Med Chem Res
DOI 10.1007/s00044-012-0238-0

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

POM analyses of antitrypanosomal activity of 2-iminobenzimidazoles: favorable and unfavorable parameters for drugs optimization

Taibi Ben Hadda · Rahima Mouhoub · Rahul Jawarkar · Vijay Masand · Ismail Warad

Received: 9 April 2012 / Accepted: 13 September 2012

Abstract POM virtual screening and docking of compounds 2-iminobenzimidazoles (IBIZ) as a novel class of trypanothione reductase inhibitors are described. These 2-IBIZ display potent trypanocidal activity against *Trypanosoma brucei rhodesiense*, with low cytotoxicity. A hypothetical mechanism based on bioinformatic analyses is proposed. The ligands with two neighbor pockets leading to bimetallic (M-Ligand-M/enzyme) complexes are more active than similar ligand without the two terminal arms.

Keywords 2-Iminobenzimidazoles · Trypanocidal activity · *Trypanosoma brucei rhodesiense* · Trypanothione reductase · POM analyses

Introduction

Parasitic protozoa of the family Trypanosomatidae are the causative agent of many significant tropical diseases including African trypanosomiasis, Chagas disease, and Leishmaniasis. There are currently nine key drugs in use for the treatment of these disease states: suramin and pentamidine against early stage African trypanosomiasis and eflornithine and melarsoprol against late stage disease; nifurtimox (Nfx) and benznidazole (Bdz) against early stage Chagas disease; meglumine antimoniate and sodium stibogluconate against Leishmaniasis and amphotericin B against antimony-resistant strains. All of these drugs have severe limitations including long treatment regimes, life-threatening side effects, varied efficacy against late stage diseases, and increasing incidence of drug resistance (Paulino *et al.*, 2005; Sundar *et al.*, 2000; Croft *et al.*, 2006).

Recently, Holloway *et al.* (2007) have analyzed various series by using a high-throughput screening campaign of a library of 100.000 lead-like compounds and identified 2-iminobenzimidazoles (IBIZ) (Fig. 1) as a novel class of trypanothione reductase inhibitors. These 2-IBIZ display potent trypanocidal activity against *Trypanosoma brucei rhodesiense*, which do not inhibit closely related human glutathione reductase and have low cytotoxicity against mammalian cells.

Pharmacology

Molecular properties calculations

For compound **7** and certainly for its 2-IBIZ analogs bearing two functionalized arms, the compounds **3**, **5**, and **8**, depending on the pH and position of the dissociate hydroxyl hydrogen atoms, two possible pockets can be described for the neutral forms. These relevant structures which are ready to coordinate two transition metal atoms are sketched in Fig. 2.

T. Ben Hadda (✉) · R. Mouhoub
Laboratoire de Chimie des Matériaux, Département de Chimie, Faculté des Sciences d'Oujda, Université Mohammed Premier, 60000 Oujda, Morocco
e-mail: tbenhadda@yahoo.fr

R. Jawarkar
Department of Pharmaceutical Chemistry, Sahyadri College of Pharmacy, Methawde, Sangola, Solapur, Maharashtra, India

V. Masand
Department of Chemistry, Vidya Bharati Mahavidyalaya, Camp, Amravati 444602, Maharashtra, India

I. Warad
Department of Chemistry, King Saud University, P. O. Box 2455, Riyadh 11451, Saudi Arabia

Published online: 26 September 2012

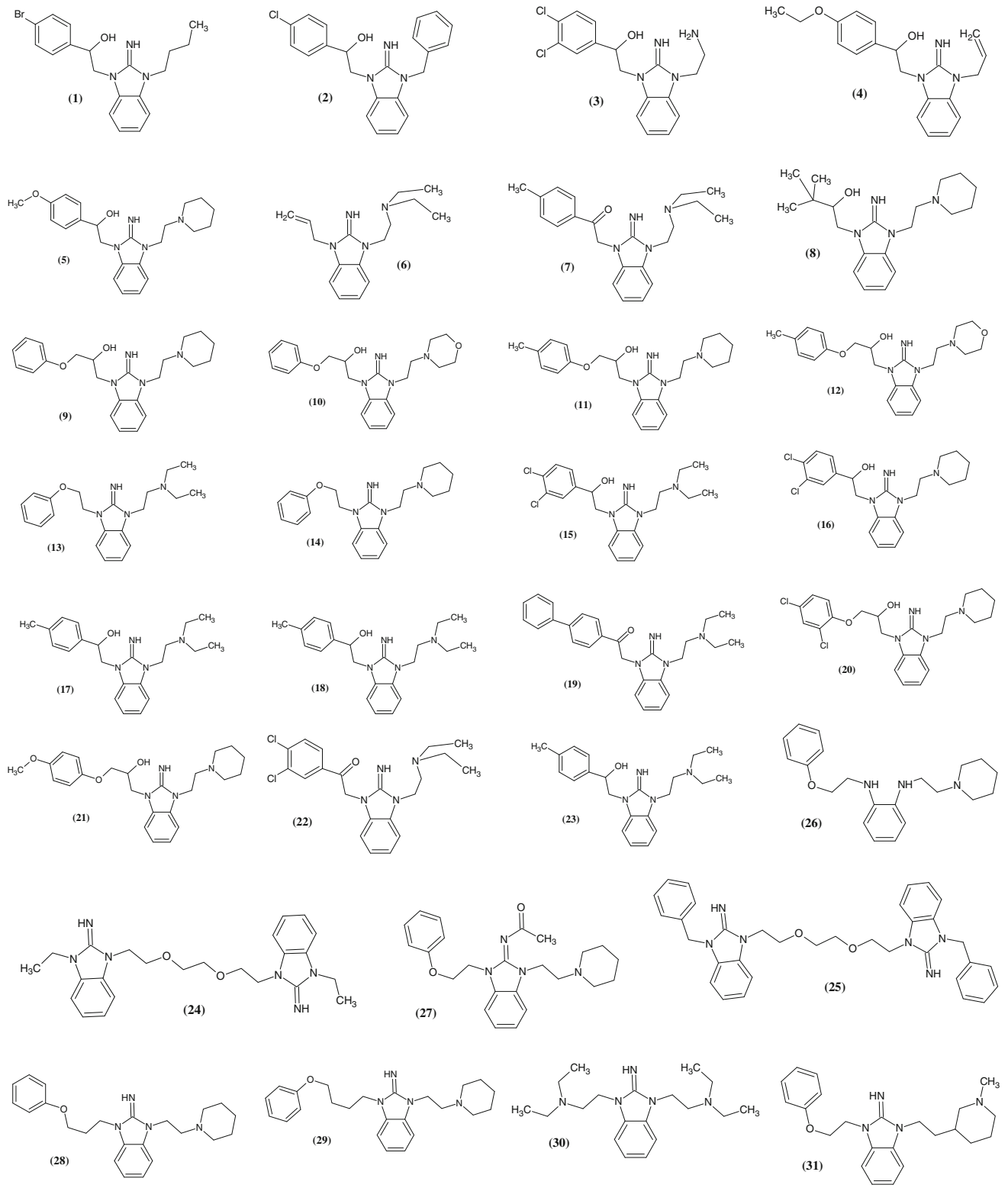

Fig. 1 Structure of 2-IBIZ compounds **1–31**

In the past, for example, in structure of curcumin derivatives, attention was mainly devoted to the diketo form. However, from a chemical point of view, all other forms (tautomers and their conformers) are possible.

For the development of binding approaches for IBIZ in the environment, the identification of the active sites in structures is important. Neither experimental nor theoretical data is available for the identification of possible

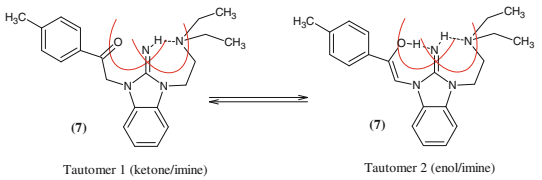

Fig. 2 Combined (O–H$^{\delta+}$–$^{\delta-}$N) and (NH$^{\delta+}$–$^{\delta-}$N) pseudo hexa/hepta-cyclic-membered antitrypanosomal pharmacophore sites

paramagnetic water-solved metal-IBIZ species. Theoretically, no NMR spectroscopy is able to identify paramagnetic chemical structures. In addition, calculations of energetics, atomic charges, minimum energy structures, geometry, and natural bond orbital (NBO) could indicate the electronic density distribution of each atom in free ligands. Finally, by taking NBO results showing the presence of C–O single bonds in consideration, realistic Lewis structures can be determined. These systematic data, regarding the variation of molecular properties, are important for the chemical structure and could therefore provide first insights into the still poorly understood chemical bonding of IBIZ complexes to soil.

In brief, the objective of this study is to investigate the potential pharmacophore sites of IBIZ species using antitrypanosomal screenings dependence on pH and comparison with the calculated molecular properties. To verify these structures, further Petra/Osiris/Molinspiration (POM) analyses were carried out for example calculation of net atomic charges, bond polarity, atomic valence, electron delocalization, and lipophilicity.

Finally, to investigate the antitrypanosomal bioactivity of the IBIZ class, tautomeric forms were derived. Current investigation in the generation of specific drug leads embodies the concept of achieving high molecular diversity within the boundaries of reasonable drug-like properties. Examples of clinical antitrypanosomal drugs are Bdz and Nfx; the two limited reference drugs have limited chemical diversity, no biochemical specificity, and Bdz has resistance properties that make it not favorable as lead and standard references (SR) structure for drug discovery, and which serve to differentiate them from libraries of synthetic and combinatorial compounds.

Various investigators have used computational methods to understand differences between natural products and other sources of drug leads. Modern drug discovery is based on large part on high-throughput screening of small molecules against macromolecular disease targets requiring that molecular screening libraries contain drug- or lead-like compounds. We have analyzed known SR for drug- and lead-like properties. With this information in hand, we have established a strategy to design specific drug- or lead-like Bdz and Nfx **1–31**.

Virtual screening and molecular properties calculations

Osiris calculations

Structure-based design is now fairly routine but many potential drugs fail to reach the clinic because of ADME-Tox liabilities. One very important class of enzymes, responsible for many ADMET problems, is the cytochrome P450. Inhibition of these or production of unwanted metabolites can result in many adverse drug reactions. Of the most important program, Osiris is already available online. With our recent publications (Sheikh *et al.*, 2011; Jawarkar *et al.*, 2010; Parvez *et al.*, 2010a, b, c, d; Chohan *et al.*, 2010a, b, c, d; Jarrahpour *et al.*, 2010) of the drug design combination of various pharmacophore sites by using heterocyclic structure, it is now possible to predict activity and/or inhibition with increasing success in two targets (bacteria and HIV virus). This is done using a combined electronic/structure docking procedure and an example will be given here. The remarkably well-behaved mutagenicity of diverse synthetic molecules classified in data base of CELERON Company of Switzerland can be used to quantify the role played by various organic groups in promoting or interfering with the way a drug can associate with DNA. Toxicity risks (mutagenicity, tumorigenicity, irritation, reproduction) and physicochemical properties [clog*P*, solubility, drug likeliness, and drug score (DS)] of compounds **1–31** are calculated by the methodology developed by Osiris as a sum of fragment-based contributions and correction factors (Tables 1, 2).

Prediction results are valued and color coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red. Whereas a green color indicates drug-conform behavior (http://www.organic-chemistry.org/prog/peo).

The toxicity risk predictor locates fragments within a molecule which indicate a potential toxicity risk. Toxicity risk alerts are an indication that the drawn structure may be harmful concerning the risk category specified. From the data evaluated in Tables 1, 2 indicate that, all structures are supposed to be mutagenic when run through the mutagenicity assessment system but as far as irritating and reproductive effects are concerned, all the compounds are at low risk comparable with standard drugs used. The log *P* value of a compound, which is the logarithm of its partition coefficient between *n*-octanol and water, is a well-established measure of the compound's hydrophilicity. Low hydrophilicity and, therefore, high log *P* values may cause poor absorption or permeation. It has been shown for compounds to have a reasonable probability of being well absorb their log *P* value which must not be greater than 5.0. On this basis, all the series is having log *P* values under the acceptable criteria. Along with this, compounds with two

Table 1 Toxicity risks prediction and experimental screening data of compounds **1–31** (Color figure online)

Compds.	Toxicity risks				Antitrypanosomal activity (Chohan et al. 2010c)	
	MUT	TUM	IRRI	REP	%Inhib	IC_{50} μM)
1					42	>100
2					32	>100
3					92	10
4					6	>100
5					85	24
6					31	>100
7					91	7
8					66	>100
9					–	5
10					–	>100
11					–	9
12					–	>100
13					–	8
14					–	4
15					–	9
16					–	4
17					–	29
18					–	35
19					–	25
20					–	5
21					–	16
22					–	24
23					–	19
24					–	>100
25					–	4
26					–	>100
27					–	>100
28					–	7
29					–	8
30					–	59
31					–	>100
Bdz					–	–
Nfx					–	–

MUT mutagenic, *TUMO* tumorigenic, *IRRI* irritant, *REP* reproductive effective; *Bdz* benznidazole and *Nfx* nifurtimox, the reference drugs

terminal functionalized arms which have shown good antitrypanosomal screening results are having low log *P* values as compared to other compounds with no or one arm, in the series. The aqueous solubility of a compound significantly affects its absorption and distribution characteristics. Typically, a low solubility goes along with a bad absorption and therefore the general aim is to avoid poorly soluble compounds. Our estimated log *S* value is a unit stripped logarithm (base 10) of a compound's solubility measured in mol/l. There are more than 80 % of the drugs on the market, which have an (estimated) log *S* value greater than −4. In case of compounds **19** and **25**, values of log *S* are low as compared to others in the series. Furthermore, Table 2 shows drug likeliness of compounds **1–31** which is in the comparable zone with that of standard drugs used.

We have calculated overall DS for the compounds **1–31** and compared with that of standard drugs, Bdz and Nfx, used as shown in Tables 2 and 3. The DS combines drug

Table 2 Osiris calculations of compounds **1–31** and references

Compds.	Substituents	Osiris calculations				
		MW	CLP	*S*	DL	DS
1	R1: 4-BrPhCH(OH)CH_2	387	3.52	−4.25	1.62	0.63
	R2: $CH_2CH_2CH_2CH_3$					
2	R1: 4-ClPhCH(OH)CH_2	377	3.44	−4.64	6.74	0.66
	R2: CH_2Ph					
3	R1: 3,4-diClPhCH(OH)CH_2	392	2.37	−3.47	6.89	0.79
	R2: $CH_2CH_2NMe_2$					
4	R1: 4-(EtO)PhCH(OH)CH_2	337	2.39	−3.4	1.29	0.74
	R2: $CH_2CH{=}CH_2$					
5	R1: 4-(MeO)PhCH(OH)CH_2	394	2.17	−2.97	4.32	0.65
	R2: CH_2CH_2N piperidine					
6	R1: $CH_2{=}CHCH_2$	272	1.75	−2.22	4.22	0.92
	R2: $CH_2CH_2NEt_2$					
7	R1: 4-MePhC(O)CH_2	364	2.42	−3.67	6.47	0.79
	R2: $CH_2CH_2NEt_2$					
8	R1: $Me_3CC(OH)CH_2$	344	2.6	−2.85	0.46	0.68
	R2: CH_2CH_2N piperidine					
9	R1: $PhOCH_2CH(OH)$	394	2.22	−3.19	4.05	0.8
	R2: *N*-piperidine					
10	R1: $PhOCH_2CH(OH)$	396	1.01	−2.3	5.16	0.85
	R2: *N*-morpholine					
11	R1: 4-MePhO$CH_2CH(OH)$	408	2.53	−3.53	2.81	0.44
	R2: *N*-piperidine					
12	R1: 4-MePhO$CH_2CH(OH)$	410	1.32	−2.65	3.91	0.49
	R2: *N*-morpholine					
13	R1: $PhOCH_2$	352	2.51	−2.96	7.0	0.84
	R2: NEt_2					
14	R1: $PhOCH_2$	364	2.77	−3.32	2.82	0.78
	R2: *N*-piperidine					
15	R1: 3,4-DiClPhCH(OH)	420	3.24	−4.07	7.93	0.69
	R2: NEt_2					
16	R1: 3,4-DiClPhCH(OH)	432	3.5	−4.43	3.8	0.62
	R2: *N*-piperidine					
17	R1: 4-MePhCH(OH)	338	1.46	−2.34	5.99	0.89
	R2: NMe_2					
18	R1: 4-MePhCH(OH)	352	1.92	−2.61	6.45	0.87
	R2: CH_2NMe_2					
19	R1: 4-PhPhC(O)	426	3.78	−5.42	6.22	0.53
	R2: NEt_2					
20	R1: 2,4-diClPhO$CH_2CH(OH)$	462	3.44	−4.66	5.24	0.35
	R2: *N*-piperidine					
21	R1: 4-(MeO)PhO$CH_2CH(OH)$	424	2.11	−3.21	4.15	0.77
	R2: *N*-piperidine					
22	R1: 4-(MeO)PhCH(OH)	418	3.33	−4.8	7.42	0.62
	R2: *N*-piperidine					
23	R1: 4-MePhCH(OH)	364	2.42	−3.67	6.47	0.79
	R2: NEt_2					
24	R: Me	436	1.4	−3.44	−7.63	0.38

Table 2 continued

Compds.	Substituents	Osiris calculations				
		MW	CLP	*S*	DL	DS
25	R: Ph	560	3.27	−5.48	−7.93	0.21
26	R1: PhO	339	3.31	−3.37	2.68	0.77
	R2: *N*-piperidine					
27	R1: PhO; R2: *N*-piperidine	406	3.45	−4.48	3.18	0.64
	R3: Ac					
28	R1: $PhOCH_2$	378	3.23	−3.59	2.06	0.72
	R2: *N*-piperidine					
29	R1: $PhOCH_2CH_2CH_2$	406	4.16	−4.13	−0.54	0.44
	R2: *N*-piperidine					
30	R1: NEt_2	331	1.7	−1.74	6.86	0.91
	R2: NEt_2					
31	R1: PhO	350	2.45	−3.13	6.36	0.84
Bdz	–	261	0.6	−1.6	−3.3	0.18
Nfx	–	301	0.92	−3.4	−2.6	0.47

CLP clog*P*, *S* solubility, *DL* drug likeliness, *DS* drug score; *Bdz* benznidazole and *Nfx* nifurtimox, the reference drugs

likeliness, clog*P*, logs, molecular weight, and toxicity risks in one handy value than may be used to judge the compound's overall potential to qualify for a drug. The reported compounds **1–31** showed moderate to good DS as compared with standard drugs used.

As recapitulation, we can say that the understanding of this situation is not easy to for the multiple complex factors to which should added a supplementary factor, the coordinative site generated by heterocyclic and aryl groups.

Molinspiration calculations

cLog*P* (octanol/water partition coefficient) is calculated by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors. The method is very robust and is able to process practically all organic and most organometallic molecules. Molecular polar surface area (PSA) TPSA is calculated based on the methodology published by Ertl 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 (Parvez *et al.*, 2010c). Prediction results of compounds and molecular properties (TPSA, GPCR ligand, and ICM) are valued (Table 3). Lipophilicity (log *P* value) and PSA values are two important predictors of per oral bioavailability of drug molecules (Clark, 1999; Chang *et al.*, 2004). Therefore, we calculated log *P* and PSA values for compounds **1–31** using Molinspiration software programs and compared them to the values obtained for standard market available drugs. For all compounds the calculated log *P* values were lower than 5, which is the upper limit for drugs to be able to penetrate through biomembranes according to Lipinski's rules. The PSA is calculated from the surface areas that are occupied by oxygen and nitrogen atoms and by hydrogen atoms attached to them. Thus, the PSA is closely related to the hydrogen bonding potential of a compound (Clark, 1999). Molecules with PSAs of 140 Å or more are expected to exhibit poor intestinal absorption (Clark, 1999). Table 3 shows that all the compounds are not within this limit with all compounds is having minimum non-comparable values of log *P* and PSA to reference drugs. This is also supported by the antibacterial screening data of compounds in terms of maximum zone of inhibitions. It has to be kept in mind that log *P* and PSA values are only two important, although not sufficient criteria for predicting oral absorption of a drug. To support this contention, note that all the compounds have zero violations of the Rule of 5. The Rule of 5 is a set of parameters devised to aid the screening of potential drug hits identified through processes such as high-throughput screening (Lipinski *et al.*, 2001). Applying the Rule of 5 increases the probability that a potential chemotherapeutic will have favorable bioavailability. The criteria of Lipinski *et al.* (2001) are as follows: (i) not more than 5 hydrogen bond donors, (ii) not more than 10 hydrogen bond acceptors, (iii) formula weight less than 500, and (iv) log *P* less than 5. Two or more violations of the Rule of 5 suggest the probability of problems in bioavailability (Lipinski *et al.*, 2001). All the compounds have zero–one violations of the Rule of 5. Drug likeliness

Table 3 Molinspiration calculations of compounds **1–31**

Compds.	Physico-chemical properties calculations					Drug likeliness			
	miLog*P*	TPSA	ONI	NV	Volume	GPCRL	ICM	KI	NRL
1	3.17	53.948	2	0	319	−0.47	−0.62	−0.63	−0.81
2	3.20	54	2	0	336	−0.40	−0.51	−0.63	−0.71
3	2.24	57	2	0	341	−0.20	−0.42	−0.46	−0.83
4	2.01	63	2	0	321	−0.74	−0.89	−0.88	−0.77
5	1.92	66	2	0	379	−0.16	−0.44	−0.44	−0.59
6	1.54	37	1	0	279	−0.57	−0.86	−0.76	−1.11
7	2.49	54	1	0	358	−0.33	−0.66	−0.40	−0.96
8	2.11	57	2	0	348	−0.23	−0.50	−0.53	−0.77
9	2.08	66	2	0	379	−0.28	−0.51	−0.47	−0.76
10	1.02	76	2	0	372	−0.35	−0.56	−0.44	−0.83
11	2.53	66	2	0	396	−0.31	−0.54	−0.49	−0.78
12	1.47	76	2	0	388	−0.37	−0.59	−0.46	−0.85
13	2.57	46	1	0	348	−0.22	−0.64	−0.30	−0.58
14	2.73	46	1	0	355	−0.15	−0.58	−0.29	−0.52
15	2.98	57	2	0	374	−0.21	−0.41	−0.47	−0.76
16	3.14	57	2	0	381	−0.14	−0.37	−0.46	−0.70
17	1.40	57	2	0	330	−0.26	−0.51	−0.48	−0.82
18	1.67	57	2	0	347	−0.25	−0.48	−0.46	−0.68
19	3.83	54	1	0	413	−0.22	−0.52	−0.28	−0.72
20	3.37	66	2	0	407	−0.30	−0.50	−0.41	−0.92
21	2.14	76	2	0	405	−0.27	−0.51	−0.43	−0.74
22	3.32	54	1	0	368	−0.27	−0.57	−0.39	−0.96
23	2.15	57	2	0	364	−0.27	−0.50	−0.48	−0.75
24	0.44	86	2	0	415	−0.36	−0.61	−0.27	−0.59
25	2.88	86	2	1	525	−0.46	−1.29	−0.69	−0.88
26	4.22	37	2	0	342	0.21	−0.11	0.10	−0.02
27	3.90	52	0	0	391	−0.10	−0.50	−0.34	−0.53
28	3.01	46	1	0	371	−0.09	−0.49	−0.27	−0.63
29	3.78	46	1	0	405	−0.08	−0.41	−0.31	−0.50
30	1.67	40	1	0	347	−0.21	−0.42	−0.34	−0.78
31	2.21	46	1	0	338	−0.11	−0.58	−0.23	−0.62
Bdz	0.7	93	1	0	225	−0.39	−0.69	−0.84	−1.55
Nfx	1.2	109	0	0	246	−1.24	−1.46	−0.92	−1.49

TPSA total polar surface area, *ONI* OH–NH interaction, *NV* number of violation, *GPCRL* GPCR ligand, *ICM* ion channel modulator, *KI* kinase inhibitor, *NRL* nuclear receptor ligand; *Bdz* benznidazole and *Nfx* nifurtimox, the reference drugs

of compounds **1–31** is tabulated in Table 2. Drug likeliness may be defined as a complex balance of various molecular properties and structure features which determine whether particular molecule is similar to the known drugs. These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility, and presence of various pharmacophores features influence the behavior of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability, and many others. Activity of all nine compounds and standard drugs were rigorously analyzed under four criteria of known successful drug activity in the areas of GPCR ligand activity, ion channel modulation, kinase inhibition activity, and nuclear receptor ligand activity. Results are shown for all compounds in Table 3 by means of numerical assignment. Likewise all compounds have consistent negative values in all categories and numerical values conforming and comparable to that of standard drugs used for comparison. Therefore, it is readily seen that all the analogs are expected to have near similar activity to standard drugs used based upon these four rigorous criteria (GPCR ligand, ion channel modulator, kinase inhibitor, and nuclear receptor ligand).

Conclusion

The compounds which were found to be potent antitrypanosomal agents of the series **1–31** are those having two coordinative pockets in neighboring positions. The POM analyses show that most compounds of the series **1–31** are less toxic than Bdz. The newly POM analyzed **1–31** were also shown to posses promising bioactivity because they have better DS than both standard drug references. It is predicted that most of these compounds could be used without greater risk of toxicity in antitrypanosomal activity. Thus, the POM calculations and actual experimental verification in one handy value not only proves the compounds' overall potential to qualify for a drug but also potentially interesting for further optimization and exploration of 2-IBIZ functionality. On the other hand, this new series **1–31** represent an original and wonderful opportunity for ligation to Mg^{2+} and Mn^{2+} in goal to get new bioavailable HIV-integrase inhibitors. So the best is coming: preliminary test of coordination of ligands **1–31** to various transition metals such as Mn^{2+}, Ni^{2+}, Fe^{2+}, Ru^{2+}, and Mg^{2+} should show formation of bimetallic complexes which are able to interact exclusively with trypanothione reductase of parasite and do not inhibit closely related human glutathione reductase via glutathione disulfide target (Fig. 3).

In fact, these 2-IBIZ display potent trypanocidal activity against *Trypanosoma brucei rhodesiense*, without inhibiting related human glutathione reductase and have low cytotoxicity against mammalian cells as it was previously reported (Holloway *et al.*, 2007).

In summary, if the application of high-throughput screening of a lead discovery library of 100,000 compounds identified nine novel chemical classes of TR inhibitors, POM virtual screening has easily fixed the favorable and unfavorable parameters for hits optimization. In particular, the bioactive 2-IBIZ were found to have good development potential with strict structural conditions (bimetallic coordination). The essential pharmacophore site of **1–31** for TR inhibitory activity was identified by investigation of a series of analogs and further possible hits/trypanothione reductase interaction via two metals. This chemical series constitutes excellent model for further development as a new organometallic class of potent therapeutics for trypanosome-mediated diseases.

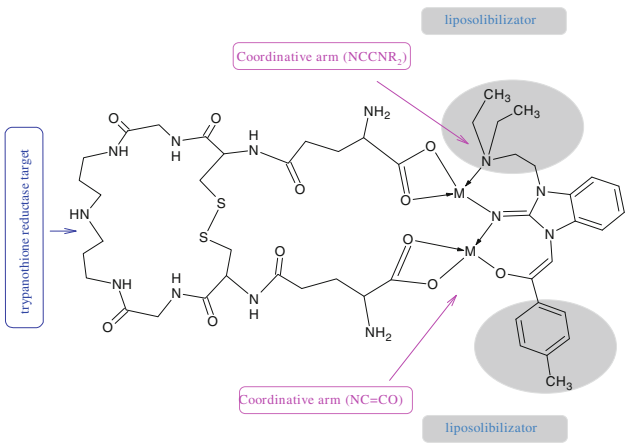

Fig. 3 Possible mechanism of inhibition of *Trypanosome crusi* via formation of a (bimetallic/trypanothione reductase/drug) complex

Acknowledgments This investigation received financial support from CNRST/Rabat of Moroccan program for research and training in contagious diseases (PROTARS I and PGR). Prof. T. Ben Hadda is sincerely thankful to the ACTELION; the Biopharmaceutical Company of Swiss, for providing necessary bioinformatics facilities.

References

Chang LCW, Spanjersberg RF, von Frijtag Drabbe K, Unzel JK, Mulder-Krieger T, van den Hout G, Beukers MW, Brussee J, Ijzerman AP (2004) 2,4,6-Trisubstituted pyrimidines as a new class of selective adenosine A1 receptor antagonists. J Med Chem 47(26):6529–6540

Chohan ZH, Sumrra SH, Youssoufi MH, Hadda TB (2010a) Design and synthesis of triazole Schiff bases and their oxovanadium(IV) complexes as antimicrobial agents. J Coord Chem 63:3981–3998

Chohan ZH, Shad HA, Toupet L, Hadda TB, Akkurt M (2010b) Structure of a new bioactive agent containing combined antibacterial and antifungal pharmacophore sites: 4-{[(E)-(5-bromo-2-hydroxyphenyl)methylidene]amino}-*N*-(5-methyl-1,2-oxazol-3-yl)benzene-sulfonamide. J Chem Crystallogr. doi: 10.1007/s10870-010-9856-x

Chohan ZH, Sumrra SH, Youssoufi MH, Hadd TB (2010c) Metal based biologically active compounds: design, synthesis and antibacterial/antifungal/cytotoxic properties of triazole derived Schiff bases and their oxovanadium(IV) complexes. Eur J Med Chem 45:2739–2747

Chohan ZH, Youssoufi MH, Jarrahpour A, Hadda TB (2010d) Identification of antibacterial and antifungal pharmacophore sites for potent bacteria and fungi inhibition: indolenyl sulfonamide derivatives. Eur J Med Chem 45:1189–1199

Clark DE (1999) Fast calculation of molecular polar surface area directly from smiles. J Pharm Sci 88:807–814

Croft SL, Sundar S, Fairlamb AH (2006) Drug resistance in leishmaniasis. Clin Microbiol Rev 19(1):111–126

Holloway GA, Baell JB, Fairlamb AH, Novello PM, Parisot JP, Richardson J, Watsona KG, Streeta IP (2007) Discovery of 2-iminobenzimidazoles as a new class of trypanothione reductase inhibitor by high-throughput screening. Bioorg Med Chem Lett 17(5):1422–1427

Jarrahpour A, Motamedifar M, Zarei M, Youssoufi MH, Mimouni M, Chohan ZH, Hadda TB (2010) Petra, Osiris and Molinspiration together as a guide in drug design: predictions and correlation structure/antibacterial activity relationships of new *N*-sulfonyl monocyclic β-lactams (Part II). Phosphorus Sulfur Silicon Relat Elem 185:491–497

Jawarkar RD, Masand VH, Patil KN, Mahajan DT, Youssoufi MH, Hadda TB, Kumbhare SL (2010) 3D-QSAR study on coumarin analogues as potent inhibitors of MAO-B using a CoMFA approach. Der Pharma Chem 2(6):302–310

Lipinski CA, Lombardo F, Dominy BW, Feeney PJ (2001) Experimental and computational approaches to estimate solubility and

permeability in drug discovery and development settings. Adv Drug Deliv Rev 46(1–3):3–26

Parvez A, Jyotsna M, Sheikh J, Tiwari V, Dongre R, Hadda TB (2010a) Predictions and correlations of structure activity relationship of some aminoantipyrine derivatives on the basis of theoretical and experimental ground. Med Chem Res 21(2):157–164

Parvez A, Meshram J, Tiwari V, Sheikh J, Dongre R, Shanti M, Khandarkar K, Ahemad M, Hadda TB (2010b) Greener synthetic and nanotechnological bridge: theoretical and practical biological approach toward the bactericidal dual action mechanism of azomethine–nanosilver hybrid. Int J Green Nanotechnol: Phys Chem 2:53–61

Parvez A, Meshram J, Youssoufi MH, Hadda TB (2010c) Theoretical calculations and experimental verification of the antibacterial potential of some monocyclic beta-lactames containing two synergetic buried antibacterial pharmacophore sites. Phosphorus Sulfur Silicon Relat Elem 7:1500–1510

Parvez A, Meshram J, Tiwari V, Sheikh J, Dongre R, Youssoufi MH, Hadda TB (2010d) Pharmacophores modeling in terms of prediction of theoretical physicochemical properties and verification by experimental correlations of novel coumarin derivatives produced via Betti's protocol. Eur J Med Chem 45: 4370–4378

Paulino M, Iribarne F, Dubin M, Aguilera-Morales S, Tapia O, Stoppani AOM (2005) The chemotherapy of Chagas' disease: an overview. Mini Rev Med Chem 5(5):499–519

Sheikh J, Parvez A, Ingle V, Juneja H, Dongre R, Chohan ZH, Youssoufi MH, Hadda TB (2011) Synthesis, biopharmaceutical characterization, antimicrobial and antioxidant activities of 1-(4′-*O*-*β*-d-glucopyranosyloxy-2′-hydroxyphenyl)-3-aryl-propane-1,3-diones. Eur J Med Chem 46(4):1390–1399

Sundar S, More DK, Singh MK, Singh VP, Sharma S, Makharia A, Kumar PCK, Murray HW (2000) Failure of pentavalent antimony in visceral leishmaniasis in India: report from the center of the Indian epidemic. Clin Infect Dis 31(4):1104–1107