Available online at www.scholarsresearchlibrary.com

Scholars Research Library

J. Comput. Method. Mol. Design, 2011, 1 (3): 57-68
(http://scholarsresearchlibrary.com/archive.html)

ISSN : 2231- 3176
CODEN (USA): JCMMDA

POM as Efficient Tools to Predict and Improve Both Antibacterial and Antifungal Activity of Aryl Aldazines

Jihane Fathi[1], Vijay Masand[2], Rahul Jawarkar[3], Rahima Mouhoub[1], Taibi Ben Hadda[1,*]

[1]Laboratoire Chimie des Matériaux, FSO, Université Med. 1[ier], Oujda-6000, Morocco.
[2]Department of Chemistry, Vidya Bharati College, Camp, Amravati, Maharashtra, India.
[3]Department of Pharmaceutical chemistry,Sahyadri College of Pharmacy,Methawade, Sangola, Solapur

---

ABSTRACT

A general, simple and straight forward approach to symmetric substituted aldazines derivatives via condensation reaction of aromatic aldehydes and ammonia precursors has been demonstrated successfully under mild reaction conditions. Their qualitative antimicrobial activities have been previously evaluated against 10 bacterial and 3 fungal species. We have reported the design and calculated molecular properties of some aldazines derivatives on the basis of hypothetical antibacterial pharmacophore site, structures which were designed to interact with both of Gram positive and Gram negative bacteria. A correlation of structure and activities relationship of these compounds with respect to molecular modeling, Lipinski rule of five, drug likeness, toxicity profiles and other physico-chemical properties of drugs are described and verified experimentally.

Keywords: Symmetrical Acyclic Aryl Aldazines, POM virtual screening, Docking, Antibacterial/ Antifungal Activity.

INTRODUCTION

Azines moiety is a four-membered group containing a pi-conjugated (C = N-N = C) fragment. It has been the focus of medicinal chemists over the past ten decades because of the outstanding pharmacological properties shown by several of its derivatives [1], e.g., Ketazines, mixed azines, etc. D. Kolbah and D. Korunčev (1967), then S. Dayagi and Y. Degani (1970) discovered Azines [2,3]. Owing to their promising antitumor [4-9], antibacterial [10-17], anti-inflammatory [18], antimalarial dyes [19], anticonvulsant activities [20,21], unsymmetrical aldazines have shown antitumor [22], antibacterial [23,24] and antioxidant [25] activity. Symmetrical 4-bromo benzaldazine has evaluated as anticonvulsant agent but shown very low activity [26]. Similar monosubstituted benzaldazines have been tested as allosteric modulators [27] and has found that

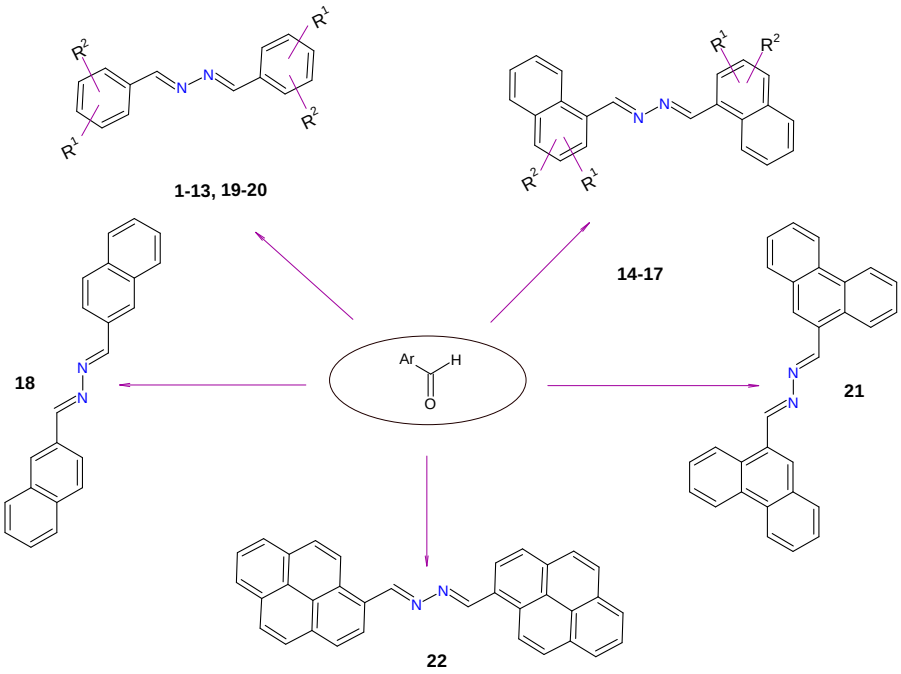
2-fluoro and 3-fluoro compounds possessed positive activity, while 4-fluoro, 3-chloro, 3- and 4-methoxy, and 3-hydroxy analogues were not active. Recently, a series of unsymmetrical and two examples of symmetrical 3-indolyl aldazines have been studied and have found to exhibit antioxidant [25] and antibacterial [24] activity. The latter presents, to the best of our knowledge, the only record in the literature on the evaluation of antibacterial and antifungal activity of symmetrical aryl aldazines.

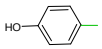
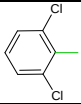
We present here the results of our virtual screening investigation into possible alternative structures for these compounds. A comparison between experiment and theoretical predictions of the antibacterial activity has enabled us to identify alternative combined pharmacophore sites structures. The nature of pharmacophore site assignment of the aldazine compounds was based on their POM analyses.

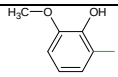
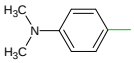
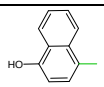
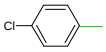
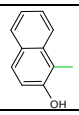
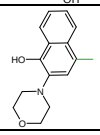
RESULTS AND DISCUSSION

2.1. Chemistry

The titled aldazines have been previously obtained by the classical protocol from aldehydes and hydrazine sulphate in ethanol [1], as shown on Scheme 1.



Compd.	Aryl	R^1	R^2		Compd.	Aryl	R^1	R^2
1		H	H		**9**		1-Cl	H
2		H	4-OH		**10**		2-Cl	6-Cl
3		H	3-OH		**11**		2-Cl	4-Cl
4		2-OH	H		**12**		2-Cl	4-F

5		2-OH	3-O-Me		**13**		H	3-F
6		H	4-N(Me)$_2$		**15**		H	4-OH
7		H	4-Cl		**16**		2-OH	H
8		H	3-Cl		**17**		3-(morpholin-4-yl)	4-OH

Scheme 1. General synthesis of symmetrical aryl aldazines 1-22.[1]

2.2. Pharmacology

The results of antibacterial and antifungal screening of the compounds **1-22** demonstrated that the bi- and polycyclic aromatics studied are remarkably more active than benzaldazines. The latter possess antibacterial activities only, which were dramatically reduced by the introduction of substituents. The tests showed that the activities are strongly dependent on the type and position of the substituents and that the effects on antibacterial and antifungal activities are the opposite. 2-Naphtaldazine was significantly more active than its position isomer 1-naphthaldazine against Saccharomyces cerevisiae and Penicillium chrysogenum, whereas both compounds possess commensurable activities towards Candida tropicalis and the bacterial strains. From the other side, the presence of 4-hydroxy substituent in 1-naphthaldazine reduced the antibacterial and increased the antifungal activities, while the influence of 2-hydroxy group led to reversed results (Tables 1 & 2).

Table 1. Aldazines with antibacterial activity; zone of inhibitiona in mm [1]

Azine	*Bacillus subtilis*	*Bacillus idosus*	*Bacillus megat.*	*Bacillus mycoides*	*Bacillus cereus*	*Acinetob. johnst.*	*Staph. aureus*	*Sarcina lutea*	*Microc. luteus*	*E. coli*
1[b]	20	21	20	16	17	24	18	20	19	30
2[b]	10	18	17	15	26	17	17	17	16	20
12[b]	-	15	14	16	17	-	12	14	15	25
14[b]	19	18	20	11	22	18	21	23	21	24
15[b]	13	19	12	18	16	16	14	14	14	25
16[c]	17	26	24	19	25	27	15	25	22	25
17[c]	11	12	11	10	12	11	12	11	12	12
18[c]	20	23	21	16	20	25	22	25	23	30
19[c]	15	19	20	15	19	17	17	18	20	37
20[c]	22	25	25	14	22	26	23	20	25	23
22[c]	15	19	14	15	19	13	12	18	21	33
Ref 1[b,e]	35	30	30	35	30	30	32	27	30	35
Ref 2[d,f]	30	35	36	32	29	39	35	34	38	31

[a]DMSO solutions with different concentrations; indicated for each compound: [b]25 mg/ml; [c]12.5 mg/ml; [d]20 mg/ml; [e]*Streptomycin*; [f]*Gentamycin*.

Surprisingly but interestingly, we observed that inside the benzaldazine series **1-13**, the unsubstituted compound **1** exhibited good activities, while the introduction of substituents (OH, Cl, F, NMe_2)in the phenyl ring led to loss of antibacterial activity in general.

A comparison between the active compounds (Table 2) shows that inside the naphthaldazine series, 2-naphtal- dazine **18** is remarkably more active than its position isomer 1-naphthaldazine **14** against *Saccharomycescer- evisiae* and *Penicillium chrysogenum*, while both com-pounds possess the same activity towards *Candida tropicalis*. From the other side, the position of the hydroxy substituent in 1-naphthaldazine displayed a reversed effect in respect to antibacterial tests. The presence of a 4-hydroxyl substituent, **14** *vs* **15**, led to slight increase of the activity towards the yeast strains tested and reduced activity against the fungal strain, while 2-hydroxy derivative **16** was not active in general.

Table 2. Aldazines with antifungal activity [1]; zone of inhibittion[a] in mm

Compound	*Candida tropicalis*	*Saccharomyces cerevisiae*	*Penicillium chrysogenum*
14[b]	20	18	18
15[b]	24	25	15
18[c]	20	30	35
20[c]	21	23	20
Fluconazol[b]	35	-	-
Itraconazole[c]	-	30	-

[a]DMSO solutions with different concentrations; indicated for each com-pound: [b]25 mg/ml; [c]12.5 mg/ml.

3. Virtual screenings and molecular properties calculations

3.1. Molecular properties calculations

For aldazine **5** and certainly for its analogues (**1-13**) and (**19-20**), depending on the pH and position of the dissociate alcohol hydrogen atom, two possible aldazine principal conformations can be described for the neutral forms. These relevant structures are sketched in Figure 1.

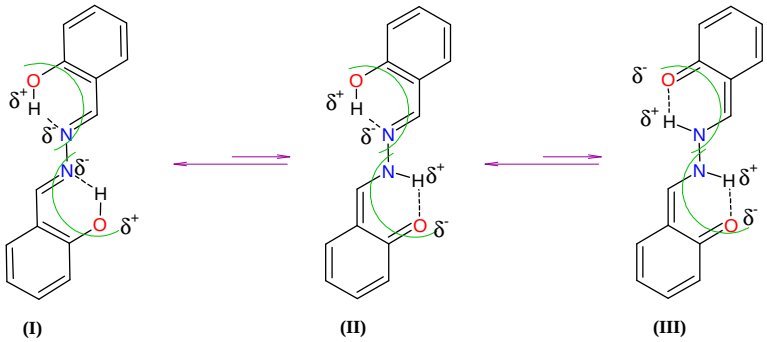


Figure 1. Possible tautomeric structures (I-III) of aldazine compound 5.

In past, attention was mainly devoted to one *E,E*-conformer structure. However, from a chemical point of view, the second structure is possible. For the development of binding approaches for aldazine and its analogues (**1-13**) and (**19-20**) in the environment, the identification of the active

aldazine structures present is important. Neither experimental nor theoretical data is available for the identification of water-solved aldazine species. Theoretically, NMR spectroscopy could be useful for identifying chemical structures. Theoretical ab initio studies could supplement these measurements. Additionally, calculations of energetics, atomic charges, minimum energy structures, geometry, and natural bond orbital (NBO) could indicate the electronic density distribution of each atom. Finally, by taking NBO results showing the presence of (N–H --- O) and (N --- H–O) bridge 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 aldazine complexes to bio-targets.

In brief, the objective of this study is to investigate the potential pharmacophore sites of aldazine species using antibacterial and antifungal 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 lipophicity. Finally, to investigate the combined antibacterial/antifungal bioactivity of the aldazine species, tautomeric structure were performed.

Current thinking in the generation of specific drug leads embodies the concept of achieving high molecular diversity within the boundaries of reasonable drug-like properties [28]. Natural and semi-natural products, examples Streptomycin, Gentamycin, Fluconazol and Itraconazole have high chemical diversity, biochemical specificity and other molecular properties that make them favorable as lead and standard references (SR) structures 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 [29]. 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 will be able to establish a strategy to design specific drug-like or lead-like aldazine (**1–22**).

3.2. Petra Calculations

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. We previously tested factor by fator and seen that the delocalised-charge has a direct and crucial impact on nature and efficiency of the candidate pharmacophore site [30-50].

The series **1-22** of symmetrical acyclic aryl aldazines have been subjected to delocalised-charge calculations using Petra method of the non-hydrogen common atoms (Figure 1), obtained from the partial pi-charge of the heteroatoms, have been used to model the bioactivity against bacteria. We give here, as example, the compounds **5** and **16**.

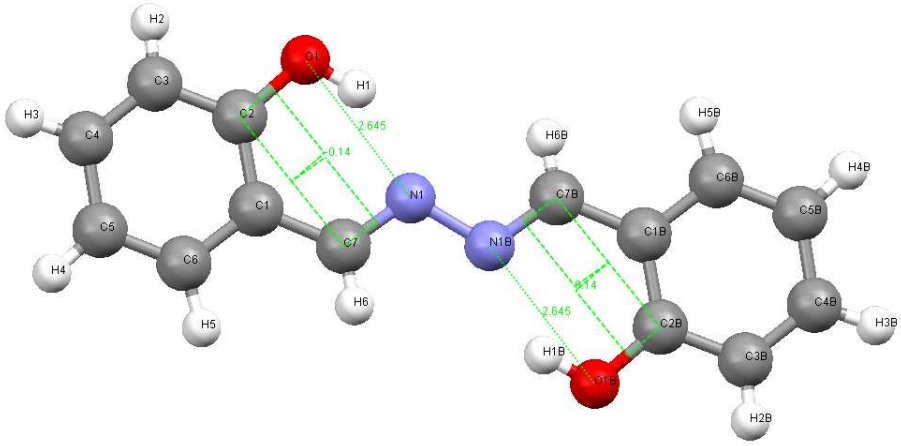


Figure 2. Crystalline structure of compound 5, showing the two strongly closed six-pseudo-member-cyclohexa-ring as weak antibacterial pharmacophore sites ($OH^{\delta+}$ --- N^{δ}) with distance d_{OH---N} = 2.645Å and dihedral angle (O1-C2-C1-N) = 0.14 degree.

It is found that the negative charges of the nitrogen atoms of aldazine group and the partial positive charge of hydrogen atom of arm 2-OH contribute positively in favour of an antibacterial activity, more, and this is in good agreement with the mode of antbacterial action of the compounds bearing ($X^{\delta+}$ --- $Y^{\delta-}$) pharmacophore(s) site(s). [30-50]

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 and fungous. It is further found that the activity increases with increase in negative charge of one heteroatom of the common pharmacophore fragment of the compounds (**5** and **16**). This synergistic and streamlined working procedure led to highly active isomeric/ tautomeric Gram(+/-)receptor ligands. On the basis of this analogue system described above, in compound **5**, sets of isomeric and tautomeric aldazine derivatives I–III could be generated in-situ in the presence of bacteria or fungi.

This synergistic and streamlined working procedure led to highly active isomeric/tautomeric Gram(+/-) and fungi receptor ligands. However, a little difference in their respective binding affinities was consistently found for all isomeric pairs I–III. The analysis of conformational differences due to heteroatom interactions in tautomers I–III revealed a strong favorable (OH/N) or (NH/O) interaction in tautomers I-III, whereas there is no other aldazine showed a repulsive interaction.

So the antifungal activity is related with possible secondary electronic interaction with the positively charged side chains of the virus target(s). Attempt was made to evaluate steric and indicator parameters which emerged as important contributors from previous pharmacologic analysis. The present results support the previous observations that phenolic ring in adjacent position of imine C=N could generate two tautomeric forms, in less and two distinct closed five-member pharmacophore sites are conducive to the low activity to both antibacterial (OH/N) and antifungal activity (O/N).

3.3. 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.

Table 3. Osiris calculations of aldazines compounds 1-22 and references

Compd.	Substituents	Osiris calculations [a]					Toxicity Risks [b]			
	Ar	MW	CLP	S	DL	D-S	MUT	TUM	IRRI	REP
1	Ph	208	4.44	-4.13	1.59	0.53				
2	4-OH-C_6H_4	240	3.84	-3.54	1.73	0.72				
3	3-OH-C_6H_4	240	3.84	-3.54	1.65	0.72				
4	2-OH-C_6H_4	240	3.84	-3.54	1.35	0.7				
5	3-OMe-2-OH-C_6H_3	300	3.63	3.58	0.3	0.61				
6	4-NMe_2-C_6H_4	294	4.44	-4.2	0.88	0.34				
7	4-Cl-C_6H_4	276	5.67	-5.6	2.81	0.43				
8	3-Cl-C_6H_4	276	5.67	-5.6	1.57	0.4				
9	2-Cl-C_6H_4	276	5.67	-5.6	2.14	0.42				
10	2,6-Cl_2-C_6H_3	344	6.89	-7.08	2.8	0.28				
11	2,4-Cl_2-C_6H_3	344	6.89	-7.08	3.05	0.29				
12	2-Cl-4-F-C_6H_3	312	5.78	-6.23	0.55	0.31				
13	3-F-C_6H_4	244	4.56	-4.76	-0.99	0.31				
14	1-naphthyl	308	6.8	-7.34	0.97	0.2				
15	4-OH-1-naphthyl	340	6.21	-6.75	0.08	0.12				
16	2-OH-1-naphthyl	340	6.21	-6.75	-1.71	0.12				
17	4-OH-3-R-1-naphthyl	510	4.98	-6.96	2.94	0.15				
18	2-naphthyl	308	6.8	-7.34	-0.77	0.16				
19	4-Ph-C_6H_4	360	7.8	-8.3	1.31	0.23				
20	2-fluoryl	244	4.56	-4.76	0.27	0.48				
21	9-phenanthryl	408	0.17	-10.56	1.64	0.12				
22	1-pyrenyl	456	10.54	-13.04	1.59	0.19				
AMP [c]	-------	349	-0.04	-1.57	1.07	0.91				
STREP[c]	-------	581	-7.83	-0.96	0.83	0.43				

[a] CLP: cLogP, S: Solubility, DL: Druglikness, DS: Drug-Score. [b] MUT: mutagenic; TUMO: tumorigenic; IRRI: irritant; REP: reproductive effective. [c] AMP: Ampicillin; STREP: Streptomycin.

With our recent publications of the drug design combination of various pharmacophore sites by using spiro-heterocyclic and sulfonamide structures, it is now possible to predict activity and /or inhibition with increasing success in two targets (bacteria and HIV) [40] or (bacteria and fungus) [48]. This was 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 Compagny 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 DNA.

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.

Table 4. Molinspiration calculations of compounds 1-22

Compd.	Physico-Chemical Properties Calculations [a]					Drug-likeness [b]			
	cLogP	TPSA	ONI	Volume	NV	GPCRL	ICM	KI	NRL
1	3.21	25	0	202	0	-0.35	-0.52	-0.64	-0.61
2	2.25	65	2	218	0	-0.23	-0.41	-0.47	-0.18
3	2.20	65	2	218	0	-0.23	-0.42	-0.48	-0.17
4	3.09	65	2	218	0	-0.24	-0.56	-0.62	-0.27
5	2.29	84	2	269	0	-0.34	-0.51	-0.49	-0.28
6	3.41	31	0	294	0	-0.20	-0.40	-0.35	-0.17
7	4.56	25	0	229	0	-0.27	-0.44	-0.51	-0.52
8	4.52	25	0	229	0	-0.26	-0.44	-0.54	-0.55
9	4.47	25	0	229	0	-0.34	-0.54	-0.62	-0.46
10	5.73	25	0	256	1	-0.27	-0.44	-0.48	-0.45
11	5.78	25	0	256	1	-0.30	-0.47	-0.53	-0.53
12	4.75	25	0	239	0	-0.35	-0.41	-0.39	-0.20
13	3.49	25	0	212	0	-0.17	-0.36	-0.39	-0.34
14	5.53	25	0	290	1	-0.09	-0.44	-0.40	-0.27
15	4.99	65	2	306	0	-0.07	-0.38	-0.32	-0.23
16	5.41	65	2	306	1	-0.20	-0.41	-0.36	-0.16
17	4.75	90	2	462	1	-0.11	-0.72	-0.41	-0.34
18	5.58	25	0	290	1	-0.21	-0.38	-0.36	-0.22
19	6.80	25	0	345	1	-0.15	-0.27	-0.26	-0.13
20	3.44	25	0	212	0	-0.21	-0.43	-0.46	-0.43
21	7.80	25	0	378	1	-0.09	-0.38	-0.31	-0.20
22	8.69	25	0	411	1	-0.08	-0.58	-0.28	-0.28
AMP [c]	-0.87	113	4	299	0	-0.56	-0.55	-0.90	-0.87
STREP [c]	-5.35	336	16	497	3	-0.67	-1.15	-0.76	-1.11

[a] TPSA: Total Polar Surface Area; ONI: OH-NH Interraction; NV: Number of Violation. [b] GPCRL: GPCR ligand; ICM: Ion Channel Modulator; KI: Kinase Inhibitor; NRL: Nuclear Receptor Ligand. [c] AMP: Ampicillin; STREP: Streptomycin.

3.4. 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 (Table 4).

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. [51] 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 **1-22** molecular properties (TPSA, GPCR ligand and ICM) are valued (Table 4).

A number of important points emerge concerning the electronic and steric factors which have direct impact on bioactivity properties. The positive results we have recorded, while encouraging for purposes of new organometallic drug design, confirm that very likely most of these compounds could be used as potential antibacterial activity after minor modifications. Based on their structural properties, these compounds may be useful as chelating agents with higher potential activity.

CONCLUSIONS

The results of present investigation support the suggested antibacterial pharmacophore sites of symmetrical acyclic aryl aldazines. It has been suggested that some functional groups such as substituted phenol present in these aldazine compounds displayed role of biological activity that may be responsible for the increase of hydrophobic character and liposolubility of the molecules. This in turn, enhances activity of the compounds and biological absorbance, so as, all the synthesized symmetrical acyclic aryl aldazines containing more than one antibacterial pharmacophore site have good antibacterial properties.

These results prompt several pertinent observations: (i) This type of symmetrical acyclic aryl aldazines can furnish an interesting model for studying the interaction of antibiotics with bacterial, fungal and viral targets because the possible charge modification of substituents and O/N of pharmacophore groups; (ii) The future flexible pharmacophore site (s) geometric conformation will enable us to prepare molecules for multi-therapeutic materials with high efficiency (Figure 3).

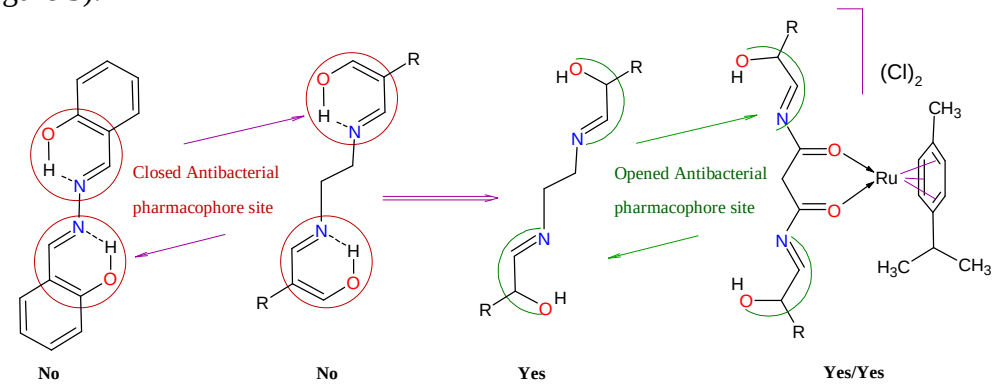


Figure 3. The involvement of antibacterial or antiviral activity is possible on the basis of coordination of symmetrical acyclic aryl aldazines 5 squeleton. The University of Pennsylvania receives US $ 9.5 million grant as part of American screening network to discover of bioactive organometallic ruthenium (II) [52].

Acknowledgements

We are grateful to Prof. Vanya B. Kurteva from Bulgarian Academy of Sciences, Sofia, Bulgaria for discussion. Prof. T. Ben Hadda would like to thank the ACTELION; the Biopharmaceutical Company of Swiss, for the on-line molecular properties calculations.

REFERENCES

[1] V. B. Kurteva, S. P. Simeonov, M. Stoilova-Disheva, *Pharmacology & Pharmacy*, 2 (**2011**), 1-9.
[2] D. Kolbah and D. Korunčev, Methoden zur Herstellung und Umwandlung von Azinen, In: *Methoden der Organischen Chemie* (*Houben-Weyl*), Georg Thieme Verlag, Stuttgart, 10 (**1967**), 85-122.
[3] S. Dayagi and Y. Degani, Formation of the Carbon- Nitrogen Double Bond, In: S. Patai, Ed., *The Chemistry of the Carbon-Nitrogen Double Bonds*, Interscience, New York, 1970, 61-147.
[4] W. J. Haggerty and C. C. Cheng, *Journal of Medicinal Chemistry*, 13 (**1970**) 574-575.
[5] J. R. Dimmock, P. Kumar, J. W. Quail, U. Pugazhenthi, J. Yang, M. Chen, R. S. Reid, T. M. Allen, G. Y. Kao, S. P. C. Cole, G. Batist, J. Balzarini and E. De Clercq, *European Journal of Medicinal Chemistry*, 30 (**1995**) 209-217.
[6] A.I. Khodair and P. Bertrand, *Tetrahedron*, 54 (**1998**) 4859- 4872.
[7] H.I. Gul, M. Gul, J. Vepsälainen, E. Erciyas and O. Hänninen, *Biological andPharmaceutical Bulletin*, 26 (**2003**) 631-637.
[8] H.N. Pati, U. Das, R.K. Sharma and J.R. Dimmock, *Mini Reviews in Medicinal Chemistry*, 7(**2007**) 131-139.
[9] N. Haider, T. Kabicher, J. Käferböck and A. Plenk, *Molecules*, 12 (**2007**) 1900-1909.
[10] Y. Sawa and M. Hoten, *Sen'i Gakkaishi*, 57 (**2001**) 153-158.
[11] R.N. Asolkar, V.P. Kamat, I. Wagner-Döbler and H. Laatsch, Limnazine, *Journal of Natural Products*, 65 (**2002**) 1664-1666.
[12] I. A. Danish and K.R. Prasad, *Acta Pharmaceutica*, 54 (**2004**) 133-142.
[13] H.I. Gul, F. Sahin, M. Gul, S. Ozturk and K.O. Yerdelen, *Archiv der Pharmazie*, 338 (**2005**) 335-338.
[14] M.N. Kumaraswamy and V.P. Vaidya, *Indian Journal of Heterocyclic Chemistry*, 14 (**2005**) 193-196.
[15] J. Jayabharathi, A. Thangamani, M. Padmavathy and B. *Medicinal Chemistry Research*, 15(**2007**) 431- 442.
[16] J. Jayabharathi, V. Thanikachalam, A. Thangamani and M. Padmavathy, *Medicinal Chemistry Research*, 16 (**2007**) 266-279.
[17] G. Aridoss, S. Amirthaganesan, M.S. Kim, J.T. Kim and Y.T. Jeong, *European Journal of Medicinal Chemistry*, 44 (**2009**) 4199-4210.
[18] R.W. Lange, *Current Opinion in Anti-inflammatory and Immunomodulatory Investigational Drugs*, 2(**2000**) 338-341.
[19] J.L. Vennerstrom, M.T. Makler, C. K. Angerhofer and J.A. Williams, *Antimicrobial Agents and Chemotherapy*, 39 (**1995**) 2671-2677.
[20] F.D. Popp, *Journal of Heterocyclic Chemistry*, 21 (**1984**) 617-619.
[21] H. I. Gul, U. Calis and J. Vepsalainen, *Arzneimittel-Forschung-Drug Research*, 54 (**2004**) 359-364.
[22] I. Picón-Ferrer, F. Hueso-Ureña, N.A. Illán-Cabeza, S.B. Jiménez-Pulido, J.M. Martínez Martos, M. J. Ramírez-Expósito and M.N. *Journal of Inorganic Biochemistry*, 103 (2009) 94-100.
[23] M. Revanasiddappa, T. Suresh, S. Khasim, S.C. Raghavendray, C. Basavaraja and S. D. Angadi, *E-Journal of Chemistry*, 5 (**2008**) 395-403.
[24] G. Gürkök, N. Altanlar and S. Suzen, *Chemotherapy*, 55 (**2009**) 15-19.
[25] G. Gürkök, T. Coban and S. Suzen, *Journal of Enzyme Inhibition and Medicinal Chemistry*, 24 (**2009**) 506-515.

[26] J.R. Dimmock, K.K. Sidhu, S.D. Tumber, S.K. Basran, M. Chen, J.W. Quail, J. Yang, I. Rozas and D.F. Weaver, *European Journal of Medicinal Chemistry*, 30 (**1995**) 287-301.
[27] J.A. O'Brien, W. Lemaire, T.-B. Chen, R. S. L. Chang, M.A. Jacobson, S.N. Ha, C. W. Lindsley, H. J. Schaffhauser, C. Sur, D.J. Pettibone, P.J. Conn and D.L. WilliamsJr, *Molecular Pharmacology*, 64 (**2003**) 731-740.
[28] F.E. Koehn, G.T. Carter, *Nat. Rev. Drug Discov*, 4 (**2005**) 206-220.
[29] A.R. Carroll, R.J. Quinn, N. B. Pham, G.K. Pierens, S. Muresan, L. Suraweera, M.E. Palframan, P. Baron, J.E. Neve, Building a Drug-like Natural Product Library; *Congres of Drug Design Amongst The Vine*s, Hunter Valley, NSW, Australia 3-7 December **2006**.
[30] R.D. Jawarkar, D.T. Mahajan, V.H. Masand, T. Ben Hadda, G.H. Kurhade. *Der Pharmacia Lettre*, 2 (**2010**) 350-357.
[31] R. D. Jawarkar, V. H. Masand, K.N. Patil, D.T. Mahajan, M.H. Youssoufi, T. Ben Hadda and S.L. Kumbhare. *Der Pharma Chemica*, 2 (**2010**) 302-310.
[32] A. Parvez, M. Jyotsna, J. Sheikh, V. Tiwari, R. Dongre, T. Ben Hadda. *European Journal of Medicinal Chemistry*. Paper has been accepted for publication at Nov 03-**2010**.
[33] A. Parvez; J. Meshram; V. Tiwari; J. Sheikh; R. Dongre; M. Shanti; K. Khandarkar; M. Ahemad; T. Ben Hadda. *International Journal of Green Nanotechnology: Physics and Chemistry*, 2 (**2010**) 53–61.
[34] Z.H. Chohan, S.H. Sumrra, M.H. Youssoufi, and T. Ben Hadda. *Journal of Coordination Chemistry* (**2010**). Paper has been accepted for publication.
[35] Z.H. Chohan, H.A. Shad, L. Toupet, T. Ben Hadda and M. Akkurt. *J. Chem. Crystallogr*. (**2010**). DOI 10.1007/s10870-010-9856-x.
[36] A. Parvez, M. Jyotsna, M. Hfid Youssoufi, and T. Ben Hadda. *Phosphorus, Sulfur, and Silicon And the related Elements*, 7 (**2010**) 1500-1510.
[37] A. Parvez, J. Meshram, V. Tiwari, J. Sheikh, R. Dongre, M.H. Youssoufi, Taibi Ben Hadda. *European Journal of Medicinal Chemistry* 45 (**2010**) 4370-4378.
[38] Z.H. Chohan, S.H. Sumrra, M.H. Youssoufi, and T. Ben Hadda. *European Journal of Medicinal Chemistry* 45 (**2010**) 2739-2747.
[39] Z.H. Chohan, M.H. Youssoufi, A. Jarrahpour, T. Ben Hadda. *European Journal of Medicinal Chemistry* 45 (**2010**) 1189–1199.
[40] A. Jarrahpour, M. Motamedifar, M. Zarei1, M.H. Youssoufi, M. Mimouni, Z.H. Chohan and T. Ben Hadda. *Phosphorus, Sulfur, and Silicon and the Related Elements (PSSI)*, 185 (**2010**) 491-497.
[41] A. Parvez, M. Jyotsna, M.H. Youssoufi and T. Ben Hadda. *Phosphorus, Sulfur, and Silicon and the Related Elements* (*PSSI), 185* (**2010**) 1500 – 1510.
[42] O.T. Benjelloun, M. Akkurt, S.Ö. Yýldýrým, M. Daoudi, T. Ben Hadda, A. Boukir, O. Büyükgüngör, and A.F. Jalbout. *Arkivoc* (ii) (**2008**) 80-93.
[43] Z.H. Chohan, C.T. Supuran, T. Ben Hadda, F-U-H. Nasim, & K. M. Khan. *Journal of Enzyme Inhibition and Medicinal Chemistry*, (**2008**) 1–12.
[44] G. Al Houari, A. Kerbal, B. Bennani, M.F. Baba, M. Daoudi, and T. Ben Hadda. *Arkivoc* (xii), (**2008**) 42-50.
[45] T. Ben Hadda, B. Rahima, A. Kerbal, B.F. Baba, M. Akkurt, G. Demailly, M. Benazza, *Arkivoc*, (ii), (**2008**) 1-13.
[46] B. Bennani, A. Kerbal, M. Daoudi, B.F Baba, G. Al Houari, A.F. Jalbout, M. Mimouni, M. Benazza, G. Demailly, M. Akkurt, S.Ö.Yýldýrým, and T. Ben Hadda. *Arkivoc* (xvi), (**2007**) 19-40.
[47] T. Ben Hadda, R. Badri, A. Kerbal, B.F Baba, M. Akkurt, G. Demailly and M. Benazza. *Arkivoc* (XIV), (**2007**) 276-288.

[48] J. Sheikh, A. Parvez, V. Ingle, H. Juneja, R. Dongre, Z.H. Chohan, M.H. Youssoufi and T. Ben Hadda. Synthesis, Biopharmaceutical Characterization, *European Journal of Medicinal Chemistry*. Paper has been accepted for publication at Janv 29-**2011**.
[49] P. Ertl, B. Rohde, P. Selzer, *J. Med.Chem.* 43 (**2000**) 3714-3717.
[50] Note: The University of Pennsylvania received **USA $ 9.5 million** grant from NIH as part of a national screening network to discover active molecules. E. Megers group is involved in this center with the design of bioactive organometallic ruthenium (II) compounds containing staurosporine derivatives as ligand. For confirmation, contact Prof. E. Meggers by e-mail: <meggers@chemie.uni-marburg.de>.