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Physicochemical Properties and Toxicity Profile of Synthesized Thiazolyl-1,3,4-oxadiazolethiols and their Derivatives by *In silico* Study

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ABSTRACT

The diverse biological activity, medicinal and agricultural importance of 1,3,4-oxadiazole and thiazole derivatives is well known. Earlier, some compounds were synthesised, by one of the Authors, having both 1,3,4-oxadiazole and thiazole moieties in it. In present paper assessment for physiochemical parameters and toxicity profile of synthesized thiazolyloxadiazolethiols and corresponding thiazolyloxadiazolethiomethyl derivatives has been reported. All studies are carried out using *In silico* tools. For physicochemical properties, like logP, logD, logS, HLB and pKa, online web server Chemicalize ChemAxon was used. Toxicity profile was evaluated using Protox-II server for acute toxicity, toxicity targets like organ toxicity and toxicological end points. Various aspects for data of these studies have been evaluated and discussed.

Key words: Thiazolyloxadiazolethiol derivatives, logP, logD, logS, HLB, pKa, Toxicity profile, toxicological end points, Chemicalize ChemAxon server, Protox-II web server.

INTRODUCTION

The 1,3,4-oxadiazoles and thiazoles are reported to exhibit diverse pharmacological and biological activities [**1**]. A few examples of commercially available drugs containing 1,3,4-oxadiazole ring [**2, 3, 4**] are, Furamizole [**2, 4, 5a**] an antibacterial, Raltegravir [**5b, 6, 7, 8**] an antiviral to treat

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HIV/AIDS and Nesapidil [**3, 5c**] an anti-arrhythmic agent. In a similar manner drugs containing thiazole ring [**9**] include Tiazofurin [**10a**] an anticancer, Niridazole [**10b**] a schistosomicide, Aminophenazole [**10c**] an antidote for barbiturate/opiate overdose and Thiabendazole [**10d**] an antihelmintic. Thiazole derivatives are also well-known pesticides, a few examples are Bentaluron [**11a,12**] a fungicide, Methabenzthiazuron [**11b,12**] an herbicide, Thiacloprid [**11c,13**] an insecticide and Clothianidin [**11d,14**] a neonicotinoid insecticide. All these examples along with their structure and uses are summarized in **Figure 1.**

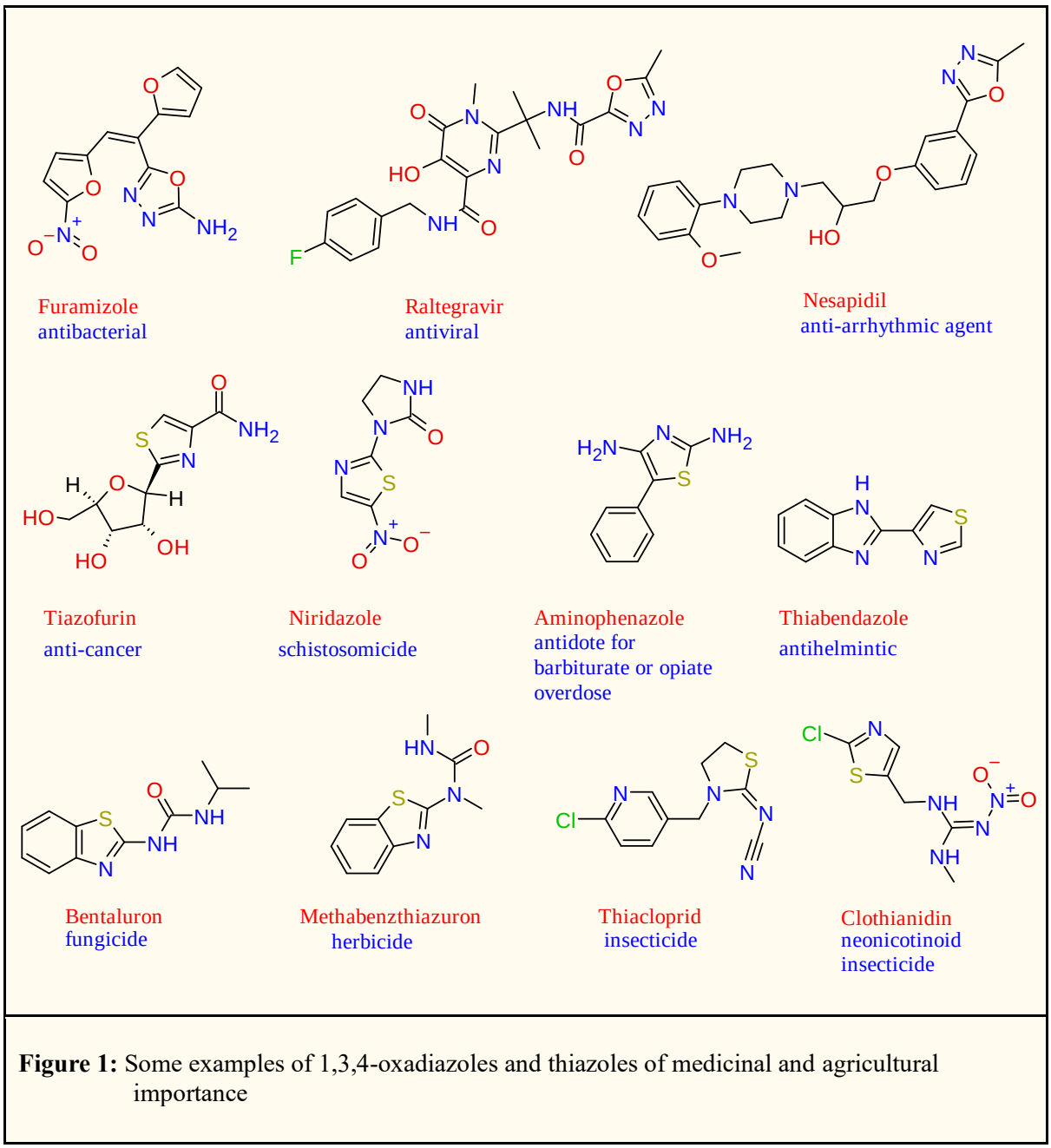

Figure 1: Some examples of 1,3,4-oxadiazoles and thiazoles of medicinal and agricultural importance

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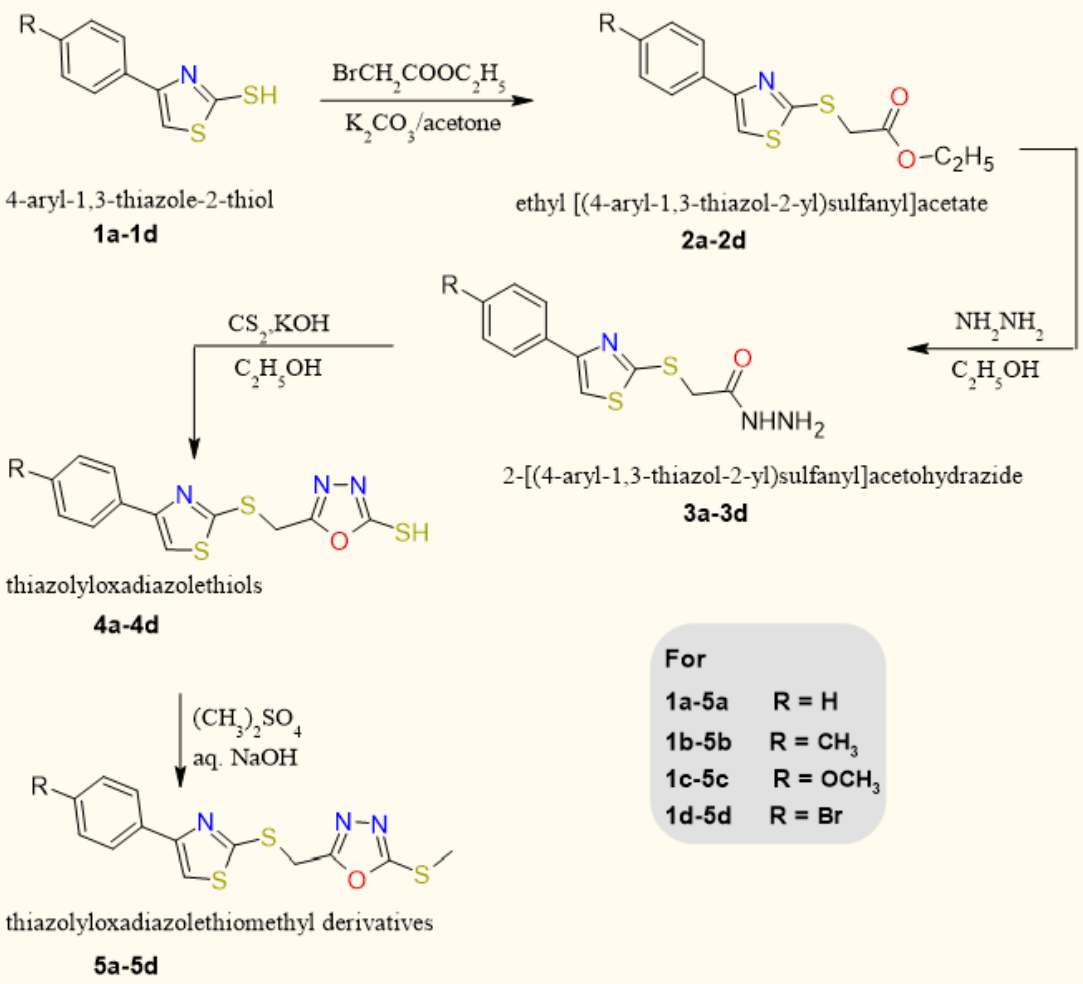
The biological activities of 1,3,4-oxadizoles and thiazoles are well known for several decades. Its nearly three and half decades ago that some compounds were synthesised, by one of the Authors, having both 1,3,4-oxadiazole and thiazole moieties in it [**15**] namely 5-{[(4-aryl-1,3-thiazol-2-yl)sulfanyl] methyl}1,3,4-oxadiazole-2-thiol (4a-4d) and 2-(methylsulfanyl)-5-{[(4-aryl-1,3-thiazol-2-yl) sulfanyl] methyl}1,3,4-oxadiazole (5a-5d). Here in, (4a-4d) will be referred in this text as thiazolyloxadiazolethiols and (5a-5d) will be referred as thiazolyloxadiazolethiomethyl derivatives.



Scheme 1: Synthesis of thiazolyloxadiazolethiols (4a-4d) and thiazolyloxadiazolethiomethyl derivatives(5a-5d) [IUPAC names given in **Table 1**.]

The reaction sequence for the synthesis of thiazolyloxadiazolethiols (4a-4d) and thiazolyloxadiazolethiomethyl derivatives(5a-5d) has been summarized in **Scheme 1**. The compounds prepared were evaluated for their *in-vitro* antifungal and antibacterial activities [**15**]. The IUPAC name for the synthesized compounds (4a-4d and 5a -5d) are summarized in **Table 1**.

Table 1. IUPAC names of oxadiazolylthiazolethiol (4a-4d) and oxadiazolylthiazolethiolmethyl derivatives (5a-5d)

4a	5-{[(4-phenyl-1,3-thiazol-2-yl)sulfanyl]methyl}-1,3,4-oxadiazole-2-thiol
4b	5-({[4-(4-methylphenyl)-1,3-thiazol-2-yl]sulfanyl}methyl)-1,3,4-oxadiazole-2-thiol
4c	5-({[4-(4-methoxyphenyl)-1,3-thiazol-2-yl]sulfanyl}methyl)-1,3,4-oxadiazole-2-thiol
4d	5-({[4-(4-bromophenyl)-1,3-thiazol-2-yl]sulfanyl}methyl)-1,3,4-oxadiazole-2-thiol
5a	2-(methylsulfanyl)-5-{[(4-phenyl-1,3-thiazol-2-yl)sulfanyl]methyl}-1,3,4-oxadiazole
5b	2-({[4-(4-methylphenyl)-1,3-thiazol-2-yl]sulfanyl}methyl)-5-(methylsulfanyl)-1,3,4-oxadiazole
5c	2-({[4-(4-methoxyphenyl)-1,3-thiazol-2-yl]sulfanyl}methyl)-5-(methylsulfanyl)-1,3,4-oxadiazole
5d	2-({[4-(4-bromophenyl)-1,3-thiazol-2-yl]sulfanyl}methyl)-5-(methylsulfanyl)-1,3,4-oxadiazole

With the development of computational chemistry over the years, several *In-silico* tools are developed to study the physicochemical properties and toxicity profile of unknown or synthesized compounds. The present work includes the study of physicochemical properties and toxicity profile of synthesized thiazolyloxadiazolethiols and corresponding thiazolyloxadiazolethiomethyl derivatives using Chemicalize ChemAxon [**16, 17**] and Protox-II online web server [**18, 19, 20**].

RESULT AND DISCUSSION

We have explored the physicochemical properties and toxicity profile of earlier synthesized thiazolyloxadiazolethiols and corresponding thiazolyloxadiazolethiomethyl derivatives. All studies were carried out using *In silico* tools. For physicochemical properties, like logP (octanol/water partition coefficient), logD (distribution coefficient), logS (intrinsic solubility), pKa (*acidic* and *basic*) and HLB (hydrophilic-lipophilic balance), online web server Chem Axon chemicalize was used **Table 2**.

Toxicity profile was evaluated using Protox-II server for lethal dose values (LD_{50}, Oral toxicity),

Organ toxicity (Hepatotoxicity) and Toxicity endpoints (Mutagenicity, Carcinogenicity, Cytotoxicity, Immunotoxicity) **Table 3**.

Physicochemical properties: The phenylthiazolyloxadiazolethiol derivative 4a**,** has been found to have acidic pka value 6.5 and basic pka as 0.59. The compounds 4b-4d showed acidic and basic pka in the same range. The thiomethyl derivative 5a showed only basic pKa of 0.59 as it does not have the free thiol group **Figure 2**. Similarly, compounds 5b-5d showed basic pKa of 0.59.

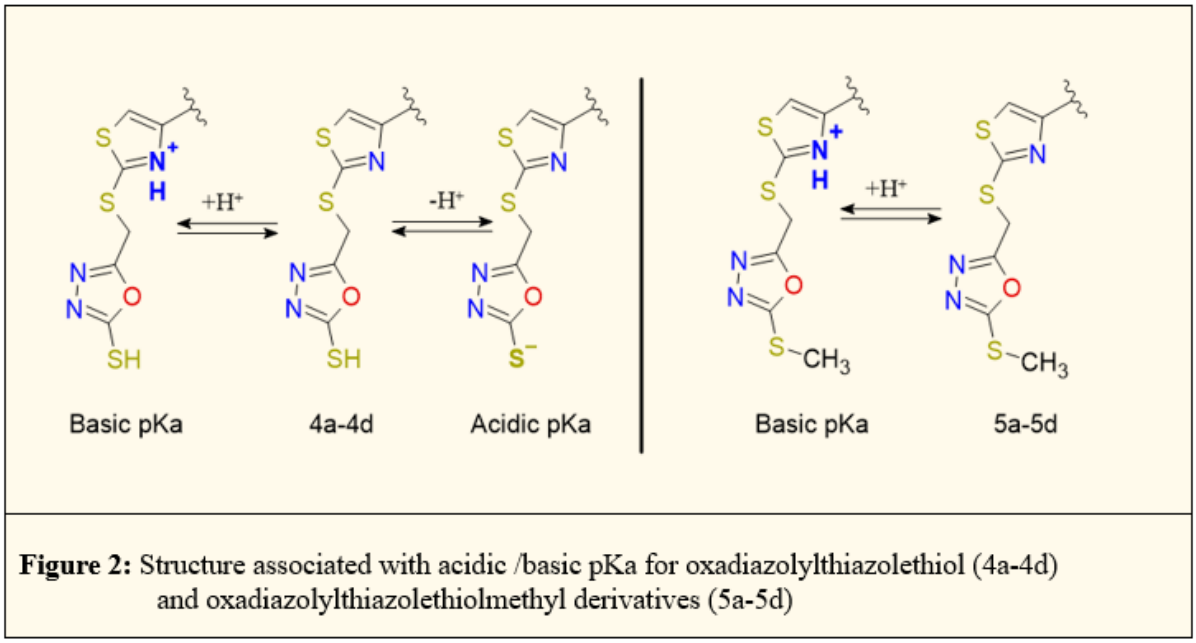


Figure 2: Structure associated with acidic /basic pKa for oxadiazolylthiazolethiol (4a-4d) and oxadiazolylthiazolethiolmethyl derivatives (5a-5d)

The logP value for compound 4a is 3.22 and is lower than its corresponding thiomethyl derivative 5a (logP 3.75). The same pattern was observed for compounds 4b-4d and their corresponding thiomethyl derivatives 5b-5d.

The logD pH 7.4 for compounds 4a-4d was found to be lower than their corresponding thiomethyl derivatives 5a-5d. The higher logP and logD values of thiomethyl derivative (5a-5d) compared to corresponding thiol derivatives (4a-4d) is attributed to their high lipophilicity. The hydrophilic lipophilic balance (HLB) measures the degree of a molecule being hydrophilic or lipophilic. The HLB values of thiol derivatives 4a-4d are higher compared to their corresponding thiomethyl derivatives 5a5d. These observations indicate high lipophilicity of thiomethyl derivatives. The logS values for all compounds 4a-4d and 5a-5d are low (< 0.01mg/mL) and indicate their poor solubility.

Table 2. Physicochemical data of oxadiazolylthiazolethiol (4a-4d) and oxadiazolylthiazolethiolmethyl derivatives (5a-5d)

Compound No.	Formula (Molar mass g/mol)	Acidic pKa	Basic pKa	logP	HLB	logD (pH 7.4)	logS
4a	$C_{12}H_9N_3OS_3$ (307.4)	6.5	0.59	3.223	9.642	2.38	-5.608
4b	$C_{13}H_{11}N_3OS_3$ (321.43)	6.5	0.59	3.736	9.111	2.90	-6.104
4c	$C_{13}H_{11}N_3O_2S_3$ (337.43)	6.49	0.59	3.065	10.654	2.22	-5.584
4d	$C_{12}H_8BrN_3OS_3$ (386.3)	6.48	0.59	3.992	8.736	3.14	-6.566
5a	$C_{13}H_{11}N_3OS_3$ (321.43)	N.A.	0.59	3.758	9.099	3.76	-5.708
5b	$C_{14}H_{13}N_3OS_3$ (335.46)	N.A.	0.59	4.271	8.574	4.27	-6.203
5c	$C_{14}H_{13}N_3O_2S_3$ (351.46)	N.A.	0.59	3.6	10.082	3.60	-5.679
5d	$C_{13}H_{10}BrN_3OS_3$ (400.33)	N.A.	0.59	4.527	8.205	4.53	-6.651

Note: The logP values are also reported in Table 3 as predicted by Protox II.

Toxicity profile*:* The LD50 (oral toxicity) of the compound 4a is predicted as 300 mg/kg. The LD50 of the compounds 4b,4d,5a,5b, and 5d is predicted as 140 mg/kg. All these compounds are placed in toxicity class 3. The LD50 of the compounds 4c and 5c (methoxy- substituted) is predicted as 1000 mg/kg and are placed in toxicity class 4. All the compounds were found to be hepatoxicity active. All compounds, except for compounds 4d and 5d (bromo- substituted), are predicted to be carcinogenic. All compounds were found to be inactive towards Immunotoxicity, Mutagenicity and Cytotoxicity. The topological polar surface area (TPSA) value for 4c (methoxy- substituted) is 153.38 $Å^2$, which is higher than the value of 144.15 $Å^2$ for compounds 4a,4b and 4d . Similarly, TPSA value for 5c (methoxy-substituted) is 139.88 $Å^2$ which is higher than the value of 130.65 $Å^2$ for compounds 5a,5b and 5d.

Table 3. Toxicity profile of oxadiazolylthiazolethiol (4a-4d) and oxadiazolylthiazolethiolmethyl derivatives (5a-5d**)**

Compound No.	logP	TPSA Å²	LD50 mg/kg *Toxicity Class*	Hepa-toxicity	Carcino-genicity	Immuno-toxicity	Muta-genicity	Cyto-toxicity
4a	3.77	144.15	300 *Class 3*	Active	Active	Inactive	Inactive	Inactive
4b	4.08	144.15	140 *Class 3*	Active	Active	Inactive	Inactive	Inactive
4c	3.78	153.38	1000 *Class 4*	Active	Active	Inactive	Inactive	Inactive
4d	4.54	144.15.	140 *Class 3*	Active	**Inactive**	Inactive	Inactive	Inactive
5a	4.21	130.65	140 *Class 3*	Active	Active	Inactive	Inactive	Inactive
5b	4.52	130.65	140 *Class 3*	Active	Active	Inactive	Inactive	Inactive
5c	4.22	139.88	1000 *Class 4*	Active	Active	Inactive	Inactive	Inactive
5d	4.97	130.65	140 *Class 3*	Active	**Inactive**	Inactive	Inactive	Inactive

Note: The logP values are also reported in Table 2 as predicted by Chemicalize chemAxon.

CONCLUSION

The compounds 5-{[(4-aryl-1,3-thiazol-2-yl)sulfanyl]methyl}-1,3,4-oxadiazole-2-thiol (4a-4d) and 2-(methylsulfanyl)-5-{[(4-aryl-1,3-thiazol-2-yl)sulfanyl]methyl}-1,3,4-oxadiazole (5a-5d) were synthesized earlier. The study of their physicochemical properties is carried out using online web server Chemicalize chemAxon. The toxicity profile study is carried out using Protox-II server. The logP, logD and HLB values of thiomethyl derivatives (5a-5d) indicate their high lipophilicity compared to corresponding thiol derivatives (4a-4d). The predicted value of logP in **Table 2** and **Table 3** are different due to difference in data set used for computation by individual servers. However, the same pattern is observed in their lipophilicity. The logS values for all compounds 4a-4d and 5a-5d is low and indicate

their poor solubility. The compounds 4a-4d showed acidic and basic pka in the same range, however their thiomethyl derivatives 5a-5d showed only basic pKa, as these do not have the free thiol group.

Computational study shows these compounds to be toxic and all these compounds are placed in toxicity class 3, except for compounds 4c and 5c (methoxy- substituted) that are placed in toxicity class 4. Toxicity classes are defined according to the Globally Harmonized System (GHS) of classification of labelling of chemicals. LD50 values are given in mg/kg (a) **Class 1**: fatal if swallowed (LD50 ≤ 5) (b) **Class 2**: fatal if swallowed (5 < LD50 ≤ 50) (c) **Class 3**: toxic if swallowed (50 < LD50 ≤ 300) (d) **Class 4**: harmful if swallowed (300 < LD50 ≤ 2000) (**e**) **Class 5**: may be harmful if swallowed (2000 < LD50 ≤ 5000) (f) **Class 6**: non-toxic (LD50 > 5000).

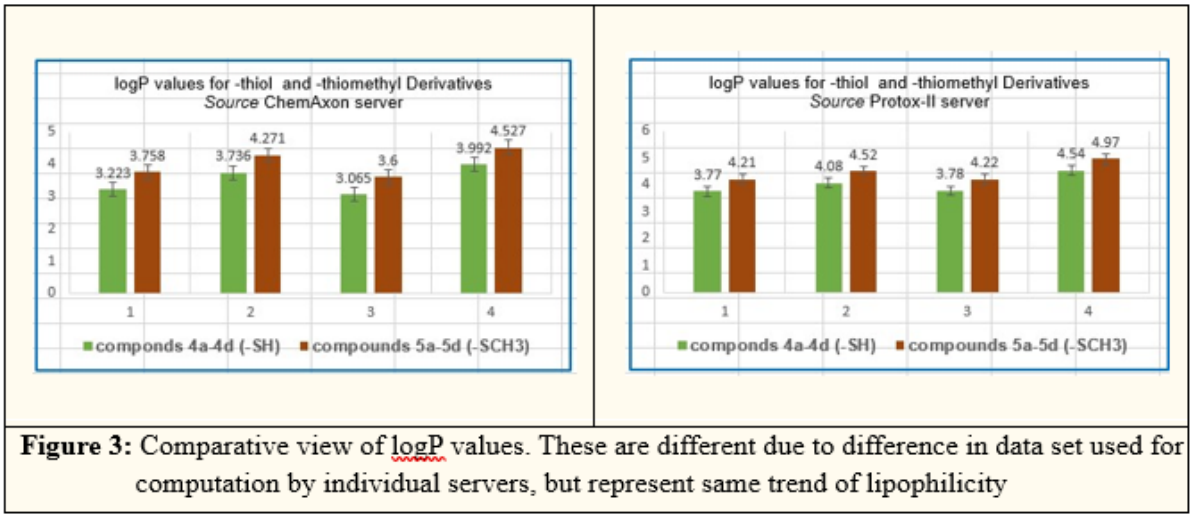


Figure 3: Comparative view of logP values. These are different due to difference in data set used for computation by individual servers, but represent same trend of lipophilicity

The topological polar surface area (TPSA) value for methoxy- substituted compounds 4c and 5c is higher than the corresponding compounds 4a,4b, 4d and compounds 5a,5b ,5d respectively.

All these compounds are found to be hepatoxicity active. Except for compounds 4d and 5d (bromo-substituted) all other compounds are predicted to be carcinogenic. All compounds are found to be inactive towards Immunotoxicity, Mutagenicity and Cytotoxicity.

From toxicity profile it can be concluded that these compounds are not a safe choice for further investigations to be used as agrochemicals.

REFERENCES

1. Tyrell, J. A., & Quin, L. D. (2010). *Fundamentals of heterocyclic chemistry: importance in nature and in the synthesis of pharmaceuticals*. John Wiley & Sons.
2. Bala, S.; Kamboj, S.; Kumar, A. Heterocyclic 1, 3, 4-oxadiazole compounds with diverse biological activities: A comprehensive review. J. Pharm. Res 2010, 3, 2993–2997.

3. Somani, R. R., & Shirodkar, P. Y. (2011). Oxadiazole: A biologically important heterocycle. Der Pharma Chemica; 2009, 1 (1): 130-140 (Google Scholar)
4. Singh R, Chauhan A (2013) Biological importance of 1,3,4-Oxadiazole derivatives. Int J Adv Biol Res 3:140–149
5. PubChem CID for the Chemical compounds used in this article: (a) Furamizole (PubChem CID: 5378303), (b) Raltegravir (PubChem CID: 54671008), (c) Nesapidil (PubChem CID :175512),
6. British national formulary: BNF 69 (69 ed.). British Medical Association. 2015. p. 429. ISBN 9780857111562.
7. Summa, V., Petrocchi, A., Bonelli, F., Crescenzi, B., Donghi, M., Ferrara, M., & Rowley, M. (2008). Discovery of raltegravir, a potent, selective orally bioavailable HIV-integrase inhibitor for the treatment of HIV-AIDS infection. *Journal of medicinal chemistry*, *51*(18), 5843-5855.
8. Caputo, F.; Corbetta, S.; Piccolo, O.; Vigo, D. Seeking for Selectivity and Efficiency: New Approaches in the Synthesis of Raltegravir. Org. Process Res. Dev. 2020, 24, 1149–1156.
9. Abdu-Rahem, L. R., Ahmad, A. K., & Abachi, F. T. (2021). Synthesis and medicinal attributes of thiazole derivatives: A review. *Sys. Rev. Pharm*, *12*, 290-295.
10. PubChem CID for the Chemical compounds used in this article: (a) Tiazofurin (PubChem CID: 457954), (b) Niridazole (PubChem CID: 6093), (c) Amiphenazole (PubChem CID: 10275), (d) Thiabendazole (PubChem CID: 5430)
11. PubChem CID for the Chemical compounds used in this article: (a) Bentaluron (PubChem CID: 4408229), (b) Methabenzthiazuron (PubChem CID: 29216), (c) Thiacloprid (PubChem CID :115224), (d) Clothianidin (PubChem CID: 86287519)
12. Mendieta-Wejebe, J. E., Rosales-Hernández, M. C., Padilla-Martínez, I. I., García-Báez, E. V., & Cruz, A. (2023). Design, Synthesis and Biological Activities of (Thio) Urea Benzothiazole Derivatives. *International Journal of Molecular Sciences*, *24*(11), 9488.
13. Beketov, M. A., & Liess, M. (2008). Acute and delayed effects of the neonicotinoid insecticide thiacloprid on seven freshwater arthropods. *Environmental Toxicology and Chemistry: An International Journal*, *27*(2), 461-470.
14. Uneme, H. (2011). Chemistry of clothianidin and related compounds. *Journal of Agricultural and Food Chemistry*, *59*(7), 2932-2937.
15. Ahluwalia, V.K, Arora, K.K and Mehta, B. (1988). Synthesis of Some 4-Aryl-2-(5′-mercapto-1′, 3′, 4′-oxadiazol-2′-ylmethylmercapto) thiazoles and Their Derivatives, Indian Journal of Chemistry Section B. (1988), **27B**, 183-184
16. Calculator Plugins were used for structure property prediction and calculation of logP, pKa, logD , Solubility Predictor ;ChemAxon (http://www.chemaxon.com)
17. Chemicalize was used for name to structure generation/prediction of *physicochemical* properties/etc, https://chemicalize.com/ developed by ChemAxon (http://www.chemaxon.com)
18. ProTox-II - Prediction of TOXicity of chemicals (charite.de); https://tox-new.charite.de/protox_II/
19. Banerjee, P., Eckert, A. O., Schrey, A. K., & Preissner, R. (2018). ProTox-II: a webserver for the prediction of toxicity of chemicals. *Nucleic acids research*, *46*(W1), W257-W263.
20. Drwal, M. N., Banerjee, P., Dunkel, M., Wettig, M. R., & Preissner, R. (2014). ProTox: a web server for the in-silico prediction of rodent oral toxicity. *Nucleic acids research*, *42*(W1), W53W58.