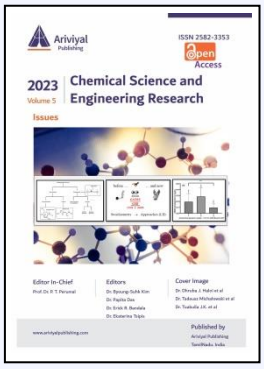
Chemical Science & Engineering Research

Ariviyal Publishing

Research Article

DOI: 10.36686/Ariviyal.CSER.2023.05.12.070

Chem. Sci. Eng. Res., 2023, 5(12), 18-23.



In *Silico* Drug Activity Prediction of Chemical Components of *Justicia adhatoda*

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ISSN: 2582-3353

Crossref

Publication details
Received: 27th August 2022
Revised: 04th January 2023
Accepted: 11th March 2023
Published: 31st March 2023

Abstract: *Justicia adhatoda*, commonly known in English as Malabar nut, adulsa, adhatoda, vasa, and vasaka is a medicinal plant native to Asia, widely used in traditional medicine. The plant's native range is the Indian subcontinent (Assam, Bangladesh, India, Nepal, and Sri Lanka), Laos, and Myanmar. The leaves of *Justicia adhatoda* contain phytochemicals such as alkaloids, tannins, saponins, phenolics and flavonoids. The most important is Vasicine, a quinazoline alkaloid. The vasicine yield of the herbage has been measured as 0.541 to 1.1% by dry weight. bromhexine a serine protease inhibitor with mucolytic properties available over-the-counter in Europe was originally derived from *Justicia adhatoda.* To explore the drug-likeness character of the chemical compounds, present in the *Justicia adhatoda* plant, theoretical studies were carried out using software's with selected alkaloid compounds present in the leaf of the *Justicia adhatoda* plant. Biological activity scores and molecular properties were predicted using MOLINSPIRATION and PASS ONLINE softwares. Binding energy was calculated using GAUSSIAN software. Many of the pharmacokinetic properties of the chosen compounds predicted using softwares comply with Lipinsky rule of five indicating that these compounds have drug likeness. Negative binding energy of all compounds reveals that these are capable of binding with receptors. Docking studies prove that the selected compounds are capable of binding with protein receptors of several microorganisms so that they can be considered as lead compounds for drug designing.

Keywords: *Justicia adhatoda;* PASS online; MOLINSPIRATION; Gaussian

1. Introduction

Justicia adhatoda is a shrub with 10-20 lance-shaped leaves 8-9 centimeters in length by four wides. They are oppositely arranged, smooth-edged, and borne on short petioles when dry they are of a dull brownish-green color. They are bitter-tasting. When a leaf is cleared with chloral hydrate and examined microscopically the oval stomata can be seen. They are surrounded by two crescent-shaped cells at right angles to the ostiole. The epidermis bears simple one- to three-celled warty hairs and small glandular hairs. cystoliths occur beneath the epidermis of the underside of the blade. The trunk has many long opposite ascending branches, where the bark is yellowish in color. Flowers are usually white and the inflorescence shows large, dense, axillary spikes. Fruits are pubescent and are with club-shaped capsules.[1]

Justicia adhatoda consists of alkaloids, containing pyrroquinazoline ring derivatives like vasicine, vasicol, vasicinone, deoxyvasicinone, adhavasicine, adhavasinone, vasicoline, vasicolinone and vasicinol.[2]

2. Medicinal applications of *justicia adhatoda*

The reason for choosing this plant for our present study is the wide spectrum of its medicinal applications as listed below.

The leaves, roots and the flowers are extensively used in indigenous medicine as a remedy for cold, cough, bronchitis and asthma. In acute stages of bronchitis, it gives unfailing relief. Especially where the sputum is thick and sticky it liquefies tilt sputum so that it is brought up more easily. For relief in asthma, the dried leaves should be smoked.[3]

In Ayurveda, a preparation made from vasaka flowers, known as gulkand is used to treat tuberculosis. A few fresh petals of vasaka flowers should be bruised and put in a pot of chill3 clay. Some sugar crystals are added and the jar kept in the sun. It should be stirred every morning and evening.[4] The preserve is ready for use in about a month. Even the juice from its leaves is useful in treating tuberculosis. About 30 ml of the juice is taken thrice a day with honey. It relieves the irritable cough by its soothing action on the nerve and by liquefying the sputum, which makes expectoration easier. 7 leaves of the plant are boiled in water, strained, and mixed with 24 grams of honey. This decoction provides relief. Similarly, a confection of vasaka flowers eaten in doses of 12 grams twice daily relieves cough. About 60 grams of flowers and 180 grams of jaggery should be mixed for preparing this confection.

Its leaves, bark, the root-bark, fruit, and flowers are useful in the removal of intestinal parasites. The decoction of its root and bark in doses of 30 grams twice or thrice a day for 3 days can be given for this purpose. The juice of its fresh leaves can also be used in doses of

Table 1. The biological activity of Adhavasicine and Adhavasinone

COMPOUND 1 (Adhavasicine)			COMPOUND 2 (Adhavasinone)		
Pa	**Pi**	**Activity**	**Pa**	**Pi**	**Activity**
0,726	0,043	Gluconate 2-dehydrogenase (acceptor) inhibitor	0,710	0,051	Gluconate 2-dehydrogenase (acceptor) inhibitor
0,615	0,008	UGT2B12 substrate	0,647	0,010	Acetylcholine neuromuscular blocking agent
0,675	0,072	Aspulvinone dimethylallyltransferase inhibitor	0,580	0,011	UGT2B12 substrate
0,591	0,034	JAK2 expression inhibitor	0,568	0,019	Antiasthmatic
0,562	0,019	Antiasthmatic	0,595	0,073	Antineurotic
0,571	0,034	Acetylcholine neuromuscular blocking agent	0,526	0,027	CYP2D substrate
0,544	0,022	Caspase 3 stimulant	0,522	0,032	Antihypoxic
0,533	0,014	1-Acylglycerol-3-phosphate O-acyltransferase inhibitor	0,586	0,103	Aspulvinone dimethylallyltransferase inhibitor
0,591	0,072	CYP2H substrate	0,492	0,011	Antineoplastic (multiple myeloma)
			0,558	0,088	CYP2H substrate

Table 2. The biological activity of Deoxyvasicinone and Vasicine

COMPOUND 3 (Deoxyvasicinone)			COMPOUND 4 (Vasicine)		
Pa	**Pi**	**Activity**	**Pa**	**Pi**	**Activity**
0,860	0,008	Antineurotic	0,682	0,008	Alopecia treatment
0,758	0,005	Antihypoxic	0,670	0,025	Ribulose-phosphate 3-epimerase inhibitor
0,745	0,018	Nicotinic alpha2beta2 receptor antagonist	0,653	0,010	4-Hydroxyproline epimerase inhibitor
0,742	0,029	Nootropic	0,657	0,031	5 Hydroxytryptamine release stimulant
0,700	0,008	(R)-6-hydroxynicotine oxidase inhibitor	0,638	0,015	(R)-6-hydroxynicotine oxidase inhibitor
0,677	0,005	HERG 1 channel blocker	0,659	0,069	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
0,639	0,012	Acetylcholine neuromuscular blocking agent	0,593	0,005	Antineoplastic (multiple myeloma)
0,621	0,014	(S)-6-hydroxynicotine oxidase inhibitor	0,665	0,077	Gluconate 2-dehydrogenase (acceptor) inhibitor
0,631	0,024	Electron-transferring-flavoprotein dehydrogenase inhibitor	0,612	0,032	Glucan endo-1,6-beta-glucosidase inhibitor
			0,612	0,042	Pseudolysin inhibitor
0,610	0,016	CYP2A8 substrate			
0,641	0,052	Glycosylphosphatidylinositol phospholipase D inhibitor			

Table 3. The biological activity of Vasicinol and Vasicinone

COMPOUND 5 (Vasicinol)			COMPOUND 6 (Vasicinone)		
Pa	**Pi**	**Activity**	**Pa**	**Pi**	**Activity**
0,716	0,005	Alopecia treatment	0,744	0,005	Antihypoxic
0,714	0,024	5 Hydroxytryptamine release stimulant	0,715	0,018	Ribulose-phosphate 3-epimerase inhibitor
0,727	0,042	Gluconate 2-dehydrogenase (acceptor) inhibitor	0,682	0,009	4-Hydroxyproline epimerase inhibitor
0,658	0,025	HIF1A expression inhibitor	0,663	0,018	Pullulanase inhibitor
0,638	0,026	Kidney function stimulant	0,667	0,024	Glucan endo-1,6-beta-glucosidase inhibitor
0,658	0,064	CYP2C12 substrate	0,695	0,057	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
0,623	0,043	TP53 expression enhancer	0,629	0,021	27-Hydroxycholesterol 7alpha-monooxygenase inhibitor
0,647	0,073	Testosterone 17beta-dehydrogenase (NADP+) inhibitor			

Table 4. The biological activity of Vasicol and Vasicoline

COMPOUND 7 (Vasicol)			COMPOUND 8 (Vasicoline)		
Pa	**Pi**	**Activity**	**Pa**	**Pi**	**Activity**
0,729	0,013	UDP-N-acetylglucosamine 4-epimerase inhibitor	0,692	0,028	Nicotinic alpha2beta2 receptor antagonist
0,690	0,022	Ribulose-phosphate 3-epimerase inhibitor	0,662	0,026	Nicotinic alpha4beta4 receptor agonist
0,699	0,055	Testosterone 17beta-dehydrogenase (NADP+) inhibitor	0,616	0,007	CYP2D2 inhibitor
			0,650	0,050	CYP2H substrate
0,600	0,023	Acetylcholine neuromuscular blocking agent	0,648	0,051	Nicotinic alpha6beta3beta4alpha5 receptor antagonist
0,587	0,015	Neurotransmitter antagonist	0,601	0,017	(S)-6-hydroxynicotine oxidase inhibitor
0,594	0,027	Platelet aggregation stimulant	0,587	0,028	General pump inhibitor
0,587	0,042	Antidyskinetic	0,563	0,011	Cognition disorders treatment
0,556	0,011	Adenosine regulator			

Table 5. The biological activity of Vasicolinone

Compound 9 (Vasicolinone)		
Pa	**Pi**	**Activity**
0,600	0,071	Antineurotic
0,548	0,024	(S)-6-hydroxynicotine oxidase inhibitor
0,613	0,112	Gluconate 2-dehydrogenase (acceptor) inhibitor
0,578	0,086	Nootropic
0,518	0,033	Antihypoxic
0,533	0,066	Nicotinic alpha2beta2 receptor antagonist
0,523	0,060	Acetylcholine neuromuscular blocking agent
0,508	0,058	Neurotransmitter uptake inhibitor

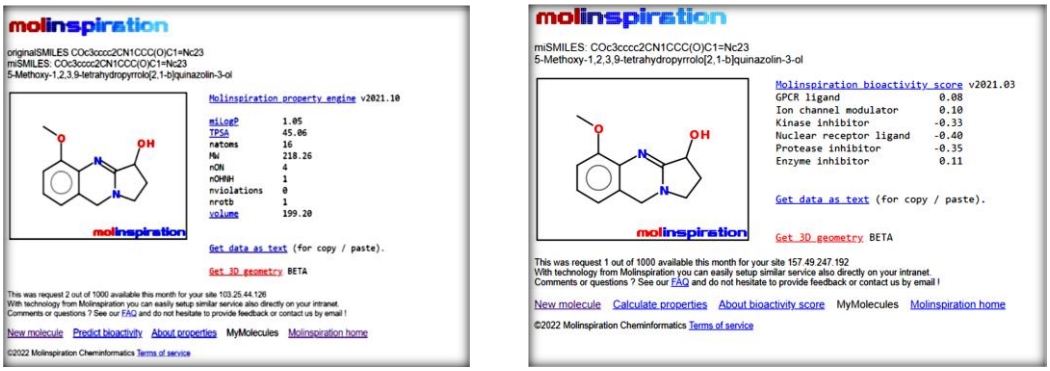

Fig. 1. Molinspiration window

a teaspoon thrice a day for 3 days. The juice from its leaves should be given in doses of 2 to 4 grams in treating diarrhoea and dysentery.[5]

A poultice of its leaves can be applied with beneficial results over fresh wounds, rheumatic joints, and inflammatory swellings. A warm decoction of its leaves is useful in treating scabies and other skin diseases.

3. Drug Designing

Drugs are chemical or organic materials that have a few forms of physiological or biochemical effect on our body and they may be single compounds or a combination of various compounds. A drug is likewise called a remedy or medicinal drug and it's far used to treatment of disease for the sake of well-being.[6]

Drug designing has received a many fold's face-lifts by the virtue of computer software dedicated to the designing of ligands and identifying biological targets. Computer generated structure serve to be good predictive models for evaluating biological activity.[7] A drug exhibits its action when it binds to its biological target usually receptors. Receptors are nothing but proteins with active sites for binding. Hence in order to design a good ligand, it is necessary to know the structure of such receptors and to identify their active sites accurately. Two important aspects in predicting a molecular interaction in (CADD) are development of pharmacophore based and molecular docking and scoring techniques. Different molecular property fields such as, electrostatic, steric, hydrophobic, hydrogen bond acceptor and donor fields[8] as well as their weighed combinations have been used to achieve a fully automated alignment of molecule.[9]

Identification of a lead compound plays a major role in drug designing. Some of the chemical components of Justicia adhatoda were selected to evaluate their drug likeness character, using softwares PASS online, Molinspiration and GAUSSIAN.[10]

4. Experimental Methods

4.1. Software's Used

Using the software's (PASS online, Molinspiration and Gaussian) the calculation of physical properties and prediction of biological activity has been done for some of the chemical components of *Justicia adhatoda* listed below:

- Compound 1 - Adhavasicine
- Compound 2 - Adhavasinone
- Compound 3 - Deoxyvasicinone
- Compound 4 - Vasicine
- Compound 5 - Vasicinol
- Compound 6 - Vasicinone
- Compound 7 - Vasicol
- Compound 8 - Vasicoline
- Compound 9 - Vasicolinone

5. Results and Discussions

5.1. Activity Prediction using PASS online

Using PASS online software, the biological activity of the selected compounds was predicted and the data obtained are given in the Tables 1 to 5.

Table 1 shows that Adhavasicine and Adhavasinone possess >70% Gluconate-2-dehydrogenaseinhibitor activityand above 50% antiasthmatic activity

Table 2 shows Deoxyvasicinone possess >75% Antineurotic and Antihypoxic activity.Vasicine is having capacity for Alopecia treatment.Both the compounds have (R) -6-hydroxynicotine oxidase inhibitor activity.

Table 3 shows both Vasicinol and Vasicinone can act as Kidney function stimulant andTestosterone 17beta -dehydrogenase (NADP+) inhibitor.

Table 4 shows Vasicol and Vasicoline are having Alopecia treatment activity.Vasicol is having >70% of UDP-N-acetylglucosamine 4-epimerase inhibitor activity and Vasicoline is having nearly 70% of Nicotinicalpha2beta2receptor antagonist activity.

Table 5 shows Vasicolinone possess around 60% of Antineurotic and Gluconate 2-dehydrogenase (acceptor) inhibitor activity. The above results show that all the compounds possess a very good spectrum of drug-like activity. Here it should be noted that Pa >> Pi. All the compounds have biological activity and may serve as lead compounds in designing new drugs for the treatment of many diseases.

Table 6. Comparison of calculated Molecular Properties of the nine compounds with the standards

Compound	mi LogP	TPSA	n - atoms	MW	n-ON	n - OHNH	n - violations	nrotb	Volume
Adhavasicine	1.05	45.06	16	218.26	4	1	0	1	199.20
Adhavasinone	0.49	64.36	17	232.24	5	1	0	1	201.38
Deoxyvasicinone	1.47	34.90	14	186.21	3	0	0	0	167.79
Vasicine	1.04	35.83	14	188.23	3	1	0	0	173.66
Vasicinol	0.53	56.06	15	204.23	4	2	0	0	181.67
Vasicinone	0.48	55.12	15	202.21	4	1	0	0	175.84
Vasicol	-0.02	66.56	15	206.25	4	3	0	2	191.51
Vasicoline	3.33	18.84	22	291.40	3	0	0	2	282.95
Vasicolinone	2.91	38.13	23	305.38	4	0	0	2	285.13
Indomethacin	3.99	68.54	25	357.79	5	1	0	4	303.24
Aspirin	1.43	63.60	13	180.16	4	1	0	3	155.57

Table 7. Comparison of calculated Bioactivity Scores of the Samples with the standards

COMPOUND	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Adhavasicine	0.08	0.10	-0.33	-0.40	-0.35	0.11
Adhavasinone	-0.24	-0.43	-0.44	-0.67	-0.86	0.07
Deoxyvasicinone	-0.98	-0.92	-0.75	-1.39	-1.22	-0.09
Vasicine	0.03	0.32	-0.43	-0.59	-0.36	0.24
Vasicinol	0.13	0.37	-0.29	-0.27	-0.30	0.33
Vasicinone	-0.40	-0.35	-0.53	-0.85	-0.97	0.03
Vasicol	-0.13	0.04	-0.29	-0.52	0.14	0.16
Vasicoline	0.25	0.15	-0.14	-0.17	-0.12	0.17
Vasicolinone	-0.04	-0.26	-0.21	-0.35	-0.48	-0.01
Indomethacin	0.24	-0.31	-0.11	0.42	-0.11	0.30
Aspirin	-0.76	-0.32	-1.06	-0.44	-0.82	-0.28

5.2. Molecular Properties and Bioactivity Prediction using Molinspiration

Theoretical drug designing studies were carried with the selected compounds. Using Molinspiration Online Software, Molecular Properties and Bioactivity Scores were calculated for the selected compounds.[11] Fig. 1 represents the molinspiration window as a sample. Comparison of Molecular Properties and Bioactivity Scores of the nine compounds with the Standards (Indomethacin & Aspirin) are given in Tables 6 and 7. From this, the drug-likeness and bioactivity of the compounds can be observed.

According to Lipinski's Rule of Five[12] if the molecule has drug-likeness, it must have

- miLogP < 5
- MW < 500,
- n-OHNH < 5,
- n-ON < 10 and also
- n-violation should not be more than one

From the Molinspiration results, we observed that all the selected compounds in the leaf of the *Adhatoda vasica* plant obey Lipinski's Rule of Five.

From the comparison table, we find that the calculated molecular properties and bioactivity scores of some of the compounds are almost nearer to the values of the chosen Standards (Indomethacin & Aspirin). So, all the selected compounds in the leaf of the *Adhatoda vasica* plant have more drug-likeness.

5.3. Energy and dipole moment calculation using Gaussian view 6.0

Hartree-Fock SCF Energy and dipole moment of the selected compounds calculated using 3-21G Basis Set of the Gaussian View 6.0 Software[13-15] and the results obtained are given in the Table 8.

Table 8. Energy and dipole moment calculation using Gaussian view 6.0

COMPOUNDS	GAUSSIAN	
	Energy (UHF)	Dipole Moment (Debye)
`Adhavasicine	-725.42614343	2.6987
Adhavasicinone	-799.44784339	3.3635
Deoxyvasicinone	-610.33888965	5.0446
Vasicine	-607.75614405	3.8811
Vasicinol	-686.13528926	2.5143
Vasicinone	-681.39524948	0.7157
Vasicol	-835.90164802	3.9493
Adhavasicinone	-799.44784339	3.3635
Deoxyvasicinone	-610.33888965	5.0446
Vasicine	-607.75614405	3.8811

If the value is negative, that compound may have more drug like activity and also that the compound is more stable. All the compounds have negative Hartree-Fock SCF Energy value and hence they can act as drug. The Dipole Moment values obtained from Gaussian View 6.0 Software are given in table. 8. Generally, active drug has the Dipole Moment value range from 3.25 – 4.58 and inactive drug have the Dipole Moment value from 1.77 – 2.52. Aadhavasicinone, Vasicine, and Vasicol have their dipole moment values in the active range.

5.4. HOMO-LUMO Analysis

The highest occupied molecular orbitals (HOMOs) and the lowest-lying unoccupied molecular orbitals (LUMOs) are named as Frontier Molecular Orbitals (FMOs)[16] as they lie at the outermost boundaries of the electrons of the molecules. The FMOs play an important role in the optical and electric properties, as well as in quantum chemistry.[17] The HOMO-LUMO energies are popular quantum mechanical descriptors[18] which play a major role in governing wide range of chemical interactions. The Frontier Molecular orbital gives an insight about the reactivity of the molecule and the active site can be demonstrated by the distribution of Frontier orbital. The Frontier orbital gap helps characterize the chemical reactivity and the kinetic

Table 9. Global Reactivity

Molecule	Energy of HOMO	Energy of LUMO	Electro negativity (χ)	Hardness (η)	Softness (S)	Free Energy (ΔG)
Adhavasicine	0.01166	0.18765	0.099655	0.087995	5.68197	-0.17599
Vasicinol	0.01349	0.19094	0.102215	0.088725	5.63539	-0.17745
Adhavasicinone	0.04256	0.21693	0.151025	0.065905	7.59667	-0.17437
Vasicol	0.04154	0.23315	0.137345	0.095805	5.21893	-0.19161
Vasicine	0.01503	0.19819	0.10661	0.009158	5.459707	-.18316

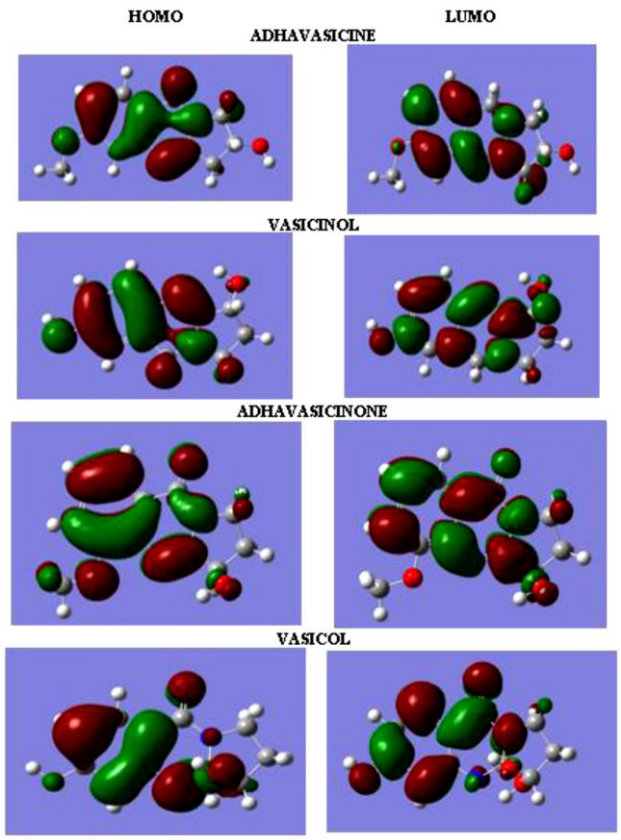

Fig. 2. HOMO & LUMO of Selected compounds

stability of the molecule. A molecule with a small Frontier orbital gap is generally associated with a high chemical reactivity, low kinetic stability and is also termed as soft molecule.[19,20] The 3D plots of the frontier orbitals HOMO and LUMO figures of some selected components calculated with DFT are given in Fig. 2.

5.5. Global Reactivity Descriptors

The energy gap between HOMO and LUMO is a critical parameter to determine molecular electrical transport properties. By using HOMO and LUMO energy values for a molecule, the global chemical reactivity descriptors of molecules such as hardness (η), softness (S), electronegativity (χ) and free energy ΔG have been defined.[21,22] On the basis of E HOMO (A) and E LUMO (B), these are calculated using the below equations. Fig. 2 represents the HOMO and LUMO images of selected compounds

- ELECTRO NEGATIVITY (χ) = A+B/2,
- HARDNESS (η) = A-B/2
- SOFTNESS (S) = 1/2η
- FREE ENERGY (ΔG) = A-B

All the calculated values of electronegativity, hardness, softness and free energy are shown in Table 9. Compound with smaller frontier orbital gap is more polarizable and is associated with a high chemical reactivity, low kinetic stability and is also termed as soft molecule.[23-25] The calculated values indicate that all the compounds are having similar properties and are more reactive.

6. Conclusions

Identification of a lead compound plays a major role in drug designing. Some of the chemical components of *Justicia adhatoda* were selected to evaluate their drug likeness character, Using Gaussian software the binding energy of the compounds were calculated. If the value of binding energy is negative the drug may be more active and it is more stable. All the compounds have negative value of binding energy. All compounds can act as drug. Using molinspiration, physical properties and bioactivity score were calculated for all the chosen compounds. Comparison of the properties of the compounds with standard values revealed that all the compounds have drug likeness character. Pharmacological activities of all compounds were predicted using PASS software and all of them were found to have a list of biological activities.

Conflicts of Interest

The authors declare no conflict of interest.

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