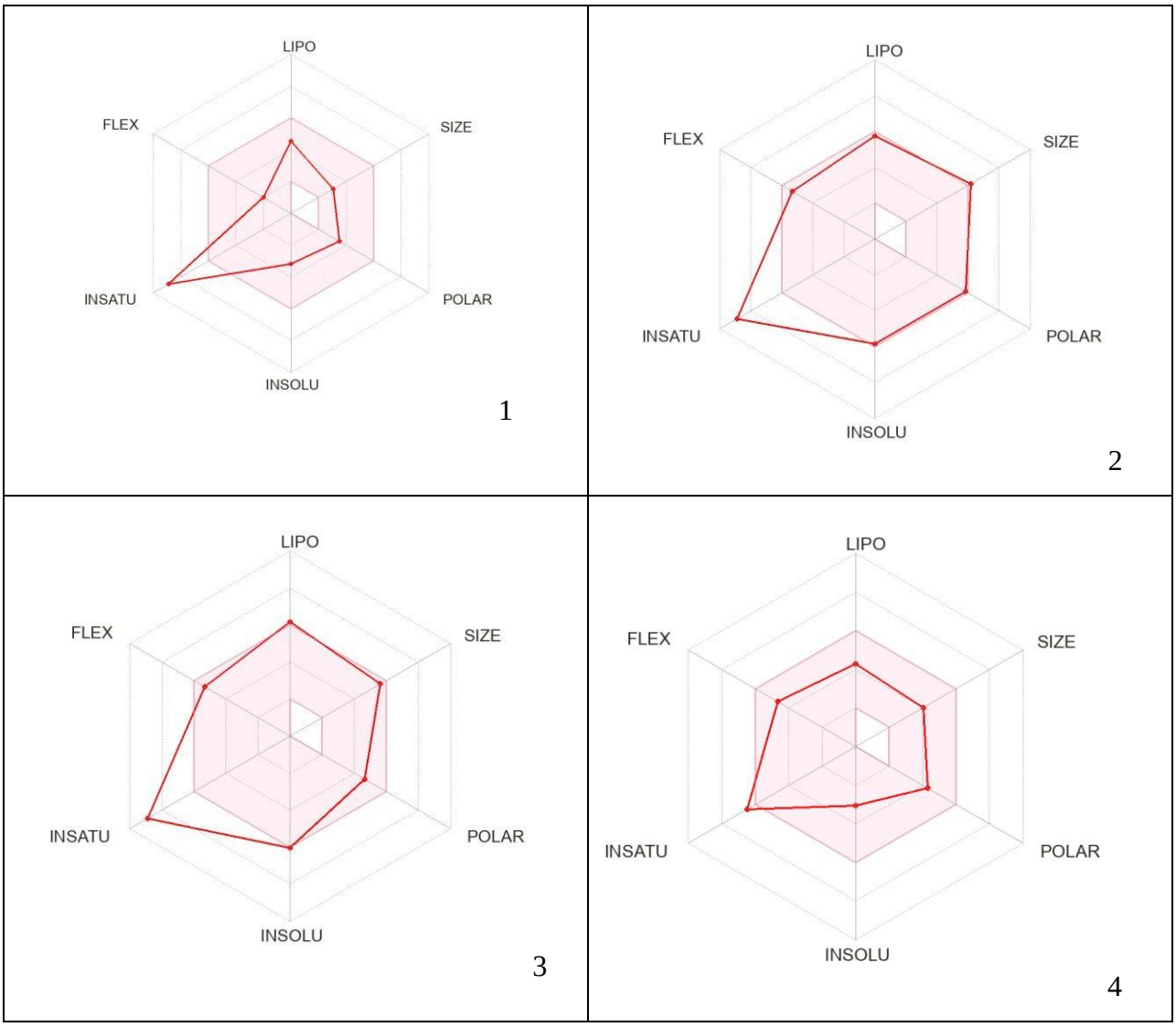


Fig 4. BOILED-Egg Representation of Schiff bases

Bioavailability Radar:

The bioavailability radar displays rapid appraisal of a molecule to become an oral drug (**Fig 5**). The suitable physiochemical space for oral bioavailability is the pink zone, and the radar plot of the molecule has to entirely fall in the pink zone to be reviewed drug-like[22]. The pink zone displays the optimal range for eachof the properties: LIPO (Lipophilicity): -0.7 < XLOGP 3 < +5.0; SIZE: 150g/mol< MW < 500 g/mol; POLAR (polarity):20Å2< TPSA < 130Å2; INSOLU (Insolubility): 0 < Log S (ESOL) < 6; INSATU (Insaturation): 0.25 <Fraction of Csp3 < 1; FLEX (Flexibility): 0 < Num. rotatable bonds < 9. From the Swiss ADME prediction, it is evident that all compounds were in the optimal range of all the 5 properties, except for few properties, enabling them to be considered to possess proficient chemotherapeutic potentials.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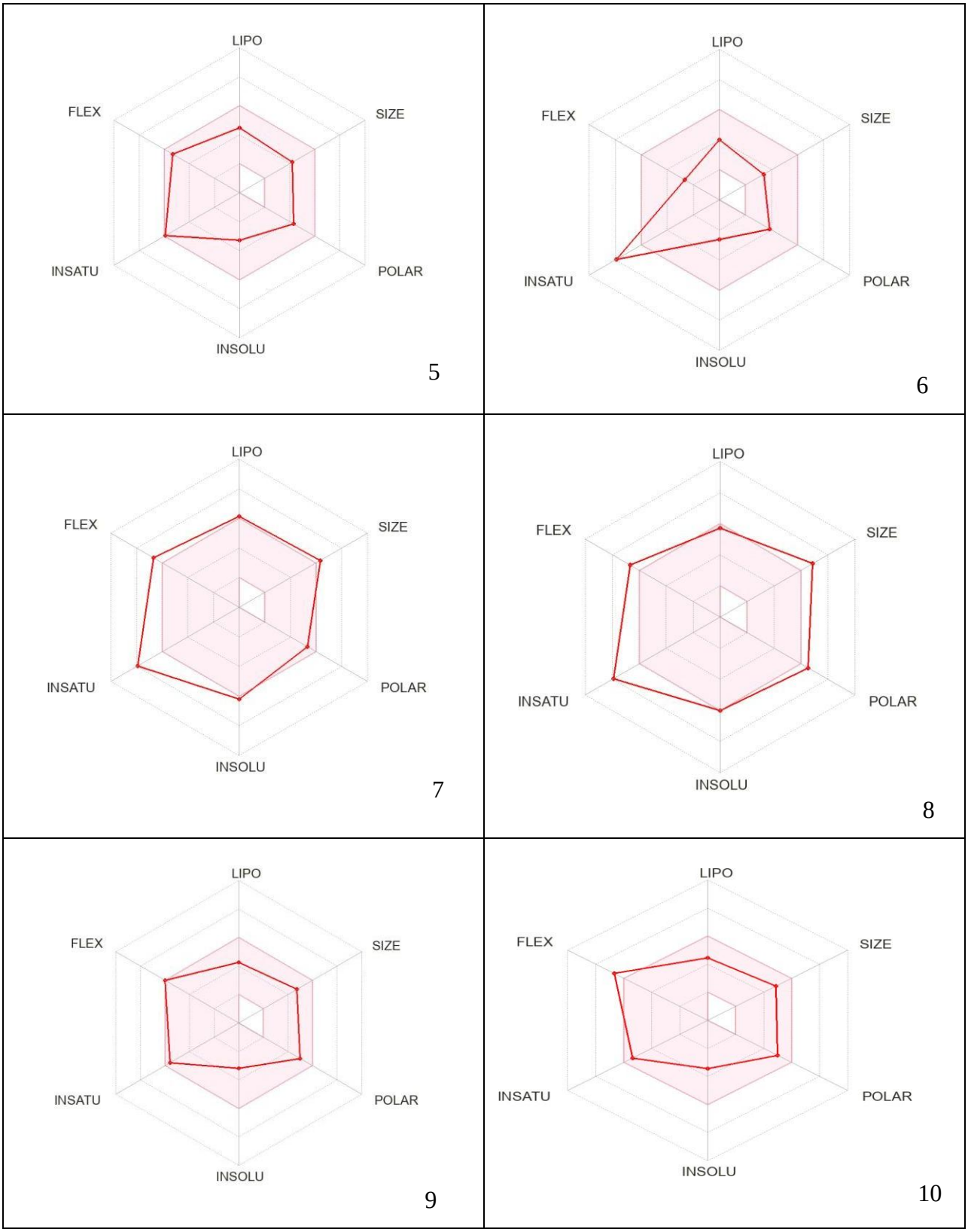


Fig 5.Bioavailability Radar of the Compounds.

Molecular Docking Studies of Compounds:

The results of the docking are shown in **Table 6**. All the compounds were bound deeply into the active sitesof the receptor (Figures 6-8). The possible hydrophobic interactions detected by compounds with active site residues (ALA 42, ILE 46, ILE 121, VAL 168, TYR 183, LEU 171, ALA 172, LEU 215, LEU 217, ILE 218, ALA 223, ALA 65, MET 93, VAL 142, LEU 126, TYR 177, VAL 180, VAL 231, ALA 123, MET 233, LEU 128, PHE 129, ILE 133, MET 179, ALA 181, ALA 182, ILE 218, ALA 226, ILE 89, ALA 90, MET 96, PHE 98, ALA 99, VAL 149, VAL 152,

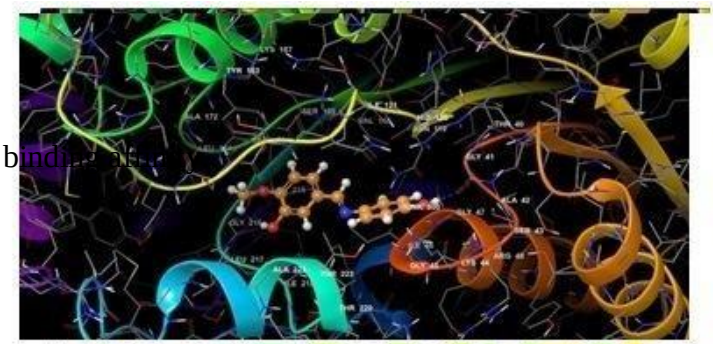
Compounds	Docking score kcal.mol^{-1}	Active sites with a mode of interaction		
		H-bond	π-π stacking	Hydrophobic contacts (at 5Å)
1	-6.334	GLY 216 GLY 41	--	ALA 42, ILE 46, ILE 121, VAL 168, TYR 183, LEU 171, ALA 172, LEU 215, LEU 217, ILE 218, ALA 223
2	-5.965	ILE 46 THE 220	--	ILE 46, ALA 65, MET 93, VAL 142, ILE 121, LEU 126, LEU 171, ALA 172, TYR 177, VAL 180, TYR 183, ALA 223, VAL 231
3	-7.287	LEU 215	--	ILE 46, ALA 65, MET 93, ALA 123, ILE 121, LEU 126, VAL 142 LEU 171, ALA 172 LEU 217, ILE 218, LEU 215, TYR 177 VAL 180, TYR 183, VAL 231, MET 233
4	-5.892	ASP 131 SER 125	--	LEU 126, LEU 128, PHE 129, ILE 133, MET 179, VAL 180, ALA 181, ALA 182
5	-7.511	SER 168 LYS 187 ILE 121 MET 93	--	ILE 46, MET 93, ALA 65, ILE 121, VAL 142, VAL 168, TYR 183, LEU 171, LEU 215, ILE 218
6	-5.6	ARG 66 THR 220	--	ILE 46, MET 93, ALA 65, ILE 121, VAL 142, ALA 223, ILE 218
7	-7.436	--	LYS 44	ILE 46, MET 93, ALA 65, ILE 121, LEU 126,VAL 142, VAL 180, TYR 183, LEU 215, ALA 172, LEU 171, LEU 215, ILE 218, ALA 223, ALA 226
8	-2.808	ILE 89	ARG 137	ILE 89, ALA 90, MET 96, PHE 98, ALA 99, ILE 133, VAL 149, VAL 152, ALA 153
9	-6.006	MET 93 THR 220	--	ALA 42, ILE 46, PHE 98, MET 93, ALA 65, ILE 121, VAL 142, VAL 168, TYR 183, LEU 215, ILE 218, ALA 223
10	-4.051	MET 93 TYR 183	--	ALA 65, MET 93, PHE 98, ALA 42, ILE 46,ILE 121, VAL 142, TYR 147, VAL 168, TYR 183 ALA 223, MET 224, ALA 226, LEU 215

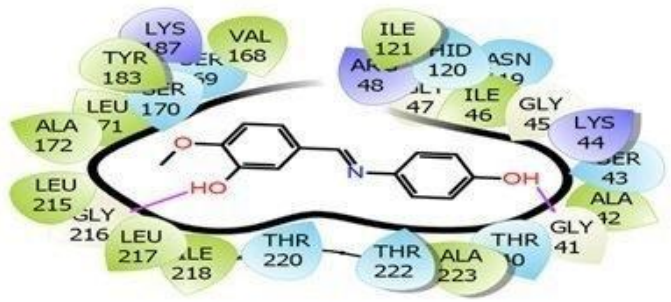
ALA 153, TYR 147, MET 224) may play a vital role in the interaction profile of the mentioned Schiff base diols compounds (Figures 6-8). The hydrogen bond interaction between the docked compounds and receptor active sites were displayed in Table 6. The results from Table 6 indicate that the compounds 1, 2, 4,6, 8, 9&10 have relatively higher binding energies and found to lesser affinity for binding with targeted protein and consequently would show weak inhibition effect to the organism. The lower the relative binding energy, the more effective is the binding affinity between

Table 6.Molecular docking score of 1 to 10 with receptor cortisone reductase deficiency 2 (CORTRD2).

the ligand molecules and the receptors. The Schiff base compounds 3, 5 and 7 were found to possess relatively lower binding energy values (**Table 6**) indicating their higher affinity to the target sites. The attained results from molecular docking simulations emphasize that the interaction between Schiff base diol compounds and the target protein was conquered by strong hydrogen bonding, hydrophobic forces and π- interactions. The docking study thus, proposes the compounds 3, 5, and 7 as the most promising analogs predicted to bind to the CORTRD2 receptor with stronger

1





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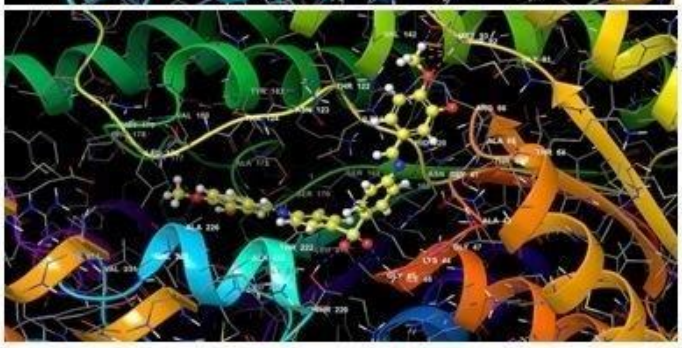

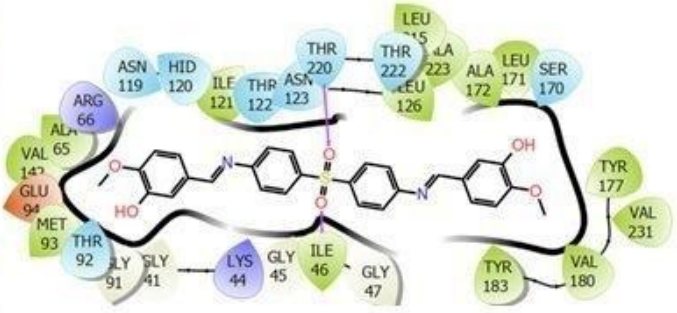

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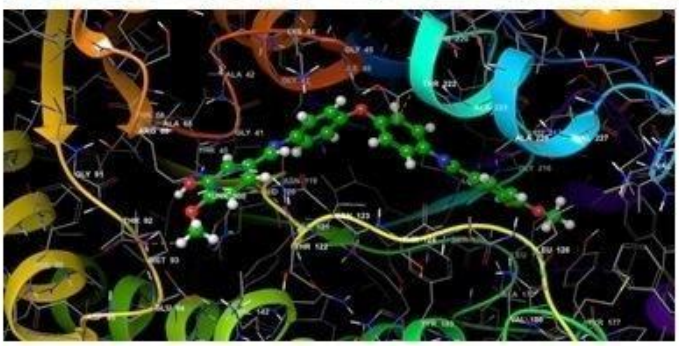

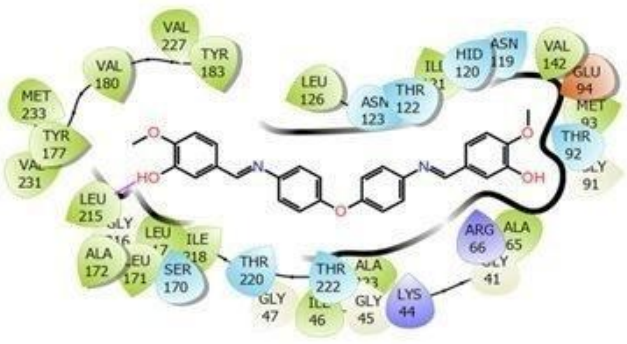

Fig.6 Molecular docking studies of synthesized monomers such as 1,2,3 and 4with receptor cortisone reductase deficiency 2 (CORTRD2).

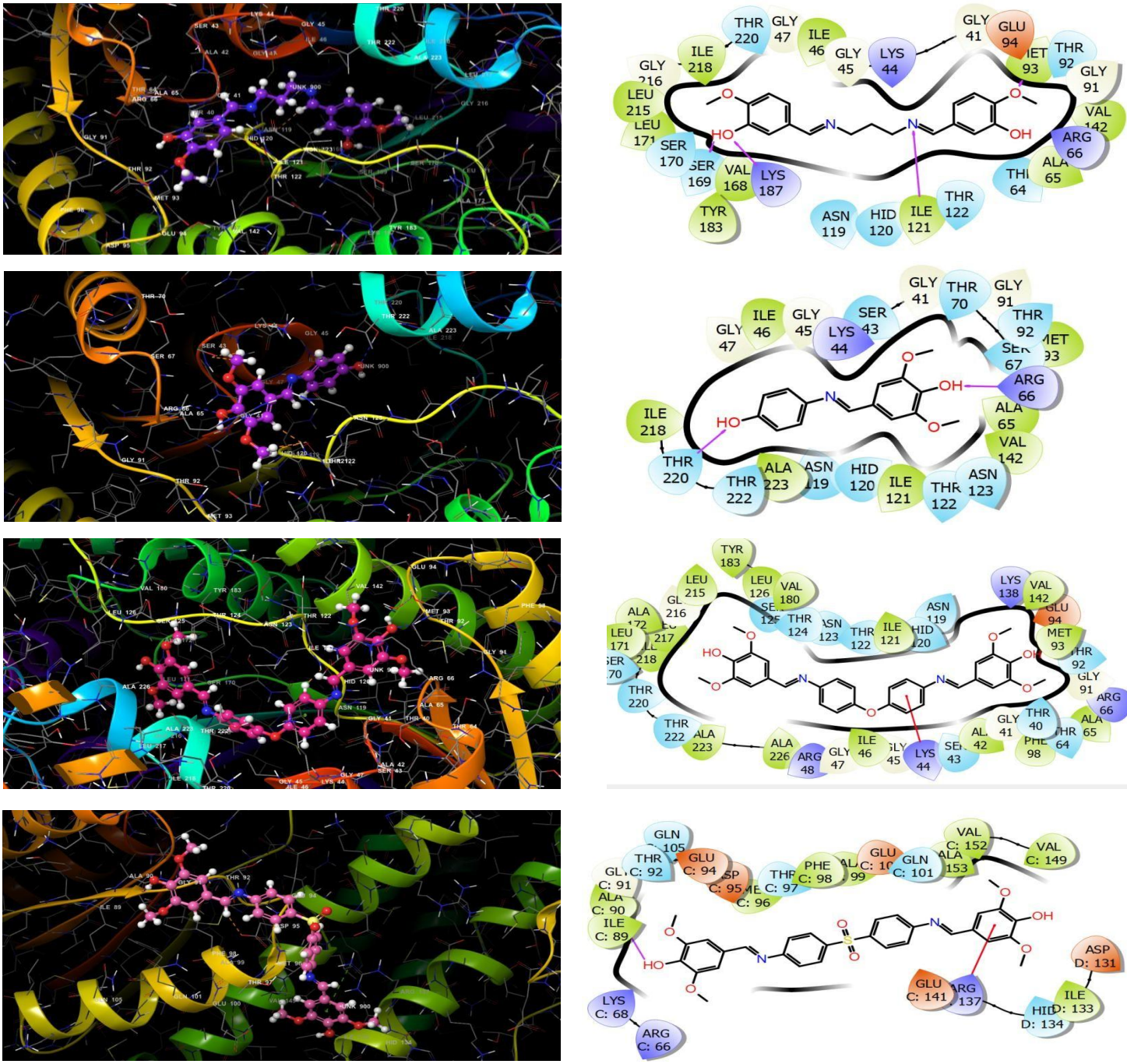

Fig.7 Molecular docking studies of synthesized monomers such as 5,6,7 and 8 with receptor cortisone reductase deficiency 2 (CORTRD2).

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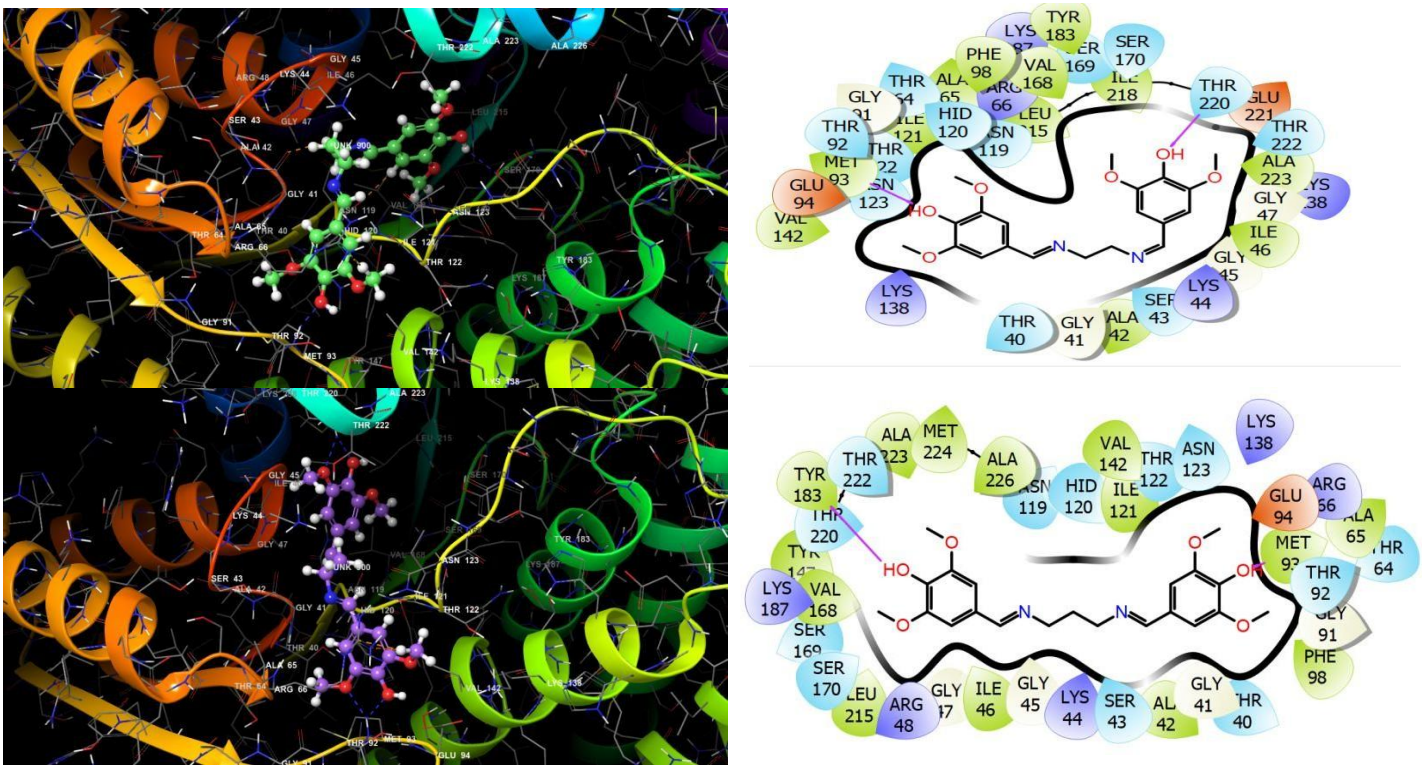


Fig.8 Molecular docking studies of synthesized monomers such as 9 and 10 with receptor cortisone reductase deficiency 2 (CORTRD2).

FRONTIER MOLECULAR ORBITALS:

The FMO theory is an implementation of molecular orbital theory which describes HOMO and LUMO which play predominant role in geometrical investigation. The highest occupied molecular orbital (HOMO) which represents the ability to donate an electron, and lowest unoccupied molecular orbital (LUMO)which represents the ability to obtain an electron are the key orbitals in chemical stability. The HOMO and LUMO correspond to the transitions from ground state tofirstexcitedstate.The molecular stability and chemical reactivity of molecules are measured byglobal hardness and softness of the molecules. The softmoleculeshavesmallenergygaparemorereactivethan that of hard molecules with large energy gap. Among thecompounds1–10, compound 5 is most stable, whereas thecompound9ismostreactivewithlowestenergygap (figure 9) .The large energy gap determinesthestability of the complexes, and small energy gap allows easy intramolecular charge transfer enhancing the biological activity ofthecompounds[23].The calculated quantum chemical parameters of the Schiff base diol compounds obtained from the

calculationssuchasenergiesofHOMO(E_{HOMO}),energiesofLUMO (E_{LUMO}), ionization potential (IP), electron affinity(EA),chemicalpotential(μ),globalhardness(η),global softness (S), and electrophilicity (ω). The calculations were carried out based on the Koopman'stheorem,usingthefollowingequations, andare tabulated inTable7.

$$\Delta E = E_{LUMO} - E_{HOMO}$$

$$IP = -E_{HOMO}$$

$$EA = -E_{LUMO}$$

$$\mu = \frac{\text{IP} + \text{EA}}{2}$$

$$\chi = \frac{-(E_{HOMO} + E_{LUMO})}{2}$$

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2}$$

$$S = \frac{1}{2\eta}$$

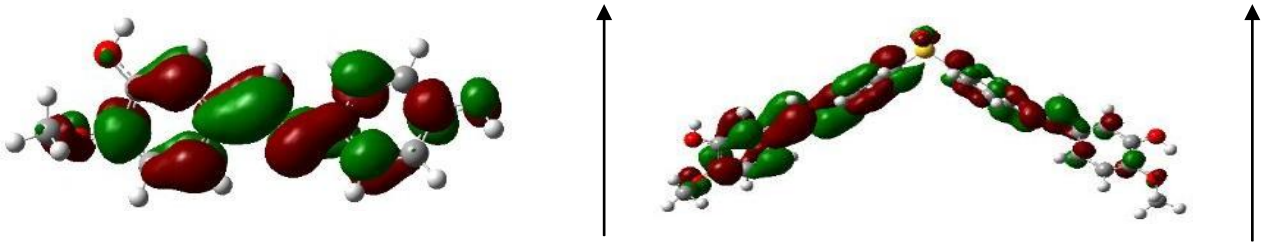
$$\omega = \frac{\mu^2}{2\eta}$$

Table 7. The calculated quantum chemical parameters of the Schiff base diol compounds.

Parameter (eV)	1	2	3	4	5	6	7	8	9	10
E_{LUMO}	0.03838	0.02275	0.03203	0.04843	0.05152	0.04562	0.03563	0.02723	0.00584	0.06204
E_{HOMO}	-0.1189	-0.1258	-0.1164	-0.1275	-0.1261	-0.1091	-0.1117	-0.1203	-0.0296	-0.1118
ΔE	0.157	0.149	0.148	0.176	0.178	0.155	0.147	0.148	0.035	0.174
IP	0.119	0.126	0.116	0.127	0.126	0.109	0.112	0.12	0.03	0.112
EA	-0.038	-0.023	-0.032	-0.048	-0.052	-0.046	-0.036	-0.027	-0.006	-0.062
μ	0.041	0.052	0.042	0.04	0.037	0.032	0.038	0.047	0.012	0.025
Ƞ	0.079	0.074	0.074	0.088	0.089	0.077	0.074	0.074	0.018	0.087
S	6.329	6.757	6.757	5.682	5.618	6.494	6.757	6.757	27.778	5.747
Ω	0.011	0.018	0.012	0.009	0.008	0.007	0.01	0.015	0.004	0.004

HOMO LUMO

1.



ΔE=0.157 ΔE=0.149

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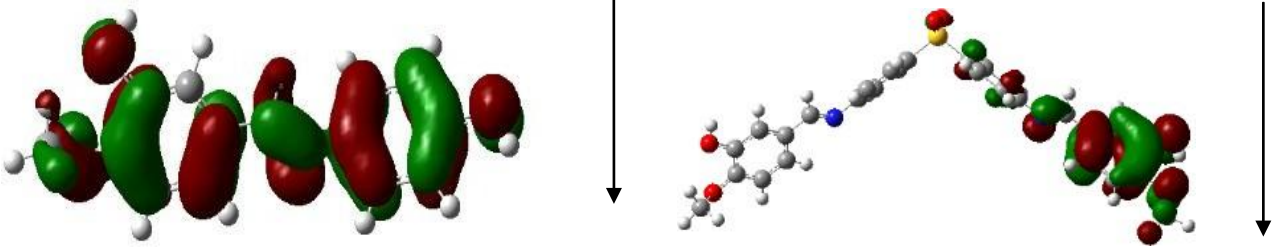

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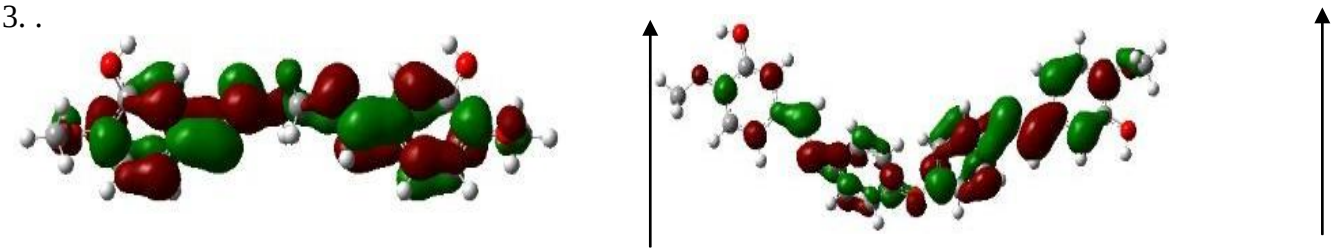

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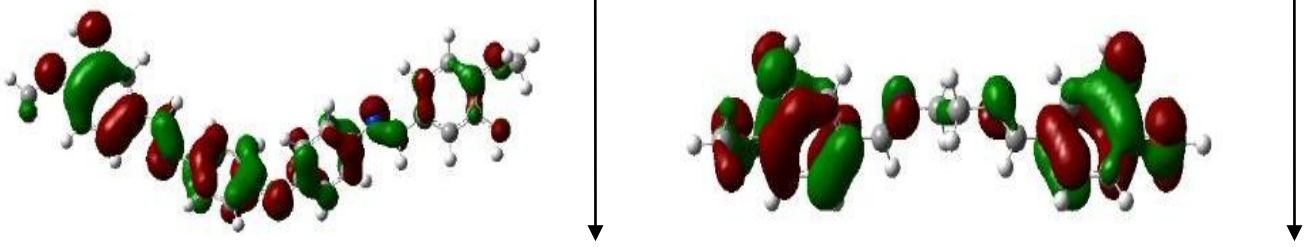
ΔE=0.148ΔE=O.176



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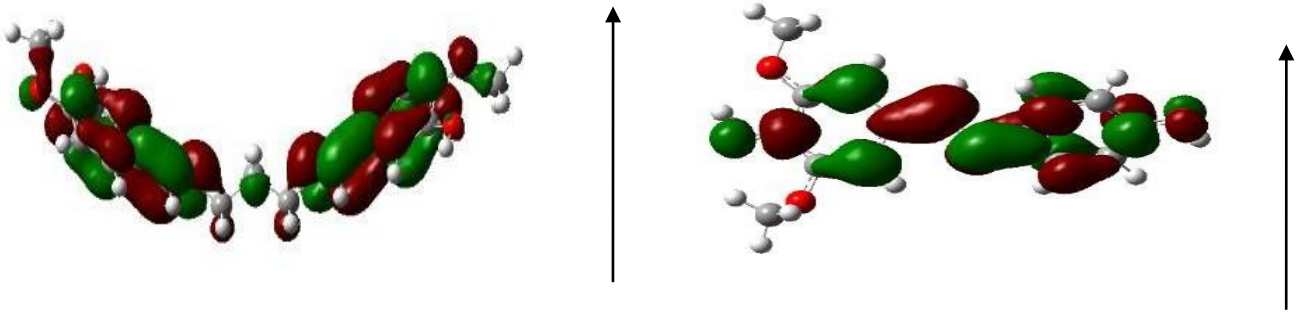

ΔE=0.178

ΔE=0.155

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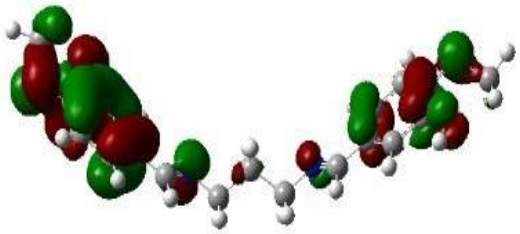

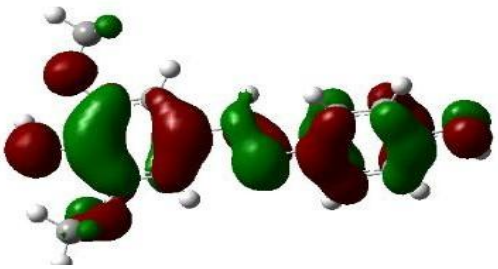

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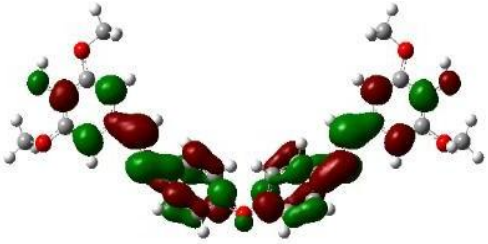

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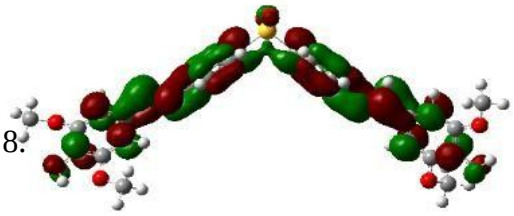

ΔE=0.147

ΔE=0.148

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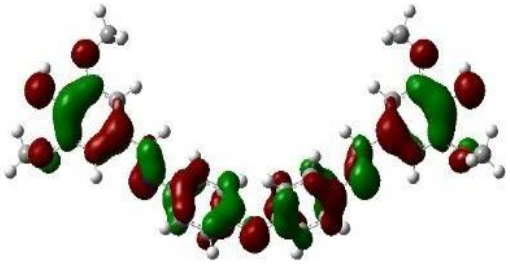

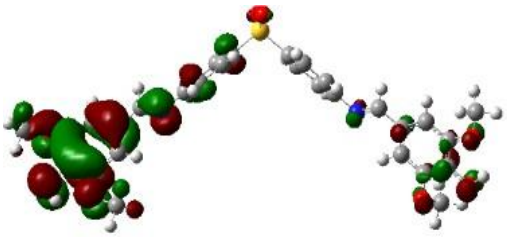

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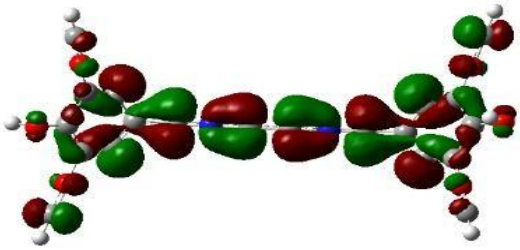
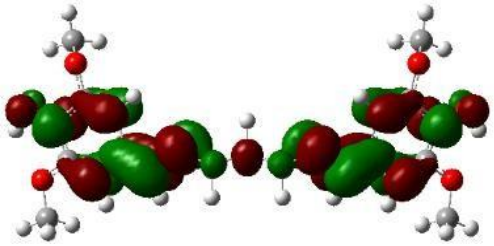
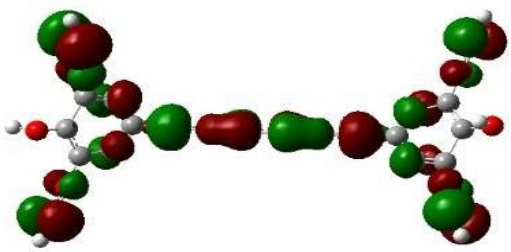




ΔE=0.035

ΔE=0.174

10.



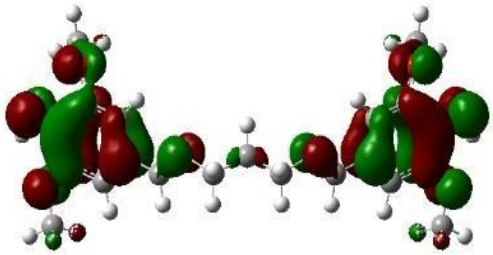
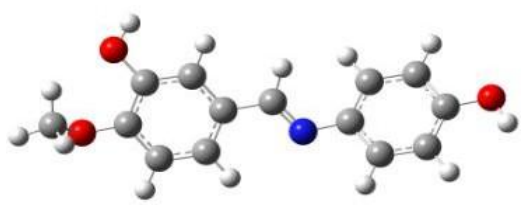


Fig.9 Frontier Molecular orbital of investigated complexes namely compound 1 to 10 monomers using B3LYP/LACVP++ basis set.



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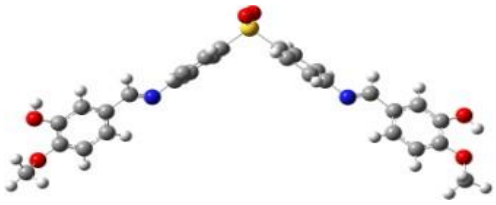

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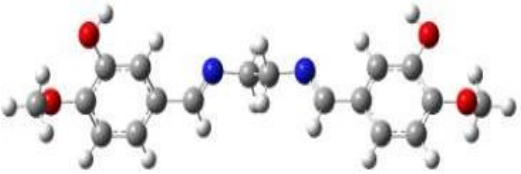

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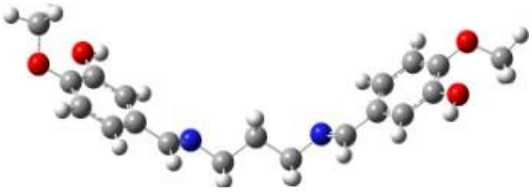

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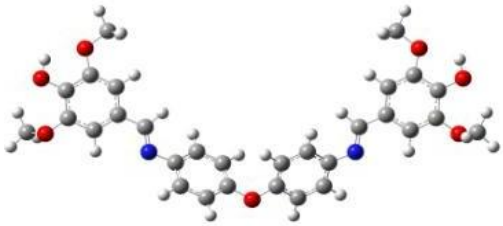

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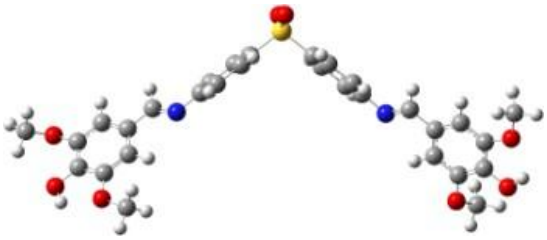

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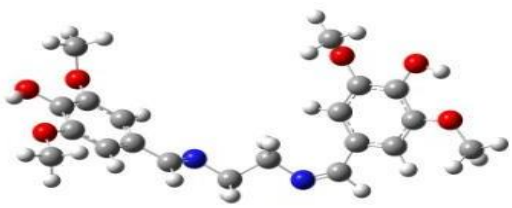

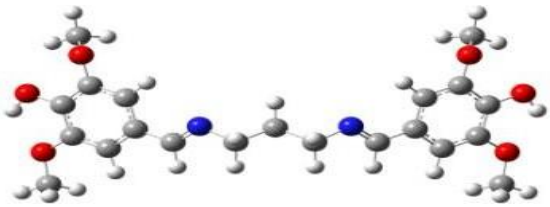

9 **10**

MULLIKEN ATOMIC CHARGES

Mulliken atomic charges for some important atoms were calculated and the data are listed in Table 7. The calculation of atomic charges plays an important role in the application of quantum mechanical calculations to molecular systems.[24] The calculated charge values for N and O are −0.406 and −0.527a.u.(**Table 7**) , indicates the high electronegativity around them and high probability of electron transfer from these atoms. Oxygen and nitrogen atoms in the compound had more negative charges than the other atoms. The C_7, C_8 and C_{18}atoms had higher positive atomic charges than the other carbon atoms. This was due to the electronegative atoms such as oxygen and nitrogen attached to carbon atoms. Mulliken method was used for predicting the suitable sites of coordination to the metal ions present in Schiff base diols.

Table 7: Mulliken Charge Analysis for Compound 5.

Atom	Mulliken charges
1C	0.127896
2O	-0.239630
3C	0.093659
4C	-0.061314
5C	-0.065089
6C	-0.023876
7C	0.314042
8C	0.321335
9O	-0.527507
10C	0.173159
11N	-0.406333
12C	0.128956
13C	0.051270
14N	-0.401477
15C	0.168970
16C	-0.009205
17C	0.303901
18C	0.319139
19C	-0.111482
20C	-0.017584
21C	0.096987
22O	-0.527387
23O	-0.242270
24C	0.266307
25C	0.267535

VIBRATIONAL PROPERTIES:

FTIR spectra of compounds recorded in the region of 4000-500 cm^{-1} showed various modes of vibrations which substantial characterize peaks of the synthesized compounds. Theoretical modes of vibrations for the deigned Schiff base diols were computer using DFT analysisreasonable correlations have been found between the calculated and experimental spectra value (**Table 8**).The characteristic peaks are found at 3465-3254cm-1 for hydroxyl stretching, at 1526-1540 cm-1 for aromatic C=C stretching, at 1654-1671 cm-1 for imine stretching and at 2848-2910 cm-1 for aliphatic C-H stretching for compound 5.

Compounds	**Stretching frequency(cm^{-1})**							
	$C=C_{Ar}$		**-C=N-**		**$-OCH_{(methoxy)}$**		**-OH**	
	Expt	**Theort**	**Expt**	**Theort**	**Expt**	**Theort**	**Expt**	**Theort**
M1	1589	1565	3445	3823	2825	3030	3445	3823
M2	1567	1565	3507	3773	2815	3010	3507	3773
M3	1588	1544	3386	3774	2864	3025	3386	3774
M4	1526	1564	3465	3819	2848	2990	3465	3819
M5	1518	1633	3551	3824	2882	3029	3551	3824
M6	1552	1544	3439	3756	2874	3023	3439	3756
M7	1543	1542	3503	3756	2789	3028	3503	3756
M8	1591	1546	3439	3748	2899	3025	3439	3748
M9	1536	1547	3387	3757	2817	3022	3387	3757
M10	1546	1546	3565	3757	2863	3027	3565	3757

Table8:FT-IRabsorption peaksof compounds(1-10)

CONCLUSION:

Pharmacokinetics plays an important role in the validation of a lead compounds. Many a time the compounds obtained from different sources are left without being taken to the next level of becoming an appropriate drug. These studies have taken our compounds of interest to the various PBPK models which helped our research to identify the best lead compounds. The Schiff base diols have been analyzed by virtual ADME screening and a optimized by density functional theory. The entire sets of compounds are polar with good to moderate water solubility and are therefore expected to have good oral absorption and bioavailability. The predicted gastro-intestinal absorption was displayed high and could assess the absence of toxicity at CNS level, due to non-permeation across the blood-brain barrier. The synthesized compounds **(1,4,5,6,9, and 10)** were observed to have a high intestinal absorption and hence do not affect the CNS. Hence base on ADME, docking and DFT studies, we propose Schiff base diols 3, 5 and 7 can be developed as lead compounds against cortisone deficiency syndrome disorder. The geometry optimizations of the Schiff base diols were done using DFT calculations. The molecular stability and chemical reactivity of molecules were measured by global hardness and softness of the molecules. The soft molecules have small energy gap and are reactive than that of hard molecules with large energy gap. Among the compounds 1–10, compound 5 is the most stable, whereas the compound 9 is the more reactive with lowest energy gap. The DFT studies showed acceptable agreement between the theoretical and experimental IR data. The Schiff base diols showed inhibitory activity against CORTRD2 receptor. The diols 3, 5 and 7 exhibited strong interaction with the receptor via hydrophobic interactions and hydrogen bonding. Analysis of ADME properties and pharmacokinetics evidenced the good drug likeness of the Schiff base diols.

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