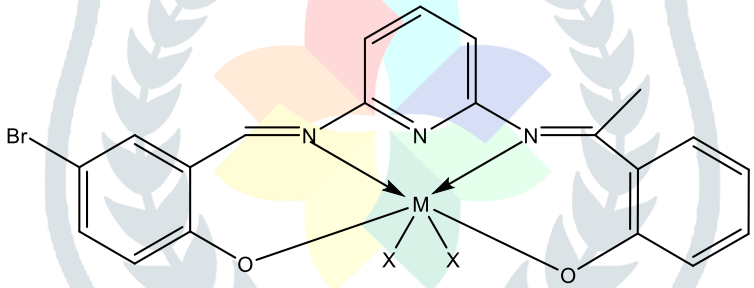
Quantum mechanical and pharmacophore analyses of transition metal complexes of N-(5-bromo-2-hydroxyacetophenone)-N'-(2-hydroxyacetophenone)-2,6-diaminopyridine

Atish K. Maldhure[1]*, Vijay H. Masand[2],Nilima A. Kalambe[3], Mahendrasingh J. Pawar[1], Anil R. Somwanshi[4]

[1]Department of Chemistry, Arts, Commerce and Science College, Kiran Nagar, Amravati, Maharashtra, India
[2]Department of Chemistry, VidyaBharati College, Camp, Amravati, Maharashtra, India
[3]Department of Chemistry, ShriShivaji Science College, Amravati, MS, India,
[4]Department of Chemistry, J. D. PatilSangludkarMahavidyalaya, Daryapur, MS, India.

Abstract: Unsymmetrical Schiff Base transition metal (Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Cr^{2+} and Fe^{2+}) complexes with tetradentate unsymmetrical Schiff base ligand N-(5-bromo-2-hydroxyacetophenone)-N'-(2-hydroxyacetophenone)-2,6-diaminopyridinehas been synthesized by a simple method using DMF as a solvent and alcoholic ammonia to maintained the pH 7.5 -8.00. This ligand has been prepared by condensation reaction between 5-bromo-2-hydroxyacetophenone and *o*-hydroxyacetophenone with 2,6-diaminopyridine. The ligand and the prepared complexes have shown good to better antimicrobial activity against bacteria *Staphalococcusaureus*, *Bacillus Subtilis*, *Salmonella typhimurium* and *Escherichia coli* and fungi *Aspergillusoryzae* and Fusarium species. Furthermore, quantum mechanical and pharmacophore analyses of transition metal complexes and ligand reveals that on coordinating with metal, the pharmacophore pattern as well as the electron density distribution of a metal ligand changes significantly. This could be used for achieving specific type of pharmacophore pattern for deriving novel compounds with desired pharmacophore with targeted activity profile.



Keywords: Unsymmetrical Schiff Base, Antimicrobial Activity, Pharmacophore analysis.

Introduction:

The chemistry of Schiff's bases, named after Hugo Schiff (Frankfurt, 26 April 1834-Florence, 8 September 1915), is more than hundred years old. Schiff bases, also known as azomethines or imines, are compounds that in a broad sense possess the general formula $R_3R_2C=NR_1$. The substituents R_2 and R_3 may be alkyl, phenyl, heteroaryl, hydrogen. The substituent R_1 at the N-imino (C=N) may be alkyl, phenyl, heteroaryl, hydrogen or a metal (generally Si, Al, B, Sn). A Schiff base derived from aniline, where R_3 is a phenyl or a substituted phenyl, can be called an *anil*. Thus, Schiff bases can be considered as a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (C=O) has been replaced by an imine or azomethine group. The name "Organic Bases" first appeared in a German paper entitled "*EineneueReiheorganischerBasen*" ("A New Series of Organic Bases") [1], though, they are not used as bases in the conventional sense, the designation of these compounds as bases, has persisted up to the present time.

The chemistry of Schiff's bases originated, when Schiff [1-9] reported the reaction between aniline with aldehydes. The method involved Dean Stark apparatus for removal of water molecule.

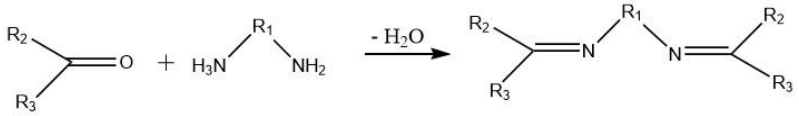


Figure 1 Synthetic protocol and general structure of amine

Schiff's bases readily form complexes with a variety of metals. The imino N atom is frequently employed for co-ordination with the metals. This has led to opening of new avenues for the chemical and biological profiles of Schiff's bases. Literature survey reveals that metal-Schiff's base complexes exhibits a range of anti-bacterial, anti-fungal, anti-cancer, etc. in micro to sub nanomolar range. This promising aspect of Schiff's base complexes has been the subject of study in the last decade [1-9].In the present work, the newly synthesized ligands and their complexes [10] with different 3D-series elements have been subjected to pharmacophore analysis.

Experimental Methodology:

Dataset: The dataset consists of complexes of N-(5-bromo-2-hydroxyacetophenone)-N'-(2-hydroxyacetophenone)-2,6-diaminopyridinewith a variety of d-block elements. Therefore, the selected dataset is useful to develop a pharmacophore model.

Structure drawing, optimization and alignment:A typical protocol and methodology reported in literature have been followed to develop a consensus pharmacophore model [11-13]. The different steps encompassed are:

Step-1: Drawing all structures: The structures were drawn using Chemsketch Freeware 12 (www.acdlabs.com) using default settings.

Step-2: Structure optimization of all the structures using MMFF94 force field: In this step, Avogadro version 1.2 was used using default settings using the semi-empirical force field (MMFF94).

Step-3: This step involved extensive use of PyMOl 1.8.6 and its plugin LIQUID for pharmacophore development using the default settings for different complexes and the free ligand.

Results and discussion:

The developed pharmacophore model for free and complexed ligand reveals a good number of differences. A comparison of pharmacophore model for free and complexed ligand, depicted in figure 1, reveals that some of the features are not affected by complexation but little influence on pharmacophoric pattern and good impact on molecular shape. There are six pharmacophoric features in both the free and complexed ligands. Out of six features, three are aromatic moieties and rests are H-bond acceptor, which form respective triangles with each other.

In the case of free ligand, the free –OH groups present on the terminal aromatic rings are available for H-bonding but not in the case of complexed ligand. The Nitrogen atom of diaminopyridine is not available for H-bond acceptation due to complex formation while free ligand can use it for H-bond formation.

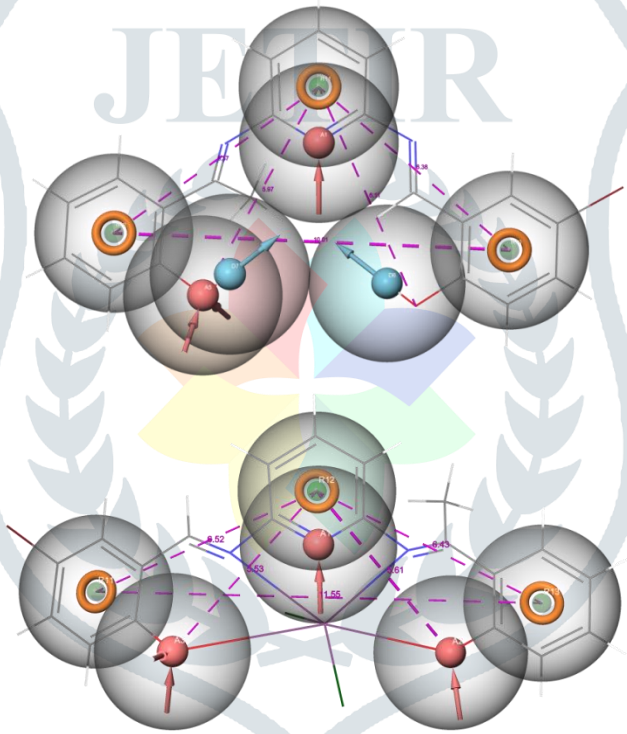


Figure 1. Comparison of pharmacophore pattern for free and complexed ligand (a) free ligand (b) Complex of ligand (shown using Mn as a representative only)

The present work indicates that complex formation inhibits the approach of any moiety toward the central Nitrogen atom present in the diaminopyridine of N-(5-bromo-2-hydroxyacetophenone)-N'-(2-hydroxyacetophenone)-2,6-diaminopyridine. It also changes the shape of the molecule. The –OH groups present on terminal moieties are not available for future H-bonding due to complex formation.

Conclusion:

In the present work, a thriving analysis has been accomplished using Quantum mechanical and pharmacophore analyses of transition metal complexes of N-(5-bromo-2-hydroxyacetophenone)-N'-(2-hydroxyacetophenone)-2,6-diaminopyridine and the free ligand. The analysis could be useful in future optimizations.

References:

[1] Schiff H (1864) MittheilungenausdemUniversitätslaboratorium in Pisa: eineneueReiheorganischerBasen. Justus Liebigs*Ann Chem 131*: 118–119.

[2] Schiff H (1866) EineneueReiheorganischerDiamine. Justus Liebigs*Ann Chem 140*: 92–137.

[3] Claisen L (1896) UebereineeigenthümlicheUmlagerung. *BerDtschChemGes 29*: 2931–2933.

[4] Langheld K (1909) Über das Verhalten von α-AminosäurengegenNatriumhypochlorit. *BerDtschChemGes42*: 2360–2374.
[5] Reddelien G (1920) Über die Zersetzung von Anilen. (Über die katalytische Wirkungsweise von Halogenwasserstoffsäuren bei Kondensationen, II). *BerDtschChemGes 53*: 355–358.
[6] Houben J, Fischer W (1929) Formation of aromatic nitriles by basic hydrolysis of trichloromethyl aryl ketimines. Acidic hydrolysis yields ketones. J PraktChem 123: 262–313.
[7] Pickard PL, Young CW (1951) Ketimines. III. ι-Cyclohexylalkyl Alkyl Type[1].*J Am ChemSoc 73*: 42–43.
[8] Porai-Koshits BA, Remizov, AL (1956) Probl. mekhanizma org. reaktsii. *Chem. Abstr 50:* 16686.
[9] Pickard PL, Tolbert TL (1961) An improved method of ketimine synthesis. *J Org Chem 26:* 4886–4888.
[10] Maldhure AK, Aswar AS (2013) Synthesis, Characterization and Antimicrobial studies of Some Transition metal complexes of N-(5-chloro-2-hydroxyacetophenone)-N'-(2-hydroxyacetophenone)-ethylenediamine *Am. J PharmTech Res3*: 462-486.
[11] Masand, V. H., El-Sayed, N. N. E., Bambole, M. U., Patil, V. R., & Thakur, S. D. (2019).
[12] Multiple quantitative structure-activity relationships (QSARs) analysis for orally active trypanocidal N-myristoyltransferase inhibitors.*Journal of Molecular Structure, 1175*, 481-487. doi:10.1016/j.molstruc.2018.07.080
[13] Masand, V. H., El-Sayed, N. N. E., Bambole, M. U., &Quazi, S. A. (2018). Multiple QSAR models, pharmacophore pattern and molecular docking analysis for anticancer activity of α, β-unsaturated carbonyl-based compounds, oxime and oxime ether analogues. *Journal of Molecular Structure, 1157*, 89-96. doi:10.1016/j.molstruc.2017.12.045
[14] Masand, V. H., Mahajan, D. T., Alafeefy, A. M., Bukhari, S. N., &Elsayed, N. N. (2015). Optimization of antiproliferative activity of substituted phenyl 4-(2-oxoimidazolidin-1-yl) benzenesulfonates: QSAR and CoMFA analyses. *Eur J Pharm Sci, 77*, 230-237. doi:10.1016/j.ejps.2015.06.001