IOSR Journal of Applied Chemistry (IOSR-JAC)
e-ISSN: 2278-5736.Volume 10, Issue 7 Ver. III (July. 2017), PP 23-28
www.iosrjournals.org

Synthesis, Structural characterization and Nucleic acid interaction of (E)-(2-(2-hydroxybenzylidene) hydrazinyl)(pyridin-4-yl)methaniminium

M. Sennappan [a, b], P. Murali Krishna [c*], N.B. Gopal Reddy [d], Praveen B.Managutti [e]

[a]*Department of Chemistry, Dayananda Sagar College of Engineering, Bengaluru-560078, India*
[b]*Visvesvaraya Technological University, Belagavi-590018, India*
[c]*Department of Chemistry, Ramaiah Institute of Technology, Bengaluru-560054, India*
[d]*Department of Chemistry, The Oxford College of Science, Bengaluru-560102, India*
eSolid State and Structural Chemistry Unit, Indian Institute of Science, Bengaluru-560012, India
*Corresponding Author: *P.Murali Krishna*

Abstract: *An environmentally benign and efficient reaction was developed for the preparation of (E)-(2-(2-hydroxybenzylidene)hydrazinyl)(pyridin-4-yl)methaniminium in the presence of water acting solvent and also catalyst with very high yield. In which, amine exchange and condensation reaction taken place between N-salicylidene aniline and isonicotinic acid hydrazide yields a novel methaniminium hydrazone at one step and very short time. The compound was structurally characterized by using single crystal X-RD and spectroscopy (FT-IR and NMR) techniques. The single X-RD results indicate that the ligand crystallizes in monoclinic system with P21/n space group.The investigation of DNA binding of the prepared compound was undertaken by electronic absorption titration method. The methaniminium hydrazone was showed hypochromism of 1.96% at 301nm; intrinsic DNA binding constant is 6.3111x106 M-1.*

Keywords-*Amine exchange reaction, Condensation reaction, Hypochromism, Methaniminium, Spectroscopy.*

Date of Submission: 17-07-2017 Date of acceptance: 31-07-2017

I. Introduction

Hydrazone Schiff bases are well known organic compounds containing azomethine group, having lone pair of electrons in SP2 hybridized orbital of nitrogen atom combined with one or more donor atoms close to this group [1]. This is considerable for chemical and biological importance and imparts excellent chelating ability with metal ions to produce complexes[2, 3] and cyclization ability to produce ring containing heteroatoms such as 1,3,4-oxadiazolines[4], 2-Azetidinones[5] and 4-Thiazolidinones[6]. Methaniminium cations are prepared by photoionization of alkyl amine in mass spectrometry [7-10], heating a guanidine with sulfonyl chloride and triethylamine [11] etc. Methaniminium cations are having positively charged nitrogen in sp2 hybridization with general formula –C=NH2+. This cation is isoelectronic structure with ethylene carbon but lost one electron to become positive charge. This is may be mildly acidic in nature. Methaniminium cation containing organic molecules are used in varies fields such as dye chemistry, biological, pharmacological, forensic science etc. Malachite green (MG) is used in fungal infections of farmed fish and aquaculture to control protozoan. This is also used in food, medical and textile industries [12].

In cell biology, DNA is the primary target molecule for most anticancer and antiviral therapies. Investigations on DNA interactions with small molecules have aroused, especially for those containing heteroatoms and aromatic rings. Since, it has potential applications as new therapeutic agents and interesting properties which make them as possible probes of DNA structure and conformation [13, 14]. Interaction of peptides, small organic and inorganic molecules with DNA intervene a number of processes like translation, transcription and replication [15]. By considering above principle various disorders like cancer, cystic fibrosis etc., can be cured by using DNA as targets, which is called DNA drug interaction. Schiff's bases have been found to be potential to bind DNA through multitude of interactions such as intercalation binding, groove binding and electrostatic binding. The drugs has been developed in this way may be less toxic and more prone to exhibit anti-proliferative activity against tumors [16, 17]. In the present study, methaniminium hydrazone Schiff base was prepared by amine exchange reaction, which has been described by Reddelien and Danilof in 1921 simultaneously taken place condensation reaction between amide carbonyl group of isonicotinic acid hydrazide and amine group of replaced amine at one step. The structure of the compound was established on the basis of

single crystal X-ray diffraction studies and spectroscopic data's. In addition, the investigation of DNA binding ability of the compound was undertaken by electronic absorption spectroscopy method.

II. Experimental

2.1. Materials

Aniline and salicylaldehyde were purchased from Merck, Bangalore, India. Isonicotinic acid hydrazide was purchased from Tokyo Chemical Industry.Co.Ltd, India. Distilled water was used throughout experiments.

2.2. Physical Measurements

Melting points of the compounds were recorded by using capillaries in Sigma melting point apparatus, Sigma instruments, Chennai, India. Infrared spectra were recorded in the 400–4000 cm-1 region (KBr disc) on a SHIMADZU, FTIR-8400S. 1H-NMR spectrum obtained in d6-DMSO using tetramethylsilane (TMS) as an internal reference on Advanced 200.12MHz NMR spectrometer. 13C-NMR spectrum was obtained in d6-DMSO using Bruker- 300 MHz NMR. Single X-ray diffraction data was recorded on a Bruker Kappa Apex2 CCD diffractometer at 293(2) K and refined at IISC, Bangalore, India.

2.3. Synthesis of (E)-(2-(2-hydroxybenzylidene)hydrazinyl)(pyridin-4-yl) methaniminium

A hot solution of isonicotinic acid hydrazide (0.696g, 5.076 mmol) in water was added slowly to a hot solution of N-Salicylidene aniline [1g, 5.076 mmol] in methanol with constant stirring at room temperature for 15 minutes. The formed precipitate was filtered, washed with cold methanol and dried. Yield: 92 %, M.P: 294-296^{0}C. ^{1}H-NMR (200.12MHz, DMSO-d^6, ppm) δ: 2.49 (s, 2H, $NH2^+$), 3.62 (s, DMSO), 6.87-8.78(m, Ar), 8.78 (s, 1H, -CH=N), 11.17 (s, 1H, -NH), 12.36 (s, 1H, -OH). ^{13}C NMR (300MHZ, DMSO-d6 and CHCl3) δ: 161.86 (C-OH), 157.90 (C=N,), 150.75(C=$NH2^+$) 149.59- 132.20(C, pyridine), 129.74-116.86(C, phenyl), 40.57-38.91(C, DMSO). FT-IR (KBr, cm^{-1}) 3452(-OH), 3192(-$NH2^+$), 1678(-C=N), 1278(Pyridine(C=N)).The synthetic route of the compound was illustrated in scheme-1.

Scheme 1. Synthesis of the methaniminium hydrazone.

2.4. X-ray crystallography

Single crystal of compound was grown by solvent evaporation method using the mixture of 1:1 methanol and tetrahydrofuran at room temperature for four days. A crystal size 0.26 × 0.25 × 0.24 mm^3 was taken for the X-ray crystallographic study. Single crystal X-ray diffraction data for the compound was collected at 298(2) K on a Bruker APEX-II CCD diffractometer using graphite monochromater Mo Kα (λ=0.71073A°). The structure was solved using OLEX2 [18] with SHELXS by direct methods [19]. The structure was refined by full-matrix least-squares minimization with SHELXL [19]. The non-hydrogen atom positions were found and refined anisotropically. Whereas, hydrogen atoms were positioned geometrically and treated as riding atoms where C–H = 0.93 Å with Uiso(H) = 1.2 Ueq(C) for aromatic carbon atoms and C–H = 0.96 Å with Uiso(H) = 1.5 Ueq(C) for methyl carbon atoms [20]. The crystallographic data collection and refinement parameters are presented in **Table I**.

Table 1. Crystal data and structure refinement of compound.

CCDC No	1529789
Empirical formula	$C_{13}H_{13}N_4O$
Formula weight	241.27
Temperature/K	298(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	8.1906(12)
b/Å	15.625(2)
c/Å	9.5795(13)
α/°	90

β/°	105.610(6)
γ/°	90
Volume/Å^3	1180.8(3)
Z	4
ρ_{calc}g/cm^3	1.357
μ/mm^{-1}	0.091
F(000)	508.0
Crystal size/mm^3	0.26 × 0.25 × 0.24
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.128 to 49.996
Index ranges	-9 ≤ h ≤ 9, -18 ≤ k ≤ 18, -10 ≤ l ≤ 11
Reflections collected	15430
Independent reflections	2077 [R_{int} = 0.0402, R_{sigma} = 0.0189]
Data/restraints/parameters	2077/0/208
Goodness-of-fit on F^2	1.040
Final R indexes [I>=2σ (I)]	R_1 = 0.0495, wR_2 = 0.1405
Final R indexes [all data]	R_1 = 0.0537, wR_2 = 0.1439
Largest diff. peak/hole / e Å^{-3}	0.32/-0.54

2.5. DNA Binding

The DNA binding ability of compound was examined by UV−vis spectroscopic studies in 50 mM Tris-HCl/NaCl buffered solution at pH 7.0. The concentration of CT-DNA was calculated from the Molar absorbance coefficient (6600 dm3 mol-1 cm-1) at 260 nm [21]. The solution of CT-DNA gave a ratio of UV absorbance at 260 and 280 nm (A260/A280) of 1.8-1.9 indicating the protein free nature of DNA. Electronic absorption titration experiment was performed by maintaining the concentration of methaniminium hydrazone as constant (7.0x10^{-5}M) but with variable nucleotide concentration from 0 to 7.9x10^{-7}M. Stock solutions were stored at 4^{o}C and were used after no more than 4 days. Distilled water was used to prepare buffer solutions. Solutions were prepared by mixing the methaniminium hydrazone and CT-DNA in DMSO medium. After equilibrium was reached (ca.5 min) the spectra was recorded against an analogous blank solution containing the same concentration of DNA.

The intrinsic binding constant (K_b) was calculated from the following equation (3).

$$[DNA]/ (\varepsilon a-\varepsilon b) = [DNA]/ (\varepsilon b-\varepsilon f) + 1/ Kb (\varepsilon b-\varepsilon f) \quad (3)$$

Where, [DNA] is the concentration of DNA, εa, εb and εf correspond to apparent, bound and free compounds extinction coefficients respectively. A plot of [DNA]/ (εa-εf) Vs [DNA] gave slope of 1/ (εb-εf) and a Y-intercept equal to 1/K_b (εb-εf), K_b is the ratio of the slope to the Y-intercept.

III. Results and Discussion

3.1. Single crystal X-ray diffraction studies

The numbering scheme, hydrogen bonding interactions and unit cell packing diagram of the compound is given in figure1, 2 and 3. The selected bond lengths, bond angles and hydrogen bonding data's are presented in table 2, 3 and 4. The phenyl ring showed C-C distances ranging from 1.381(3) to 1.412(3) A° reveals that delocalized bonding structure. The C13-N1 and C2-N1 bonds distances of 1.346(2) and 1.343(3) A° and ring C-C distances from 1.382(3) to 1.395(3) A° agrees with pyridyl ring [22]. The bond length of hydrazinyl (N7-N6) nitrogen atoms 1.377(2) A° is in agreement with literature reports [23, 24]. Bond length of azomethine group (C8-N7) is 1.285(2) A° as expected for formal double bond [25]. Bond length of C5-N0AA is 1.213(2) A°, may be characteristic of methaniminium group. The bond lengths of N6-C5 and C5-C4 are 1.366(2) and 1.508(3) A° respectively, which are supporting methaniminium group in the molecule. The molecular conformation is stabilized by a strong intra-molecular O2-H2….N7 (1.800 A°) hydrogen bond. Molecule is further stabilized by medium strength inter molecular N6-H6….N1hydrogen bond (1.800 A°). Strength of the hydrogen bond is confirmed by bond length.

3.2. DNA binding studies

The electronic absorption spectrum of methaniminium hydrazone in the absence and presence of increasing amounts of CT-DNA (25μL) was recorded (Fig. 4). The methaniminium hydrazone showed

hypochromism of 1.96% at 301nm; intrinsic DNA binding constant is 6.3111x106M^{-1}. This result suggested that the compound was bound with CT-DNA strand through intercalation. When compound bind into the base pairs of DNA, the π* orbital of the intercalator may couple with the π orbital of the base pairs of DNA. Thus, decreasing the π- π* transition and hence a hypochromism is observed in the compound [26].

IV. Figures and Tables

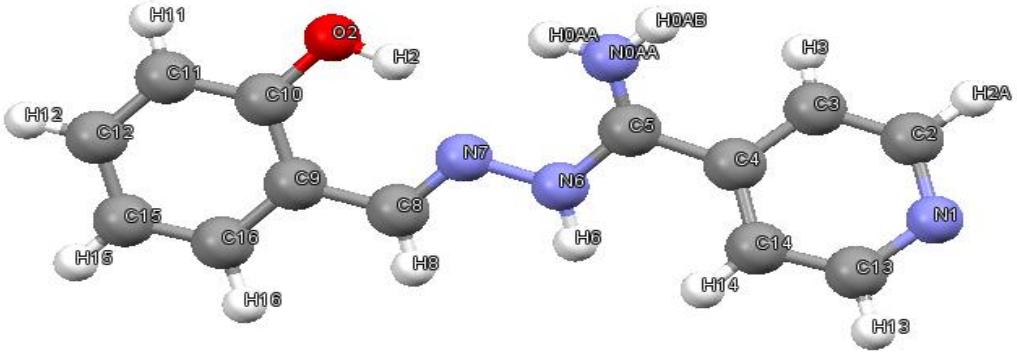

Fig. 1. ORTEP diagram of the compound with numbering scheme.

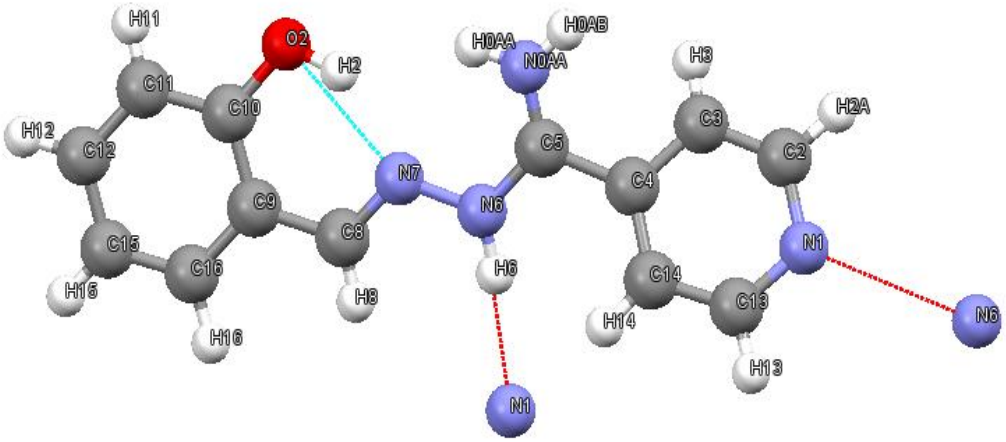

Fig. 2. ORTEP diagram of compound with hydrogen bonds.

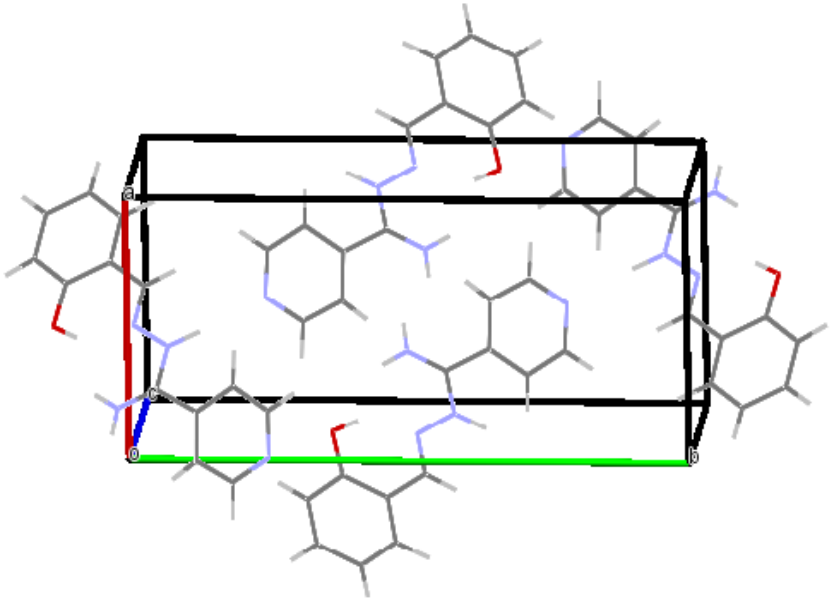

Fig. 3. Unit cell packing diagram of the methaniminium hydrazone.

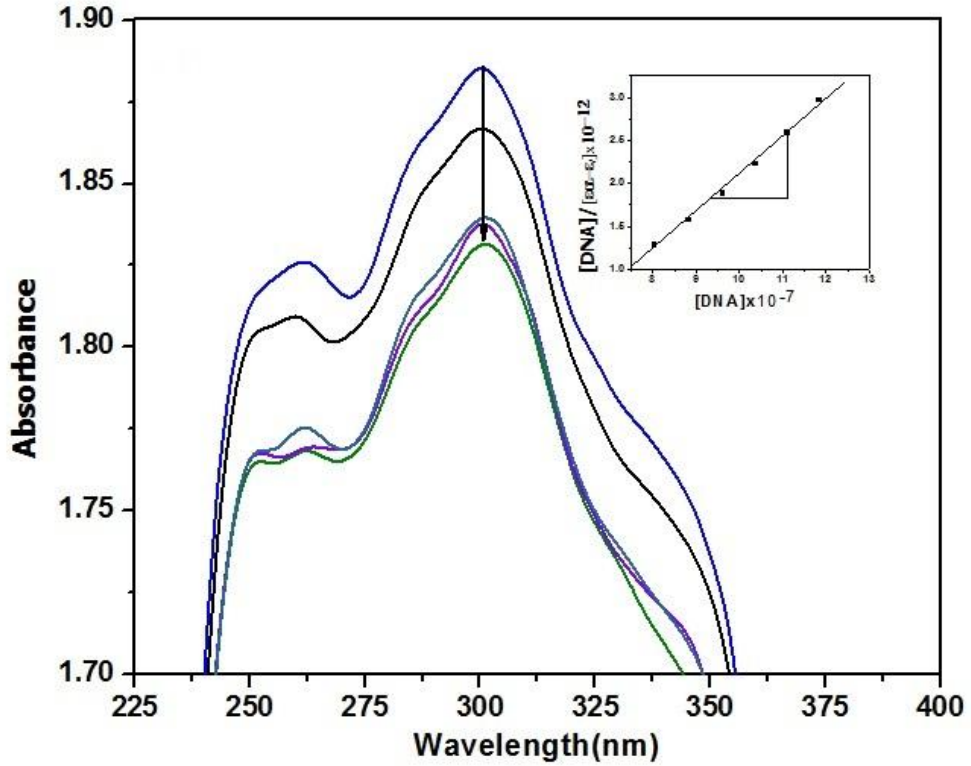

Fig. 4. Electronic absorption spectra of methaniminium hydrazone Schiff base in the absence and presence of increasing amounts of CT-DNA (25µL - 350µL). Arrow shows the decrease in absorbance with respect to an increase in the DNA concentration [Inset: plot of [DNA]/ (εa-εf) Vs [DNA].

Table 2. Selected bond lengths (Å) and bond angles (˚).

Bond	Bond length	Bond	Bond length	Bonds	Bond Angle	Bonds	Bond Angle
N0AA-C5	1.213(2)	C9-C10	1.412(3)	C2-N1-C13	116.39(16)	C10-C9-C8	121.67(16)
O2-C10	1.361(2)	C9-C16	1.403(3)	N1-C2-C3	123.75(17)	C16-C9-C8	119.90(16)
N1-C2	1.343(3)	C10-C11	1.396(3)	C2-C3-C4	119.23(18)	C16-C9-C10	118.43(17)
N1-C13	1.346(2)	C11-C12	1.383(3)	C3-C4-C5	118.27(16)	O2-C10-C9	122.26(17)
C2-C3	1.382(3)	C12-C15	1.388(3)	C14-C4-C3	117.72(17)	O2-C10-C11	118.40(18)
C3-C4	1.395(3)	C13-C14	1.383(3)	C14-C4-C5	124.00(16)	C11-C10-C9	119.34(18)
C4-C5	1.508(3)	C15-C16	1.381(3)	N0AA-C5-C4	121.83(17)	C12-C11-C10	120.6(2)
C4-C14	1.394(3)			N0AA-C5-N6	123.49(17)	C11-C12-C15	120.78(19)
C5-N6	1.366(2)			N6-C5-C4	114.67(16)	N1-C13-C14	124.10(18)
N6-N7	1.377(2)			C5-N6-N7	117.63(16)	C13-C14-C4	118.80(17)
N7-C8	1.285(2)			C8-N7-N6	117.78(16)	C16-C15-C12	118.9(2)
C8-C9	1.457(2)			N7-C8-C9	120.49(17)	C15-C16-C9	121.85(19)

Table 3. Hydrogen bonds(Å).

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
N6-H6	0.964	2.102	172.54	3.061	N1
O2-H2	0.938	1.800	143.18	2.612	N7

V. Conclusion

In this work, we have synthesized stable methaniminium hydrazone Schiff base by novel reaction. This reaction has significant advantages such as high conversion, very short reaction time, mild reaction conditions, inexpensive, simple work up and non-toxic. Generally this kind of molecules studied in organic reactions as intermediates. However, this compound may be shown versatile properties used for various fields. Several new drugs with reduced toxicity and high specificity have been developed by understanding the mechanism of DNA binding. Development of medicinal chemistry requires an understanding of the physiological processing of compounds with DNA, to provide a rational basis for the design of new drugs.

Acknowledgements

We offer our sincere thanks to Prof. T. N. Guru Row, SSCU, IISC, Bangalore; Dr. V. Murugan, DSCP, Bangalore for their supporting during Single X-RD and FT-IR analysis respectively.

References

[1] S. Patai, The Chemistry of Carbon–Nitrogen Double Bond (Interscience, New York, 1970) 149-180.
[2] Daniel J. Hutchinson, Scott A. Cameron, Lyall R. Hanton and Stephen C. Moratti, Sensitivity of Silver(I) Complexes of a Pyrimidine–Hydrazone Ligand to Solvent, Counteranion, and Metal-to-Ligand Ratio Changes, Inorg. Chem. 51(9), 2012, 5070–5081.
[3] Shane M. Wilkinson, Timothy M. Sheedy and Elizabeth J. New, Synthesis and Characterization of Metal Complexes with Schiff Base Ligands, J. Chem. Educ. 93(2), 2016, 351–354.
[4] H.N. Dogan, A. Duran, S. Rollas, G. Sener, Y. Armutak and M. Keyer-Uysal, Synthesis and structure elucidation of some new hydrazones and oxadiazolines: anticonvulsant activities of 2-(3-acetyloxy-2-naphthyl)-4-acetyl-5-substituted-1,3,4-oxadiazolines, Med. Sci. Res. 26(11),1998, 755- 758.
[5] R. Kalsi, M. Shrimali, T. N. Bhalla and J. P. Barthwal, Synthesis and anti-inflammatory activity of indolyl azetidinones, Indian J. Pharm. Sci. 41, 2006, 353-359.
[6] A. Bolognese, G. Correale, M. Manfra, A. Lavecchia, E. Novellino and V. Barone, Thiazolidin-4-one formation. Mechanistic and synthetic aspects of the reaction of imines and mercaptoacetic acid under microwave and conventional heating, Org. Biomol. Chem. 2(9), 2004, 2809-2813.
[7] D. Suarez and T. L. Sordo, Ab Initio Study of the H_2 Elimination from CH_2OH^+, $CH_2NH_2^+$ and CH_2SH^+, J. Phys. Chem. A, 101(8), 1997, 1561-1566.
[8] Tae Hoon Choi, Sang Tae Park and Myung Soo Kima, Theoretical and experimental studies of the dissociation dynamics of methaniminium cation, $CH_2NH_2^+ \rightarrow CHNH^+ + H_2$: Reaction path bifurcation, J. Chem. Phys. 114(14), 2001, 6051-6057.
[9] John C. Traeger, Gas-Phase Heats of Formation for Alkylimmonium Cations by Photoionization Mass Spectrometry, J. Phys. Chem. A, 111(21), 2007, 4643-4649.
[10] John C.Traeger and A. H. Zoe, Heat of Formation for the $CH_3CH=NH_2^+$ Cation by Photoionization Mass Spectrometry, J. Phys. Chem. A, 110(27), 2006, 8542-8547.
[11] Shaaban K. Mohamed, Mehmet Akkurt, Mahmoud A. A. Elremaily, Ali. M. Ali and Mustafa R.Albayati, Amino[(1H-benzimidazol-2-yl)amino]- methaniminium 4-methylbenzenesulfonate, Acta Cryst. E, 69, 2013, 1543–1544.
[12] Jie Yang, Xiaodan Yang, Yonghui Lin, Tzi Bun Ng, Juan Lin, Xiuyun Ye, Laccase-Catalyzed Decolorization of Malachite Green: Performance Optimization and Degradation Mechanism, PLoS ONE, 10, 2015, 1-14.
[13] M. R. Gajendragad and U. Agarwala, 1, 3, 4-Thiadiazole-2, 5-dithiol as a Complexing Agent II. Complexes of Ni^{II}, Rh^{I}, Pd^{II}, Pt^{II}, Au^{III}, and Cu^{II}, Z. anorg. Allg. Chem, 415, 1975, 84-96.
[14] L. Ronconi and P. J. Sadler, Using coordination chemistry to design new medicines, Coord. Chem. Rev, 251, 2007, 1633-1648.
[15] O. Kennard, DNA-drug interactions, Pure & App. Chem, 65, 1993, 1213-12226.
[16] A. R. Beaudoin, Teratogenic activity of 2-amino-1,3,4-thiadiazole hydrochloride in Wistar rats and the protection afforded by nicotinamide, Teratology, 7(1), 1973, 65-71.
[17] J. H. Looker and Jr. L. W. Wilson, 1, 2, 3-Thiadiazoles as potential antineoplastic agents I. Synthesis of novel 4-monosubstituted and 4,5-disubstituted derivatives, J. Heterocyclic. Chem, 2, 1965, 348-354.
[18] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program, J. Appl. Cryst. 42, 2009, 339-341.
[19] G. M. Sheldrick, A short history of SHELX, Acta Cryst. A64, 2008, 112–122.
[20] Muhammad Nadeem Arshad , Aisha Bibi, Tariq Mahmood , Abdullah M. Asiri and Khurshid Ayub, Synthesis, Crystal Structures and Spectroscopic Properties of Triazine-Based Hydrazone Derivatives; A Comparative Experimental-Theoretical Study, Molecules, 20(4), 2015, 5851-5874.
[21] Vimal K. Bhardwaj and Ajnesh Singh, Comparative DNA Binding Abilities and Phosphatase-Like Activities of Mono-, Di-, and Trinuclear Ni(II) Complexes: The Influence of Ligand Denticity, Metal–Metal Distance, and Coordinating Solvent/Anion on Kinetics Studies, Inorg. Chem, 53(19), 2014, 10731−10742.
[22] Shu-Ye Wang, Xue-Ming Song and Li-Xiang Duan, N'-Propylisonicotinohydrazide, Acta Cryst, E64, 2008, 1-6.
[23] S. Sawusch, N. Jager, U. Schilde and E. Uhlemann, Ligand Exchange Reactions of $ReOCl_3(PPh_3)_2$ with Tridentate Diacidic Ligands with the Donor Set O-N-O(N): Molecular and Electronic Structures of the Resulting Oxo-rhenium(V) Complexes, Structural Chemistry, 10(2), 1999, 105–119.
[24] L. Zhang, G.C. Xu, L. Liu, G.F. Liu and D. Jia, Synthesis, characterization and crystal structure of 1-phenyl-3-methyl-4-(salicylidene hydrazide)-phenylethylene-pyrazolone-5, Journal of Chemical Crystallography, 38(2), 2008, 151–155.
[25] Angela kriza, Lucica Viorica Ababei, Nicoleta Cioatera, Ileana rau and Nicolae Stanica, Synthesis and structural studies of complexes of Cu, Co, Ni and Zn with isonicotinic acid hydrazide and isonicotinic acid (1-naphthylmethylene)hydrazide, J. Serb. Chem. Soc, 75 (2), 2010, 229–242.
[26] Palaniswamy sathyadevi, Paramasivam Krishnamoorthy, Rachel R. Butorac, Alan H. Cowley, Nallaswamy Dharmaraj, Synthesis of novel heterobimetallic copper(I) hydrazone Schiff base complexes: A comparative study on the effect of heterocyclic hydrazides towards interaction with DNA/protein, free radical scavenging and Cytotoxicity, Metallomics. 5, 2012, 498-511.

IOSR Journal of Applied Chemistry (IOSR-JAC) is UGC approved Journal with Sl. No. 4031, Journal no. 44190.

P.Murali Krishna. "Synthesis, Structural characterization and Nucleic acid interaction of (E)-(2-(2-hydroxybenzylidene) hydrazinyl)(pyridin-4-yl)methaniminium." IOSR Journal of Applied Chemistry (IOSR-JAC) 10.7 (2017): 23-28.