IJPSR (2019), Volume 10, Issue 12 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 07 March 2019; received in revised form, 12 June 2019; accepted, 17 July 2019; published 01 December 2019

QSRT STUDIES OF 2-(5-ARYL-1, 3, 4-OXADIAZOL-2-YL)-*N*-(5-METHYLISOXAZOL-3-YL)-ACETAMIDE DERIVATIVES AS AN ANTIMICROBIAL AGENTS

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Keywords:

QSRT studies, Isoxazolyl oxadiazoles, Antimicrobial agents, Bicyclic hetero cyclic compounds

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ABSTRACT: Quantitative structure relationship techniques (QSRT) is among the most widely used computational technology for analog-based drug design. A molecular modeling approach using theoretical, computational analysis through chem sketch ACD lab online software was done for determination of probable antimicrobial activity. To develop a pharmacophoric model for inhibition, QSRT parameters PCP, ADME, and toxicity has been used. BCF (Bioconcentration factor), adsorption coefficient, log P, log D values, plasma protein binding, P-gp inhibition, AMES test, hERg inhibition, estrogen receptor, and Lipinski's type properties have been calculated. From a data set of 11 analogs, it has been concluded that all compounds are non-bio-accumulative, non-endocrine disruptors, non hERg inhibitors, genotoxic and within Lipinski's criteria. None of the compounds are practically ionizable at various body pH values, and all are zwitterionic compounds. From these data and *in-vitro* antimicrobial data compounds, 5c and 5f can be exploited for the formulation of bactericide and fungicide with a slight modification in their structure.

INTRODUCTION: Besides biological reactivity against a target, which is the primary requirement, there are so many essential properties and characteristics that are mandatory to be possessed by a molecule to be considered as a drug. The use of computational methods for designing molecules with a desired activity, reactivity or property has been a growing area in chemistry and medicine.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(12).5391-96

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(12).5391-96

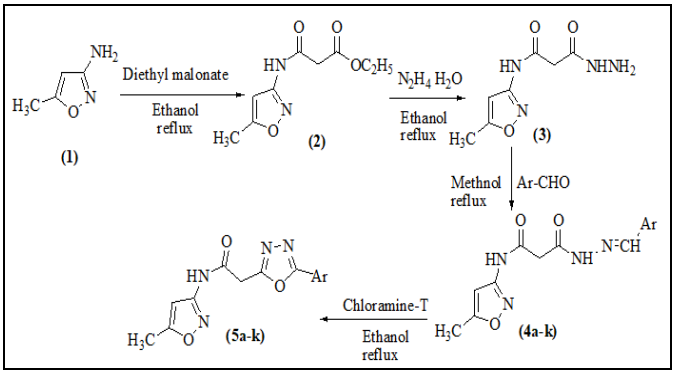
In this direction QSRT analysis has been performed considering some important activity properties like BCF (Bioconcentration factor), adsorption coefficient, partition coefficients, probable plasma binding property, p-gp inhibiting characteristics, non genotoxicity, AMES test possibilities, hERg inhibiting probabilities, endocrinal disruptor tendency, and drug's pharmacokinetics like adsorption, distribution, metabolism and elimination in the human body, and can be inferred from Lipinski's rule molecular properties.

1, 3, 4-Oxadiazoles are of great practical significance, which is primarily due to their large number of uses, in the most diverse areas, such as in drug synthesis, scintillation materials, in the

production of polymers and dyes, and uses in photography as light screening agents. 1, 3, 4-Oxadiazole derivatives are reported to exhibit antibacterial [1], antifungal [2], analgesic and anti-inflammatory [3], anticonvulsant [4], anticoagulant [5], and anticancer activity [6, 7]. A large number of synthetic derivatives of this molecule are well documented in the literature. Similarly, isoxazole derivatives are found to possess a wide variety of biological activities [8, 9, 10, 11, 12].

Literature survey indicated that the compounds bearing the isoxazole moiety are endowed with various types of biological activities. The 1, 3, 4-oxadiazoles are heterocycles of current interest due to their broad-spectrum pharmacological activity. Therefore, in the current investigation, the QSRT studies of isoxazolyl 1, 3, 4-oxadiazoles have been undertaken to correlating antimicrobial activity In this paper, we present QSRT studies of 2-(5-aryl-1, 3, 4-oxadiazol-2-yl) -*N* -(5-methyl isoxazol-3-yl)-acetamides.

MATERIALS AND METHODS: Several isoxazolyl 1,3,4-oxadiazoles have been synthesized and characterized by spectral analysis **Scheme I** and evaluated for antibacterial **Table 1** and antifungal activity [13] **Table 2**. The structures are drawn and submitted for theoretical, computational analysis using through chem sketch ACD-lab online software [14] analyzed QSRT parameters *viz.*, BCF, adsorption coefficient [15], log P, log D values, Plasma protein binding [16], P-gp inhibition[17], AMES test [18, 19], hERg inhibition[20], estrogen receptor [21, 22] genotoxicity [23, 24] and Lipinski's type properties [25]. The data is tabulated and examined for analysis between the structural aspects of molecular activity. Under the light of changes of structural aspects of the molecule, the trends in the molecules are evaluated. This will help in designing new molecules with expected behaviors.



SCHEME I: SYNTHESIS OF 2-(5-aryl-1, 3, 4-oxadiazol-2-yl)-*N*-(5-methylisoxazol-3-yl)-acetamides. 4 & 5 Ar = a: C_6H_5; b: 4-ClC_6H_4; c: 4-$OCH_3C_6H_4$; d: 4-$NO_2C_6H_4$; e: 3-$OCH_3C_6H_4$; f: 3-BrC_6H_4; g: 2-OH C_6H_4; h: 2-OH,3-$OCH_3C_6H_3$; i: 3,4,5-$(OCH_3)_3C_6H_2$; j: 3,4-$(OCH_3)_2C_6H_3$; k: 2-$CH_3C_6H_4$

TABLE 1: ANTIBACTERIAL ACTIVITY OF *N*-(5-methylisoxazol-3-yl)-2-(5-phenyl-1,3,4-oxadiazol-2-yl) acetamides [13] (5a-k)

Compound	Minimum Inhibitory Concentration (MIC)[a,b]					
	Bacterial strains					
	P. aeruginosa	*K. aerogenes*	*C. violaceum*	*B. subtilis*	*B. sphaericus*	*S. aureus*
5a	20	18	18	19	17	15
5b	11	11	8	9	8	7
5c	17	15	13	16	18	14
5d	10	8	7	6	8	6
5e	10	16	15	15	13	14
5f	13	11	14	11	12	10
5g	18	14	16	16	15	15
5h	19	16	20	17	18	21
5i	21	18	21	19	17	18
5j	23	20	22	18	16	15
5k	22	23	20	18	17	16
Ciprofloxacin	30	25	25	20	20	25

[a]Negative control (acetone)- no activity, [b]Concentration in µg/mL

TABLE 2: ANTIFUNGAL ACTIVITY OF *N*-(5-methylisoxazol-3-yl)-2-(5-phenyl-1,3,4-oxadiazol-2-yl) acetamides [13] (5a-k)

Compound	Zone of Inhibition mm[a,b]				
	Fungal strains				
	A. niger	*C. tropicum*	*R. oryzae*	*F. moniliforme*	*C. lunata*
5a	52.5	46.5	51.0	41.2	50.5
5b	69.1	70.1	72.5	69.8	65.5
5c	56.0	57.0	58.0	61.0	59.5
5d	75.0	77.2	80.5	73.2	69.5
5e	48.0	51.0	48.5	53.2	57.2

5f	63.2	65.0	72.5	60.5	73.5
5g	55.8	58.3	59.1	60.0	61.1
5h	47.2	42.5	40.2	38.5	31.5
5i	39.0	38.3	31.2	37.0	51.0
5j	51.0	55.2	49.8	48.1	59.0
5k	45.5	60.1	55.3	48.1	39.5
Clotrimazole	26.5	30.6	33.5	25.5	35.8

[a]Negative control (acetone)- no activity, [b]Concentration 100 µg/mL

RESULTS AND DISCUSSION:

QSRT Studies: In this paper, an attempt has been made to analyze 2-(5-aryl-1,3,4-oxadiazol-2-yl)-*N*-(5-methylisoxazol-3-yl)-acetamide derivatives (5a-5k) through the application of the quantitative structure relationship techniques (QSRT).

QSPR Studies: Table 3 shows the properties computed through quantitative structure-property relationship algorithm of ACD software. Very marginal variance is observed among all physical parameters.

QSAR Study: BCF of 5a-k structures is found to have a constant unity value concerning the change in pH. In the case of the adsorption coefficient, a consistent value unity has been maintained between pH range 1-9, besides that, it tends to approach a constant value, as shown in **Table 4**. Since, BCF is <1000, 5a -5k compounds are non bioaccumulative.

Therefore, there is very less chance to be incorporated into biological food chains from the environment. Since the bioconcentration factor is greater than 1; it is indicative of a hydrophobic or lipophilic chemical. In the case of 5a-5k derivatives as they have unity value indicating very low hydrophilic nature, but not having of lipophobic or hydrophilic nature.

TABLE 3: GENERAL PHYSICAL PROPERTIES OF COMPOUNDS 5a-5k

Compound	Molar Refractivity	Molar Volume	Parachor	Index of Refraction	Surface Tension	Density	Polarizability
5a	73.30	210.0	584.5	1.615	59.9	1.353	29.05
5b	78.19	221.9	620.4	1.622	61.0	1.435	30.99
5c	79.98	234.0	641.2	1.599	56.3	1.342	31.70
5d	79.84	221.8	640.0	1.639	69.2	1.484	31.65
5e	79.98	234.0	641.2	1.599	56.3	1.342	31.70
5f	80.99	226.2	635.0	1.634	62.1	1.605	32.10
5g	75.18	208.4	599.5	1.640	68.4	1.440	29.80
5h	81.86	232.4	656.2	1.621	63.5	1.420	32.45
5i	93.33	282.0	754.5	1.576	51.2	1.327	37.00
5j	86.65	258.0	697.9	1.586	53.5	1.334	34.35
5k	78.12	226.3	622.2	1.606	57.1	1.318	30.97

TABLE 4: BCF, ADSORPTION COEFFICIENT, log P AND log D VALUES OF COMPOUNDS 5a-5k

Compound	BCF BIO		log P		log D				
	BCF	K^{OC}	log P	Reliability	pH 1.6	pH 4.6	pH 6.5	pH 7.4	pH 8.2
5a	1	20.8C	1.71	0.65M	1.71	1.71	1.71	1.71	1.71
5b	1	54.3C	2.12	0.52M	2.12	2.12	2.12	2.12	2.12
5c	1	25.7C	1.73	0.48B	1.73	1.73	1.73	1.73	1.73
5d	1	19.8C	1.49	0.59M	1.48	1.49	1.49	1.49	1.49
5e	1	25.6C	1.73	0.48B	1.73	1.73	1.73	1.73	1.73
5f	1	70.5C	2.35	0.5M	2.35	2.35	2.35	2.35	2.35
5g	1	29.2C	1.3	0.55M	1.3	1.3	1.3	1.3	1.3
5h	1	27.6	0.81	0.51M	0.81	0.81	0.81	0.81	0.81
5i	1	26.4C	1.38	0.56M	1.38	1.38	1.38	1.38	1.38
5j	1	28.1C	0.96	0.47B	0.96	0.96	0.96	0.96	0.96
5k	1	37.1C	1.73	0.52M	1.73	1.73	1.73	1.73	1.73

The log P and log D computed values are found to be moderately reliable with reliability parameter between 0.56-0.65. For all compounds except for 5c, 5e, and 5j, whose reliabilities are found to be borderline. log D values for all of the derivatives at pH 1.7, 4.6, 6.5, 7.4 and 8 appears to be same for

all the compounds (5a–5k) indicating that at all those pH s no practical ionization of molecule occurs **Table 4**. Partition coefficient values are found to be in-between 0.86 to 2.83. log P, log D, adsorption coefficient, and BCF increased when halogen groups are present. By halogen substitution molecule's log P, log D, and aqueous solubility decreased. Presence of two methoxyl on aryl groups shown a decrease in log P value in 5j derivative on comparison with the un-substituted molecule, whereas the presence of either single methoxyl group or three methoxyl groups on aryl structural unit is showing a decreasing tendency.

TABLE 5: PLASMA PROTEIN BINDING AND P-gp INHIBITION POSSIBILITIES WITH RELIABILITIES OF COMPOUNDS 5a-5k

Compound	DBP				P-gp inhibition			
	PPB (%)	Reliability I	log K^{HSA}	Reliability II	Probability	Reliability	K_i	Reliability
5a	96.54	0.42B	4.32	0.4B	0.08	0.31B	0.01	0.56M
5b	97.45	0.52M	4.63	0.38B	0.1	0.2NR	0.01	0.46B
5c	95.28	0.49B	4.32	0.4B	0.11	0.2NR	0.02	0.54M
5d	95.73	0.41B	4.16	0.38B	0.1	0.2NR	0.02	0.49B
5e	95.28	0.49B	4.32	0.4B	0.11	0.2NR	0.02	0.54M
5f	96.44	0.43B	4.46	0.39B	0.1	0.21NR	0.02	0.48B
5g	93.77	0.49B	4.14	0.39B	0.05	0.13NR	0.01	0.53M
5h	90.78	0.4B	4.06	0.23NR	0.06	0.14NR	0	0.49B
5i	93.6	0.45B	4.34	0.34B	0.13	0.25NR	0.03	0.53M
5j	93.65	0.49B	4.25	0.35B	0.13	0.22NR	0.03	0.55M
5k	95.28	0.48B	4.33	0.4B	0.11	0.21NR	0.02	0.51M

% PPB of 5b is found to be moderately reliable in respect of plasma protein binding possibility and borderline for all other 5 series compounds. 5b has the highest value of 97.45, and 5h has the least value. The variation is very narrow for all as 94±4. No molecule is found to have a high probability of 0.8 or above reliability in respect to plasma protein binding parameter. log K^{HSA} values of 5a-5k compounds are very narrowly distributed so synergetic effect on the availability of molecule concerning others is very less significant. Presence of 5b can enhance the percentage of 5h in blood as the difference in their K_i value is significant to consider. All (5a-5k) are Zwitterionic compounds. These drugs are likely to bind to the majority of plasma proteins.

Further one may work except that all may bind to human serum albumin, alpha1-acid glycoprotein, and albumin although in most cases the binding is not extensive. In compound 5d nitroarenes exhibit genotoxic activity after metabolic transformation to hydroxylamines **Fig. 1**.

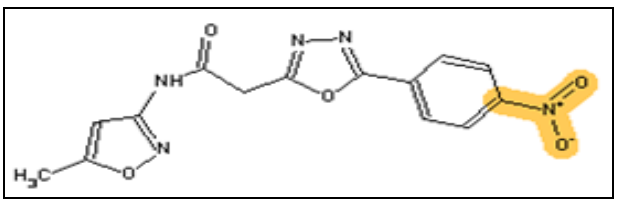


FIG. 1: GENOTOXICITY OF COMPOUND 5d

In this series, a constant value of 0.1 has been observing for most of them. From this one can conclude that there will be a least binding tendency concerning P-glycoprotein, 5a, 5h and 5g are having 0.05 order of binding aptitude that is 10 fold less than other members of the same series.

Since probability of potent P-gp inhibition (Ki<1 micro-M): 0.01, Reliability: Moderate (RI = 0.56 to 0.49) and McGowan's volume is found to be less than 200 cm^3/mol with high reliability for 5a, so it can classify as non-inhibitor, 5g, and 5h will be Probably non-inhibitor as they are weak hydrophilic acid or amphiprotic compound, acid pKa > 5, MW < 360, AB/logP < 2.5, with high reliability. In cases of 5b, 5c, 5d, 5e, 5f, 5i, 5j and 5k no prediction can be made unless data for similar compounds be available to predict through the use for probabilistic estimation [23, 26] **Table 5**.

All other molecules of this series have AMES test probabilities in the range of 0.12 to 0.16 with non-reliable values of 0.17 or 0.18, except 5d with a value of 0.68 with borderline reliability 0.38. So it may show carcinogen activity. hERg inhibiting probabilities are found to be reliable, which is borderline except 5c. Still, one may except non inhibiting character as their values estimated appear to be very low, (the range is 0.1-0.2). Only 5g has 0.09 value.

They are expected to have log RBA less than -3 and K^i less than 10 μM. Relative binding affinity values are within the criteria of expectation, so all the molecules of consideration do not tend to bind to alpha estrogens receptor **Table 6**. All compounds are found to be within the Lipinski's criteria. It has found to be a topological surface area well below 145 and 142 (borderline value) in case of 5d; it may be associated with a reduction of genotoxicity by oxadiazole ring formation **Table 7**.

TABLE 6: AMES TEST PROBABILITIES AND ESTROGEN RECEPTOR PROBABILITIES WITH RELIABILITIES OF COMPOUNDS 5a-5k

Compound	AMES test		hERg Inhibitors		Endocrine Disruptions	
	Probability	Reliability	Probability	Reliability	Log RBA>-3	Log RBA>0
5a	0.13	0.2NR	0.12	0.22NR	0.2	0
5b	0.14	0.17NR	0.28	0.27NR	0.33	0
5c	0.16	0.17NR	0.13	0.23NR	0.21	0
5d	0.68	0.38B	0.1	0.19NR	0.18	0
5e	0.16	0.17NR	0.13	0.23NR	0.24	0
5f	0.14	0.18NR	0.15	0.18NR	0.36	0
5g	0.14	0.17NR	0.09	0.18NR	0.23	0
5h	0.17	0.17NR	0.13	0.17NR	0.24	0
5i	0.1	0.19NR	0.14	0.17NR	0.11	0
5j	0.12	0.18NR	0.13	0.19NR	0.19	0
5k	0.13	0.18NR	0.12	0.23NR	0.31	0

TABLE 7: LIPINSKI'S TYPE PROPERTIES OF COMPOUNDS 5a-5k

Compound	Lipinski's type properties				
	M. Wt.	HBD	HBA	TPSA	RB
5a	284.27	1	7	94.05	4
5b	318.71	1	7	94.05	4
5c	314.3	1	8	103.28	5
5d	329.27	1	10	142.88	5
5e	314.3	1	8	103.28	5
5f	363.17	1	7	94.05	4
5g	300.27	2	8	114.28	4
5h	330.29	2	9	123.51	5
5i	374.35	1	10	121.74	7
5j	344.32	1	9	112.51	6
5k	298.3	1	7	94.05	4

CONCLUSION: QSAR and QSPR studies for 5a-5k were presented. All the Compounds (5a-5l) are found to be promising non bio-accumulative, nonendocrine disruptors, non hERg inhibitors, and within Lipinski criteria. None of the compounds are practically ionizable at various body pH values. All the compounds (5a-5k) are zwitterionic compounds. It can be concluded that compounds 5a-5k may exhibit potential antimicrobial activity based on QSRT studies. QSRT studies may help in designing the pharmacophore modes to identify more potent isoxazolyl oxadiazole as an antimicrobial agent, which will be useful for the formulation of bacteriocide and fungicide.

ACKNOWLEDGEMENT: The authors are thankful to Department of Chemistry, University College of Science, Satavahana University, Karimnagar, Department of Chemistry and Siddhartha Degree & P. G. College, Narsampet, Warangal for providing laboratory facilities and JNTU-Kakinada for their constant encouragement. All the authors are thankful to Prof. E. Rajanarendar for his valuable suggestions. The authors are also grateful to the ACD labs for providing software to analyze the structures.

CONFLICTS OF INTEREST: The authors declare no conflicts of interest.

REFERENCES:

1. Shaikh A and Meshram J: Novel 1, 3, 4-oxadiazole derivatives of dihydropyrimidinones: synthesis, anti-inflammatory, anthelmintic, and antibacterial activity evaluation. J of Heterocyclic Chem 2015; 53: 1176-82.
2. Jadhav GR, Deshmukh DG, Medhane VJ, Gaikwad VB and Bholay AD: 2, 5-Disubstituted 1, 3, 4-oxadiazole derivatives of chromeno[4,3-*b*]pyridine: synthesis and study of antimicrobial potency. Heterocyclic Communications 2016; 22: 123-30.

3. Mahajan P, Nikam M, Chate A, Nimbalkar U, Patil V, Bobade A, Chaudhari A, Deolankar D, Javale B and Gill C: Synthesis, antioxidant, anti-Inflammatory, and antimicrobial screening of newer thiophene-fused arylpyrazolyl 1,3,4-oxadiazoles. Phosphorus, Sulfur, and Silicon and the Related Elements 2015; 190: 1803-13.
4. Patil SG, Girisha M, Badiger J, Kudari SM and Purohit MG: Synthesis and anticonvulsant, antimicrobial activity of some bis-1,3,4-oxadiazole and bis-1,2,4-triazole derivatives from sebacic acid. Indian Journal of Heterocyclic Chemistry 2017; 17: 37-40.
5. Iyer VB, Inturi GBMB, Sairam KV and Pujar GV: Synthesis of 1,3,4-oxadiazoles as promising anticoagulant agents. RSC Advances 2016; 6: 24797-07.
6. Szulczyk D, Tomaszewski P, Jóźwiak M, Kozioł AE, Lis T, Collu D, Iuliano F and Struga M: Synthesis and biological activities of ethyl 2-(2-pyridylacetate) derivatives containing thiourea, 1,2,4-triazole, thiadiazole and oxadiazole moieties. Molecules 2017; 22: 409.1-409.16.
7. Abdo NYM, and Kamel MM: Synthesis and anticancer evaluation of 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, 1,2,4-triazoles and mannich Bases. Chemical and Pharmaceutical Bullet 2015; 63: 369-76.
8. Cho GH, Kim T, Son WS, Seo SH, Min SJ, Cho YS, Keum G, Jeong KS, Koh HY, Lee J and Pae AN: Synthesis and biological evaluation of aryl isoxazole derivatives as metabotropic glutamate receptor 1 antagonist: a potential treatment for neuropathic pain. Bioorganic & Medicinal Chemistry Letters 2015; 25: 1324-28.
9. Kakkerla R, Marri S, Krishna MPSM, Molgara P and Reddy YN: Synthesis and biological evaluation of 3,4-dihydro-3-(3-methylisoxazol-5- yl)-2H-benzo [e] [1,3] oxazine derivatives as anticancer agents. Letters in Organic Chemistry 2018; 15: 124-32.
10. Hamama WS, Ibrahim ME and Zoorob HH: Synthesis and biological evaluation of some novel isoxazole derivatives. Journal of Heterocyclic Chemistry 2016: 53; 2007-12.
11. Pedada SR, Yarla NS, Tambade PJ, Dhananjaya BL, Bishayee A, Arunasree KM, Philip GH, Dharmapuri G, Aliev G, Putta S and Rangaiah G: Synthesis of new secretory phospholipase A2-inhibitory indole containing isoxazole derivatives as anti-inflammatory and anticancer agents. European Journal of Medicinal Chemistry 2016; 112: 289-97.
12. Marri S, Kakkerla R, Murali Krishna MPS, Lingabathula H, Reddy YN and Merugu R: Synthesis and pharmacological evaluation of 3-(3,5-dimethylisoxazol-4-yl)-2-arylthiazolidin-4-ones as a potential antioxidant, anti-inflammatory and analgesic agents. Indian Journal of Chemistry 2019; 58B: 109-19.
13. Marri S, Kakkerla R, Murali Krishna MPS and Venkat Rajam M: Synthesis and antimicrobial evaluation of isoxazole-substituted 1,3,4-oxadiazoles. Heterocyclic Communications 2018; 24: 285-92.
14. ACD/Labs, I-Lab 2.0-ilab.acdlabs.com, Algorithm Version v12.1.0.50374, Advanced Chemistry Development Inc., Toronto, ON, Canada, 2017, www.acdlabs.com (accessed April 2017).
15. Aranda JF, Bacelo DE, Leguizamón Aparicio MS, Ocsachoque MA, Castro EA and Duchowicz PR: Predicting the bioconcentration factor through a conformation-independent QSPR study. SAR and QSAR in Environmental Research 2017; 28: 749-63.
16. Dollery C: Therapeutic drugs. Churchill Livingstone, Edition 2nd, 1999.
17. Seelig A, Blatter XL and Wohnsland F: Substrate recognition by p-glycoprotein and the multidrug resistance-associated protein MRP1: a comparison. Int J of Clinical Pharmacology & Therapeutics, 2000; 38: 111-21.
18. ACD/Tox Suite, version 2.95, Data Sheet, 2012, Advanced Chemistry Development, Inc., Toronto, On, Canada. http://www.acdlabs.com.
19. Helma C, Cramer T, Kramer S and De Raedt L: Data mining and machine learning techniques for the identification of mutagenicity inducing substructures and structure-activity relationships of noncongeneric compounds. Journal of Chemical Information and Computer Sciences 2004; 44: 1402-11.
20. Nakajima M, Ohyama K, Nakamura S, Shimada N, Yamazaki H and Yokoi T: Inhibitory effects of azelastine and its metabolites on drug oxidation catalyzed by human cytochrome P-450 enzymes. Drug Metabolism and Disposition 1999; 27: 792-97.
21. Blair RM, Fang H, Branham WS, Hass BS, Dial SL, Moland CL, Tong W, Shi L, Perkins R and Sheehan DM: The estrogen receptor relative binding affinities of 188 natural and xenochemicals: structural diversity of ligands. Toxicol Science 2000; 54: 138-53.
22. Fang H, Tong W, Shi LM, Blair R, Perkins R, Branham W, Hass BS, Xie Q, Dial SL, Moland CL and Sheehan DM: Structure-activity relationships for a large, diverse set of natural, synthetic, and environmental estrogens. Chemical Research in Toxicology 2001; 14: 280-94.
23. Tiemersma EW, Voskuil DW, Bunschoten A, Hogendoorn EA, Witteman BJM, Nagengast FM, Glatt H, Kok FJ and Kampman E: Risk of colorectal adenomas in relation to meat consumption, meat preparation, and genetic susceptibility in a dutch population. Cancer Causes & Control 2004; 15: 225-36.
24. Westwood IM, Holton SJ, Rodrigues-Lima F, Dupret JM, Bhakta S, Noble MEM and Sim E: Expression, purification, characterization and structure of *Pseudomonas aeruginosa* arylamine N-acetyl transferase. Biochemical Journal 2005; 385: 605-12.
25. Lipinski CA, Lombardo F, Dominy BW and Feeney PJ: Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews 1997; 23: 3-25.
26. Guengerich F: Heterologous expression of human drug-metabolizing enzymes. Drug Metabolism Disposition 1997; 25: 1234-41.

How to cite this article:
Marri S, Kakkerla R and Krishna MPSM: QSRT studies of 2-(5-aryl-1, 3, 4-oxadiazol-2-yl)-*N*-(5-methylisoxazol-3-yl)-acetamide derivatives as an antimicrobial agents. Int J Pharm Sci & Res 2019; 10(12): 5391-96. doi: 10.13040/IJPSR.0975-8232.10(12).5391-96.