Computational Drug-Likeness Studies of Selected Thiosemicarbazones: A Sustainable Approach for Drug Designing

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Abstract

Drug intake, its absorption in the body, removal, and various side effects are factors considered when designing the drugs. Here, the *in silico* tools act as virtual shortcuts assisting in the prediction of several important physicochemical properties like molecular weight, polar surface area (PSA), molecular flexibility etc. to evaluate probable drug leads as potential drug candidates. Moreover, these tools also play an important role in the prediction of the bioactivity score of probable drug lead against various human receptors. This paper presents a virtual combinatorial library of selected thiosemicarbazone (TSC) ligands and their metal complexes. Different properties like physicochemical, bioactivity score, absorption, distribution, metabolism, excretion and toxicity (ADMET) parameters were assessed. Structures of ligands and complexes were drawn and downloaded in PDB format using ChemDraw Ultra 12.0. Physicochemical parameters were calculated using Molinspiration, SwissADME and ADMET properties were calculated using admetSAR (2.0). Molecular docking was performed using PyRx Python Prescription 0.8. with two proteins namely Transforming Growth Factor Beta (Tgf- β) and Janus Kinase. Transforming Growth Factor Beta (Tgf- β) and Janus Kinase are some cytokines involved in cell development, proliferation, and death. Salicyldehyde thiosemicarbazone, acenaphthenequinone thiosemicarbazone and 2-chloronicotinic thiosemicarbazone and their virtually designed complexes exhibited appreciable *in silico* results. Most ligands and complexes had good bioactivity values against all the biological targets.

Keywords: Thiosemicarbazones; *in silico* studies; bioactivity score; molecular docking

Introduction

➢Schiff bases are condensation products of primary amines and carbonyl compounds [1].

➢ Thiosemicarbazones (TSCs) of various aldehydes and ketones occupy a special place among Schiff based ligands due to the various donor atoms present in them [2-3].

➢ Transition metal ion complexes of TSCs have been the subject of many studies [4]. These compounds possess a range of biological applications that include antitumor [5], antifungal], antiviral and antibacterial activities.

➢ The mechanism of action of TSCs is due to their ability to inhibit DNA biosynthesis, probably by blocking the enzyme ribonucleotide diphosphate reductase; binding to the nitrogen bases of DNA, hindering or blocking base replication, or creating lesions in the DNA strands by oxidative rupture [3].

Materials and Methods

- Structures of ligands and complexes were drawn and downloaded in PDB format using ChemDraw Ultra 12.0.
- Physicochemical parameters were calculated using online softwares viz. Molinspiration, SwissADME and ADMET properties were calculated using admetSAR (2.0).
- Molecular docking was performed using PyRx Python Prescription 0.8.

Results and Discussion

Table 1 Common names of the selected TSCs for virtual screening

S. No.	Chemical Formula	Name of the Compound
1	$C_6H_{11}N_3OS$	Acetyl-acetone thiosemicarbazone
2	$C_8H_9N_3S$	Benzaldehydethiosemicarbazone
3	$C_9H_{11}N_3O_2S$	Vanillin thiosemicarbazone
4	$C_8H_7Cl_2N_3S$	2,4-dichlorobenzaldehyde thiosemicarbazone
5	$C_8H_7Cl_2N_3S$	2,6-dichlorobenzaldehyde thiosemicarbazone
6	$C_{10}H_{14}N_4S$	4-(dimethylamino)benzaldehydethiosemicarbazone
7	$C_9H_{11}N_3S$	Acetophenonethiosemicarbazone
8	$C_{10}H_{10}N_4S$	Indole-3-carboxaldehyde thiosemicarbazone
9	$C_2H_5N_3S$	Formaldehyde thiosemicarbazone
10	$C_8H_9N_3OS$	Salicyldehydethiosemicarbazone
11	$C_{13}H_7N_3OS$	Acenaphthenequinonethiosemicarbazone
12	$C_7H_7ClN_4OS$	2-chloronicotinic acid thiosemicarbazone

Table 2 Pharmacokinetic parameters of the selected TSCs and their complexes

S. No.	Compound	Volume	TPSA	MW	M log p	nOHNH	nON	nRB
1	$C_6H_{11}N_3OS$	156.35	67.48	173.24	0.02	3	4	4
2	$C_8H_9N_3S$	158.86	50.41	179.25	1.88	3	3	3
3	$C_9H_{11}N_3O_2S$	192.42	79.88	225.27	1.22	4	5	4
4	$C_8H_7Cl_2N_3S$	185.93	50.41	248.14	3.17	3	3	3
5	$C_8H_7Cl_2N_3S$	185.93	50.41	248.14	3.14	3	3	3
6	$C_{10}H_{14}N_4S$	284.76	53.65	222.32	1.99	3	4	4
7	$C_9H_{11}N_3S$	175.42	50.41	193.28	1.80	3	3	3
8	$C_{10}H_{10}N_4S$	187.83	66.20	218.28	2.03	4	4	3
9	$C_2H_5N_3S$	87.76	50.41	103.15	0.23	3	3	2
10	$C_8H_9N_3OS$ (L_1)	166.87	70.64	195.25	1.82	4	4	3
11	$C_{13}H_7N_3OS$ (L_2)	210.99	67.48	255.30	2.48	3	4	2
12	$C_7H_7ClN_4OS$ (L_3)	176.25	83.53	230.68	0.51	4	5	3
13	$[Fe(L_1)_2]SO_4$	428.39	201.43	617.30	-1.44	8	14	4
14	$[Co(L_1)_2]Cl_2$	398.10	123.03	524.37	2.61	8	8	4
15	$[Cu(L_1)_2]SO_4$	409.58	175.64	554.13	0.18	8	12	4
16	$[Zn(L_1)_2]SO_4$	409.58	175.64	555.98	0.90	8	12	4
17	$[Fe(L_2)_2]SO_4$	497.87	169.33	666.54	1.38	6	12	2
18	$[Co(L_2)_2]Cl_2$	486.38	116.72	644.48	4.09	6	8	2
19	$[Cu(L_2)_2]SO_4$	497.87	169.33	674.25	1.66	6	12	2
20	$[Zn(L_2)_2]SO_4$	497.87	169.33	676.09	2.38	6	12	2
21	$[Fe(L_3)_2]SO_4$	428.39	201.43	617.30	-1.44	8	14	4
22	$[Co(L_3)_2]Cl_2$	416.91	148.82	595.23	1.27	8	10	4
23	$[Cu(L_3)_2]SO_4$	428.39	201.43	625.00	-1.16	8	14	4
24	$[Zn(L_3)_2]SO_4$	428.39	201.43	626.85	-0.44	8	14	4

TPSA= Topological polar surface arca (defined as a sum of surfaces of polar atoms in a molecule)
LogP = Logarithm of compound partition coefficient between n-octanol and water.
OHNH= number hydrogen bond donor.
ON= number hydrogen bond acceptor.
nRB= number of rotatable bonds
MW= molecular weight.

Table 3 Drug-likeness of the selected TSCs and their metal complexes

S.No.	Compound	Physiochemical Properties		Medicinal Feasibility	
		FRACTION Csp^3	Molar Refractivity	PAINS	Synthetic accessibility
1	$C_6H_{11}N_3OS$	0.50	48.14	0 alert	2.92
2	$C_8H_9N_3S$	0.00	53.20	0 alert	2.17
3	$C_9H_{11}N_3O_2S$	0.11	61.72	1 alert	2.24
4	$C_8H_7Cl_2N_3S$	0.00	63.22	0 alert	2.43
5	$C_8H_7Cl_2N_3S$	0.00	63.22	0 alert	2.39
6	$C_{10}H_{14}N_4S$	0.20	67.41	0 alert	2.17
7	$C_9H_{11}N_3S$	0.11	58.01	0 alert	2.13
8	$C_{10}H_{10}N_4S$	0.00	65.06	0 alert	2.12
9	$C_2H_5N_3S$	0.00	28.71	0 alert	2.83
10	$C_8H_9N_3OS$ (L_1)	0.00	55.22	1 alert	2.21
11	$C_{13}H_7N_3OS$ (L_2)	0.00	73.98	1 alert	2.68
12	$C_7H_7ClN_4OS$ (L_3)	0.00	57.58	0 alert	2.28
13	$[Fe(L_1)_2]SO_4$	0.25	131.03	1 alert	5.70
14	$[Co(L_1)_2]Cl_2$	0.25	131.61	1 alert	5.59
15	$[Cu(L_1)_2]SO_4$	0.25	131.03	1 alert	5.60
16	$[Zn(L_1)_2]SO_4$	0.25	131.03	1 alert	5.55
17	$[Fe(L_2)_2]SO_4$	0.15	168.55	0 alert	6.56
18	$[Co(L_2)_2]Cl_2$	0.15	169.12	0 alert	6.48
19	$[Cu(L_2)_2]SO_4$	0.15	168.55	0 alert	6.45
20	$[Zn(L_2)_2]SO_4$	0.15	168.55	0 alert	6.44
21	$[Fe(L_3)_2]SO_4$	0.29	134.92	0 alert	5.90
22	$[Co(L_3)_2]Cl_2$	0.29	135.49	0 alert	5.76
23	$[Cu(L_3)_2]SO_4$	0.29	134.92	0 alert	5.83
24	$[Zn(L_3)_2]SO_4$	0.29	134.92	0 alert	5.82

Table 4 ADMET properties of the selected TSCs and their metal complexes

S. No.	Compound	HIA	Caco-2	BBB	HOB
1	$C_6H_{11}N_3OS$	(+) 0.9342	(-) 0.6104	(+) 0.9793	(+) 0.6857
2	$C_8H_9N_3S$	(+) 0.9692	(+) 0.9335	(-) 0.9828	(+) 0.8000
3	$C_9H_{11}N_3O_2S$	(+) 0.9785	(+) 0.7591	(+) 0.9731	(+) 0.6286
4	$C_8H_7Cl_2N_3S$	(+) 0.9694	(+) 0.8509	(+) 0.9773	(+) 0.7000
5	$C_8H_7Cl_2N_3S$	(+) 0.9694	(+) 0.9434	(+) 0.9773	(+) 0.8857
6	$C_{10}H_{14}N_4S$	(+)0.9700	(+)0.8595	(+)0.9775	(+)0.6857
7	$C_9H_{11}N_3S$	(+)0.9948	(+)0.8765	(+)0.9844	(+)0.7429
8	$C_{10}H_{10}N_4S$	(+)0.9729	(+)0.7011	(+)0.9729	(+)0.6571
9	$C_2H_5N_3S$	(+)0.9014	(+)6085	(+)0.9844	(+)0.7286
10	$C_8H_9N_3OS$ (L_1)	(+)0.9698	(+)0.8413	(+)0.9732	(+)0.7571
11	$C_{13}H_7N_3OS$ (L_2)	(+)0.9921	(+)0.6885	(+)0.9749	(+)0.7143
12	$C_7H_7ClN_4OS$ (L_3)	(+)0.9910	(+)0.5565	(+)0.9748	(+)0.8571
13	$[Fe(L_1)_2]SO_4$	(+) 0.9562	(-) 0.7028	(+) 0.9704	(+) 0.5857
14	$[Co(L_1)_2]Cl_2$	(+) 0.9605	(-) 0.6077	(+) 0.9730	(+) 0.6571
15	$[Cu(L_1)_2]SO_4$	(+)0.9562	(-)0.7028	(+)0.9704	(+)0.5143
16	$[Zn(L_1)_2]SO_4$	(+)0.9562	(-)0.7028	(+)0.9704	(+)0.6143
17	$[Fe(L_2)_2]SO_4$	(+) 0.9829	(-) 0.7916	(+) 0.9689	(+) 0.5429
18	$[Co(L_2)_2]Cl_2$	(+) 0.9847	(-) 0.7685	(+) 0.9729	(+) 0.6000
19	$[Cu(L_2)_2]SO_4$	(+)0.9829	(-)0.7916	(+)0.9689	(-)0.5000
20	$[Zn(L_2)_2]SO_4$	(+)0.9829	(-)0.7916	(+)0.9689	(+)0.6286
21	$[Fe(L_3)_2]SO_4$	(+) 0.9463	(-) 0.7818	(+) 0.9688	(+) 0.6000
22	$[Co(L_3)_2]Cl_2$	(+) 0.9515	(-) 0.7468	(+) 0.9722	(+) 0.6143
23	$[Cu(L_3)_2]SO_4$	(+)0.9463	(-)0.7818	(+)0.9688	(-)0.5000
24	$[Zn(L_3)_2]SO_4$	(+)0.9463	(-)0.7818	(+)0.9688	(+)0.5714

Table 5 Bioactivity scores of the selected thiosemicarbazones and metal complexes

S. No.	Compound	Parameters of Boactivity Score					
		GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear Receptor Ligand	Protease Inhibitor	Enzyme Inhibitor
1	$C_6H_{11}N_3OS$	-2.60	-1.86	-3.10	-2.98	-1.88	-1.04
2	$C_8H_9N_3S$	- 2.85	- 1.59	- 1.86	- 2.42	- 1.60	- 0.91
3	$C_9H_{11}N_3O_2S$	-1.51	-1.25	-1.30	-1.67	-1.26	-0.59
4	$C_8H_7Cl_2N_3S$	-1.72	-1.35	-1.53	-2.08	-1.40	-0.77
5	$C_8H_7Cl_2N_3S$	-1.62	-1.30	-1.55	-2.01	-1.33	-0.71
6	$C_{10}H_{14}N_4S$	-1.48	-1.21	-1.24	-1.70	-1.17	-0.62
7	$C_9H_{11}N_3S$	-1.83	-1.42	-1.93	-1.96	-1.22	-0.70
8	$C_{10}H_{10}N_4S$	-1.14	-1.04	-1.04	-1.66	-1.07	-0.41
9	$C_2H_5N_3S$	-4.01	-3.94	-3.96	-4.07	-3.74	-3.72
10	$C_8H_9N_3OS$ (L_1)	-1.79	-1.55	-1.63	-1.99	-1.33	-0.74
11	$C_{13}H_7N_3OS$ (L_2)	-0.94	-0.94	-0.96	-1.21	-1.02	-0.43
12	$C_7H_7ClN_4OS$ (L_3)	-1.41	-0.69	-1.24	-1.79	-1.04	-0.46
13	$[Fe(L_1)_2]SO_4$	0.21	-0.04	-0.05	-0.07	0.18	0.11
14	$[Co(L_1)_2]Cl_2$	0.06	-0.03	-0.04	-0.07	0.05	0.01
15	$[Cu(L_1)_2]SO_4$	0.16	-0.04	-0.05	-0.07	0.18	0.16
16	$[Zn(L_1)_2]SO_4$	0.16	-0.04	-0.05	-0.07	0.18	0.23
17	$[Fe(L_2)_2]SO_4$	0.11	-0.47	-0.33	-0.38	0.06	-0.10
18	$[Co(L_2)_2]Cl_2$	0.04	-0.24	-0.20	-0.25	-0.05	-0.11
19	$[Cu(L_2)_2]SO_4$	0.07	-0.47	-0.33	-0.38	0.06	-0.12
20	$[Zn(L_2)_2]SO_4$	0.07	-0.47	-0.33	-0.38	0.06	-0.06
21	$[Fe(L_3)_2]SO_4$	0.25	0.12	0.04	-0.14	0.20	0.22
22	$[Co(L_3)_2]Cl_2$	0.12	0.15	0.06	-0.15	0.08	0.05
23	$[Cu(L_3)_2]SO_4$	0.20	0.12	0.04	-0.14	0.20	0.19
24	$[Zn(L_3)_2]SO_4$	0.20	0.12	0.04	-0.14	0.20	0.26

Table 6 Binding energies (kJ/mol) of the selected TSCs and their complexes

S.No.	Chemical Formula	Binding energy (kJ/mol) against Target Protein	
		Transforming Growth Factor Beta	Janus Kinase
1.	$C_6H_{11}N_3OS$	-5.1	-5.3
2.	$C_8H_9N_3S$	-6.2	-6.2
3.	$C_9H_{11}N_3O_2S$	-6.2	-6.6
4.	$C_8H_7Cl_2N_3S$	-6.6	-6.4
5.	$C_8H_7Cl_2N_3S$	-6.3	-6.7
6.	$C_{10}H_{14}N_4S$	-6.1	-6.3
7.	$C_9H_{11}N_3S$	-6.5	-6.3
8.	$C_{10}H_{10}N_4S$	-7.0	-7.0
9.	$C_2H_5N_3S$	-4.1	-3.9
10.	$C_8H_9N_3OS$ (L_1)	-6.1	-6.3
11.	$C_{13}H_7N_3OS$(L_2)	-7.8	-8.5
12.	$C_7H_7ClN_4OS$(L_3)	-6.1	-6.3
13.	$[Fe(L_1)_2]SO_4$	-6.5	-7.8
14.	$[Co(L_1)_2]Cl_2$	-6.3	-6.1
15.	$[Cu(L_1)_2]SO_4$	-6.3	-6.7
16.	$[Zn(L_1)_2]SO_4$	-6.3	-6.3
17.	$[Fe(L_2)_2]SO_4$	-8.4	-7.6
18.	$[Co(L_2)_2]Cl_2$	-6.3	-6.2
19.	$[Cu(L_2)_2]SO_4$	-5.1	-7.1
20.	$[Zn(L_2)_2]SO_4$	-6.2	-6.2
21.	$[Fe(L_3)_2]SO_4$	-6.2	-6.2
22.	$[Co(L_3)_2]Cl_2$	-6.5	-7.5
23.	$[Cu(L_3)_2]SO_4$	-7.0	-7.4
24.	$[Zn(L_3)_2]SO_4$	-6.3	-6.1

Conclusion

The paper has highlighted the significance of virtual screening and computational drug designing which is cost and time effective. However, thiosemicarbazone complexes have received considerable attention for their pharmaceutical utility. Studies involving Quantitative Structure Activity Relationship (QSAR) and Structure Activity Relationship (SAR) must be undertaken to gain insight of the influence of structural modification upon activity.

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