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ARTICLE

Prediction of *in silico* ADMET Properties and Molecular Docking Study of Substituted Thiadiazole for Screening of Antibacterial and Antifungal Activities against Protein Targets Helicobacter pylori α-Carbonic Anhydrase and *Trypanosoma brucei* Pteridine Reductase

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ABSTRACT

The aim of this work was to evaluate the physico-chemical, pharmacokinetic parameters (absorption, distribution, metabolism, excretion and toxicity) and pharmacodynamic parameters (bioactivity and adverse reactions) of substituted thiadiazole by means of *in silico* computational prediction. Online softwares such as Pre-ADMET, Molinspiration and rule of five were used for the analysis. Substituted thiadiazole fits the characteristics of drug-likeness, pharmacokinetic properties appropriate to the predicted patterns and activities within the scope for the treatment of infection in the stomach or duodenum (first part of the small intestine), gastritis and trypanosomiasis. Therefore, *in silico* results allow us to conclude that substituted thiadiazole is predicted to be a potential future drug candidate, due to its relevant Drug-likeness profile, bioavailability, excellent liposolubility and adequate pharmacokinetics, including at the level of CNS, penetrating the blood-brain barrier. Molecular docking studies have also been performed to screen the antibacterial and antifungal activities of the 50 designed compounds against protein targets *Helicobacter pylori* α-carbonic anhydrase (PDB: 5TUO) and *Trypanosoma brucei* Pteridine Reductase (PTR1) (PDB: 4WCD) respectively. Among all the compounds C11 exhibited the most significant affinity score against *Helicobacter pylori* α-carbonic anhydrase and C37 exhibited the most significant affinity score against *Trypanosoma brucei* pteridine reductase (PTR1) best significant hydrogen bonds interaction at the active site of protein.

KEYWORDS

Toxicity prediction, Molecular Docking, Molinspiration, PreADMET, Rule of five, Substituted thiadiazole.

INTRODUCTION

Heterocyclic chemistry is one of the most fascinated areas in the field of research. Thiazoles, thiadiazoles, oxadiazoles, indoles and pyrroles are some of the most important classes of heterocyclic compounds due to their interesting biological activities [1]. Heterocyclic compounds may found in considerable number of organic molecules that exhibit antimicrobial efficiencies. The antimicrobial efficiencies of these molecules have is fundamentally contingent by structures of these molecules [2].

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Thiadiazoles exhibit a broad spectrum of biological activities possibly due to the presence of the toxophoric -*N*-C-S moiety [3]. Heterocycles bearing a symmetrical 1,3,4-thiadiazole moiety are reported to show a broad spectrum of biological and pharmacological activities such as antimicrobial, anti-inflammatory, anticancer, antituberculosis, antiparasitic, anticonvulsants, antioxidant, herbicidal and insecticidal properties [4,5].

In recent years, the search for novel drug has utilized sophisticated procedures involving computational techniques such as Docking and Pharmacophore modeling, which are widely used in virtual screening studies [6]. The resistance towards available drugs is rapidly becoming a major worldwide problem. The need to design new compounds to deal with this resistance has become one of the most important areas of research today. Thiadiazole is a versatile moiety that exhibits a wide variety of biological activities. Thiadiazole moiety acts as hydrogen binding domain and two-electron donor system. It also acts as a constrained pharmacophore [7]. In present study, the novel derivatives of thiadiazole have been designed and docked for possible targets followed by antimicrobial and antifungal activities.

COMPUTATIONAL DETAIL

The structure of thiadiazole derivatives examined are presented in Fig. 1 and their names are shown in Table-1. These compounds contain several functional groups which differ in polarity: hydroxyl, methyl, acetyl group, chloro, iodo, nitro, bromo, amino, *etc.* Molecular properties such as Pre-ADMET, Molinspiration and rule of five were evaluated for the analysis using online program [8]. The results are presented in Table-2.

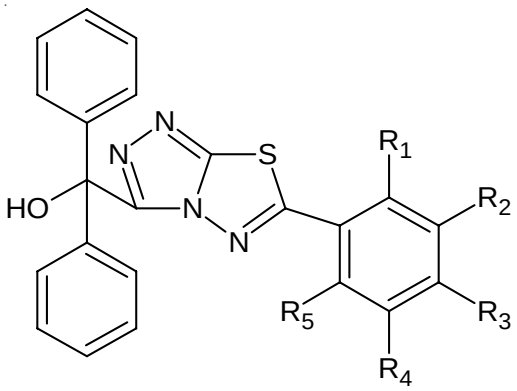

Fig. 1 Structure of substituted thiadiazole

Lipinski's rule of five calculations: The Lipinski's rule of five calculations were performed to determine the degree of absorption or permeability of compounds against lipid bilayers in the human body. The Lipinski rule is a parameter that demonstrates the oral bioavailability of a compound. Good bioavailability will satisfy the Lipinski rule where the maximum molecular weight of the compound is 500, the log P is not greater than 5, the hydrogen bond donor is less than 5 and hydrogen bond acceptor is less than 10 [9].

Lipinski's rule of five helps in distinguishing between drug like and non drug like molecules. It predicts high probability of success or failure due to drug likeness for molecules complying with 2 or more of the following:

1. Molecular mass less than 500 Dalton
2. High lipophilicity (expressed as Log P less than 5)
3. Less than 5 hydrogen bond donors
4. Less than 10 hydrogen bond acceptors
5. Molar refractivity should be between 40-130

TABLE-1
THIADIAZOLES WITH DIFFERENT SUBSTITUTIONS

S. No	Code	R_1	R_2	R_3	R_4	R_5	S. No	Code	R_1	R_2	R_3	R_4	R_5
1	C1	H	$-NH_2$	H	H	H	26	C26	$-NH_2$	H	Cl	H	H
2	C2	H	H	$-NH_2$	H	H	27	C27	$-NH_2$	CH_3	H	H	H
3	C3	H	H	H	H	H	28	C28	H	NH_2	CH_3	H	H
4	C4	Br	H	H	H	H	29	C29	COC_6H_5	H	H	H	H
5	C5	H	H	Br	H	H	30	C30	H	H	COC_6H_5	H	H
6	C6	Cl	H	H	H	H	31	C31	Cl	H	NO_2	H	H
7	C7	H	Cl	H	H	H	32	C32	NO_2	H	H	Cl	H
8	C8	H	H	Cl	H	H	33	C33	H	H	CN	H	H
9	C9	H	$-NH_2$	H	$-NH_2$	H	34	C34	H	NH_2	NH_2	H	H
10	C10	Cl	H	Cl	H	H	35	C35	Cl	H	H	H	Cl
11	C11	H	$-NO_2$	H	$-NO_2$	H	36	C36	OH	H	OH	H	H
12	C12	$C_6H_5N_2O$	$-NO_2$	H	$-NO_2$	H	37	C37	OH	H	H	H	OH
13	C13	H	H	-OH	H	H	38	C38	H	OH	OH	H	H
14	C14						39	C39	H	OH	H	OH	H
15	C15	I	H	H	H	H	40	C40	OCH_3	OCH_3	H	H	H
16	C16	OCH_3	H	H	H	H	41	C41	OCH_3	H	H	H	OCH_3
17	C17	H	H	OCH_3	H	H	42	C42	H	OCH_3	OCH_3	H	H
18	C18	H	H	CH_3	H	H	43	C43	H	OCH_3	H	OCH_3	H
19	C19	H	CH_3	H	H	H	44	C44	H	$N(CH_3)_2$	H	H	H
20	C20	CH_3	H	H	H	H	45	C45	H	H	$N(CH_3)_2$	H	H
21	C21	H	$-NO_2$	H	H	H	46	C46	H	CH_3	CH_3	H	H
22	C22	H	H	$-NO_2$	H	H	47	C47	H	CH_3	H	CH_3	H
23	C23	H	-OH	-OH	-OH	H	48	C48	H		H	H	NO_2
24	C24	I	I	H	I	H	49	C49	F	H	H	H	H
25	C25	$COCH_3$	H	H	H	H	50	C50	H	F	H	H	H

TABLE-2
RESULTS OF LIPINSKI'S RULE OF FIVE CALCULATIONS

Compd. code	Mass	HBD	HBA	Log P	Molar refractivity	Compd. code	Mass	HBD	HBA	Log P	Molar refractivity
C1	399.0	3	5	3.719198	113.492195	C26	433.5	3	6	3.918788	112.631172
C2	399.0	3	6	4.037308	110.552177	C27	413.0	3	6	4.345729	115.289177
C3	384.0	1	5	4.455109	106.139771	C28	413.0	3	6	4.345729	115.289177
C4	462.0	1	5	5.217611	113.839775	C29	488.0	1	6	5.687521	137.939819
C5	462.0	1	5	5.217611	113.839775	C30	488.0	1	6	5.686110	136.014328
C6	418.5	1	5	4.391299	108.484764	C31	463.5	1	7	4.299499	115.139160
C7	418.5	1	5	4.391299	108.484764	C32	463.5	1	7	3.787608	114.222664
C8	418.5	1	5	4.391299	108.484764	C33	409.0	1	6	4.326789	110.854767
C9	414.0	5	7	3.619509	114.964577	C34	414.0	5	7	3.619509	114.964577
C10	453.0	1	5	4.272779	110.563766	C35	453.0	1	5	4.327489	110.829765
C11	474.0	1	9	4.271509	119.448555	C36	416.0	3	7	3.866308	109.469368
C12	594.0	2	12	4.828831	154.543472	C37	416.0	3	7	3.866308	109.469368
C13	400.0	2	6	4.160708	107.804565	C38	416.0	3	7	3.866308	109.469368
C14	385.0	1	6	3.850109	103.934776	C39	416.0	3	7	3.866308	109.469368
C15	511.0	1	5	5.059711	118.856766	C40	444.0	1	7	4.926009	118.917763
C16	414.0	1	6	4.463708	112.691765	C41	444.0	1	7	4.472308	119.243767
C17	414.0	1	6	4.463708	112.691765	C42	444.0	1	7	4.472308	119.243767
C18	398.0	1	5	4.763529	110.876770	C43	444.0	1	7	4.472308	119.243767
C19	398.0	1	5	4.763529	110.876770	C44	427.0	1	6	4.521109	120.466766
C20	398.0	1	5	4.763529	110.876770	C45	427.0	1	6	4.521109	120.466766
C21	429.0	1	7	4.363308	112.794159	C46	412.0	1	5	4.839250	114.680771
C22	429.0	1	7	4.363308	112.794159	C47	412.0	1	5	5.071950	115.613770
C23	432.0	4	8	3.571908	111.134163	C48	658.0	2	11	658.0	164.563965
C24	765.0	1	5	6.268912	144.290863	C49	402.0	1	5	4.594210	106.097771
C25	426.0	1	6	4.657709	116.144264	C50	402.0	1	5	4.594210	106.097771

Log P (octanol/water partition coefficient): Log P is calculated by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors. Method is very robust and is able to process practically all the organic and most organometallic molecules.

Molecular polar surface area TPSA: It's calculation is based on the methodology reported by Zabiulla *et al.* [1] as a sum of fragment contributions. O- and N-centered polar fragments are considered. PSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability and blood-brain barrier penetration.

Molecular volume: Method for calculation of molecule volume developed at Molinspiration is based on group contributions. These have been obtained by fitting sum of fragment contributions to "real" 3D volume for a training set of about twelve thousand, mostly drug-like molecules. 3D molecular geometries for a training set were fully optimized by the semi empirical AM1 method.

Rule of 5 properties: A set of simple molecular descriptors used by Lipinski in formulating his "Rule of 5" [2]. The rule states, that most "drug-like" molecules have log P <= 5, molecular weight <= 500, number of hydrogen bond acceptors <= 10 and number of hydrogen bond donors <= 5. Molecules violating more than one of these rules may have problems with bioavailability. The rule is called "Rule of 5", because the border values are 5, 500, 2*5 and 5.

RESULTS AND DISCUSSION

Number of rotatable bonds-nrotb: This simple topological parameter is a measure of molecular flexibility. It has been shown to be a good descriptor of oral bioavailability of drugs. Rotatable bond is defined as any single non-ring bond, bounded to non-terminal heavy (*i.e.* non-hydrogen) atom. Amide C-N bonds are not considered because of their high rotational energy barrier [9]. The results of molecular properties are shown in Table-3.

***in silico* ADME properties, drug likeness and toxicity study of designed compounds:** At the Ames test endpoint of PreADMET, there are 41 mutagenic compounds and 9 other compounds are non-mutagenic compounds. The positive test results on Ames test indicate that the compound is mutagenic and has the possibility as carcinogenic. In the prediction of carcinogenicity in rat produced 2 carcinogenic positive compounds and 48 other compounds are negative carcinogenic. While in the prediction of carcinogenicity in mouse 47 compounds are not carcinogenicity. At the hERG Inhibition, 36 compounds show low risk while others are ambiguous. The results are presented in Tables 4 and 5.

***in silico* ADME properties of designed compounds:** In this study, the designed compounds were screened using *in silico* Pre-ADMET software to predict their overall ADME properties and toxicity hazards (Table-6), since they play a vital role in drug discovery and environmental riskiness [10-12]. Different parameters have been screened such as:

Blood-brain barrier (BBB) penetration, which served in reducing the side effects and toxicity or improving the efficacy of drugs whose pharmacological activity of the brain. Predicting BBB penetration means predicting whether the target pass across the Blood Brain Barrier. All tested targets showed positive values, indicating that they can easily cross the BBB, but their values are less than 1 (CBrain/Cblood) [13,14].

TABLE-3
RESULT OF MOLECULAR PROPERTIES USING ONLINE PROGRAM (MOLINSPIRATION)

Code	miLog P	TPSA	N atoms	m.w.	nON	nOHNH	N violations	nrotb	Volume
C1	3.85	89.34	29	399.48	6	3	0	4	341.68
C2	3.82	89.34	29	399.48	6	3	0	4	341.68
C3	4.77	63.32	28	384.46	5	1	0	4	330.39
C4	5.53	63.32	29	463.36	5	1	1	4	348.28
C5	5.58	63.32	29	463.36	5	1	1	4	348.28
C6	5.40	63.32	29	418.91	5	1	1	4	343.93
C7	5.43	63.32	29	418.91	5	1	1	4	343.93
C8	5.45	63.32	29	418.91	5	1	1	4	343.93
C9	2.85	115.36	30	414.49	7	5	0	4	352.97
C10	6.06	63.32	30	453.35	5	1	1	4	357.46
C11	4.62	154.97	34	474.46	11	1	1	6	377.06
C12	6.26	199.92	43	594.57	14	2	3	8	475.59
C13	4.29	83.55	29	400.46	6	2	0	4	338.41
C14	3.70	76.21	28	385.45	6	1	0	4	326.24
C15	5.81	63.32	29	510.36	5	1	2	4	354.38
C16	4.78	72.55	30	414.49	6	1	0	5	355.94
C17	4.83	72.55	30	414.49	6	1	0	5	355.94
C18	5.22	63.32	29	398.49	5	1	1	4	346.95
C19	5.20	63.32	29	398.49	5	1	1	4	346.95
C20	5.17	63.32	29	398.49	5	1	1	4	346.95
C21	4.71	109.14	31	429.46	8	1	0	5	353.73
C22	4.73	109.14	31	429.46	8	1	0	5	353.73
C23	3.51	124.00	31	432.46	8	4	0	4	354.45
C24	7.88	63.32	31	762.15	5	1	2	4	402.36
C25	4.62	80.39	31	426.50	6	1	0	5	365.94
C26	4.86	89.34	30	433.92	6	3	0	4	355.22
C27	4.61	89.34	30	413.51	6	3	0	4	358.24
C28	4.63	89.34	30	413.51	6	3	0	4	358.24
C29	6.18	80.39	36	488.57	6	1	1	6	420.78
C30	6.23	80.39	36	488.57	6	1	1	6	420.78
C31	5.34	109.14	32	463.91	8	1	1	5	367.26
C32	5.34	109.14	32	463.91	8	1	1	5	367.26
C33	4.53	87.11	30	409.47	6	1	0	4	347.25
C34	3.67	115.36	30	414.49	7	5	0	4	352.97
C35	6.03	63.32	30	456.35	5	1	1	4	357.46
C36	4.00	103.78	30	416.46	7	3	0	4	346.43
C37	4.24	103.78	30	416.46	7	3	0	4	346.43
C38	3.80	103.78	30	416.46	7	3	0	4	346.43
C39	3.47	103.78	30	416.46	7	3	0	4	346.43
C40	4.59	81.79	32	444.52	7	1	0	6	381.48
C41	4.79	81.79	32	444.52	7	1	0	6	381.48
C42	4.42	81.79	32	444.52	7	1	0	6	381.48
C43	4.81	81.79	32	444.52	7	1	0	6	381.48
C44	4.85	66.56	31	427.53	6	1	0	5	376.30
C45	4.88	66.56	31	427.53	6	1	0	5	376.30
C46	5.60	63.32	30	412.52	5	1	1	4	363.51
C47	5.60	63.32	30	412.52	5	1	1	4	363.51
C48	6.56	192.27	45	658.70	13	2	3	10	511.73
C49	4.89	63.32	29	402.45	5	1	0	4	335.32
C50	4.91	63.32	29	402.45	5	1	0	4	335.32

TABLE-4
RESULT OF TOXICITY STUDIES OF DESIGNED COMPOUNDS

Toxicity		Compounds
Ames_test	Mutagen	C1, C2, C3, C4, C5, C6, C7, C8, C9, C11, C12, C14. C15, C16, C17, C18, C19, C20, C21, C22, C25, C26, C27, C28, C30, C31, C32, C33, C34, C35, C40, C41, C42, C43, C44, C45, C46, C47, C48, C49, C50
	Non-Mutagen	C10, C13, C23, C24, C29, C36, C37, C38, C39
Carcino_Mouse	Negative	C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C25, C26, C27, C28, C29, C30, C31, C32, C33, C34, C35, C36, C37, C38, C39, C40, C41, C42, C43, C44, C45, C46, C47, C48
	Positive	C24, C49, C50
Carcino_Rat	Negative	C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C14, C16, C17, C18, C19, C20, C21, C22, C23, C25, C26, C27, C28, C29, C30, C31, C32, C33, C34, C35, C36, C37, C38, C39, C40, C41, C42, C43, C44, C45, C46, C47, C48, C49, C50
	Positive	C15, C24
hERG_inhibition	Ambiguous	C1, C2, C9, C12, C13, C23, C26, C27, C28, C34, C36, C37, C38, C39
	Low-risk	C3, C4, C5, C6, C7, C8, C10, C11, C14, C15, C16, C17, C18, C19, C20, C21, C22, C24, C25, C29, C30, C31, C32, C33, C35, C40, C41, C42, C43, C44, C45, C46, C47, C48, C49, C50

TABLE-5
RESULT OF DRUG LIKENESS OF DESIGNED COMPOUNDS

Drug likeness		Compounds
CMC_like_Rule	Qualified	C1, C2, C3, C4, C5, C6, C7, C8, C9, C11, C13, C14, C16, C17, C18, C19, C20, C21, C22, C23, C25, C26 C27, C28, C31, C32, C33, C34, C36, C37, C38, C39, C40, C41, C42, C43, C44, C45, C49, C50
	Not qualified	C10, C12, C15, C24, C29, C30, C35, C46, C47, C48
MDDR_like_Rule	Mid structure	C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C25, C26, C27, C28, C30, C31, C32, C33, C34, C35, C36, C37, C38, C39, C44, C45, C46, C47,
	Drug like	C29, C30, C40, C41, C42, C43, C48
Rule_of_Five	Suitable	C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C13, C14, C16, C17, C18, C19, C20, C21, C22, C23, C25, C26, C27, C28, C29, C30, C31, C32, C33, C34, C35, C36, C37, C38, C39, C40, C41, C42, C43, C44, C45, C46, C47, C49, C50
	Not suitable	C12, C15, C24, C48

TABLE-6
In silico ADME PROPERTIES OF DESIGNED COMPOUNDS

Code	Alog P98 value	BBB	Caco2	HIA	Plasma protein binding	Skin permeability
C1	4.0951	1.09412	6.86278	96.04468	93.01192	-2.66559
C2	4.0951	1.09412	6.86278	96.04468	93.01192	-2.66559
C3	4.8417	2.84962	34.3121	96.73425	93.91195	-2.29074
C4	5.5901	1.97573	25.1985	97.27943	100.00000	-2.18889
C5	5.5901	1.45922	25.2594	97.27943	100.00000	-2.20517
C6	5.5061	2.00967	34.3276	97.0224	95.40413	-2.29703
C7	5.5061	1.50055	34.2449	97.0224	95.29732	-2.3173
C8	5.5061	1.44493	34.2449	97.0224	96.13766	-2.31845
C9	3.3485	0.381788	5.06403	95.31979	91.53968	-3.41396
C10	6.1705	0.572776	33.1334	97.39162	100.00000	-2.24731
C11	4.6305	0.080501	0.65952	88.42942	97.65392	-2.41542
C12	6.7325	0.126487	0.49612	84.27578	94.82345	-2.40154
C13	4.5743	1.02929	9.34075	95.50092	92.79012	-2.75769
C14	3.6911	0.525556	24.268	97.15625	94.41168	-2.81454
C15	5.4199	2.04044	24.4127	98.23237	100.00000	-2.22967
C16	4.8253	1.40955	37.1127	96.853094	95.458894	-2.41139
C17	4.8253	1.76564	36.5086	96.85309	92.51566	-2.43632
C18	5.3279	1.98632	37.9229	96.77718	93.11167	-2.23196
C19	5.3279	1.70812	37.9229	96.77718	96.9019	-2.23246
C20	5.3279	1.98632	37.9229	96.77718	93.11167	-2.23196
C21	4.7361	0.08878	0.886104	98.28660	95.04202	-2.31343
C22	4.7361	0.09214	0.886431	98.28660	94.01742	-2.3138
C23	4.0395	0.359701	4.97113	90.42746	93.78927	-3.64304
C24	6.5763	0.248263	30.0264	97.27923	100.00000	-2.0858
C25	4.5816	1.02094	21.9952	97.07481	100.00000	-2.381
C26	4.7595	0.909313	19.3328	96.09204	95.86122	-2.62483
C27	4.5813	0.920038	9.20661	96.01463	91.51665	-2.47881
C28	4.5813	0.980131	8.993	96.0159	91.72933	-2.49808
C29	6.2459	1.03586	31.0922	97.14275	96.60008	-1.886*
C30	6.2459	0.331425	26.607	97.14275	96.75739	-1.89518*
C31	5.4005	0.124268	5.74856	98.7369	94.69687	-2.30181
C32	5.4005	0.121677	5.53408	98.7369	97.81694	-2.30001
C33	4.7206	0.345915	12.0434	97.60774	94.60318	-2.24946
C34	3.3485	0.360929	5.06403	95.31524	89.08189	-3.42898
C35	6.1705	0.923301	33.0228	97.39162	99.70124	-2.22691
C36	4.3069	0.617244	5.07931	93.58152	93.53218	-3.43893
C37	4.3069	0.851859	5.28606	93.57984	93.46258	-3.41434
C38	4.3069	0.495773	4.8632	93.57902	92.64665	-3.46085
C39	4.3069	0.670919	4.86977	93.58314	96.61893	-3.45159
C40	4.8089	0.861336	38.3846	97.16901	97.86846	-2.50718
C41	4.8089	0.966683	38.8437	97.16901	96.31664	-2.51032
C42	4.8089	0.918493	37.8926	97.16901	95.50593	-2.54701
C43	4.8089	0.883139	37.8926	97.16901	99.51763	-2.56797
C44	5.0039	1.157160	42.0424	96.85178	97.31214	-2.24293
C45	5.0039	1.780960	42.0424	96.85178	93.77445	-2.24416
C46	5.8141	0.702357	40.7967	96.83136	96.63823	-2.17064
C47	5.8141	0.680797	40.7967	96.83136	100.00000	-2.18667
C48	6.9439	0.06079*	0.556342	85.41073	92.11564	-2.39776*
C49	5.0472	2.00440	37.3463	96.73704	93.54327	-2.50895
C50	5.0472	1.38135	36.4797	96.73704	96.07351	-2.5407

Human intestinal absorption (HIA) is the process through which the drug was administrated orally from the intestine. All compounds exhibited higher values in the range 70-100% belonging to the well-absorbed compounds and, therefore, may be assimilated through human intestine [14].

Caco2 cell permeability (CCP) as a human colon epithelial cancer cell line generally used to estimate the *in vitro* human intestinal permeability of the drug in comparison to human enterocytes and express the transporter and the efflux of proteins. All tested compounds displayed positive CCP justifying their middle permeability [15]. Plasma protein binding (PPB) affects the time that a drug stays in the body and can also have an effect upon the drug's efficiency. The degree of binding to plasma proteins dramatically influences the pharmacodynamic and pharmacokinetic behaviour of a drug. Values of % bound < 90 were classified as low and ≥ 90 as high. As shown, compounds **1**, **2**, **3** and **4** showed affinity for a plasmatic protein with the potent value close to 95% binding observed for compound **1**; contrariwise, compound **6** present a lower binding. Likewise, it should be noted that the drug distribution process was highly affected by its ability of binding to protein plasma.

The skin permeability rate is an essential parameter for the transdermal delivery of drugs. In the pharmaceutical fields, skin permeability rate is important factor to predict as a crucial parameter for the transdermal delivery of drugs. PreADMET program is used to predicts *in vitro* skin permeability and the result value is given as log K_p. K_p (cm/h) is defined as [16]:

$$K_p = \frac{K_m \cdot D}{h}$$

where, K_m = Distribution coefficient between stratum corneum and vehicle; D = Average diffusion coefficient (cm^2/h); H = thickness of skin (cm).

The drug must diffuse into the intercellular lipid matrix, which is recognized as the major determinant of drug absorption by the skin [17]. All tested compounds showed negative values of skin permeability, ranging from –2.29 (compounds **3** and **4**) to –1.74 (compound **2**), meaning that it is not important that the compounds be administered *via* transdermal routes.

Calculation of bioactivity scores (Molinspiration program): Online Molinspiration server is used for the prediction of bioactivity scores for G protein-coupled receptors ligand (GPCR), ion channel modulation (ICM), kinase inhibition (KI), nuclear receptor ligand (NRL), protease inhibition (PI) and enzyme inhibition (EI). The values obtained indicate binding affinity of examined compounds to the mentioned receptors and enzymes (negative values indicate low affinity, while positive values indicate greater affinity towards receptors).

Drug score values indicate overall potential of a compound to be a drug candidate. Molinspiration is a web-based tool used to predict the bioactivity score of the synthesized compounds against regular human receptors such as GPCRs, ion channels, kinases, nuclear receptors, proteases and enzymes [18]. The pharmacological activity describes the beneficial effects of drugs in living beings. The drug is supposed to bind with a biological target. Biological targets are the most common proteins such as enzymes, ion channels and receptors. The biological target is also referred to as drug target. The bioactivity scores of the synthesized complexes were calculated for different parameters such as binding to G protein-coupled receptor (GPCR) ligand and nuclear receptor ligand, ion channel modulation, kinase inhibition, protease inhibition and enzyme activity inhibition. All the parameters were calculated with the help of online software Molinspiration (www.molinspiration.com), which predicted moderate biological activity for the synthesized complexes. It is known that for metal complexes, if the bioactivity score is more than 0.0, then the complex is active; if it is between –5.0 and 0.0, then the complex is moderately active and if the bioactivity score is less than –5.0, then it is inactive. As seen in Table-7, the bioactivity scores of the ligand as well as all the four complexes were between –5.0 and 0.0, which clearly indicate that they possess such properties as are required for the complexes to act as potential drugs with some modifications in chemical structure [19,20].

TABLE-7
BIOACTIVITY SCORE OF THE LIGAND AND ITS COMPLEXES

Compound Code	Molinspiration biological activity					
	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
C1	-0.43	-0.77	0.05	-0.71	-0.66	-0.25
C2	-0.42	-0.77	0.07	0.70	-0.66	-0.23
C3	-0.47	-0.84	-0.04	-0.67	-0.74	-0.33
C4	-0.57	-0.89	-0.09	-0.77	-0.83	-0.40
C5	-0.55	-0.87	-0.07	-0.75	-0.82	-0.38
C6	-0.47	-0.87	-0.03	-0.67	-0.80	-0.34
C7	-0.46	-0.82	-0.05	-0.65	-0.77	-0.34
C8	-0.46	-0.81	-0.05	-0.67	-0.76	-0.34
C9	-0.42	-0.77	0.07	-0.73	-0.64	-0.24
C10	-0.45	-0.83	-0.04	-0.66	-0.78	-0.34
C11	-0.52	-0.76	-0.13	-0.68	-0.73	-0.36
C12	-0.54	-1.11	-0.35	-1.02	-0.68	-0.51
C13	-0.43	-0.78	-0.00	-0.55	-0.73	-0.29
C14	-0.40	-0.81	0.13	-0.68	-0.71	-0.25
C15	-0.49	-0.87	-0.05	-0.72	-0.79	-0.40
C16	-0.47	-0.90	-0.06	-0.66	-0.83	-0.36
C17	-0.49	-0.85	-0.07	-0.64	-0.75	-0.35
C18	-0.50	-0.87	-0.07	-0.68	-0.77	-0.37

C19	-0.48	-0.86	-0.05	-0.64	-0.75	-0.35
C20	-0.45	-0.83	-0.09	-0.65	-0.81	-0.34
C21	-0.56	-0.81	-0.13	-0.69	-0.80	-0.38
C22	-0.56	-0.81	-0.15	-0.70	-0.80	-0.40
C23	-0.43	-0.74	0.01	-0.58	-0.70	-0.24
C24	-0.53	-0.85	-0.04	-0.71	-0.77	-0.32
C25	-0.45	-0.72	-0.23	-0.70	-0.72	-0.32
C26	-0.45	-0.77	-0.08	-0.81	-0.71	-0.33
C27	-0.51	-0.85	0.00	-0.72	-0.75	-0.29
C28	-0.45	-0.80	0.07	-0.73	-0.70	-0.27
C29	-0.32	-0.65	0.01	-0.43	-0.63	-0.16
C30	-0.34	-0.67	0.03	-0.42	-0.60	-0.20
C31	-0.56	-0.84	-0.14	-0.69	-0.87	0.41
C32	-0.61	-0.84	-0.21	-0.81	-0.88	-0.40
C33	-0.43	-0.78	0.05	-0.55	-0.69	-0.27
C34	-0.44	-0.77	0.08	-0.67	-0.66	-0.20
C35	-0.44	-0.80	-0.05	-0.66	-0.72	-0.35
C36	-0.43	-0.85	-0.00	-0.55	-0.79	-0.33
C37	-0.43	-0.78	-0.03	-0.59	-0.71	-0.31
C38	-0.43	-0.76	0.01	-0.56	-0.73	-0.27
C39	-0.43	-0.77	0.01	-0.53	-0.72	-0.27
C40	-0.47	-0.84	-0.08	-0.66	-0.80	-0.37
C41	-0.43	-0.78	-0.07	-0.61	-0.70	-0.31
C42	-0.47	-0.80	-0.04	-0.63	-0.73	-0.32
C43	-0.46	-0.81	-0.05	-0.60	-0.72	-0.32
C44	-0.43	-0.79	-0.01	-0.60	-0.71	-0.30
C45	-0.43	-0.78	-0.01	-0.61	-0.71	-0.32
C46	-0.45	-0.84	-0.04	-0.61	-0.73	-0.33
C47	-0.46	-0.84	-0.06	-0.62	-0.72	-0.34
C48	-0.60	-1.42	-0.62	-1.04	-0.72	-0.60
C49	-0.46	-0.83	-0.00	-0.70	-0.78	-0.34
C50	-0.43	-0.81	-0.01	-0.60	-0.72	-0.32

Molecular docking: Molecular modelling studies were performed to investigate the potential interactions between target compound and targeted protein active sites residues to produce targeted protein inhibitory activity by using Molegro virtual docker 6.0.1. The docking protocol was validated by re-docking the co-crystallized ligand into the targeted protein binding pocket.

The 3D structure of protein targets *Helicobacter pylori* α-carbonic anhydrase (PDB: 5TUO) and *Trypanosoma brucei* Pteridine Reductase (PTR1) (PDB: 4WCD) was downloaded from protein data bank. The best score affinity results of the docked simulation are listed in Table-8. Among all synthesized compounds, **5b** and **6b** exhibited the most significant affinity score against *Helicobacter pylori* α-carbonic anhydrase (PDB:

TABLE-8
DOCKING SCORES OF TARGET CONFORMER FOR ENZYMES/PROTEINS OF *Helicobacter pylori* α-CARBONIC ANHYDRASE (PDB: 5TUO) AND *Trypanosoma brucei* PTERIDINE REDUCTASE (PTR1) (PDB: 4WCD)

Compd. code	*Helicobacter pylori* α-carbonic anhydrase (PDB: 5TUO)		*Trypanosoma brucei* Pteridine Reductase (PTR1) (PDB: 4WCD)	
	Dock score	H-bond interaction	Dock score	H-bond Interaction
C1	-114.238	Thr 191, Thr 83	-136.571	Leu208, Ser207
C2	-118.394	Ala 192	-134.697	Leu208, Ser 207
C3	-112.542	Thr 191, Ala 192	-131.080	Cys 168
C4	-113.404	Ala 192	-122.188	Tyr174, Ser95, Lys178
C5	-117.996	Ala 192	-137.572	Cys 168, Asp 161
C6	-115.944	0	-132.764	Cys 168, Asp161
C7	-117.763	Ala 192	-132.300	Leu208
C8	-118.142	Ala 192	-128.955	Tyr 174, Cys 168
C9	-117.590	Thr 83, Ala 192	-136.919	Leu208, Ser 207, Met163, Gly 166
C10	-119.839	Ala 192	-144.921	Leu208,
C11	-138.524	Thr 83, Thr 191, Tyr 25, Asn 227, His 84	-151.862	Leu208, Ser 207,Gly16, Lys178, Asn93
C12	-165.475	His 110, His 84, Trp23	-188.008	Pro 204, Leu208, Gly16, Ile15, Asn 93
C13	-114.408	Thr 191, Ala 192	-136.368	Cys168, Phe171
C14	-117.092	His 84, Thr 191, Lys 88	-30.1175	Tyr 174, Gly205,, Pro 204
C15	-112.640	Ala 192	-127.813	Gly 205, Asp161
C16	-115.439	Asn 108, Lys 88, His 110	-135.483	Cys168, Tyr174
C17	-115.486	Thr 191, Thr 83, Ala 192	-152.245	Leu208, Ser207, Cys168
C18	-118.233	Ala 192	-142.210	Leu208, Ser207

C19	-118.241	Ala 192	-140.588	Ser207, Leu208,
C20	-115.340	Thr 191, Ala 192	-143.944	Ser207, Leu208
C21	-123.743	Lys 88, Trp 23	-146.64	Cys168, Asn175, Tyr174
C22	-119.162	Ala 192, Trp 23	-155.358	Leu208, Ser207, Gly 16, Asn 175
C23	-116.233	Pro 193	-132.421	Leu208, Ser207, Gly16, Asn93
C24	-115.890	Lys 88	-130.059	Tyr 174
C25	-120.000	Lys 88, His 110	-143.786	Leu208, Ser207, Cys168, Asp161
C26	-118.931	Thr 191, Ala 192	-140.937	Asp161, Leu208, Cys168
C27	-115.469	Thr 191, Ala 192	-141.020	Asp161, Leu208
C28	-115.438	Pro 193	-132.908	Asn93, Tyr174
C29	-147.147	His 110, His 84, Thr 83, Lys 88	-175.926	Ser95, Tyr 174, Leu208
C30	-130.823	Thr 83, Thr 191	-167.841	Tyr174, Lys13, Gly16, Asn93
C31	-121.783	Lys 88	-155.357	Leu208, Asn175, Cys168
C32	-126.817	Ala 192, Thr 191	-146.073	Asp161, Ser207, Cys168
C33	-116.656	Ala 192	-145.998	Leu208, Ser 207, Phe171
C34	-114.386	Thr 191	-145.016	Ser207, Leu208,
C35	-117.283	Ala 192	-130.460	Leu208, Ser 207
C36	-117.599	Ala 192, Thr 191	-140.310	Asp161, Leu208
C37	-112.571	Lys 88, Pro 193	-137.596	Asp 161, Tyr174, Ser 207, Gly205, Cys168
C38	-118.606	Ala 192	-138.446	Leu208, Ser207
C39	-119.931	Pro 193	-132.721	Tyr174, Asn 175, Cys168
C40	-119.261	Thr 191, Lys 88, His 84	-141.271	Cys168, Tyr174, Lys178
C41	-126.357	Thr 191	-145.905	Cys168, Asp161, Ser207
C42	-121.323	Ala 192	-136.721	Cys168
C43	-125.695	Thr 83, Thr 191, Tyr 25, Asn 227, His 84	-146.596	Leu208
C44	-121.144	Ala 192	-150.915	Leu208
C45	-113.594	Lys 88	-163.136	Ser207, Leu208, Cys168
C46	-117.084	0	-132.929	Tyr174
C47	-112.447	Lys 88	-138.336	Cys168, Tyr174
C48	-172.621	Ser 90, Lys 78, Lys 133, Thr 191	-204.443	Leu208, Ser207, Tyr174, Ser95
C49	-114.764	Thr 191	-130.329	Tyr 174
C50	-118.338	Ala 192	-136.171	Tyr 174
1SA_303 [A]	-77.762	His 129, Thr 191, His 110, His 84, Tyr 25	-83.1666	Leu208, Ser207, Tyr174
Cefixime	-111.996	Thr191, Lys88	–	–
Ketoconazole	–	–	-151.684	Tyr174, Asn 93, Ala 212

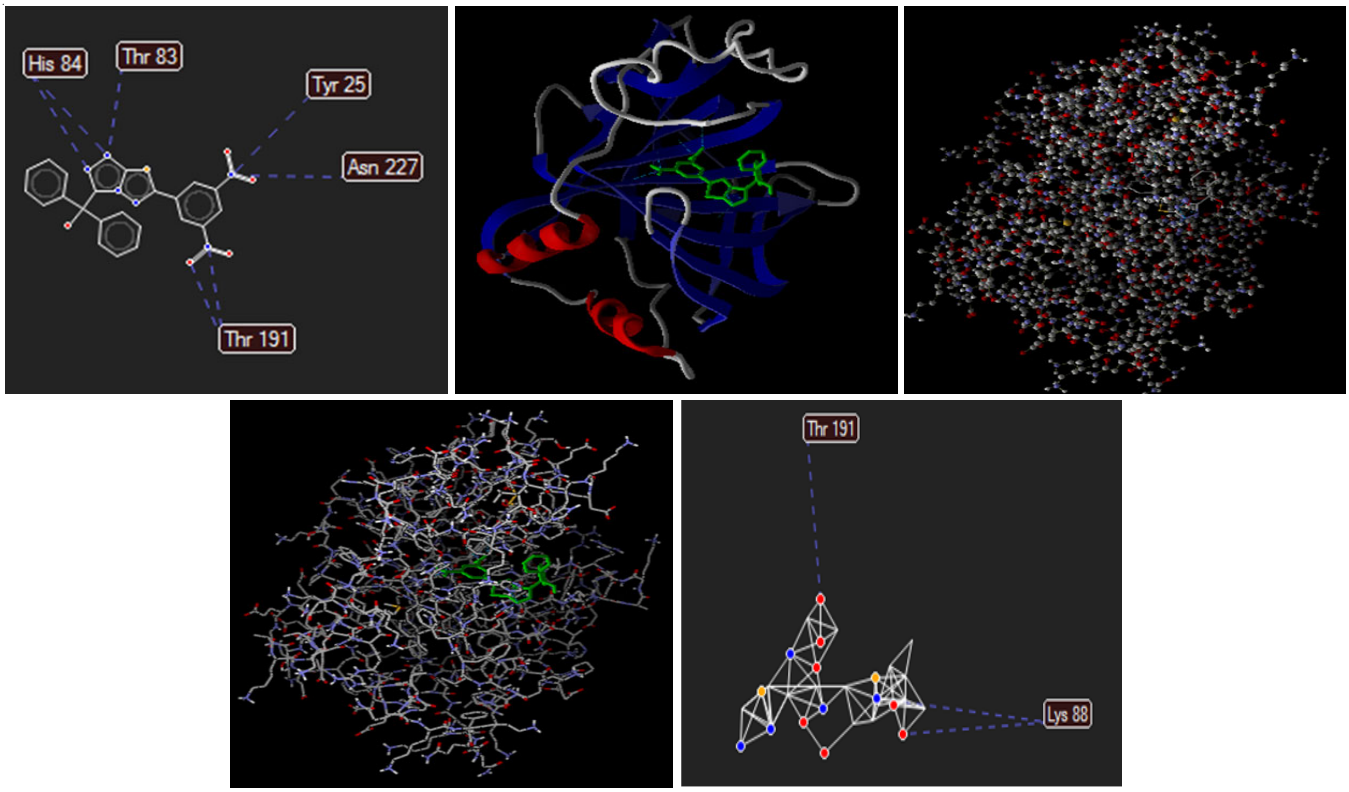

Fig. 2. Representation of most active compound C11 and cefixime for *Helicobacter pylori* α-carbonic anhydrase (PDB: 5TUO). Hydrogen bond interactions are represented as dotted lines

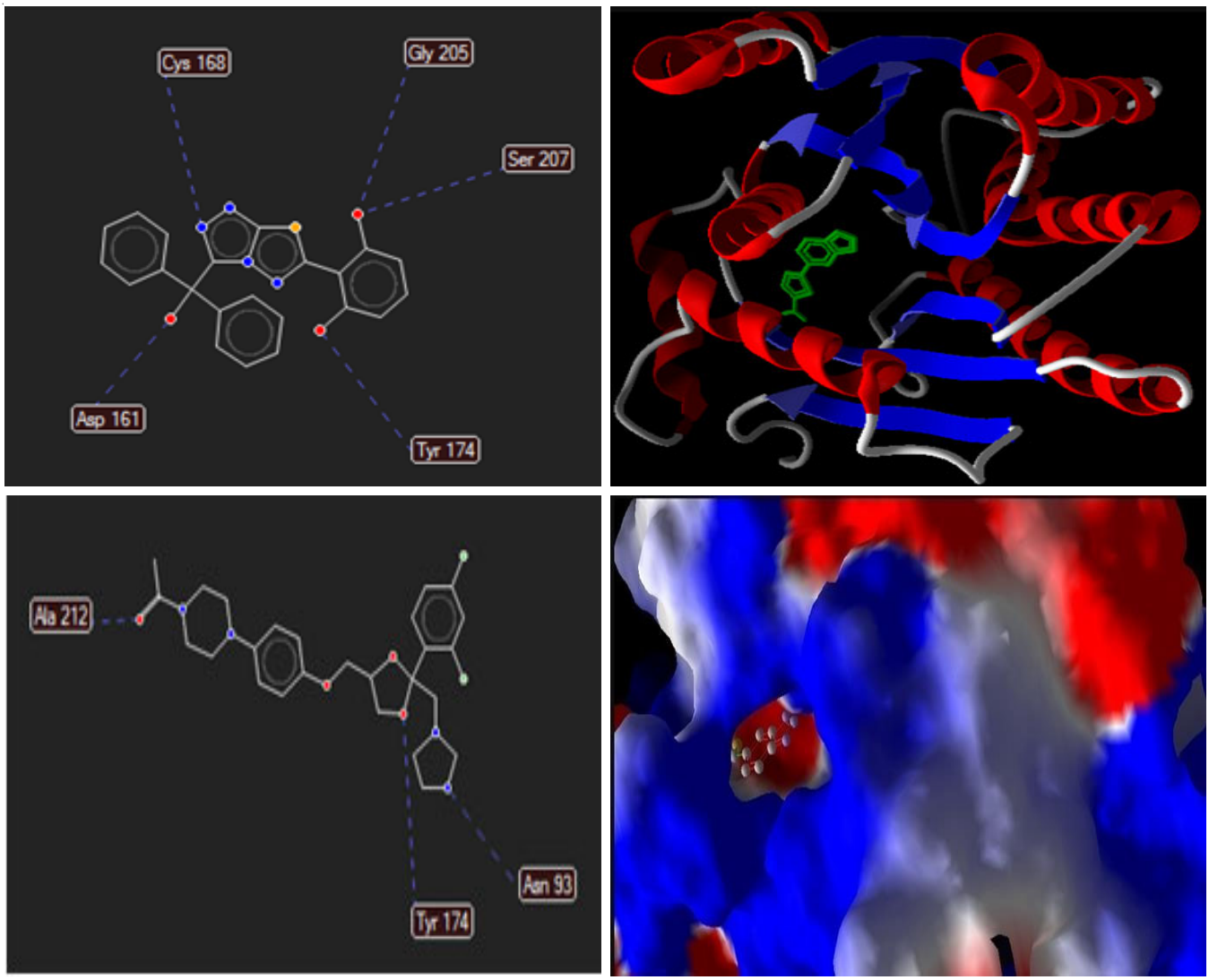

Fig. 3. Representation of most active compound C37 and ketoconazole *Trypanosoma brucei* Pteridine Reductase (PTR1) (PDB: 4WCD). Hydrogen bond interactions are represented as dotted lines

5TUO) and *Trypanosoma brucei* pteridine reductase (PTR1) (PDB: 4WCD).

Conclusion

It is concluded that a series of novel biologically active substituted thiadiazole compounds **c1** to **c50** were designed and screened for antibacterial and antifungal activities. It also concludes From the molecular docking study of *Helicobacter pylori* α-carbonic anhydrase (PDB: 5TUO) and *Trypanosoma brucei* pteridine reductase (PTR1) (PDB: 4WCD) (docking score -138.524 and -137.596, respectively), it was observed that the top ranked conformation of the most active compound **C11** (Fig. 2) for *Helicobacter pylori* α-carbonic anhydrase (PDB: 5TUO) established five hydrogen bonds through amine and hydroxyl group with the binding site residues Thr 83, Thr 191, Tyr 25, Asn 227, His 84 and C37 (Fig. 3) *Trypanosoma brucei* pteridine reductase (PTR1) (PDB: 4WCD) established five hydrogen bonds through amine and hydroxyl group with the binding site residues Asp 161, Tyr174, Ser 207, Gly205, Cys168. Based on results of molecular properties using online program and molecular properties using online program (Molinspiration) and Lipinski's rule of five calculations, all of substituted thiadiazole derivatives conform Lipinski's rule. Boactivity score values of C1, C2, C9, C14, C27, C28, C29, C30 shows positive values indicate greater affinity towards the kinase and nuclear receptors.

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