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Synthesis and SAR Study of 2-(4-cyano-2-methylphenoxy)acetohydrazide

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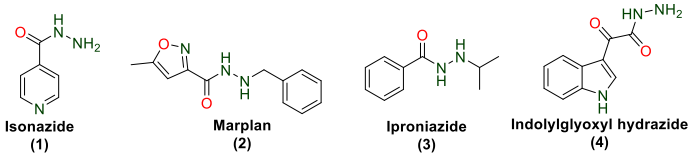
ABSTRACT

In drug development process, if physical sample is limited then computer models constitutes valid alternative to experiment. Here, we used different web tools such as ChemDraw, Spartan, Cresset, Avogadro, MarvinSketch 18.10, Forge, SwissADME, SwissTargetPrediction, Swiss Similarity, and Molinspiration, etc. to predict drugllikeness character of the hydrazide. The 2-(4-cyano-2-methylphenoxy)acetohydrazide was synthesized from 4-cyano-2-methylphenol and study their antimicrobial activity.

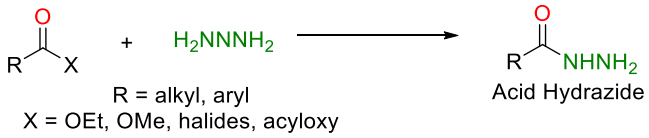
Keywords: *Avogadro, Statron, Forge, SwissADME, Antimicrobial, Hydrazine*

INTRODUCTION

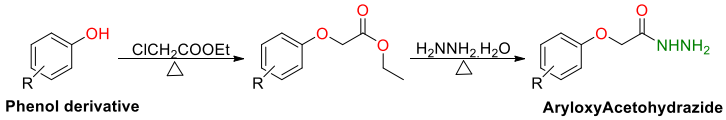
The great focus on the hydrazides and their derivatives was due to their properties and applications such as drugs, chemical preservers for plants, polymer synthesis, glues, etc [1]. Vast groups of organic derivatives containing the active functional group –C(=O)NHNH$_2$. Acid hydrazides and their derivatives such as hydrazones was the important precursor for the synthesis of heterocyclic compounds of different sizes with one or more heteroactoms that exhibit interesting applications such as Pharmaceuticals [2,3], herbicides [4], antibacterial agents [5] and dyes [6,7]. Hydrazides analogues possesses different biological activities such as anticonvulsant [8], antidepressant [9], anti-inflammatory [10], antimalarial [11], antimycobaterial [12], anticancer [13], and antimicrobial [14-17] activities. Examples of some known drugs containing acid hydrazide groups are Isonicotinic acid hydrazide known an isonazide (tuberculosis therapy) [18], Marphan (monoamine oxidase inhibitor; anti-depressant) [19], Iproniazid (anti-depressant; psychostimulators) [20] and indolylglyoxylyl hydrazide (potent 5-hydroxytryptophan decarboxylators) [21].



Usually acid hydrazides are synthesized from various acyl derivatives which includes esters, cyclic anhydrides, and acyl halides by condensing with hydrazine. A general scheme for the synthesis of acid hydrazides is given below.



Different substituted phenols are treated with ethyl chloroacetate in dry acetone or DMF in presence of excess potassium carbonate under reflux condition followed by the treatment of hydrazine hydrate in ethanol forming aryloxy acetohydrazide [22].



Molecular visualization tools:

Spartan and Cresset, both are combines a powerful set of molecular modeling and calculation tools within one graphical user interface. The electron density models of the molecules shows the locations of the electrons around the skeleton of molecules.

Spartan:

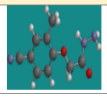
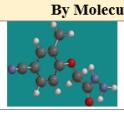
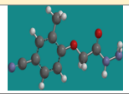
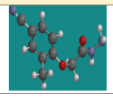
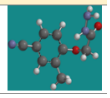
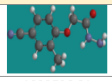
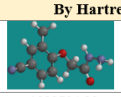
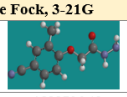
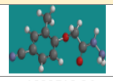
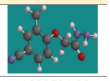
Molecular surfaces can be calculated from a wide range of in built quantum chemistry methods. This provides essential connections between important chemical observable - structure, stability, reactivity and selectivity - and energy. Spartan has the ability to calculate surface properties for various molecules. This can aid in calculations of molecular equilibrium and transition-state geometry as well as thermodynamic and kinetic information as the follow on from interpretation of surfaces.

Spartan is a powerful tool for computer aided drug design. The easy-to-use interface delivers a new suite of molecular modeling features as well as quantum calculation tools for chemists working in drug discovery. Pharmaceutical scientists can perform conformational analysis and can quantify 3D molecular similarity based on structure, chemical function, and pharmacophore models. Many of the leading Pharmaceutical companies are already using Wave function software to fast-track development of new drugs.

Spartan allows chemists to investigate a wide range of molecular properties from within one intuitive graphical interface:

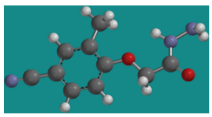
- Mulliken, electrostatic-fit and natural charges,
- Dipole and higher moments, polarizabilities and hyperpolarizabilities,
- Free energies, aqueous solvation energies HOMO and LUMO energies,
- Polar Surface Area and polar area based on ESP,
- Log P, ovality, electronegativity, and hardness,
- NMR chemical shifts with Hartree-Fock and Density Functional Theory.

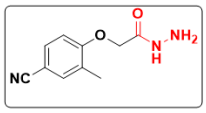
There are total 108 different conformations possible for the hydrazide; out of which five are more stable and low energetic given below.

By Molecular Mechanics					
Structure					
E (kJ/mol)	431.38	435.38	449.46	453.19	455.29
Boltzmann Dist. const.	0.834	0.166	0.000	0.000	0.000
By Hartree Fock, 3-21G					
Structure					
E (kJ/mol)	-1822735.81	-1822734.39	-1822706.49	-1822718.86	-1822734.39
Boltzmann Dist. const.	0.542	0.305	0.000	0.000	0.152
Dipole moment (D)	2.71	4.68	5.64	7.00	4.69

Molecular descriptors:

Properties are calculated by using Hartree Fock, 3-21G. Molecular descriptors are those calculated readily from the molecular formula, the molecular graph or from one or more computed 3D conformations. These descriptors refer the properties of whole molecule or properties of individual atoms or relationship between molecular structure and its properties. Some commonly used descriptors are listed below. The stereo-electronic properties such as nature and size of substituent's, molar refractivity, volume, surface area, molecular electrostatic potential, partition coefficient, H-donor and H-acceptor, etc. Using the ChemDraw panel, we can draw 2D structure and convert them to 3D models. Alternatively, we can also build a 3D model and convert it to a 2D drawing that displays in the panel. The various properties listed below of the molecule can be studied by using ChemBio3D and Avogadro software:





Formula: $C_{10}H_{11}N_3O_2$

Energy: - **694.242824** au

Energy (aq): - **694.256372** au

Solvation E: - **35.57** kJ/mol

E-HOMO: -**9.29** eV.	E-LUMO: **2.56** eV.	Dipole moment: **2.71** debye.
Tautomers: **01**.	Weight: **205.217** amu.	Point group: C_1.
Conformers: **108**.	Area: **235.48** A^2.	Volume: **206.02** A^3.
PSA: **74.747** A^2.	Ovality: **1.40**.	Log P: **0.56** - **0.80**.
Polarizability: **55.30**	HBA count: **3**	HBD count: **5**

Geometrical Descriptors

Dreiding energy: 399.04 kcal/mol
Minimal projection area: 28.22
Minimal projection radius: 4.27
Length perpendicular to the max area: 4.37
van der Waals volume: 201.76 A^3
MMFF94 energy: 333.96 kcal/mol
Maximal projection area: 80.69
Maximal projection radius: 8.03
Length perpendicular to the min area: 16.05
Van der Waals surface area: 293.03 A^2

Partition coefficient (*log P*) is measured how hydrophilic (water loving) or hydrophobic (water fearing) nature of the chemical molecule. It is use to estimate the distribution of drugs within the body. It also used to explain time required to reach its intended target of body, how strong it effect the target, and how long it present in active form in the body.

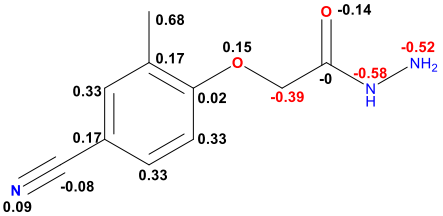
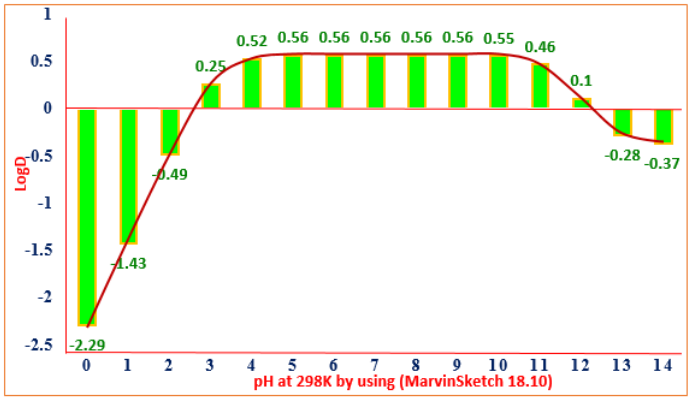


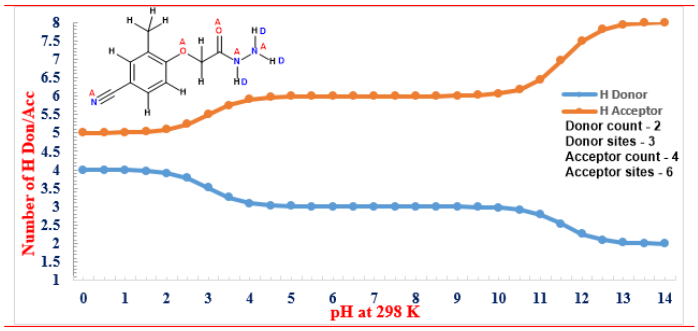
Image of log P of heavy atoms of molecule (MarvinSketch 18.10)

Ovality of the molecule is obtained from calculated molecular volume and surface area. The ovality index is one for spherical top molecule and increasing with increasing linearity of the molecule. When any organic solute enter into the liquid phase of octanol and water, it create hole which is directly related to the ovality, molecular surface area and volume. These molecular descriptors are very useful to decide soft analogs based on the various concepts which has desired physical, chemical and activity properties.

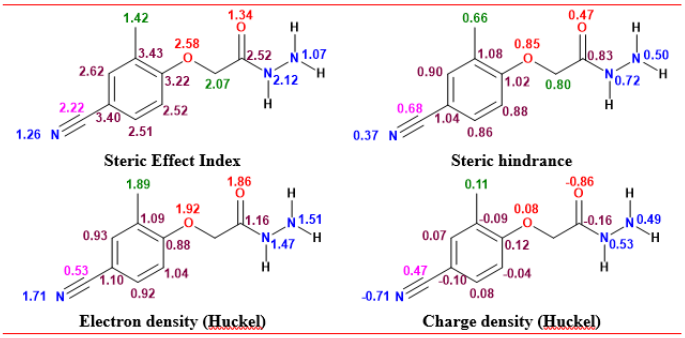
The variation of distribution of the molecule (log D) against pH of the target molecule at 298K is plotted in following graph. Log P = 0.56.



Hydrogen donor and acceptor count and sites are changes by changing the pH of the solution because of protonation and deprotonation of the atoms or groups of the molecule. Some atom or group shows dual nature either hydrogen bond acceptor or donor which is function of pH of solution. This can be explain by using following graph (plotted from data generated by MarvinSketch 18.10).



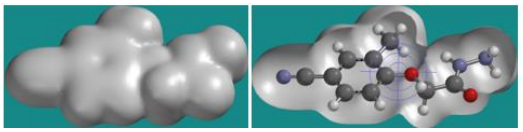
The steric hindrance, steric effect index, electron density (Huckel analysis), charge density (Huckel analysis), etc. of the target molecule at pH 7.40 is calculated by MarvinSketch 18.10.



Density of the molecule:

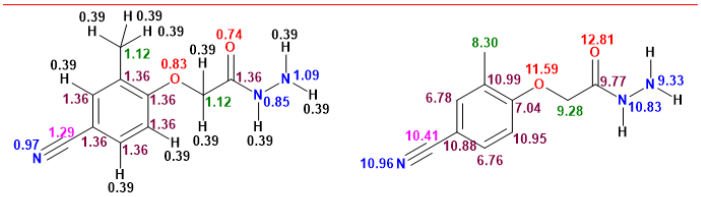
The size of the electron density surfaces indicates the size of

electron clouds around that particular atom or bond. The large size/values of the electron density will first indicate the position of atom in the molecule and then slowly decreases resolution, showing the presence of chemical bonds.



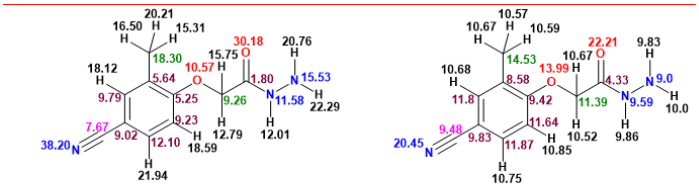
IsoVal: **0.002**
Area: **226.27** A^2.
Vol: **206.68** A^3.
Acc. Area: **172.77** A^2.

Polarizability of the target molecule is 20.94 at pH 7.4 and 298K calculated by MarvinSketch 18.10. The sp^2 hybridized carbons has highest polarizability (1.36) while all hydrogen has least (0.39). Orbital electronegativity i.e. electronegativity of the heavy atoms is calculated; the sp2 hybrid oxygen has highest electronegativity.



Polarizability of each atom | Orbital electronegativity of heavy atoms

The total molecular surface area (solvent accessible and Van der Waals) of the target molecule is calculated by MarvinSketch 18.10.



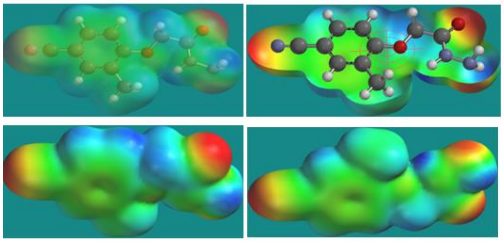
ASA: **388.40** ASA+: **239.57** ASA-: **148.82**
ASA_H: **229.94** ASA_P: **158.45**
Solvent accessible surface area at pH 7.40

Van der Waals surface area: **293.07**
Van der Waals surface area at pH 7.40

Electrostatic potential of the molecule:

The electrostatic potential electron density layout was important to understand the location or shifting of electron density within the molecule which was used to explain electrophilic and nucleophilic centers of the molecules. This was also used to explain the electronic effects present in the molecule such as inductive and resonance effects. The electronegative atom attracts bonding electron toward itself and giving rise to an unequal distribution of charge in a molecule. As the electrostatic potential around the molecule explain its reactivity towards electrophile or nucleophile, also it was used to distinguish the reactivity difference between the molecules and their positions. The electrophilic and Nucleophilic strength of electrostatic potential can be mapped by using color. The red color of potential indicates negative value (more electron density or region with excess negative charge), while colors towards blue indicate the positive values (electron deficient centers or region with excess positive charge) and the green color indicate the neutrality. The intensity of blue colour around hydrogen attached to nitrogen and carbon atoms of ring and methyl group is – N > ring > methyl. It indicates that hydrogen (202.03 kJ/mol) attached to nitrogen are more electrophilic. The nitrogen of cyano group and oxygen of carbonyl group are red in colour which are nucleophilic in nature. The oxygen of carbonyl was more nucleophilic (-226.41 kJ/mol) than nitrogen. From the total molecular area 226.27 A^2; polar surface area of the molecule is 72.46 A^2. These polar surfaces are useful for the long range electrostatic interactions between the molecules. The electrophile reacts faster at nitrogen of –CN, $-NH_2$ and >C=O than the other while nucleophilic attack takes place faster on hydrogen of –NH- and $–CH_2$- group. Polar surface area (PSA) was the useful descriptor for the quick estimation of biological barrier crossing such as absorption and brain access.

Property range (electrostatic properties): - 200 to 200 kJ/mol. (Min -226.41 & Max 202.03).

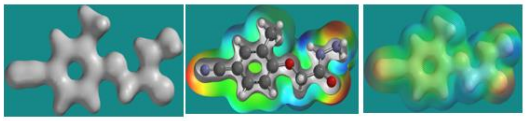


isoVal: 0.002
Val: 86.7 kJ/mol
p-Area: 72.46 A^2.
Area: 226.27 A^2.
Volume: 206.68 A^3.
Acc. Area: 172.77 A^2.
Acc. P-Area: 59.59 A^2.

The electrostatic potential map was provides the information about the distribution of the charges, delocalization of charges or electrons by resonance, etc. in a molecule. These surfaces was used to explain h-bonding, van der Waal interactions and solvation by polar solvent. The hydrazide and –CN groups of the molecules are highly polar so easily forming hydrogen bonding with polar protic solvent.

Density of bonds of the molecule:

The electron density model was also used to explain the bonding present in the molecule and transition state which was formed during the course of reaction where bond are partially break and formed.



IsoVal: 0.08
Area: 120.12 A^2.
Vol: 43.66 A^3.
Acc. Area: 65.45 A^2.

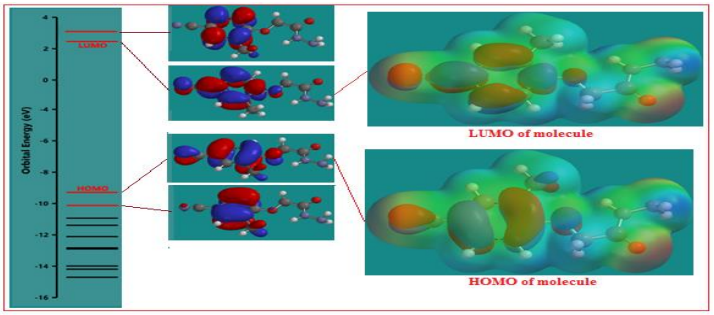
HOMO and LUMO of the molecule:

The electron density distribution of highest occupied molecular orbitals (HOMO) and the lowest unoccupied molecular orbital (LUMO) are important because these orbitals are involved in most of the chemical reactions. The red and blue circles identify regions where the orbitals takes on significant value; either positive (shaded) or negative (unshaded). The molecular orbital surfaces can be extended over varying number of atoms; if the molecular orbital surface (or surfaces) is spread over single atom or to atoms which are not close together, are called as non-bonding while the orbital contains surface that extends continuously over the two or more neighboring atoms are called as bonding molecular orbital. Such orbital is also called as bonding orbital with respect to these atoms. The lowest unoccupied molecular orbital (LUMO), in particular provides the information of the location of positive charge in a molecule. The electron deficient centers of the molecules benzene ring and carbon of cyano group. The mapping of the electron density model and the LUMO of the molecule clearly gives the positions on the molecules where the affinity for electrophilic or Nucleophilic reactions. The LUMO has lower energy will be have lowest resistance to accept electrons.

Area of HOMO: 99 A^2.	**Area of LUMO: 107.20 A^2.**
Vol of HOMO: 28.17 A^3.	Vol of LUMO: 29.30 A^3.
IsoVal of HOMO: 0.032	IsoVal of LUMO: 0.032
Energy: -9.29 eV	Energy of LUMO: 2.56 eV

The electron density of HOMO was mostly available to participate for the reactions. The energy of the HOMO is which was important for the chemical reaction and charge transfer complexes. As the energy of the HOMO increases the ability of the orbital to donate the electrons was get increase and vice versa.

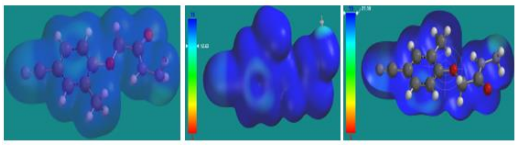
The energy difference between the HOMO-LUMO orbitals (gap) is an important indicator for the molecular stability. The energy gap is lower then the molecule was generally more reactive, while molecules with higher gap has high stability and therefore low reactivity for different chemical reactions.



Local ionization potential map of the molecule:

These electrostatic potential map provide the information of the sites which are susceptible for electrophilic attack. It explain electrophilic attack and substitution as well as activation and deactivation of electrophilic site and therefor reaction. It provide the information of the site of the molecule from where electron was more easily ionized. The nitrogen atom of $–NH_2$ group (12.59 eV) has lower value while oxygen of ether (21.82 eV) has higher value indicate the electrophilic attacking sites.

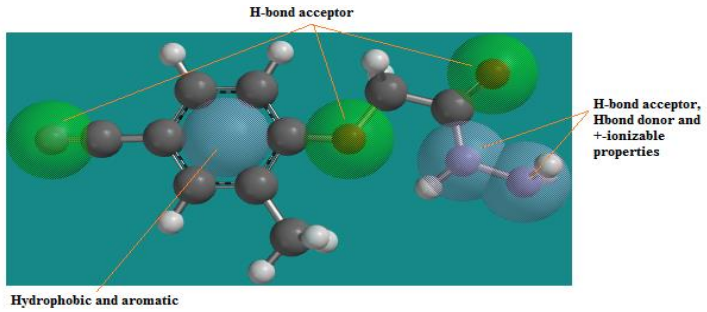
Property range: 05 – 15 eV. (Min 12.59 and Max 21.82)



Isoval: 0.002
Area: 226.27 A^2.
Vol: 206.68 A^3.
Acc. Area: 172.77 A^2.
Val: 18.438160

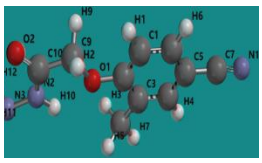
CFD (chemical function descriptors) or pharmacophores properties:

The pharmacophore modeling was typically performed by extracting common chemical features from 3D structure. A set of decriptors (typically steric and electronic features) such as hydrogen-bond acceptors or donors, positive or negative ionizable sites, and aromatics and other hydrophobes used to explain chemical functionality and used to correlate the molecule is a pharmacore or not. The molecules may either has similar molecular structures or has similar CFD's with proper arrangement. It has not only used for hits and lead identification but also for subsequent lead optimization. The hydrazide has 3-sites acts as H-bond acceptor; 2-sites acts both H-bond acceptor, H-bond donor and ionizable centers; and the aromatic ring acts as hydrophobic and aromatic center.



Atomic properties of the molecule:

Chirality: Molecule does possesses any type of chirality.



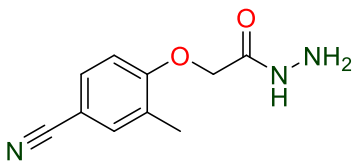


Table 1: Atomic charges and exposed area was calculated by using Avogadro 1.1.1 (Git revision: 3248586) and ChemDraw:

Atom No	Electrostatic charges	Mulliken charges	Natural charges	Exposed area in A^2
O1	-0.408	-0.764	-0.592	4.210
O2	-0.625	-0.639	-0.668	14.945
C9	-0.453	-0.152	-0.172	11.467
C10	0.749	0.835	0.759	12.619
N1	-0.468	-0.506	-0.305	15.168
N2	-0.179	-0.724	-0.589	4.840
N3	-0.925	-0.541	-0.689	10.396
H11	0.426	0.333	0.384	8.925
H12	0.426	0.333	0.384	8.924
H10	0.299	0.405	0.450	7.340
C2	0.515	0.452	0.390	7.851
C1	-0.427	-0.268	-0.335	12.107
C3	0.015	-0.112	-0.096	5.756
H2	0.233	0.258	0.239	5.294
H9	0.234	0.258	0.239	5.294
C8	-0.661	-0.563	0.666	17.917
H3	0.205	0.231	0.245	5.319
H5	0.204	0.231	0.245	5.319
H7	0.206	0.217	0.236	5.297

Bond lengths of the molecule: The bond length is measured in A^0 which is used to determine bond order (single, double, triple or partial bond). The distance between any non-bonded atoms in a molecule is used to determine orientation of the atoms in group and stereochemistry of the molecule. The stereochemistry and planarity of the atoms or groups of the molecule was also explain with the help of torsion bond angles.

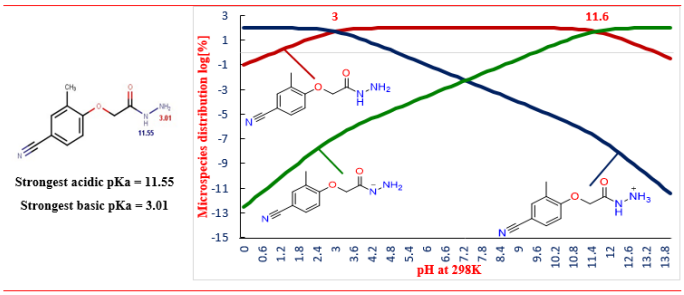
Table 2: Bond lengths of the molecule:

Bond	Bond length in A	Bond	Bond length in A	Bond	Bond length in A
H11-N3	1.006	**H12-N3**	1.006	**N2-N3**	1.423
N2-H10	0.993	**C10-N2**	1.337	**C10-O2**	1.219
C9-C10	1.518	**C9-H2**	1.081	**C9-H9**	1.081
C9-O1	1.434	**C2-O1**	1.371	**C1-C2**	1.380
C1-H1	1.069	**C2-C3**	1.396	**C3-C8**	1.511
C8-H5	1.084	**C8-H7**	1.082	**C8-H3**	1.084
H10-O1	2.130	**H2-O2**	2.672	**H9-O2**	2.671
O2-H12	2.770	**O2-H11**	2.771	**H1-H2**	2.402
H9-H1	2.401	**H10-H3**	2.826	**H10-H5**	2.826

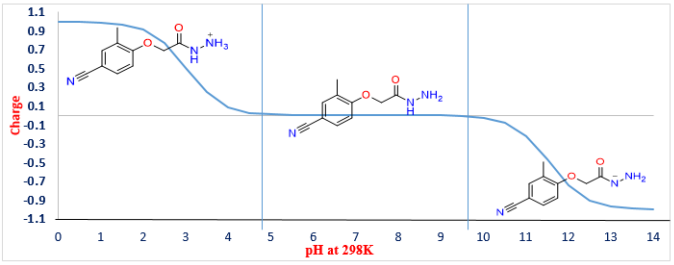
Table 3: Bond angles of the molecule:

H11-N3-H12	**110.42**	**H11-N3-N2 & H12-N3-N2**	**109.63**
N3-N2-H10	117.29	**H10-N2-C10**	121.72
N2-C10-O2	26.33	**N3-N2-C10**	120.98
C9-C10-O2	120.18	**C10-C9-H2**	108.17
C9-C10-H9	28.99	**H2-C9-H9**	108.91
H2-C9-O1	111.21	**H9-C9-O1**	39.87
C9-O1-C2	28.35	**O1-C2-C3**	115.78
C1-C2-O1	123.43	**H1-C1-C2**	120.85
C2-C3-C8	119.32	**H3-C8-C3**	110.53

Different macro-species distribution (in log[%]) between min basic pKa (-2.0) to max acidic pKa (16) at 298K is calculated by **MarvinSketch 18.10**. The graph shows abidance of the molecule in three different forms (neutral, cationic and anionic) in log[%]; neutral molecule (red line; exist between pH 1.0 to 13.5), NH get deprotonated (green line; exist pH less than 5) and NH_2 protonated (blue line; exist pH more than 9.5).



Therefore overall charge present on the molecule was varied with pH at 298K. It can be explain by descriptor called isoelectronic point (where charge get reverse). Isoelectronic point is 7.28 of the molecule.



SAR study:

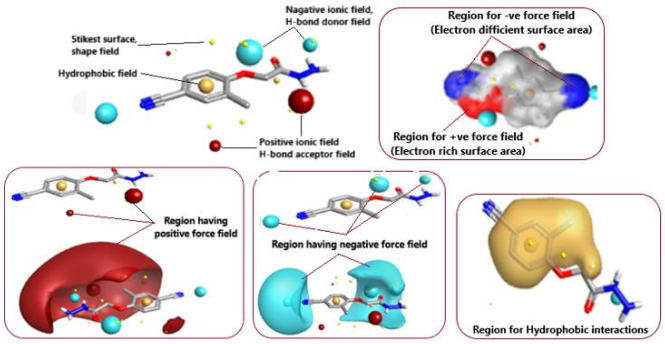
Forge (software) is a molecular design and SAR interpretation tool. It will generate detailed 3D models of binding and pharmacophores that will help to define the requirements of the protein of interest, aiding the synthetic chemist in the designing of new actives. It also gives rationale for the polarization of the molecules for synthesis.

Fore describe the molecules based on their molecular fields not on their structure. The interaction between a ligand and a protein involves electrostatic fields and the surface properties (e.g. H-bonding, hydrophobic surface, etc). If any two molecules binds to a common active sites tends to make a similar interactions with protein and hence have highly similar field properties. Accordingly, using these properties to describe molecules is a powerful tool for the medicinal chemist as it concentrates on the aspects of the molecules that are important for biological activity.

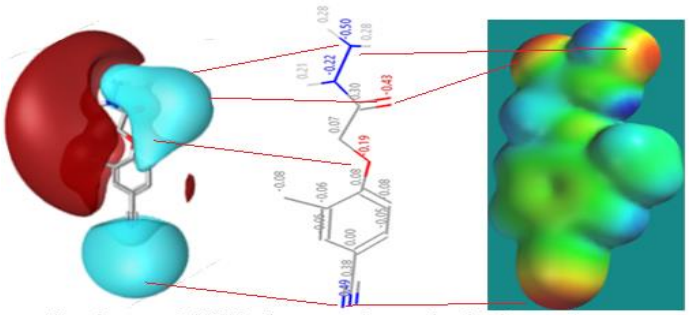
Forge condense the molecular field down to a set of points around the molecule termed field points. The field points are local extrema of the electrostatic, van der Waals and hydrophobic potential of the molecule. They have size/strength information associated with them i.e. all H-bond donor are not treated the same; some make stronger bonds than the others. The bigger fields points are generated by charged groups such as ammonium or carbonyl group or highly polar group. The colours of the field points indicates – Blue – Negative field points (like to interact with positives or H-bond donor present on protein); Red – Positive field points (like to interact with negatives or H-bond acceptors present on protein); Gold or Orange – Hydrophobic field points (describe the regions with high polarizability or hydrophobicity); Yellow – van der Waal field points (describe possible surface or rdW interactions). In general, ionic groups including those forming hydrogen bonding; give rise to the strongest electrostatic field. Aromatic groups encode both electrostatic and hydrophobic fields. Aliphatic groups give rise to hydrophobic and surface points but are essential electrostatically neutral.

Activity atlas of Forge actually performs three types of analysis: useful for quantitative information can be gained from 3D model. This model shows the average SAR of the molecule by comparing its structural parameters with the active molecules used commonly. The average electrostatic of actives (red or blue) shows the region where the active molecule in general shows either a positive or a negative field. As, this field of reference molecule which having high biological activity and the new molecules under study shows same either positive or negative fields should also be active. The average hydrophobic of the actives (yellow) contributions shows the regions where the active molecules in general make hydrophobic interactions with the target of interest.

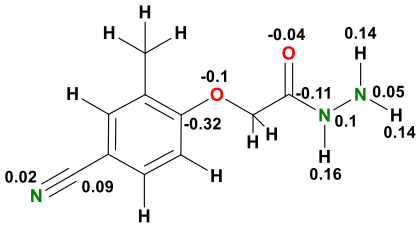
The molecule containing -CO–NH-NH_2 and –CN groups which will be confirmed from its FTIR spectrum. The –NH-NH_2 group shows strong absorption band at 3324, 3256 and 3201 cm-1 is due to strong symmetric stretching vibrations of N-H bond. The carbonyl group of acid hydrazide (-CO-NH-) linkage shows strong absorption at 1667 cm^{-1} while aromatic double bonds show strong absorption bands in 1613 and 1584 cm^{-1}. The cyanide group shows strong absorption band at 2226 cm^{-1}. The molecule containing two oxygen and three nitrogen atoms, all having different chemical environments. The electron density nitrogen of –NH_2 is -0.50 while that of carbon of –CN group is +0.38 which was higher than the carbon (+0.30) of carbonyl group. Therefore, electrophile should be react preferentially with amino group while nucleophile attack on carbon of cyano-group.



The order of electron density is - N (NH2)>N (CN)>O (C=O)>N (NH)>O (ether)



The nitrogen of -NH2 having more electron density than any heteroatom
The C of CN group is more electron deficient C of carbonyl group



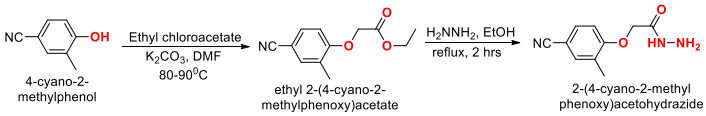
The oxygen and nitrogen atom are act as H-bond bond donor while hydrogen atom attached to nitrogen atom acts as H-bond acceptor. The phenyl ring shows mixed hydrophobic and electrostatic character and is reflected in a combination of in plane positive field points, pi-cloud points and hydrophobic points are at its center.

Synthesis of 2-(4-cyano-2-methylphenoxy)acetohydrazide:

An equimolar mixture of 4-cyano-2-methylphenol and ethyl chloroacetate, 1.5 molar anhydrous potassium carbonate in dry

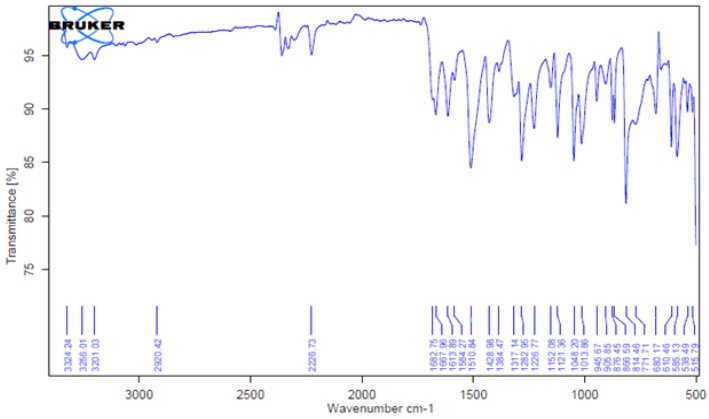
DMF was heated on a water bath at 80-90^{0}C for 4-5 hr. The completion of reaction was monitored by performing TLC. Cool the reaction mixture and pour into excess ice; extract the product by ethyl acetate. Dry the organic layer by anhydrous sodium sulphate and distilled out the solvent under reduced pressure. Record the yield and recrystallize the ethyl 2-(4-cyano-2-methylphenoxy) acetate by alcohol. Use the ester as it is for further reaction.

To a suspension of above synthesized ester in absolute ethanol, add 1.2 equivalent of hydrazine hydrate (99%) slowly with stirring and the reaction mixture was refluxed for 2 hrs. The solution was concentrated, cool and resulting solid obtained was filtered, washed with cold ethanol and recrystallized from absolute alcohol. Record the yield and characterized by IR.



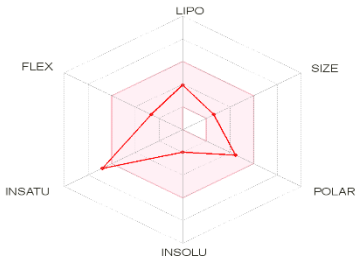
Color: white solid; **m.p.**: ^{0}C.

FT-IR (Frequency, cm^{-1}): 3324, 3256, 3201, 2920, 2226, 1686, 1667, 1613, and 1584.



Biological Study:

SwissADME (Absorption, Distribution, Metabolism and Excretion), SwissTargetPrediction and Swiss Similarity are the free web tool used to predict physiochemical properties, pharmacokinetics, drug-likeness and medicinal chemistry friendliness of the different chemical structures [23].



Bioavailability Radar: It is a displayed for a rapid appraisal of drug-likeness. The color zone is suitable physicochemical space for oral bioavailability. The six phycochemical properties are taken into account for prediction of bioavailability radar as: lipophilicity (-0.7 to 5.0), size (150 g/mol to 500 g/mol), polarity (20 A^2 to 130 A^2), solubility (ESOL; insolubility 0 to 6), flexibility (num. rotatable bonds 0 to 9) and saturation (insaturation; fraction Csp3 0.25 to 1) [24,25]. The molecule has less contribution of saturation character than the ideal (0.20 < 0.25). Other remaining parameters are in ideal range (Lipo = 1.35; MV = 205.21 g/mol; polarity = 88.14 A^2; Solubility = 2.08).

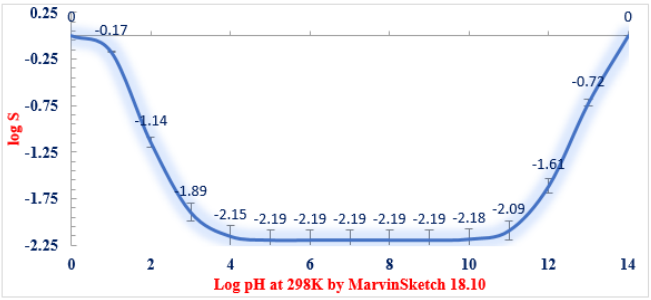
Lipophilicity and water solubility:

Lipophilicity was the classical descriptor (log of partition coefficient between n-octanol and water) used in pharmacokinetics drug discovery. This was most important in physicochemical screening and biological behavior of the molecule as drug. Lipophilicity was affecting number of pharmacokinetic parameters such as higher lipophilicity decreases solubility and increase permeability in the gastrointestinal tract, across the blood–brain barrier, other tissue membranes, affinity to metabolizing enzymes and efflux pumps, and has higher protein binding.

For the discovery of oral administrative drugs, solubility is one of the major descriptor. Highly water solubility was useful for deliver active ingredient in sufficient quantity in small volume of such pharmaceutical dosage. These values are the decimal logarithm of the molar solubility in water (log S).

Lipophilicity		**Solubility**	
Predictive Methods	**Values (LogS)**	**Topological Methods**	**Values**
XLogP3	1.35	ESOL Model	LogS (ESOL) = -1.99
WLogP	0.24		Solubility = 2.08 mg/ml 1.01e-02 mol/l
MLogP	0.31		
SILICOS-IT	0.57		Class = Highly Soluble
iLogP	1.26	Ali Model	LogS (Ali) = -2.80
Continuous LogP	**0.75**		Solubility = 0.323 mg/ml 1.57e-03 mol/l
			Class = Soluble
		SILICOS-IT	**LogS = -2.66**
			Solubility = 0.445 mg/ml 2.17e-03 mol/l
			Class = Soluble

The effect pH on solubility of target molecule was shown in following diagram.



Pharmacokinetics Study: The skin permeability coefficient (K_p) was given linear correlation of molecular size and lipophilicity. The more negative the log K_p (with K_p in cm/s), the less skin permeant is the molecule. The target molecule has -6.59 cm/s indicate that the target molecule is low skin permeant. A passive human gastrointestinal absorption (HIA) and blood brain barrier (BBB) was predicted from the BOILED-Egg model [25]. It depends mostly on two physicochemical descriptors WLogP and TPSA (lipophilicity and apparent polarity). The egg-shaped plot including yolk (high probable BBB permeation) and white (highly probable gastrointestinal absorption). Both compartments are not mutually exclusive. The target molecule has high gastrointestinal absorption and appears on white part.

Other binary classification models focus on the molecule act as substrate or inhibitor of proteins governing important pharmacokinetics behaviors. The result of the compound being substrate or non-substrate of the permeability glycoprotein (P-gp) is key to appraise active efflux through biological membranes, for instance from the gastrointestinal wall to the lumen or from the brain [26]. P-gp is protecting the central nervous system from xenobiotics and is also over expressed in cancerous cells [27]. The

cytochrome P450 (CYP) was the superfamily of isoenzymes play key role in drug elimination through drug metabolic biotranformation [28] therefore interaction of the molecule with cytochrome is important. The inhibition of the isoenzymes by the target molecule leading toxicity or other unwanted adverse effects due to the less excretion or metabolism and accumulation of the drug or its metabolites [29]. Therefore, it was essential to predict the interaction of target molecule with different isoforms of CYPs through inhibition and determine which isoforms are affected. SVM was the better machine learning algorithm predict the molecule is substrate or non-substrate of P-gp and inhibitor or non-inhibitor of a given CYP [26]. SwissADME was use to estimate a chemical to be substrate of P-gp or inhibitor of the most important CYP isoenymes. The predictive capacity of SwissADME classifier is grossly equivalent to the related SVM methods both in terms of external accuracy (ACC_{ext}) and external area under ROC curve (AUC_{ext}). The graphical output of the molecule is used to predict passive absorption (inside/outside the white), passive brain assess (inside/outside the yolk) and active efflux from CNS or to the gastrointestinal lumen by color-coding (blue dot for P-gp substrate (PGP+) and red dots for P-gp non-substrate (PGP-).

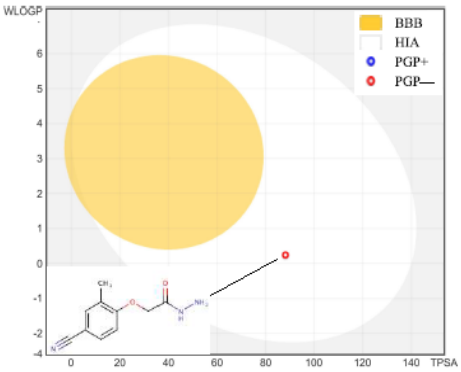


Fig: BOILED-Egg model

Table: Statistical performance of SVM classification models for substrate or inhibitor of pharmacokinetics-relevant protein, P-gp and CVP

Model (10 fold model)	TR/TS (Training set/Tested set)	Cross validation		External validation	
		ACC_{CV}	AUC_{CV}	ACC_{ext}	AUC_{ext}
P-gp substrate	1033/415	0.72	0.77	0.88	0.94
CYP1A2 inhibitor	9145/3000	0.83	0.90	0.84	0.91
CYP2C19 inhibitor	9272/3000	0.80	0.86	0.80	0.87
CYP2C9 inhibitor	5940/2075	0.78	0.85	0.71	0.81
CYP2D6 inhibitor	3664/1068	0.79	0.85	0.81	0.87
CYP3A4 inhibitor	7518/2579	0.77	0.85	0.78	0.86

Rule	**Conditions**	**Drug likeness character**
Lipinski rule	MW < 500; MLogP < 4.15; N or O < 10; NH or OH < 5	Yes; 0 violation
Ghose rule	160 < MW < 480; -0.4 < WLogP < 5.6; 40 < MR < 130; 20 < atoms < 70	Yes; 0 violation
Veber rule	Rotatable bond < 10; TPSA < 140	Yes; 0 violation
Egan Rule	WLogP < 5.88; PTSA < 131.6	Yes; 0 violation
Muegge Rule	200 < MW < 600; -2 < XLogP < 5; TPSA < 150; Num. of rings < 7; Num. of carbons > 4; Num. of heteroatoms > 1; Num. rotatable bonds < 15; H-bond accept. < 10; H-bond donor < 5.	Yes; 0 violation
	Bioavailability score	**= 0.55**

Drug likeness: Drug likeness as a oral drug candidate was established from structural and physicochemical inspection of the target molecule. SwissADME gives access to five different rule based filters with diverse ranges of properties inside of which the molecule is defined as drug-like. The basic rules are Lipinski (Pfizer), Ghose (Amgen), Veber (GSK), Egan (Pharmacia) and Muegge (Bayer) methods. The bioavailability score [30] was predicted based on total charge, TPSA and violation to the Lipinski filter. It is primary fast screening of molecule with available known chemical libraries before the synthesis and further study by chemist. Druglikeness was the complex balance between molecular properties and structural features which are used to predict the target molecule is similar to known drug or not. These properties are mainly, hydrogen bonding, electronic distribution, hydrophobicity, molecular volume and size, flexibility, etc. and various pharmacophoric features influences the behavior of the molecule in living organisms, including bioavailability, transport properties, affinity to proteins, reactivity, metabolic stability, toxicity, etc. The bioactivity score was predicted by using molinspiration tool (based on Bayesian statistics).

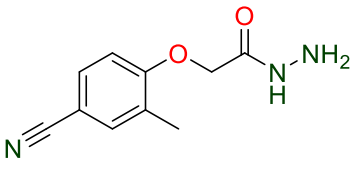
GPCR ligand	: -0.99	Nuclear receptor ligands	: -1.09
Ion channel modulator	: -1.25	Protease inhibitor	: -0.91
Kinase inhibitor	: -0.85	Enzyme inhibitor	: -0.50

Medicinal Chemistry: This help to medicinal chemist to identify potentially promatic fragments of the molecule. PAINS (for pan assay interference compounds, a.k.a. frequent hitters or promiscuous compounds) are substructures of the molecule shows potent response in assay irrespective of the protein target. Such fragments, yielding false positive biological output in analyzing six orthogonal assay and breakdown the molecules active on 2 or more assay into 481 recurrent fragments, considered as potentially leading to promiscuous compounds [31]. SwissADME gives warning if such moieties are found in the molecule. Besides that, the Brenk filters can identify the fragments which are putatively

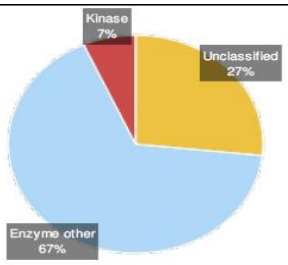
toxic, chemically reactive, metabolically unstable or to be bear properties responsible for poor pharmacokinetics [32]. By applying these filters and other physicochemical filters for the screening of molecular libraries and found the compound satisfy criteria for *leadlikeness*. This concept is similar to drug-likeness, yet focusing on physicochemical boundaries defining a good lead, i.e. a molecular entity suitable for optimization. By definition, leads are subjected to chemical modifications that will most likely increase size and lipophilicity [33]. As a consequence, leads are required to be smaller and less hydrophobic than drug-like molecules. One of the key aspects of CADD activities is help for the selection of most promising molecule which was synthesized and subjected for biological study is the synthetic accessibility (SA). For given molecule, SA score is the summation of the fragments and corrected by the terms describing size and complexity such as macrocycles, chiral centers, or spiro functions. The SA score ranges from 1 (very easy) to 10 (very difficult).

PAINS alert	: Zero alert
Brenk alert	: 2 alert – acyl-hydrazine (-CONHNH$_2$) and hydrazine (N-NH$_2$)
Leadlikeness	: No; 1 violation (Mol. Wt. < 250)
Synthetic accessibility: 2.01 (r^2 = 0.94)	

Biological Target Prediction Report: Biological target of 2-(4-cyano-2-methylphenoxy)acetohydrazide was predicted by using SwissTargetPrediction tool [24]. The prediction data show that the target molecule was more efficient against enzyme (basically Amine oxidase [flavin-containing] A and B; Carbonic anhydrase 1-3, 7, 13; Carbonic anhydrase 5A and 5B, mitochondrial; Tyrosyl-DNA phosphodiesterase 1; etc.) while less effective against Kinase (Dual specificity tyrosine phosphorylation-regulated kinase 1A) as shown in following wheel diagram.

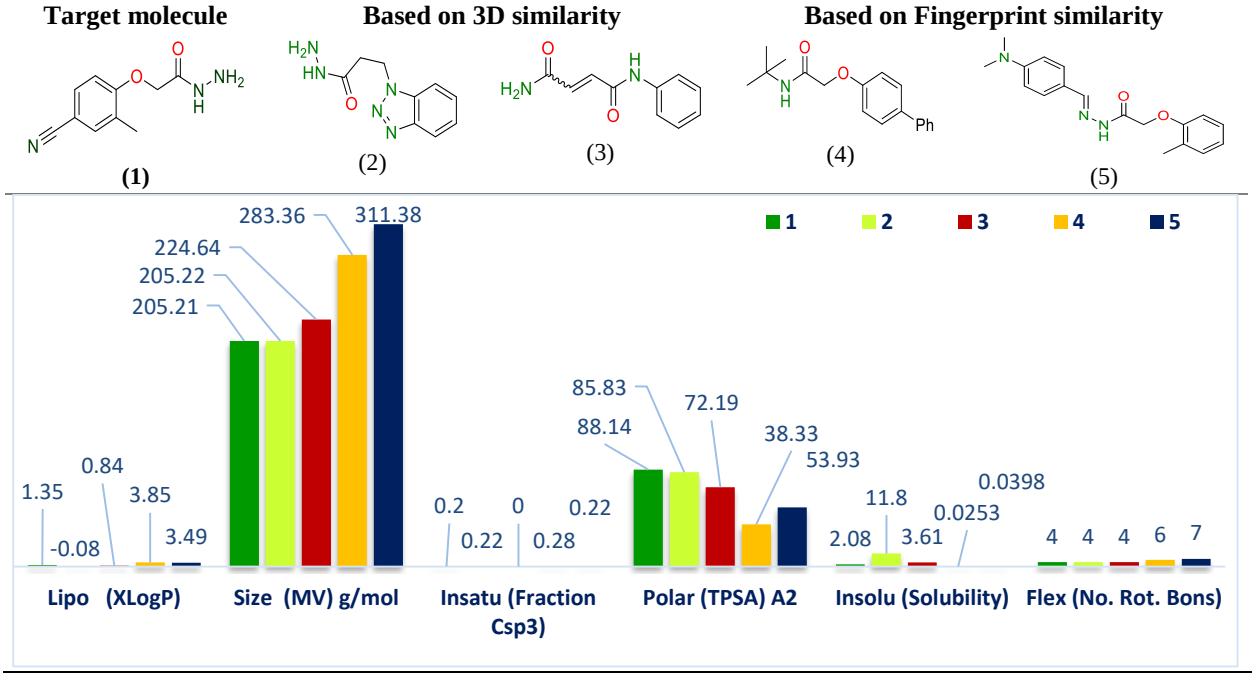


Query Molecule

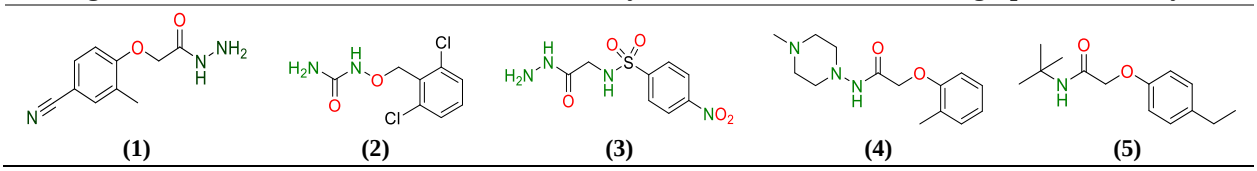


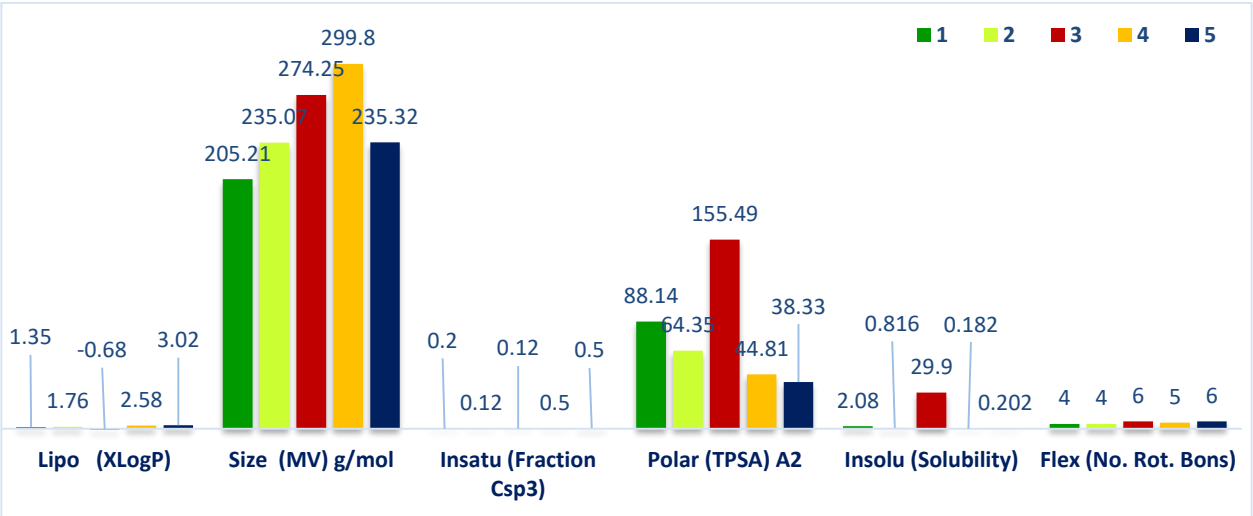
Frequency of Target Class

Target: Ligands associated with Microtubule associated protein tau (Score > 0.8)

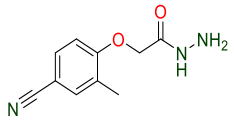
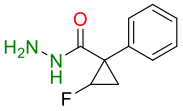
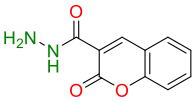
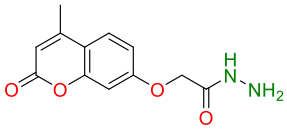
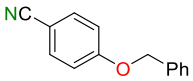


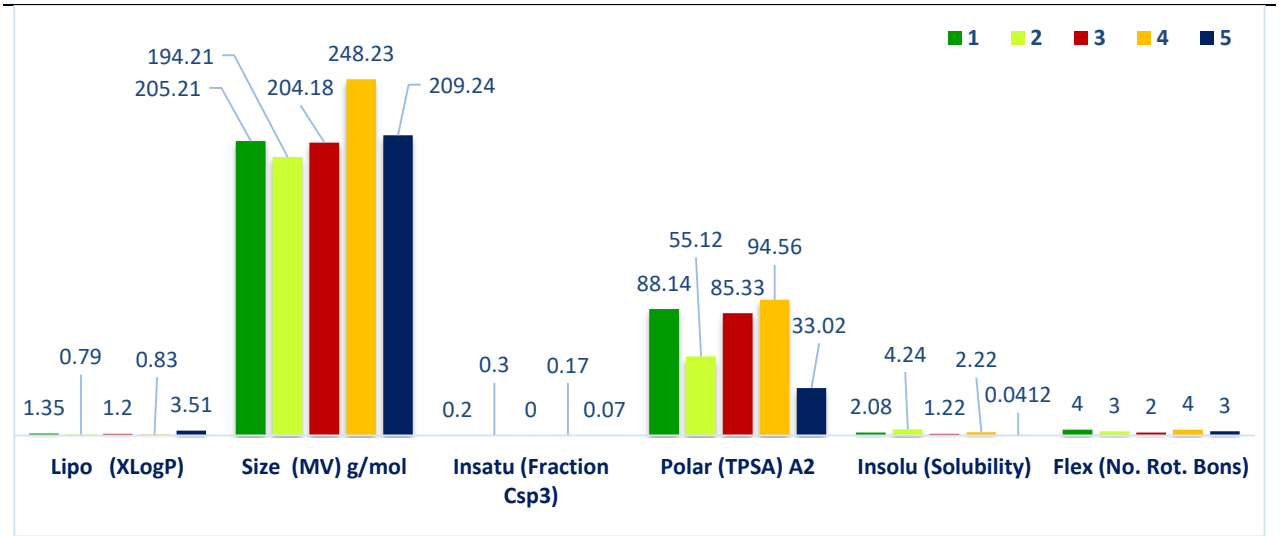
Target: Ligands associated with Muscleblind-like protein 1 (Score > 0.8)



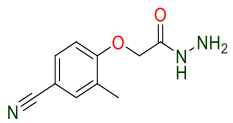
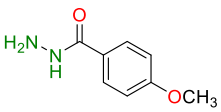
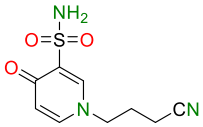
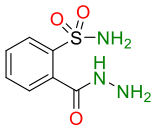
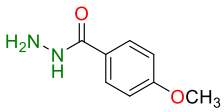


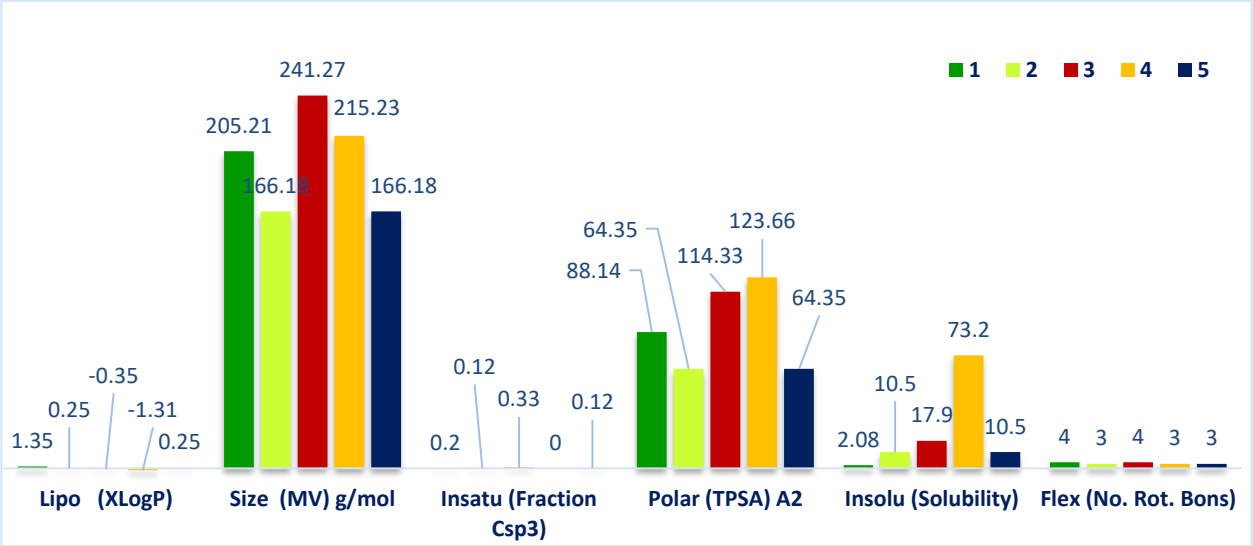
Target: Ligands associated with Amine oxidase A (Score > 0.8)

Target molecule	Based on 3D similarity			Fingerprint similarity
				
(1)	(2)	(3)	(4)	(5)

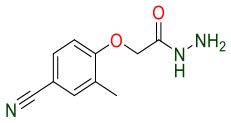
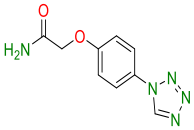
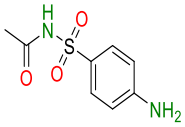
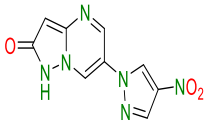
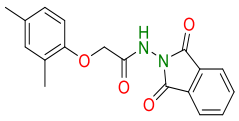


Target: Ligands associated with Carbonic anhydrase 1 (Score > 0.8)

Target molecule	Based on 3D similarity			Fingerprint similarity
				
(1)	(2)	(3)	(4)	(5)



Target: Ligands associated with Tyrosyl-DNA Phosphodiesterase 1 (Score > 0.8)

Target molecule	Based on 3D similarity			Fingerprint similarity
				
(1)	**(2)**	**(3)**	**(4)**	**(5)**

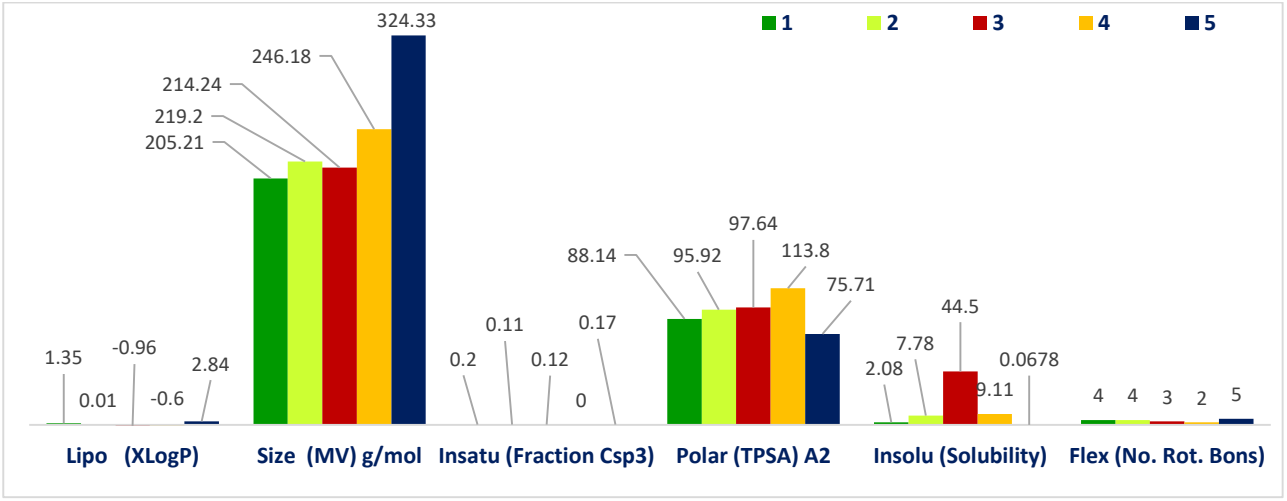
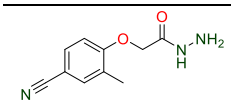
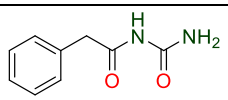
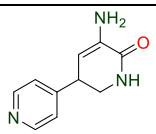
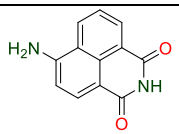
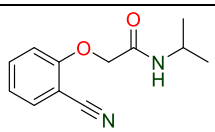
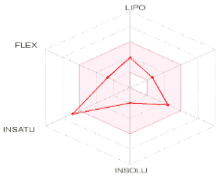
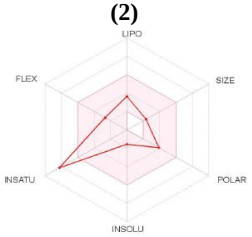
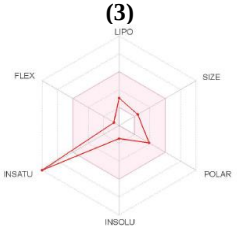
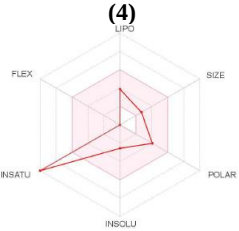
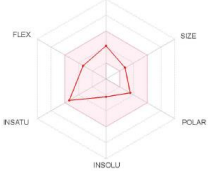
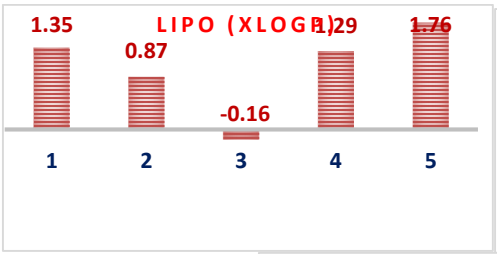
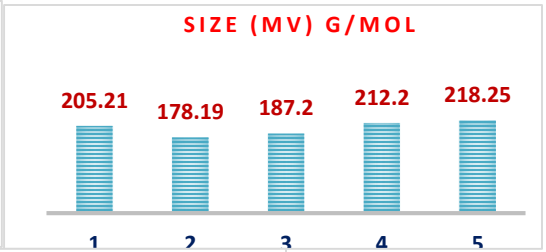
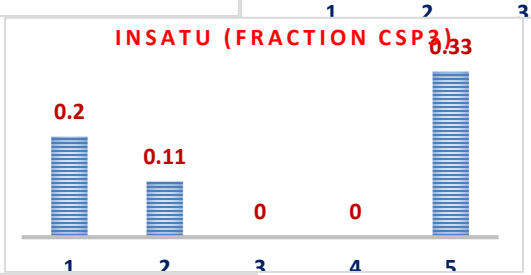


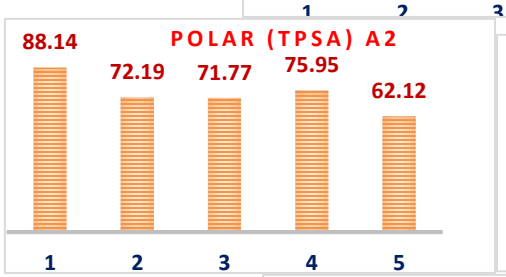
Table: SwissSimilarity provides several 2D and 3D screening methods with score

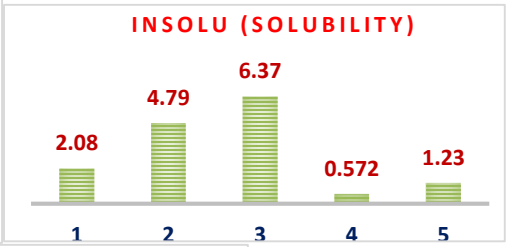
2D/3D screening method – Combine Approach				
Target Molecule	**FDA approved drugs**		**PDB extracted molecules**	**Kinase inhibitor**
				
(1)	**DB01121, Phenacemide 0.272 (2)**		**DB01427, Amrinone 0.253 (3)**	**0.266 (4)**	**0.280 (5)**
				

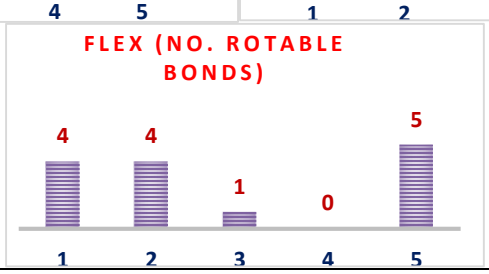




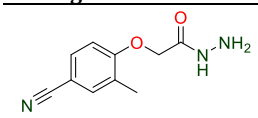
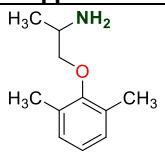
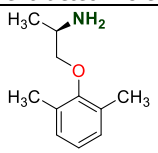
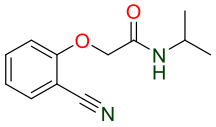
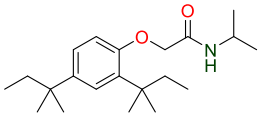
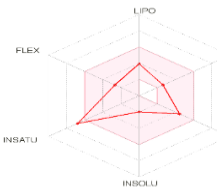
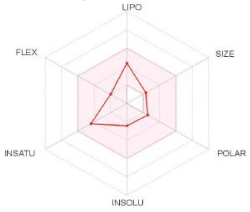
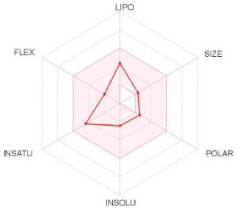
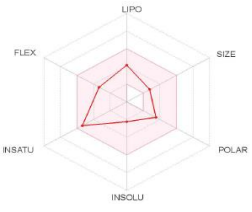
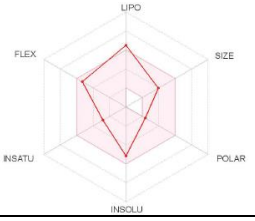




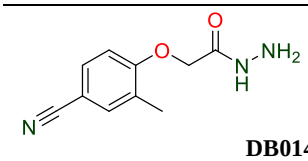
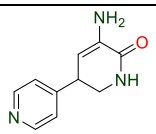
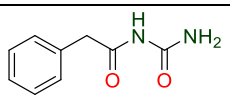
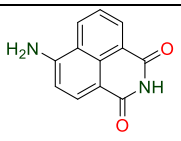
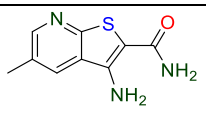
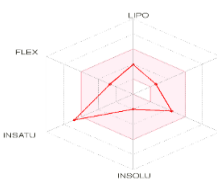
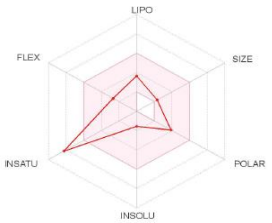
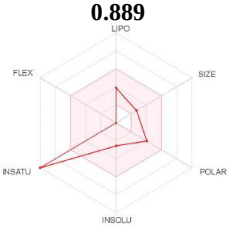
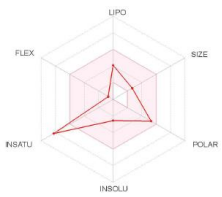


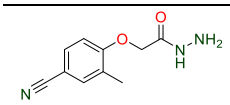
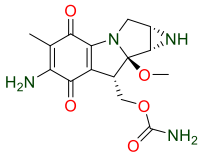
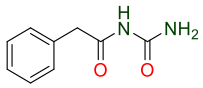
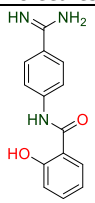
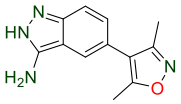
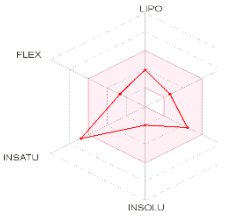
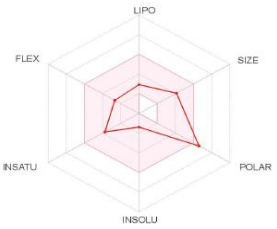
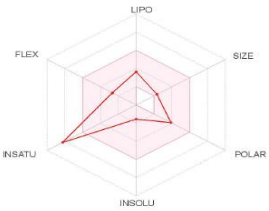
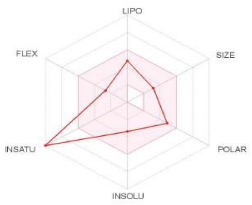
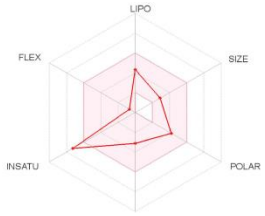


2D/3D screening method – FP2 screening

Target Molecule	FDA approved drugs	PDB extracted molecules	Kinase inhibitor	
	 DB00379, Mexiietine 0.561	 DB00379, Mexiietine 0.561	 0.689	 0.571
				

3D screening method – Electroshape-5D

Target Molecule	FDA approved drugs	PDB extracted molecules	Kinase inhibitor
	 DB01427, Amrinone 0.884	 DB01121, Phenacemide 0.891	 0.889	 0.889
				

3D screening method – Spectrophores screening				
Target Molecule	**FDA approved drugs**		**PDB extracted molecules**	**Kinase inhibitor**
	 **DB00305, Mitomycin 0.870**	 **DB01121, Phenacemide 0.867**	 **0.893**	 **CHEMBL481584 0.873**
				

Prediction of similar bioactive compounds: SwissSimilarity [34] is a web tool used for rapid ligand based virtual screening of small molecules with libraries of molecules include drugs, bioactive and commercial molecules, etc. It is online tool for computer-aided drug design provided by SIB Swiss Institute of Bioinformatics. SwissSimilarity offers four categories of small molecular libraries containing bioactive and commercially available molecules – (a) Drugs [35] – Approved drugs (1500), experimental and investigated (4800 and 500 respectively), withdraw drugs (160), illicit molecules (170) and neutraceuticals (78); (b) Bioactive small molecules – molecular entries present in structural entries of the PDB (19500) [36] all highly-curated molecules from ChEMBL [37] with an activity lower than 10 µM against a well-defined target (177,000 compounds), molecules from ChEBI [38] (28,000 compounds), kinase and GPCR inhibitors from ChEMBL and GLASS [39] (480'000 compounds) and metabolites from HMDB [40] (39,000 compounds). (iii) Collections of commercially available molecules taken from ZINC [41], with drug-like, lead-like and fragment-like properties (10,600,000, 4,300,000 and 700,000 compounds, respectively), or grouped by vendors (for a total of 9,700,000 compounds). (iv) A collection of 205 million virtual compounds readily synthesizable from commercially available reagents, and filtered for stability, non-toxicity and lack of promiscuous character.

SwissSimilarity provides several 2D and 3D screening methods – 2D similarity can be assess by using FP2 fingerprint and 3D similarity can be estimated by four approaches as Electroshape-5D and Spectrophores (fast non-superpositional shape based approaches), Shape-IT and Align-IT (superpositional shape based and pharmacophore approaches). Both 2D and 3D screening are score based ranges from 0 (totally dissimilar molecules) to 1 (for perfectly identical). The target molecule was screened against FDA approved drugs, Ligand from PDB, and kinase inhibitors ligand by using both 2D and 3D screening methods.

The similarity score (Tanimoto score for FP2 fingerprint, Align-IT and Shape-IT; Manhattan based score for Electroshape-5D and Spectrophores), structure and bioavailability radar was shown below.

Antimicrobial study:

The 2-(4-cyano-2-methylphenoxy)acetohydrazide was evaluated for their antibacterial activity against the Gram-negative and Gram-positive bacterial strains *viz. Escherichia coli, S. Aureus, K. pneumonia, S. typhi* and *C. difficile* and antifungal activity against strain *Aspergillus niger* by the disk method. The acid hydrazide under study shows moderate anti-bacterial and weak anti-fungal activity.

REFERENCES

1. Grekov, A. P. Organic Chemistry of Hydrazine; Technika Publishers: Kiev, **1966**; p 23.
2. Elnagdi, M. H.; Erian, A. W. W. New routes to polyfunctionally substituted pyridine, pyridopyridine, quinoline, and pyridazine derivatives, *Arch. Pharm.* 324 (**1991**), 853-858.
3. Gilman, A. G.; Goodman, L. S. Pharmaceutical Basis of Therapeutics; Macmillan: New York, **1985**; p 1109.
4. Costales, M. J.; Kleschick, W. A.; Ehr, R. J.; Weimer, M. R. U.S. Patent 5,763,359, **1998**; *Chem. Abstr.* 129 (**1998**), 67792k.
5. De Marinis, R. M.; Hoover, J. R. E.; Dunn, G. L.; Actor, P.; Uri, J. V.; Weisbach, J. A. *J. Antibiot.* 28 (**1975**), 463.
6. Fahmy, S. M.; Badran, A. H.; Elnagdi, M. H. Synthesis of some new azopyrazole dyes, *J. Chem. Technol. Biotechnol*. 30 (**1980**), 390-395.
7. Fahmy, S. M.; El-Hosami, M.; Elgamal, S.; Elnagdi, M. H. *J. Chem. Technol. Biotechnol*. 32 (**1982**), 1042.
8. Ragavendran, J.; Sriram, D.; Patel, S.; Reddy, I.; Bharathwajan, N.; Stables, J.; Yogeeswari, P. Design and synthesis of anticonvulsants from a combined phthalimide-GABA-anilide and hydrazone pharmacophore, *Eur. J. Med. Chem*. 42 (**2007**), 146-151.
9. Ergenc, N.; Gunay, N. S. Synthesis and antidepressant evaluation of new 3-phenyl-5- sulfonamidoindole derivatives, *Eur. J. Med. Chem*. 33 (**1998**), 143-148.
10. Todeschini, A. R.; Miranda, A. L.; Silva, C. M.; Parrini, S. C.; Barreiro, E. J. Synthesis and evaluation of analgesic, antiinflammatory and antiplatelet properties of new 2-pyridylarylhydrazone derivatives, *Eur. J. Med. Chem.* 33(3) (**1998**), 189 - 199.

11. Gemma, S.; Kukreja, G.; Fattorusso, C.; Persico, M.; Romano, M.; Altarelli, M.; Savini, L.; Campiani, G.; Fattorusso, E.; Basilico, N. Synthesis of *N*1-arylidene-*N*2-quinolyl- and *N*2-acrydinylhydrazones as potent antimalarial agents active against CQ-resistant *P. falciparum* strains, *Bioorg. Med. Chem. Lett*. 16(20) (**2006**), 5384 - 5388.
12. Bijev, A. Lett. New Heterocyclic Hydrazones in the Search for Antituber- cular Agents: Synthesis and In vitro Evaluations, *Drug Des. Discovery* 3(7) (**2006**), 506 - 512.
13. Gursoy, E.; Guzeldemirci-Ulusoy, N. Synthesis and primary cytotoxicity evaluation ofi new imidazo[2,1- b]thiazole derivatives, *Eur. J. Med. Chem*. 42(3) (**2007**), 320 - 326.
14. Masunari, A.; Tavaris, L. C. A new class of nifuroxazide analogues: synthesis of 5-nitrothiophene derivatives with antimicrobial activity against multidrug-resistant Staphylococcus aureus, *Bioorg. Med. Chem*. 15(12) (**2007**), 4229 - 4236.
15. Loncle, C.; Brunel, J.; Vidal, N.; Dherbomez, M.; Letourneux, Y. Synthesis and antifungal activity of cholesterol-hydrazone derivatives, *Eur. J. Med. Chem.* 39(12) (**2004**), 1067 - 1071.
16. Kucukguzel, S. G.; Mazi, A.; Sahin, F.; Ozturk, S.; Stables, J. P. Synthesis and biological activities of diflunisal hydrazide-hydrazones, *Eur. J. Med. Chem.* 38 (11-12) (**2003**), 1005 - 1013.
17. Vicini, P.; Zani, F.; Cozzini, P.; Doytchinova, I. Hydrazones of 1,2-benzisothiazole hydrazides: synthesis, antimicrobial activity and QSAR investigations, *Eur. J. Med. Chem.* 37(7) (**2002**), 553 - 564.
18. Seydel, J. K.; Schoper, K. J.; Wempe, E.; Cordes, H. P. *J. Med. Chem.* 19 (**1976**), 483.
19. Vardanyan, R.; Hruby, V. Synthesis of Essential Drugs, 1st Ed.; Elsevier Science: Maryland Heights, **2006**; p 111.
20. Mashkovskiy, M. D. Khim.-Farm. Zh. 10 (**1976**), 3.
21. (a) Heinzelman, R. V.; Szmuszkovicz, J. Prog. Drug Res. 6 (**1963**), 85. (b) Nogrady, T.; Morris, L. *J. Med. Chem*. 9 (**1966**), 438.
22. Hassan Abdalla Almahy Dafalla, Preparation Four Derivatives Compounds of acetyl-1*H*-pyrazole-4-carbaldehyde and Their Antimicrobial Activity, *Chemical Science Review and Letters*, 3(12) (**2014**), 1091-1096.
23. Daina, A. *et al.* SwissADME: a free web tool to evaluate pharmacokinetics, druglikeness and medicinal chemistry friendliness of small molecules. *Sci. Rep.* 7 (**2017**), 42717; doi: 10.1038/srep42717.
24. Gfeller D., Michielin O. & Zoete V. Shaping the interaction landscape of bioactive molecules, *Bioinformatics* 29 (**2013**), 3073-3079.
25. Daina, A. & Zoete, V. A BOILED-Egg To Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules. *Chem MedChem* 11 (**2016**), 1117–1121.
26. Montanari, F. & Ecker, G. F. Prediction of drug-ABC-transporter interaction–Recent advances and future challenges. *Adv. Drug Deliv. Rev.* 86 (**2015**), 17–26.
27. Szakacs, G., Varadi, A., Ozvegy-Laczka, C. & Sarkadi, B. The role of ABC transporters in drug absorption, distribution, metabolism, excretion and toxicity (ADME-Tox). *Drug Discov. Today* 13 (**2008**), 379–393.
28. Testa, B. & Kraemer, S. D. The Biochemistry of Drug Metabolism – An Introduction - Testa - 2007 - Chemistry & Biodiversity -Wiley Online Library. *Chem. Biodivers* (**2007**).
29. Kirchmair, J. *et al.* Predicting drug metabolism: experiment and/or computation? *Nature Rev. Drug Discov.* 14 (**2015**), 387–404.
30. Martin, Y. C. A Bioavailability Score. *J. Med. Chem.* 48 (**2005**), 3164–3170.
31. Baell, J. B. & Holloway, G. A. New substructure filters for removal of pan assay interference compounds (PAINS) from screening libraries and for their exclusion in bioassays. *J. Med. Chem.* 53 (**2010**), 2719–2740.
32. Brenk, R. *et al.* Lessons learnt from assembling screening libraries for drug discovery for neglected diseases. *ChemMedChem* 3 (**2008**), 435–444.
33. Hann, M. M. & Keserű, G. M. Finding the sweet spot: the role of nature and nurture in medicinal chemistry. *Nature Rev. Drug Discov.* 11 (**2012**), 355–365.
34. Zoete, V., Daina, A., Bovigny, C., & Michielin, O. SwissSimilarity: A Web Tool for Low to Ultra High Throughput Ligand-Based Virtual Screening. *J. Chem. Inf. Model.*, 56(8) (**2016**), 1399-1404.
35. Law, V.; Knox, C.; Djoumbou, Y.; Jewison, T.; Guo, A. C.; Liu, Y.; Maciejewski, A.; Arndt, D.; Wilson, M.; Neveu, V.; Tang, A.; Gabriel, G.; Ly, C.; Adamjee, S.; Dame, Z. T.; Han, B.; Zhou, Y.; Wishart, D. S. DrugBank 4.0: Shedding New Light on Drug Metabolism. *Nucleic Acids Res*. 42 (**2014**) (Database issue), D1091–D1097.
36. Feng, Z.; Chen, L.; Maddula, H.; Akcan, O.; Oughtred, R.; Berman, H. M.; Westbrook, J. Ligand Depot: a Data Warehouse for Ligands Bound to Macromolecules. *Bioinformatics* 20 (**2004**), 2153–2155.
37. Bento, A. P.; Gaulton, A.; Hersey, A.; Bellis, L. J.; Chambers, J.; Davies, M.; Krüger, F. A.; Light, Y.; Mak, L.; McGlinchey, S.; Nowotka, M.; Papadatos, G.; Santos, R.; Overington, J. P. The ChEMBL Bioactivity Database: an Update. *Nucleic Acids Res*. 42 (**2014**), (Database issue), D1083–D1090.
38. Degtyarenko, K.; de Matos, P.; Ennis, M.; Hastings, J.; Zbinden, M.; McNaught, A.; Alcantara, R.; Darsow, M.; Guedj, M.; Ashburner, M. ChEBI: a Database and Ontology for Chemical Entities of Biological Interest. *Nucleic Acids Res*. 36 (**2007**) (Database), D344–D350
39. Chan, W. K. B.; Zhang, H.; Yang, J.; Brender, J. R.; Hur, J.; Özgür, A.; Zhang, Y. GLASS: a Comprehensive Database for Experimentally Validated GPCR-Ligand Associations. *Bioinformatics* 31 (**2015**), 3035–3042.
40. Wishart, D. S.; Jewison, T.; Guo, A. C.; Wilson, M.; Knox, C.; Liu, Y.; Djoumbou, Y.; Mandal, R.; Aziat, F.; Dong, E.; Bouatra, S.; Sinelnikov, I.; Arndt, D.; Xia, J.; Liu, P.; Yallou, F.; Bjorndahl, T.; Perez-Pineiro, R.; Eisner, R.; Allen, F.; Neveu, V.; Greiner, R.; Scalbert, A. HMDB 3.0--the Human Metabolome Database in 2013. *Nucleic Acids Res.* 41 (**2013**) (Database issue), D801–D807.
41. Irwin, J. J.; Sterling, T.; Mysinger, M. M.; Bolstad, E. S.; Coleman, R. G. ZINC: a Free Tool to Discover Chemistry for Biology. *J Chem Inf Model* 52 (**2012**), 1757–1768.

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