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IN SILICO DESIGN, PREDICTION OF DRUG-LIKENESS AND TOXICITY OF NOVEL 3-(SUBSTITUTED PHENYL)-2-[5-(PYRIDIN-3-YL)-1,3,4-OXADIAZOL-2-YL]ACRYLONITRILES

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Abstract - A series of novel 3-(substituted phenyl)-2-[5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl]acrylonitriles were designed computationally based on the therapeutic benefits of 1,3,4-oxadiazole, nicotinoyl and arylacrylonitrile derivatives. The drug-likeness of title compounds were predicted by calculating molecular properties using Molinspiration Cheminformatics and OSIRIS Property Explorer. In addition, the bioactivity score and toxicity of all the compounds were estimated. The results of in silico screening indicated that all the compounds obeyed the Lipinski's rule of five indicating good oral bioavailability. All the evaluated title compounds were identified as kinase inhibitors. The drug-likeness and drug score of the title compounds were good. Among all, compound with trimethoxy substitution on phenyl ring showed highest drug score.

Keywords: Arylacrylonitriles, In silico screening, Kinase Inhibitors, Lipinski's rule, 1,3,4-Oxadiazole.

INTRODUCTION

It is well known that the nitrogen and oxygen containing heterocyclic compounds like oxadiazole, oxazole, isoxazole show various types of biological activities. Among these oxadiazole occurs in various isomeric forms reliant on nitrogen atom position in the ring. Compounds containing 1,3,4-oxadiazole displays a wide spectrum of biological activities such as antibacterial, antifungal, antiviral, antimalarial, analgesic, antiinflammatory, anticancer, antihypertensive, anticonvulsant and antidiabetic properties. Various therapeutically active drugs having 1,3,4-oxadiazole moiety are available in the market, which include Furamizole, Fenadiazole, Raltegravir, Zibotenan, Tiodazocin and Nesapidil [1, 2, 3].

Nicotinic acid is a member of vitamin B complex used to treat the human diseases like pellagra and hyperlipoproteinemias. However, very high doses are needed to achieve these therapeutic effects; due to this side effects are more common. Several nicotinic acid derivatives have been developed to reduce the side effects and necessary doses in comparison with pure nicotinic acid [4]. Recently, new nicotinic acid based 1,3,4-oxadiazoles were synthesized and evaluated as antitubercular, antibacterial agents [5, 6]. In some research reports, 5-substituted-2-cyanomethyl-1,3,4-oxadiazole was used as starting reagent for the synthesis of new compounds including arylacrylonitriles [7, 8]. Furthermore, the literature reveals that the arylacrylonitrile or phenylacrylonitrile derivatives have inhibitory effect on biosynthesis of prostaglandin and 2,3-diphenylacrylonitriles bearing halogen atom possess anticancer activity [9, 10].

In modern drug discovery process several computational or *in silico* methods used for the design and management of small molecule libraries. Identification of lead compound can be possible through virtual

screening, optimizing the affinity and selectivity, and enhancing the required physicochemical properties of hit molecules [11]. Some *in silico* methods are also used for predictive evaluation of drug toxicity to minimize the animal testing [12]. These *in silico* approaches are now widely used to study the important parameters that may guide medicinal chemist in evaluating physicochemical properties and toxicity of a compound. Hence, the present study aimed to design computationally a new series of 3-(substituted phenyl)-2-[5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl]acrylonitriles by considering the therapeutic value of 1,3,4-oxadiazole, nicotinoyl and arylacrylonitrile derivatives. The study also aimed to predict the molecular properties, drug-likeness and toxicity of title compounds by using free online software.

MATERIALS AND METHODS

The software used for the *in silico* design, prediction of drug-likeness and toxicity of novel 3-(substituted phenyl)-2-[5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl]acrylonitriles include:

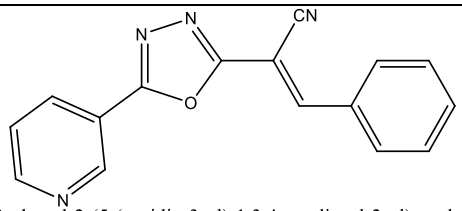
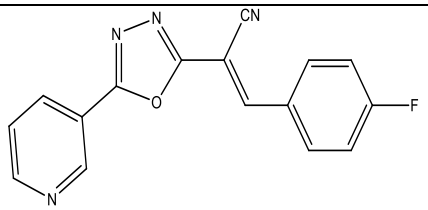
- ChemDraw Ultra 12.0
- Molinspiration Cheminformatics
- OSIRIS Property Explorer

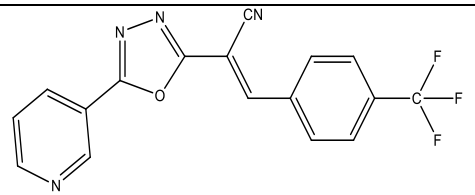
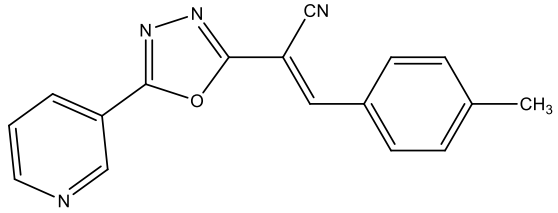
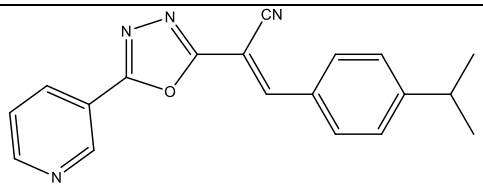
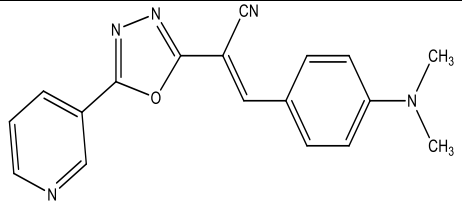
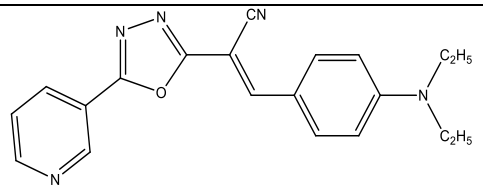
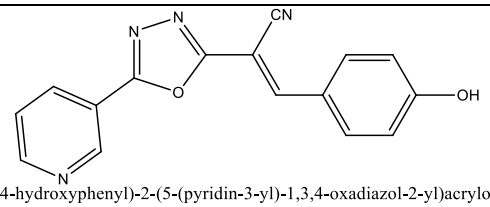
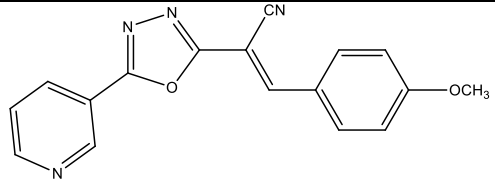
The 2D structures of novel 3-(substituted phenyl)-2-[5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl]acrylonitriles were drawn using ChemDraw Ultra 12.0. Their nomenclature and SMILES notations were generated. Molinspiration Cheminformatics software (https://www.molinspiration.com) was used to calculate the molecular properties like miLogP, TPSA, molecular weight, hydrogen bond acceptor, hydrogen bond donor, number of violations and number of rotatable bonds of title compounds. It is also used for the estimation of bioactivity score of title compounds as GPCR ligands, ion channel modulators, kinase inhibitors, nuclear receptor ligands, protease inhibitors, and enzyme inhibitors. By using OSIRIS Property Explorer, web server (http://www.organicchemistry.org/prog/peo), the properties like cLogP, solubility, molecular weight and TPSA are estimated. The software also used to predict toxicity risk factors like tumorigenic, irritant, mutagenic and reproductive effects. Drug-likeness is calculated based on the distinct substructure fragments. The overall drug score is calculated by considering the drug-likeness, cLogP, solubility, molecular weight and toxicity risks.

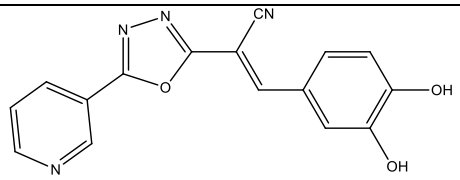
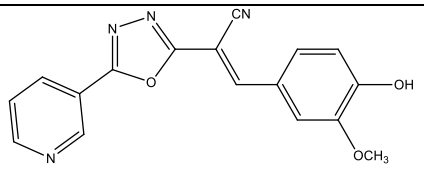
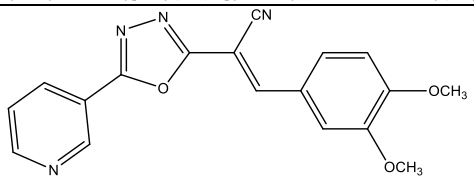
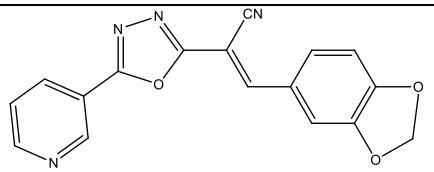
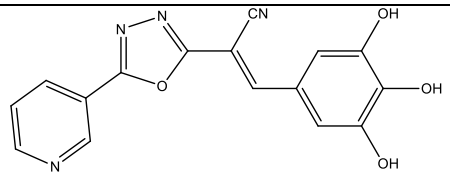
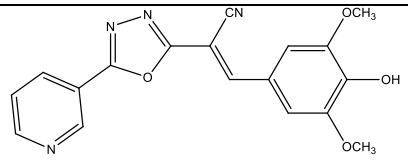
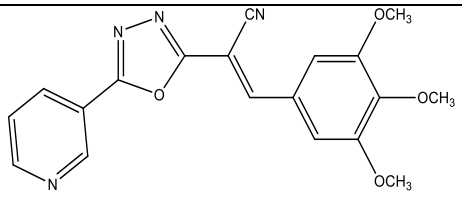
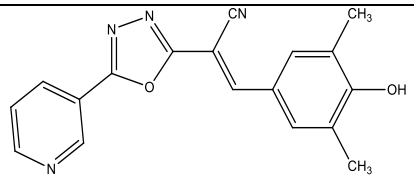
RESULTS AND DISCUSSION

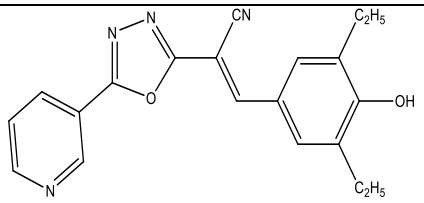
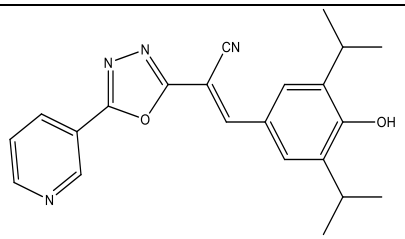
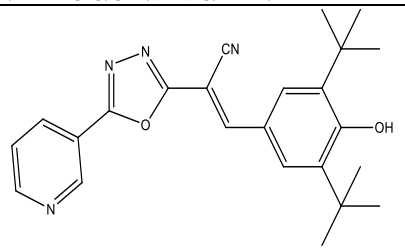
Data obtained from ChemDraw Ultra 12.0 such as structure, IUPAC name and SMILES notation for all the novel twenty compounds were included in Table-1.

Table-1: Structure, IUPAC name and SMILES notation of the compounds (C1-C20)

Com	Structure with IUPAC name	SMILES notation
C1	 (*E*)-3-phenyl-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)acrylonitrile	N#C/C(C1=NN=C(C2=CC=CN=C2)O1)=C\C3=CC=CC=C3
C2	 (*E*)-3-(4-fluorophenyl)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)acrylonitrile	FC(C=C1)=CC=C1/C=C(C#N)/C2=NN=C(C3=CC=CN=C3)O2

C3	 (*E*)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)-3-(4-(trifluoromethyl)phenyl)acrylonitrile	FC(F)(F)C(C=C1)=CC=C1/C=C(C#N)/C2=NN=C(C3=CC=CN=C3)O2
C4	 (*E*)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)-3-(*p*-tolyl)acrylonitrile	CC(C=C1)=CC=C1/C=C(C#N)/C2=NN=C(C3=CC=CN=C3)O2
C5	 (*E*)-3-(4-isopropylphenyl)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)acrylonitrile	CC(C)C(C=C1)=CC=C1/C=C(C#N)/C2=NN=C(C3=CC=CN=C3)O2
C6	 (*E*)-3-(4-(dimethylamino)phenyl)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)acrylonitrile	CN(C)C(C=C1)=CC=C1/C=C(C#N)/C2=NN=C(C3=CC=CN=C3)O2
C7	 (*E*)-3-(4-(diethylamino)phenyl)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)acrylonitrile	N#C/C(C1=NN=C(C2=CC=CN=C2)O1)=C\C3=CC=C(N(CC)CC)C=C3
C8	 (*E*)-3-(4-hydroxyphenyl)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)acrylonitrile	OC(C=C1)=CC=C1/C=C(C#N)/C2=NN=C(C3=CC=CN=C3)O2
C9	 (*E*)-3-(4-methoxyphenyl)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)acrylonitrile	N#C/C(C1=NN=C(C2=CC=CN=C2)O1)=C\C3=CC=C(OC)C=C3

C10	 (*E*)-3-(3,4-dihydroxyphenyl)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)acrylonitrile	OC(C=C1)=C(O)C=C1/C=C(C#N)/C2=NN=C(C3=CC=CN=C3)O2
C11	 (*E*)-3-(4-hydroxy-3-methoxyphenyl)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)acrylonitrile	OC(C=C1)=C(OC)C=C1/C=C(C#N)/C2=NN=C(C3=CC=CN=C3)O2
C12	 (*E*)-3-(3,4-dimethoxyphenyl)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)acrylonitrile	N#C/C(C1=NN=C(C2=CC=CN=C2)O1)=C\C3=CC(OC)=C(OC)C=C3
C13	 (*E*)-3-(benzo[*d*][1,3]dioxol-5-yl)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)acrylonitrile	N#C/C(C1=NN=C(C2=CC=CN=C2)O1)=C\C3=CC4=C(OCO4)C=C3
C14	 (*E*)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)-3-(3,4,5-trihydroxyphenyl)acrylonitrile	OC(C(O)=C1)=C(O)C=C1/C=C(C#N)/C2=NN=C(C3=CC=CN=C3)O2
C15	 (*E*)-3-(4-hydroxy-3,5-dimethoxyphenyl)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)acrylonitrile	OC(C(OC)=C1)=C(OC)C=C1/C=C(C#N)/C2=NN=C(C3=CC=CN=C3)O2
C16	 (*E*)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)-3-(3,4,5-trimethoxyphenyl)acrylonitrile	N#C/C(C1=NN=C(C2=CC=CN=C2)O1)=C\C3=CC(OC)=C(OC)C(OC)=C3
C17	 (*E*)-3-(4-hydroxy-3,5-dimethylphenyl)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)acrylonitrile	OC(C(C)=C1)=C(C)C=C1/C=C(C#N)/C2=NN=C(C3=CC=CN=C3)O2

C18	 (*E*)-3-(3,5-diethyl-4-hydroxyphenyl)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)acrylonitrile	OC(C(CC)=C1)=C(CC)C=C1/C=C(C#N)/C2=NN=C(C3=CC=CN=C3)O2
C19	 (*E*)-3-(4-hydroxy-3,5-diisopropylphenyl)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)acrylonitrile	OC(C(C(C)C)=C1)=C(C(C)C)C=C1/C=C(C#N)/C2=NN=C(C3=CC=CN=C3)O2
C20	 (*E*)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)acrylonitrile	OC(C(C(C)(C)C)=C1)=C(C(C)(C)C)C=C1/C=C(C#N)/C2=NN=C(C3=CC=CN=C3)O2

The molecular properties of twenty novel compounds were estimated by using Molinspiration Cheminformatics and the results were presented in Table-2. Lipinski's rule of five predicts the molecular properties related to the pharmacokinetic parameters of the compounds. According to this rule, the compound that have miLogP<5, molecular weight <500, the number of hydrogen bond acceptors <10 and hydrogen bond donors < 5, exhibits good oral bioavailability. According to the results obtained from the Molinspiration all the compounds obeyed Lipinski's rule of five, thus indicating good bioavailability on drug administration.

Table-2: Molecular properties of the compounds (C1-C20)

Sl.No.	miLogP	TPSA	n atoms	Molecular weight	n-ON	n-ONHNH	n violations	n rotb	Volume
C1	2.14	75.61	21	274.28	5	0	0	3	240.24
C2	2.30	75.61	22	292.27	5	0	0	3	245.17
C3	3.03	75.61	25	342.28	5	0	0	4	271.53
C4	2.58	75.61	22	288.31	5	0	0	3	256.80
C5	3.65	75.61	24	316.36	5	0	0	4	290.19
C6	2.24	78.85	24	317.35	6	0	0	4	286.14
C7	2.99	78.85	26	345.41	6	0	0	6	319.75
C8	1.66	95.84	22	290.80	6	1	0	3	248.25
C9	2.19	84.84	23	304.31	6	0	0	4	265.78
C10	1.17	116.06	23	306.28	7	2	0	3	256.27
C11	1.48	105.07	24	320.31	7	1	0	4	273.80
C12	1.78	94.08	25	334.33	7	0	0	5	291.33
C13	2.03	94.08	24	318.29	7	0	0	3	264.17
C14	0.88	136.29	24	322.28	8	3	0	3	264.29
C15	1.49	114.30	26	350.33	8	1	0	5	299.35
C16	1.77	103.31	27	364.36	8	0	0	6	316.87

C17	2.67	95.84	24	318.34	6	1	0	3	281.38
C18	3.60	95.84	26	346.39	6	1	0	5	314.98
C19	3.85	95.84	28	374.44	6	1	0	5	348.15
C20	5.19	95.84	30	402.50	6	1	1	5	380.63

(miLogP: logarithm of compound partition coefficient between n-octanol and water, TPSA: topological polar surface area, n atoms: total number of atoms in compound, n-ON: Hydrogen bond acceptor, n-ONHNH: Hydrogen bond donor, n violations: number of violations, n rotb: number of rotatable bonds)

The bioactivity score of twenty novel compounds was predicted by Molinspiration Cheminformatics and the values were listed in Table-3. A molecule having bioactivity score more than 0.00 expected to be active, while values from -0.50 to 0.00 are expected to be moderately active, if the score is less than -0.50 considered to be inactive. All the compounds were active as kinase inhibitors with the bioactivity score more than 0.00. Among the series, compound C3 containing trifluormethyl substitution was predicted as better kinase inhibitor with the score 0.20. All the compounds were moderately active as GPCR ligands, ion channel modulators, nuclear receptor ligands, protease inhibitors and enzyme inhibitors.

Table-3: Prediction of bioactivity score of the compounds (C1-C20)

Sl.No.	GPCRL	ICM	KI	NRL	PI	EI
C1	-0.26	-0.44	0.12	-0.44	-0.26	-0.15
C2	-0.22	-0.44	0.17	-0.37	-0.25	-0.16
C3	-0.12	-0.28	0.20	-0.18	-0.12	-0.12
C4	-0.28	-0.51	0.09	-0.43	-0.29	-0.21
C5	-0.19	-0.40	0.10	-0.28	-0.17	-0.13
C6	-0.19	-0.42	0.18	-0.32	-0.20	-0.15
C7	-0.16	-0.40	0.13	-0.32	-0.19	-0.18
C8	-0.18	-0.38	0.19	-0.23	-0.20	-0.08
C9	-0.26	-0.49	0.10	-0.37	-0.25	-0.19
C10	-0.17	-0.38	0.17	-0.24	-0.20	-0.09
C11	-0.21	-0.45	0.14	-0.30	-0.25	-0.13
C12	-0.24	-0.47	0.09	-0.37	-0.24	-0.18
C13	-0.20	-0.49	0.07	-0.41	-0.22	-0.17
C14	-0.17	-0.36	0.19	-0.25	-0.16	-0.04
C15	-0.22	-0.41	0.14	-0.31	-0.21	-0.10
C16	-0.24	-0.44	0.10	-0.40	-0.24	-0.17
C17	-0.20	-0.42	0.12	-0.20	-0.18	-0.11
C18	-0.13	-0.32	0.08	-0.15	-0.12	-0.05
C19	-0.14	-0.31	0.05	-0.13	-0.14	-0.05
C20	-0.10	-0.22	0.10	-0.06	-0.12	-0.02

(GPCRL: GPCR Ligand, ICM: Ion channel modulator, KI: Kinase inhibitor, NRL: Nuclear receptor ligand, PI: Protease inhibitor, EI: Enzyme inhibitor)

The prediction of toxicological risks and physicochemical properties were also performed using OSIRIS Property Explorer. The predicted physicochemical parameters were presented in Table-4. cLogP describes the lipophilicity of the molecule, the value of cLogP is less than 5, it indicates the probability of absorption. All the derivatives (C1-C20) showed values varied from 1.01 to 4.86, it indicates that the compounds will be well absorbed. The solubility (logS) of a compound is an important factor significantly affects its absorption and distribution. The compounds C1, C6, C8, C9, C10, C11, C12, C14, C15 and C16 showed the values between -3.90 and -2.96 indicates higher solubility and it leads to good absorption and distribution. The compounds C2, C3, C4, C5, C7, C13, C17, and C18 were moderately soluble and the compounds C19 and C20 were poorly soluble. Regarding the molecular weight, the compounds had values greater than 270 and less than 500 in agreement with Lipinski's rule of five. TPSA describes

topological polar surface area, the obtained TPSA values for all the compounds (C1-C20) were below 140 indicating permeability of the compounds in the cell membrane.

Table-4: Prediction of physicochemical properties for compounds (C1-C20)

Sl.No.	cLogP	logS	Molecular weight	TPSA
C1	2.05	-3.85	274.28	75.60
C2	2.15	-4.16	292.27	75.60
C3	2.89	-4.62	342.28	75.60
C4	2.39	-4.19	288.31	75.60
C5	3.23	-4.72	316.36	75.60
C6	1.94	-3.88	317.35	78.84
C7	2.76	-4.48	345.40	78.84
C8	1.70	-3.55	290.28	95.83
C9	1.98	-3.86	304.31	84.83
C10	1.35	-3.25	306.28	116.06
C11	1.63	-3.57	320.31	105.06
C12	1.91	-3.88	334.33	94.06
C13	2.16	-4.56	318.29	94.06
C14	1.01	-2.96	322.28	136.29
C15	1.56	-3.59	350.33	114.29
C16	1.84	-3.90	364.36	103.29
C17	2.39	-4.24	318.34	95.83
C18	3.22	-4.56	346.39	95.83
C19	4.07	-5.29	374.44	95.83
C20	4.86	-5.87	402.50	95.83

(cLogP: logarithm of partition coefficient between n-octanol and water; TPSA: topological polar surface)

The toxicity risks, drug-likeness and drug score of compounds were predicted using OSIRIS Property Explorer. The predicted values were listed in Table-5. The compounds showed none, low and high for its mutagenic, tumorigenic, irritant and reproductive effects. The “none” value shows that the drug-conform behaviour of compounds, the low and high values indicate about the level of toxicity of compounds. All the compounds (C1-C20) were demonstrated “high” risk of irritant effect. All the compounds expect C6, C7, C8, C13 and C18 showed “none” for its mutagenic, tumorigenic and reproductive effects. Predicted drug-likeness of all title compounds were in the range of 1.06 to -18.18. All the compounds showed drug-likeness as negative values expect compound C16. The compound C16 showed the drug likeness value 1.06. The drug score is the combination of drug-likeness, cLogP, logS, molecular weight and toxicity risks. The drug score values for all compounds (C1-C20) were in the range of 0.09 to 0.41. Among the series, compound with trimethoxy substitution on phenyl ring exhibited highest drug score.

Table-5: Prediction of toxicity risks, drug-likeness and drug score of compounds (C1-C20)

Sl.No.	Mutagenic	Tumorigenic	Irritant	Reproductive effect	Drug likeness	Drug score
C1	N	N	H	N	-3.67	0.26
C2	N	N	H	N	-3.42	0.25
C3	N	N	H	N	-10.00	0.21
C4	N	N	H	N	-4.02	0.24
C5	N	N	H	N	-4.98	0.21
C6	H	H	H	N	-6.66	0.09
C7	H	L	H	N	-8.61	0.10
C8	N	N	H	H	-2.35	0.17
C9	N	N	H	N	-2.33	0.27
C10	N	N	H	N	-1.44	0.31

C11	N	N	H	N	-1.90	0.29
C12	N	N	H	N	-0.23	0.35
C13	N	N	H	H	-2.16	0.15
C14	N	N	H	N	-2.03	0.30
C15	N	N	H	N	-1.12	0.31
C16	N	N	H	N	1.06	0.41
C17	N	N	H	N	-7.02	0.23
C18	H	N	H	N	-7.82	0.13
C19	N	N	H	N	-12.22	0.17
C20	N	N	H	N	-18.18	0.13

(N=None; H=High risk; L=Low risk)

CONCLUSION

A series of twenty novel 3-(substituted phenyl)-2-[5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl]acrylonitriles were designed by computational methods. The molecular properties, drug likeness, bioactivity score and toxicity risks of the designed compounds were predicted using Molinspiration Cheminformatics and OSIRIS Property Explorer. The results obtained from those two software concluded that all the twenty novel 3-(substituted phenyl)-2-[5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl]acrylonitriles showed good molecular properties and all the compounds followed the Lipinski's rule of five. All the compounds exhibited good kinase inhibitor activity with the bioactivity score more than 0.00. The estimated drug-likeness and drug score of the title compounds were good. The variation of score depends on the substituents on phenyl ring of title compounds modifying the molecular properties.

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