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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Computational evaluation and experimental in vitro antibacterial, antifungal and antiviral activity of bis-Schiff bases of isatin and its derivatives

Aliasghar Jarrahpour · Javed Sheikh · Ibrahim El Mounsi · Harjeet Juneja · Taibi Ben Hadda

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Abstract A computational model has been developed for the rational design of bioactive pharmacophore sites as an antibacterial, antifungal and antiviral candidates based on available X-ray structures of bis-Schiff bases (Blagus *et al.*, Maced J Chem Chem Eng 29:117–138, 2010; Nabei *et al.*, Polyhedron 28:1734–1739, 2009; Zhang *et al.*, Inorg Chem Commun 14:1636–1639, 2011; Zhong *et al.*, Eur J Med Chem 41:1090–1092, 2006; Zhou *et al.*, Inorg Chim Acta 359:1442–1448, 2006). A dozen of bis-Schiff bases **3**–**14** of isatin, benzylisatin and 5-fluoroisatin **1a**–**c** were designed using this model. The compounds were screened for antibacterial, antifugal and antiviral activity against a panel of DNA and RNA viruses. The most potent of these compounds **8** and **11** was tested in viral cultures for their ability to present a potential ($O^{\delta-}$–$N^{\delta-}$) antiviral pharmacophore site. Compounds **8** and **11** were the most cytotoxic in HEL cells. All these synthesized bis-Schiff bases were also tested for their antibacterial and antifungal activities. They did not display activity against *S. cerevisiae* (ATCC 28383) or *C. albicans* (CIP 1180-79); may be because they did not have an antibacterial pharmacophore site ($X^{\delta-}$–$Y^{\delta+}$). The best inhibitors tested in vitro against HIV-1 are genetically predisposed to be inhibited by similar pharmacophore sites. The results from all the aspects of this bioinformatic approaches are discussed as par with our experience with screening candidates.

Keywords Virtual screening · Isatin · Schiff bases · Antibacterial · Antiviral · Antifungal activity

A. Jarrahpour
Department of Chemistry, College of Sciences, Shiraz University, 71454 Shiraz, Iran

J. Sheikh (✉) · H. Juneja
Department of Chemistry, RTM Nagpur University, Nagpur 440033, India
e-mail: sheikhchemie@gmail.com; javedchemie@gmail.com

I. E. Mounsi · T. B. Hadda (✉)
Laboratoire Chimie des Matériaux, Université Mohammed Premier, 60000 Oujda, Morocco
e-mail: tbenhadda@yahoo.fr

Introduction

Invasive, all bacterial, fungal and viral infections are a serious and escalating health issue. They are associated with a high morbidity, mortality, and economic burden, especially in immuno-compromised hosts. Current therapies are limited in safety and/or efficacy and resistant fungi, bacteria, and viruses are an emerging problem (Jolliffe, 2006). It is widely recognised that there is a need for the optimization of pharmacological properties or development of new antifungal drugs that have a different mode of action to those currently in use.

Pharmacophore sites identification and then optimization (Anaflous *et al.*, 2004; Ben Hadda *et al.*, 2003, 2007, 2008; Chohan *et al.*, 2006; Hakkou *et al.*, 2002; Houari *et al.*, 2008) plays a major role in many steps of the drug discovery processes. A better understanding and modelling of the pharmacophore sites could greatly increase the efficiency for developing new efficient antibacterial (Anaflous *et al.*, 2004; Ben Hadda *et al.*, 2003, 2007, 2008; Chohan *et al.*, 2006; Hakkou *et al.*, 2002; Houari *et al.*, 2008), antitumoral (Zunino *et al.*, 2002) and combined antitubercular/anti-HIV-1 drugs (Ben Hadda *et al.*, 2005; Bennani *et al.*, 2007).

In pharmacophore site identification, an understanding of molecular properties is needed. In lead discovery and optimization, an estimate of electronic factors and

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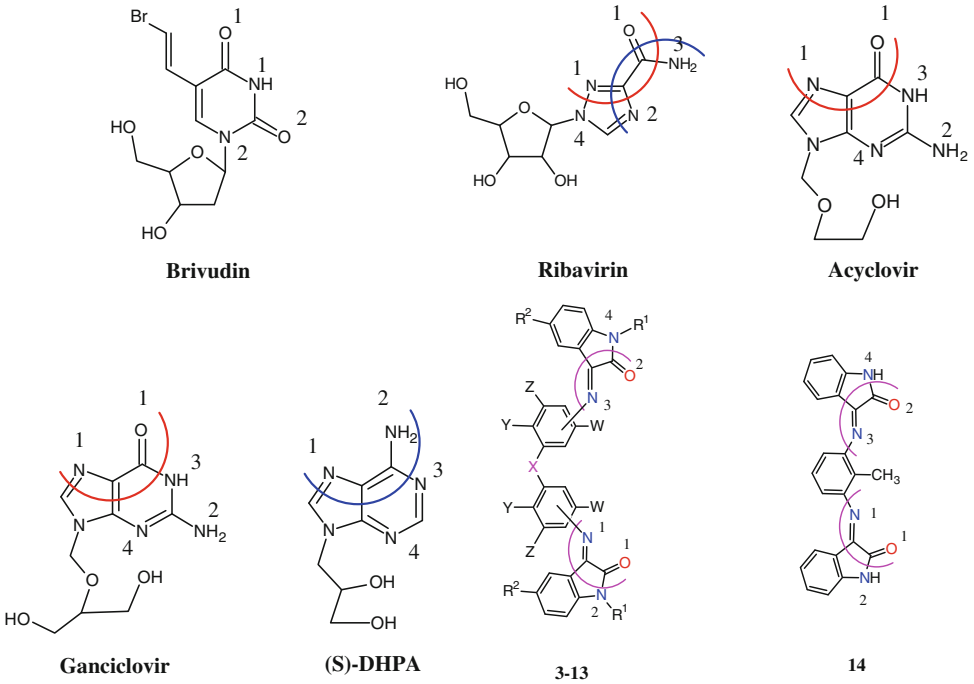


Fig. 1 Structures of SR and screened candidates **3–14**. Ribavirin is capable of adopting multiple conformations by rotating the C3–C6 bond to mimic both adenosine and guanine ribonucleosides. So it has wo different pharmacophore sites (antibacterial and antiviral) represented in *blue* and *red* colours, respectively (Color figure online)

crystallographic structure accessibility is desired, molecular properties have to be calculated, and the synthesis of a pharmacology library asks for knowledge on the scope and limitations of a bioactivity type. Further, the knowledge on the stability of the drugs of a library is necessary.

The estimation of heteroatoms charge and their orientation in space and bioavailability properties of resultant candidate has to model the interaction between drugs and their target(s) and to predict the drug-likeness values. Furthermore, many bioactivity modes of action are the results of drug conformation.

In fact, molecular recognition between a drug and its receptor is generally dictated by the correct three dimensional presentations of the 'essential' functionalities of the ligand to the binding site of the receptor. The challenge in peptidomimetic drug discovery lies in placing these pharmacophoric groups in an identical spatial arrangement to elicit the desired biological response. Although some classes of molecules have been discovered that seems to be privileged structures for at least some drug-receptor interactions, the challenge to design and synthesize small molecules with high specific affinity to pharmacologically important targets are still remains. With their high density of stereo information and their relative rigid Schiff bases of isatin provides excellent platform to display a number of substituent in a variety of sterically defined ways, hence offering the opportunity to explore these unique features for the drug discovery processes. In collaboration with NCI and TAACF of United States, we have developed a technology platform that enables easy access to structurally diverse libraries based on antibacterial, antitumoral and anti-HIV pharmacophore sites. We have employed this technology to discover potent viral inhibitors by modelling the antiviral pharmacophore sites.

In this study, we have exemplified the principles of the technology with the successful discovery of potent antiviral activity in vitro against 13 viruses (Fig. 1).

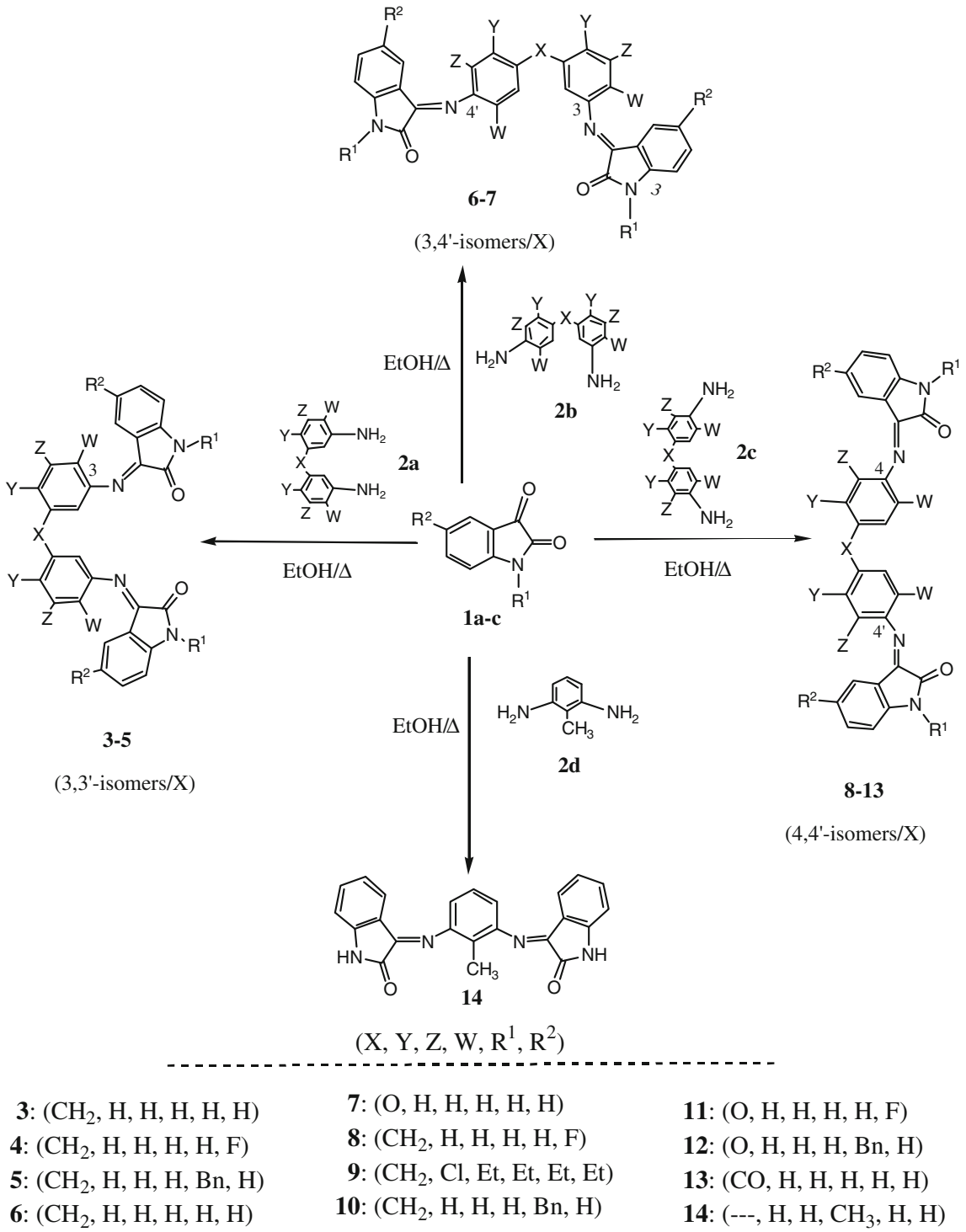
We presented here the results of our virtual screening investigation into possible alternative structures for these compounds. A comparison between experimental and theoretical predictions of the antibacterial and antiviral activity has enabled us to identify alternative antiviral structures.

Results and discussion

Synthesis

The efficient formal synthesis of various bis-Schiff bases **3–14** have previously been reported by the reaction between isatin, benzylisatin or 5-fluoroisatin **1a–c** and primary aromatic amines **2a–d** (Scheme 1). The chemical structures of the products have been confirmed by ^{1}H- and ^{13}CNMR, IR and mass spectral data (Jarrahpour *et al.*, 2007).

The structurally simpler and symmetric diamino-aryl **2d** was used as an initial precursor to allow for the exploration of a symmetric Schiff base structure **14** and to serve as a platform for the synthesis of synthetically more challenging therapeutic agents **3–13**. Compounds **3–14** were obtained in one-step sequence from isatins **1a–c**, the



Scheme 1 General synthesis of bis-Schiff bases **3**–**14**

symmetric structure of 3,3′-isomers in (**3**–**5**) and 4,4′-isomers in (4,4′-isomers) was rapidly assembled from a novel symmetric diamines **2a** or **2c** via a Keto/amine condensation. That was extended to dissymmetric structure 3,4′-isomers (**6**–**7**) by using dissymmetric diamine **2b.** So this efficient synthesis for a range of symmetric and dissymmetric-substituted Schiff bases molecules **3**–**14** has been established. The flexibility of the synthesis could allow for further development of a wide range of derivatives able to coordinate selectively one or two transition metal centres. The direct impact of structure symmetry and nature of various substituents at different positions, on

Table 1 Antibacterial activities of Schiff bases **3–14**

Compds.	Substituants							Anibacterial Activity. MIC (μg/mL)			
	X	Y	Z	W	R1	R2	C=N/X	*S. cerevisiae*	*S. aureus*	*C. albicans*	*E. coli*
3	CH_2	H	H	H	H	H	3,3′	<50	<50	<50	<50
4	CH_2	H	H	H	H	F	3,3′	<50	<50	<50	<50
5	CH_2	H	H	H	Bn	H	3,3′	<50	<50	<50	<50
6	CH_2	H	H	H	H	H	3,4′	<50	<50	<50	<50
7	O	H	H	H	H	H	3,4′	<50	<50	<50	<50
8	CH_2	H	H	H	H	F	4,4′	<50	<50	<50	<50
9	CH_2	Cl	Et	Et	H	H	4,4′	<50	<50	<50	<50
10	CH_2	H	H	H	Bn	H	4,4′	<50	<50	<50	<50
11	O	H	H	H	H	F	4,4′	<50	<50	<50	<50
12	O	H	H	H	Bn	H	4,4′	<50	<50	<50	<50
13	C=O	H	H	H	H	H	4,4′	<50	<50	<50	<50
14	–	–	–	–	–	–	–	<100	<100	<100	<100

Table 2 Cytotoxic and antiviral activity of bis-Schiff bases **3–14**

Compds.	Minimum cytotoxic concentration (μg/mL)			Minimum virus-inhibitory concentration (μg/mL)												
	HEL	Vero	Hela	A	B	C	D	E	F	G	H	I	J	K	L	M
3	80	80	≥16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	9.6	>16	>16
4	80	80	80	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	9.6	>16	>16
5	200	200	200	>40	>40	>40	>40	>40	>40	>40	>40	>40	>40	>40	>40	>40
6	80	80	≥16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	3.2	>16	>16
7	400	400	≥16	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>16	>16	>16
8	16	≥16	80	>3.2	>3.2	>3.2	>3.2	>3.2	>16	>16	>16	>16	>16	>16	>16	>16
9	80	16	16	>16	>16	>16	>16	>16	>3.2	>3.2	>3.2	>3.2	>3.2	>3.2	>3.2	>3.2
10	40	40	200	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>40	>40	>40
11	8	40	≥16	>1.6	>1.6	>1.6	>1.6	>1.6	>8	>8	>8	>8	>8	>16	>16	>16
12	400	80	80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>16	>16	>16
13	80	≥16	80	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	48	>16	>16
14	400	400	≥400	>80	>80	>80	>80	16	>80	>80	>80	>80	>80	>400	>400	>400
Brivudin	>500	500	500	0.16	>500	60	>500	500	>100	>100	>100	>100	>100	>500	>500	>500
Ribavirin	>500	>500	>500	500	>500	300	>500	>500	300	300	300	>500	60	60	>500	60
Acyclovir	>500	–	–	2.4	20	>500	>500	300	–	–	–	–	–	–	–	–
Ganciclovir	>100	–	–	0.48	4	>100	>100	12	–	–	–	–	–	–	–	–
(S)-DHPA	–	500	>500	–	–	–	–	–	>100	300	>100	>100	–	500	>500	>500

A Herpes simplex virus-1(KOS), *B* herpes simplex virus-2(G) *C* vaccinia virus, *D* vesicular stomatitis virus, *E* herpes simplex virus-1 KOS ACV' (TK'), F para-influenza-3 virus, *G* reovirus-1, *H* sindbis virus, *I* coxsackie virus B4, *J* punta Toro virus, *K* vesicular stomatitis virus, *L* coxsackie virus B4, *M* respiratory syncytial virus

bioactivity was confirmed by antibacterial, antifungal and antiviral screening results analysis (Tables 1, 2, 3).

Biological activity

The compounds have been screened for antiviral activity against a panel of DNA and RNA viruses. Minimum cytotoxic and minimum virus-inhibitory concentrations of these compounds were determined (Jarrahpour *et al.*, 2007).

The compounds **8** and **11** were the most cytotoxic in HEL cells. These newly synthesized bis-Schiff bases were also tested for their antibacterial and antifungal activities. They did not display activity against *S. cerevisiae* (ATCC 28383) or *C. albicans* (CIP 1180-79) as shown in Tables 1, 2.

Table 3 Selected Petra calculations of references and compounds **3–14** (Sheikh *et al.*, 2011b; Sheikh and Ben Hadda, 2012)

Compds.	Calculated atomic property of partial π-charge of heteroatoms (in e^-)							Antiviral pharmacophore site
	N_1	N_2	N_3	N_4	O_1	O_2	X	
3	−0.083	0.227	−0.083	0.227	−0.182	−0.182	0	N=C–C=O
4	−0.080	0.232	−0.080	0.232	−0.181	−0.181	0	N=C–C=O
5	−0.082	0.221	−0.082	0.221	−0.180	−0.180	0	N=C–C=O
6	−0.083	0.227	−0.083	0.227	−0.182	−0.182	0	N=C–C=O
7	−0.083	0.230	−0.085	0.228	−0.180	−0.196	0.098	N=C–C=O
8	−0.080	0.231	−0.080	0.231	−0.182	−0.182	0	N=C–C=O
9	−0.084	0.230	−0.084	0.230	−0.180	−0.180	0	N=C–C=O
10	−0.082	0.221	−0.082	0.221	−0.181	−0.181	0	N=C–C=O
11	−0.082	0.232	−0.082	0.232	−0.193	−0.109	0.130	N=C–C=O
12	−0.084	0.222	−0.084	0.222	−0.193	−0.193	0.122	N=C–C=O
13	−0.082	0.236	−0.082	0.236	−0.178	−0.178	−0.18	N=C–C=O
14	−0.072	0.202	−0.072	0.202	−0.153	−0.153	–	N=C–C=O
Brivudin	0.185	0.238	–	–	−0.224	−0.200	–	Tautomers
Ribavirin	−0.115	−0.116	0.138	0.261	−0.186	–	–	N=C–C=O
Acyclovir	−0.125	0.201	0.209	−0.212	−0.211	–	–	N–C–C=O
Ganciclovir	−0.125	0.201	0.209	−0.212	−0.211		–	N–C–C=O
(S)−DHPA	−0.096	0.134	−0.170	−0.174	–	–	–	N–C–C–N

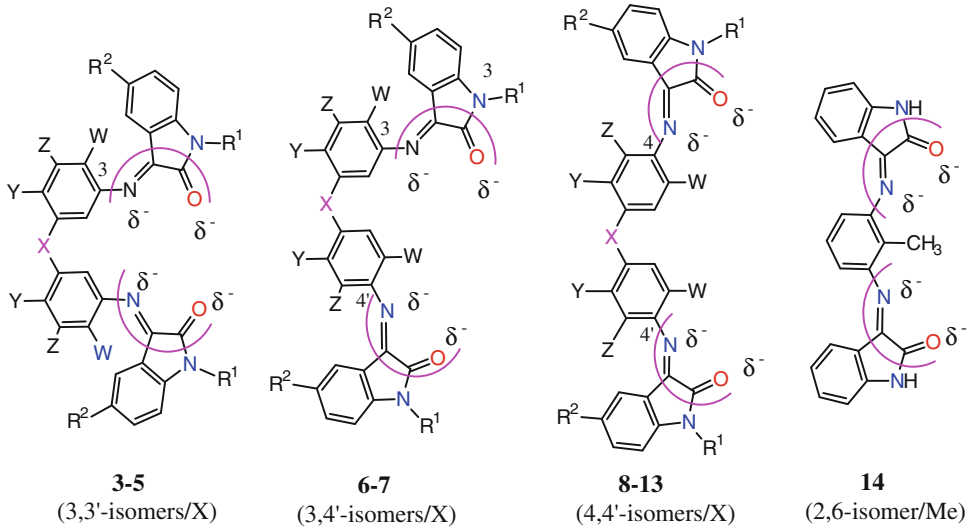


Fig. 2 Repetition of negative charge of Nsp^2 and Osp^2 atoms

Theoretical calculations of molecular properties of 3–14

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

Petra calculations

The series **3–14** of Schiff bases have been subjected to delocalised-charge calculations using Petra method of the non-hydrogen common atoms (Fig. 2), obtained from the partial pi-charge of heteroatoms, have been used to model the bioactivity against bacteria, fungal and viruses.

Table 4 Osiris calculations of compounds **3–14** and references (Color table online)

Compds.	Toxicity risks				Osiris calculations				
	MUT	TUMO	IRRI	REP	MW	CLP	S	DL	D-S
3					456	3.74	−6.91	3.71	0.4
4					492	3.86	−7.53	1.93	0.34
5					636	6.23	−9.5	5.33	0.18
6					456	3.74	−6.91	2.04	0.39
7					458	3.43	−7.49	2.7	0.39
8					492	3.86	−7.53	0.17	0.13
9					636	7.66	−10.30	3.4	0.15
10					636	6.23	−9.5	3.58	0.09
11					494	3.54	−8.12	0.95	0.25
12					674	6.03	−10.7	5.54	0.14
13					470	3.29	−7.3	0.91	0.34
14					380	2.33	−5.54	3.64	0.59
Brivudin					332	0.41	−1.87	2.02	0.31
Ribavirin					244	-2.65	−0.53	−1.37	0.21
Acyclovir					225	-1.47	−1.27	−2.42	0.31
Ganciclovir					255	-2.02	−1.1	−3.3	0.3
(S)-DHPA					209	-1.64	−1.3	−8.13	0.18

MUT mutagenic, *TUMO* tumorigenic, *IRR* irritant, *REP* reproductive effective, *CLP* cLogP, *S* solubility, *DL* *Druglikness*, *DS* drug-score

PETRA is a program package comprising various empirical methods for the calculation of physicochemical properties in organic molecules. All methods are empirical in nature and have been developed over the last 20 years in the research group of Prof. J. Gasteiger. The following chemical effects can be quantified: heats of formation, bond dissociation energies, sigma charge distribution, π-charge distribution, inductive effect, resonance effect and delocalization energies and polarizability effect (Sheikh *et al.*, 2011b; Sheikh and Ben Hadda, 2012).

It is found that the negative charges of the nitrogen Nsp^2 and oxygen Osp^2 contribute positively in favour of an antiviral activity, more than antibacterial activity, and this is in good agreement with the mode of antiviral action of the compounds bearing ($X^{\delta-}$–$Y^{\delta-}$) involving coordination of the metal within the parasite. It was hypothesized that difference in charges between two heteroatoms of the same pharmacophore site ($X^{\delta-}$–$Y^{\delta+}$) may facilitate the inhibition of bacteria, more than viruses. It is further found that the activity increases with increase in negative charge of the heteroatoms of the common pharmacophore fragment of the molecule. This is related with possible secondary electronic interaction with the positively charged side chains of the virus target(s).

Attempts were made to incorporate steric and indicator parameters which emerged as important contributors from previous pharmacologic analysis. The present results support the previous observations that bulky phenyl ring substituents and a three-member pharmacophore site attached to the isatin/aryl bridge-containing ring are conductive to the activity. The Petra software calculations confirmed that all compounds **3–14** have a clear preference for forming antiviral pharmacophore sites though their estimated partial π charges respectively for O and N neighbour atoms are of negative charges (−0.182 and −0.083 e) for compound **3**. The Petra calculations with the other azo Schiff bases **4–14** are shown and summarised in Table 3.

On the basis of the above observations, it is tentatively suggested that compounds **3–14** show two antiviral pharmacophore site in which the N,O heteroatoms act as

Table 5 Molinspiration calculations of compounds **3–14** and references

Compds.	Molinspiration calculations						Drug-likeness			
	MW g/mol	cLogP	TPSA	Number OH–NH Interract	Number violation	Volume	GPCRL	ICM	KI	NRL
3	456	6.45	90	2	1	402	−0.17	−0.46	−0.17	−0.69
4	492	4.79	90	2	0	412	−0.11	−0.55	−0.15	−0.64
5	636	9.02	68	0	2	579	−0.91	−2.45	−1.64	−1.95
6	456	6.48	90	2	1	402	−0.17	−0.46	−0.17	−0.69
7	458	6.27	99	2	1	394	−0.20	−0.47	−0.15	−0.79
8	492	4.83	90	2	0	412	−0.10	−0.54	−0.16	−0.64
9	637	9.41	90	2	2	563	−0.65	−1.48	−0.94	−1.27
10	636	9.04	68	0	2	579	−0.91	−2.44	−1.64	−1.95
11	494	4.63	99	2	0	404	−0.14	−0.55	−0.14	−0.63
12	638	8.96	78	0	2	572	−0.93	−2.45	−1.63	−1.94
13	470	5.99	108	2	1	404	−0.17	−0.54	−0.14	−0.66
14	380	4.89	90.45	2	0	331	−0.37	−0.46	−0.27	−0.96
Brivudin	333	−0.94	105	3	0	235	−0.46	−1.49	−0.30	−2.27
Ribavirin	244	−2.77	144	5	0	197	−0.32	−1.35	−0.33	−1.96
Acyclovir	225	−1.61	119	4	0	187	−0.27	−1.30	−0.32	−2.63
Ganciclovir	255	−2.17	139	5	0	212	−0.21	−1.17	−0.07	−2.40
(S)-DHPA	209	−0.97	110	4	0	178	−0.10	−0.73	0.39	−3.17

GPCRL GPCR ligand, *ICM* ion channel modulator, *KI* kinase inhibitor, *NRL* nuclear receptor ligand

ligation centres and possibly accommodate themselves between metal in such a way that a stable complex of the pharmacophore site is formed hence, giving a moderate to inactive structure to the tested antibacterial candidates.

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 cytochromes 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 (Sheikh *et al.*, 2011b; Sheikh and Ben Hadda, 2012).

With our recent publications on the drug design combinations of various pharmacophore sites by using spiro-heterocyclic structure (Bennani *et al.*, 2007), it is now possible to predict activity and/or inhibition with increasing success in two targets (bacteria and HIV). This is done using a combined electronic/structure-docking procedure and an example will be given here. The remarkably well-behaved mutagenicity of divers synthetic molecules classified in data base of CELERON Company of Swiss can be used to quantify the role played by various organic groups in promoting or interfering with the way a drug can associate with DANN (Sheikh *et al.*, 2011b; Sheikh and Ben Hadda, 2012).

The OSIRIS Property Explorer shown in this page is an integral part of Actelion's (1) inhouse substance registration system. It lets you draw chemical structures and calculates on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results are valued and colour-coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red. Whereas a green colour indicates drug-conform behaviour (Table 4).

Molinspiration calculations

CLogP (octanol/water partition coefficient) is calculated by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors (Ertl *et al.*, 2000).

The method is very robust and is able to process practically all organic, and most organometallic molecules. Molecular Polar Surface Area TPSA is calculated based on the methodology published by Ertl *et al.* (2000) 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. Prediction results of

compounds **3–14** molecular properties (TPSA, GPCR ligand and ICM) are valued (Table 5).

Conclusion

The compounds **3–14**, typically could form the highly stable aromatic pharmacophore sites (O=C–C=N). This structure leads us to design therapeutically active candidates with remarkable chemical stability in both coordination chemistry and antiviral activity. Some inactive series tested previously, in our groups, as antibacterial agents are in the same undesirable geometry (Jarrahpour *et al.*, 2011). A number of important points emerge concerning the electronic and steric factors which have direct impact on antiviral properties. The positive results we have recorded, while encouraging for purposes of new drug design, confirm that very likely most of these compounds could be used as potential antiviral activity after minor modifications. Based on their structural properties, these compounds may be useful as chelating agents with potential activity. These results prompt several pertinent observations: (i) This type of azo Schiff bases can furnish an interesting model for studying the interaction of antibiotics with viral target because the possible charge modification of substituents and O/N of pharmacophore group; (ii) The future rigid pharmacophore site (s) geometric conformation enables us to prepare molecules for multi-therapeutic materials with high selectivity and low molecular weight (MW $<$ 400 g/mol). This approach was executed with success in the case of other series of ligands and their transition metal complexes (Ben Hadda *et al.*, 2009; Chohan *et al.*, 2010a,b; Jarrahpour *et al.*, 2010; Parvez *et al.*, 2010, 2012; Rauf *et al.*, 2012; Sheikh *et al.*, 2011a,b; Sheikh and Ben Hadda, 2012).

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References

Anaflous A, Benchat N, Mimouni M, Abouricha S, Ben Hadda T, El-Bali B, Hakkou A, Hacht B (2004) Armed imidazo [1,2-a] pyrimidines (pyridines): evaluation of antibacterial activity. Lett Drug Des Discov 1:224–229

Ben Hadda T, Benchat N, El-Bali B, Abouricha S, Moueqqit M, Mimouni M (2003) Impact of dimroth rearrangement on antituberculosis activity of 3-armed-imidazo[1.2-a]pyrimidines IMP (-pyridines) IP. Med Pharm Chem 0301001:1–18

Ben Hadda T, Kotchevar AT, Daoudi M, Bennani B, Larbi NB, Kerbal A (2005) Anti-tumour activity of some polydentate *N*-ligands: *N*,*N*-bis-(3-substituted-5-methylpyrazol-1yl methyl)arylamines and *N*,*N*,*N*′,*N*′-tetra-[(3-substituted-5-methylpyrazol-1yl] paraphenylenediamines. Lett Drug Des Discov 2:584–589

Ben Hadda T, Badri R, Kerbal A, Baba BF, Akkurt M, Demailly G, Benazza M (2007) Synthesis and antitubercular activity of spiroheterocycles: 2,2′,4′,5′-tetra-substituted-1,2,2′,4′-tetrahydro-*4*H-spiro[isoquinoline-3,3′-pyrazol]-4-ones. Arkivoc XIV: 276–288

Ben Hadda T, Rahima B, Kerbal A, Baba BF, Akkurt M, Demailly G, Benazza M (2008) Looking for a new antitubercular pharmacophore site: synthesis and bioactivity of spiroheterocycles 2,3′,4′-tri-subsituted-1,2-dihydro-4H,4′H-spiro[iso-quinoline-3,5′-isoxazol]-4-ones. Arkivoc ii:1–13

Ben Hadda T, Akkurt M, Baba MF, Daoudi M, Bennani B, Kerbal A, Chohan ZH (2009) Anti-tubercular activity of ruthenium (II) complexes with polypyridines. J Enzym Inhib Med Chem 24:457–463

Bennani B, Kerbal A, Daoudi M, Baba BF, Houari GA, Jalbout AF, Mimouni M, Benazza M, Demailly G, Akkurt M, Yýldýrým SÖ, Hadda TB (2007) Combined drug design of potential *mycobacterium tuberculosis* and HIV-1 inhibitors: 3′,4′-di-substituted -4′*H*-spiro [isothiochromene-3,5′-isoxazol]-4(1*H*)-one. Arkivoc xvi:19–40

Blagus A, Cinčić D, Friščić T, Kaitner B, Stilinović V (2010) Schiff bases derived from hydroxyaryl aldehydes: molecular and crystal structure, tautomerism, quinoid effect, coordination compounds. Maced J Chem Chem Eng 29:117–138

Chohan ZH, Shaikh AU, Naseer MM (2006) Metal-based isatin-bearing sulfonamides: their synthesis, characterization and biological properties. Appl Organomet Chem 20:729–739

Chohan ZH, Sumra SH, Youssoufi MH, Ben Hadda T (2010a) 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, Ben Hadda T (2010b) Identification of antibacterial and antifungal pharmacophore sites for potent bacteria and fungi inhibition: indolenyl sulfonamide derivatives. Eur J Med Chem 45:1189–1199

Ertl P, Rohde B, Selzer P (2000) Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties. J Med Chem 43:3714–3717

Hakkou A, Bouakka M, Touzani R, Elkadiri S, Ramdani A, Kotchevar A, Ellis T, Waring M, Hadda TB (2002) 2,3-Bifunctionalized quinoxalines: synthesis, DNA interactions and evaluation of anticancer, antituberculosis and antifungal activity. Molecules 7:641–656

Houari GA, Kerbal A, Bennani B, Baba MF, Daoudi M, Hadda TB (2008) Drug design of new antitubercular agents: 1,3-dipolar cycloaddition reaction of *para*-substituted-benzadoximes and 3-*para*-methoxy-benzyliden-isochroman-4-ones. Arkivoc xii:42–50

Jarrahpour A, Khalili D, De Clercq E, Salmi C, Brunel JM (2007) Synthesis, antibacterial, antifungal and antiviral activity evaluation of some new bis-Schiff bases of isatin and their derivatives. Molecules 12:1720–1730

Jarrahpour A, Motamedifar M, Zareil M, Youssoufi MH, Mimouni M, Chohan ZH, Ben Hadda T (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

Jarrahpour A, Fathi J, Mimouni M, Ben Hadda T, Sheikh J, Chohan ZH, Parvez A (2011) Petra, Osiris and Molinspiration (POM) together as a successful support in drug design: antibacterial activity and biopharmaceutical characterization of some azo Schiff bases. Med Chem Res. doi:10.1007/s00044-011-9723-0

Jolliffe KA (2006) Inhibitors of fungal phospholipase B: novel antifungal agents. Congdes of drug design. Amongst The Vines, Hunter Valley, NSW, Australia, 3–7 December 2006

Nabei A, Kuroda-Sowa T, Shimizu T, Okubo T, Maekawa M, Munakata M (2009) Ferromagnetic interaction in iron(II)–bis-Schiff base complexes. Polyhedron 28:1734–1739

Parvez A, Meshram J, Tiwari V, Sheikh J, Dongre R, Youssoufi MH, Ben Hadda T (2010) 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

Parvez A, Meshram J, Sheikh J, Tiwari V, Dongre R, Ben Hadda T (2012) Predictions and correlations of structure activity relationship of some aminoantipyrine derivatives on the basis of theoretical and experimental ground. Med Chem Res 21:157–164

Rauf A, Liaqat S, Qureshi A, Yaqub M, Rehman AU, Hassan MU, Chohan ZH, Nasim FUH, Ben Hadda T (2012) Synthesis, characterization, and urease inhibition of 5-substituted-8-methyl-2H-pyrido[1,2-a]pyrimidine-2,4(3H)-diones. Med Chem Res 21:60–74

Sheikh J, Ben Hadda T (2012) Antibacterial, antifungal and antioxidant activity of some new water-soluble beta-diketones. Med Chem Res. doi:10.1007/s00044-012-0089-8

Sheikh J, Juneja H, Ingle V, Ali P, Ben Hadda T (2011a) Synthesis and in vitro biology of Co(II), Ni(II), Cu(II) and Zinc(II) complexes of functionalized beta-diketone bearing energy buried potential antibacterial and antiviral *O,O*-pharmacophore sites. J Saud Chem Soc. doi:10.1016/j.jscs.2011.04.004

Sheikh J, Parvez A, Juneja H, Ingle V, Chohan Z, Youssoufi M, Hadda TB (2011b) 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 46:1390–1399

Zhang N, Huang C-Y, Shi D-H, You Z-L (2011) Unprecedented preparation of bis-Schiff bases and their manganese(III) complexes with urease inhibitory activity. Inorg Chem Commun 14:1636–1639

Zhong X, Yi J, Sun J, Wei H-L, Liu W-S, Yu K-B (2006) Synthesis and crystal structure of some transition metal complexes with a novel bis-Schiff base ligand and their antitumor activities. Eur J Med Chem 41:1090–1092

Zhou X-H, Wu T, Li D (2006) Structural variations and spectroscopic properties of copper(I) complexes with bis(Schiff base) ligands. Inorg Chim Acta 359:1442–1448

Zunino F, Kotchevar AT, Waring M, Daoudi M, Larbi NB, Mimouni M, Sam N, Hadda TB (2002) Novel cytotoxic oxopyridoindolizines: iso-propyl-7,8,9-trichloro-6,7,8,9-tetrahydro-5-oxopyrido[2,3-a]-indolizine-10-carboxylates (OPIC). Molecules 7:628–640