مجلة الدراسات التربوية والعلمية - كلية التربية - الجامعة العراقية
العدد الخامس والعشرون - المجلد الثالث عشر - علوم الكيمياء - آب 2025 م
doi.org/10.52866/esj.2023.13.25.16

Synthesis, Characterization, and DFT Theoretical Studies of Some Isoniazid-Derived Hydrazones

Mohammad. F.Ahmed [*1] , Atallah B.Dekhyl[2] , Nashwan O.Tapabashi[3]
[1]Department of Chemistry, College of Education for Pure Sciences, University of Tikrit, Iraq
[2]Department of Chemistry, College of Education for Women, University of Tikrit, Iraq
[3]College of Pharmacy, Kirkuk University, Kirkuk, Iraq
Corresponding author: mf230035pep@st.tu.edu.iq

Abstract:

Aims: To synthesize isoniazid-derived imines by condensing isoniazid (INH) with substituted benzaldehydes and pyridine carboxaldehydes, and to determine their structures using spectroscopic methods.

Methodology: Isoniazid was mixed with equimolar amounts of substituted benzaldehydes and pyridine carboxaldehydes, and the mixture was refluxed for 4-7 hours.

Results: Elemental analyses and IR spectroscopy confirmed the synthesis and characterization of ten Schiff bases.

Conclusion: The analysis of the energies of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) suggests that compounds M1-M10 are stable. Hardness data indicate that molecule M8 exhibits a higher aromatic character than the other compounds.

Keywords: Isoniazid; hydrazones; Schiff bases; DFT.

تحضير وتوصيف ودراسات نظرية باستخدام نظرية الكثافة الوظيفية (DFT) لبعض الهيدرازونات المشتقة من الأيزونيازيد

[1]محمد فرمان أحمد ، [2]عطاالله برجس دخيل ، [3]نشوان عمر رشيد لطيف تبه باشى
1 - قسم الكيمياء، كلية التربية للعلوم الصرفة، جامعة تكريت، العراق
2 - قسم الكيمياء، كلية التربية للبنات، جامعة تكريت، العراق
3 - كلية الصيدلة، جامعة كركوك، العراق
mf230035pep@st.tu.edu.iq

مستخلص:

الأهداف: تمثلت الأهداف في تحضير إيمينات مشتقة من الأيزونيازيد عن طريق تكثيف الأيزونيازيد (INH) مع بنزالديهايدات ومشتقات بيريدين كربوكسالديهيد، وتحديد تراكيبها باستخدام الطرق الطيفية.

المنهجية: تم خلط الأيزونيازيد مع كميات متكافئة من بنزالديهايدات ومشتقات بيريدين كربوكسالديهيد، ثم تم غلي المزيج مع الارتداد لمدة تتراوح بين 4 إلى 7 ساعات.

النتائج: أكدت التحاليل الأولية وطيف الأشعة تحت الحمراء (IR) عملية التحضير والتوصيف لعشرة قواعد شيف.

الاستنتاج: تشير تحاليل طاقات أعلى مدار جزيئي مشغول (HOMO) وأدنى مدار جزيئي غير مشغول (LUMO) إلى أن المركبات M1-M10 مستقرة. كما تشير بيانات الصلابة إلى أن المركب M8 يتمتع بطابع عطري أعلى مقارنةً ببقية المركبات.

الكلمات المفتاحية: أيزونيازيد؛ هيدرازونات؛ قواعد شيف؛ نظرية الكثافة الوظيفية (DFT).

1. INTRODUCTION

Isoniazid, a pro-drug with recognized therapeutic uses, has been clinically employed for over five decades as a first-line medication in the prevention and treatment of tuberculosis[1], [2]. Structurally, isoniazid is a nicotinamide analog, consisting of a pyridine ring and a hydrazide moiety[3]. The reactivity of the free -NH2 group in hydrazine allows its condensation with various carbonyl compounds, forming hydrazones. These hydrazones, particularly those incorporating aldehydes and ketones, exhibit distinct chemical and biological properties[4]. Schiff bases, derived from hydrazones, are notable for their characteristic -C=N- linkage. [5]Several Schiff bases have demonstrated significant pharmaceutical applications, including antibacterial[6], antitumor[7], antifungal[8], antioxidant[9], and antitubercular activities[10]. [11]From a computational perspective, Density Functional Theory (DFT) plays a pivotal role in elucidating the electronic structures and chemical reactivity of such compounds[12]. By analyzing frontier molecular orbitals, namely the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), researchers can predict reactivity patterns and optimize compound design[13]. The integration of these experimental and computational approaches is essential for the development of novel, more effective therapeutic agents[14]. This study focuses on the synthesis, characterization, and DFT theoretical analysis of isoniazid-derived Schiff bases, aiming to explore their potential as innovative antitubercular agents and their broader pharmaceutical applications[15]. By modifying the hydrazine group of isoniazid with functional groups that inhibit acetylation, this research seeks to overcome drug resistance and enhance biological activity, contributing to advancements in therapeutic strategies[16].

2. EXPERIMENTAL

2.1. Materials

All the compounds used in this study were analytical grade (Sigma Aldrich) and were used as received, without any further purification.

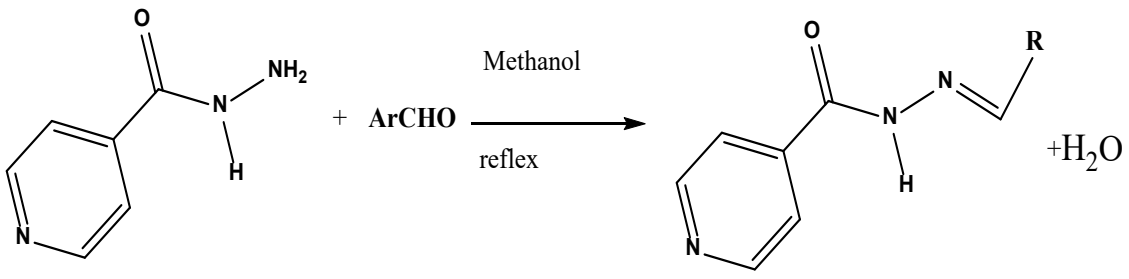
2.2. Physical Measurements

Spectra were recorded using a Per-

kin-Elmer FT-IR 100 spectrometer. The attenuated total reflectance (ATR) mode was employed to measure spectra in the range of 4000 to 600 cm^{-1}.

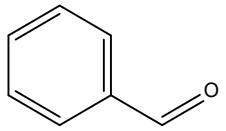
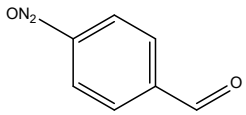
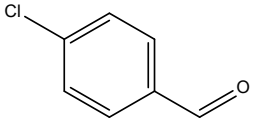
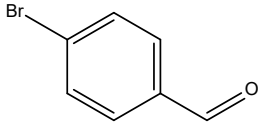
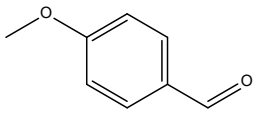
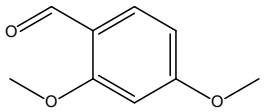
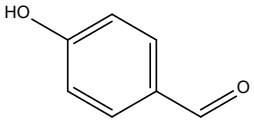
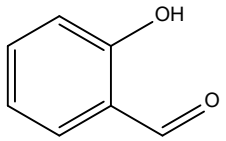
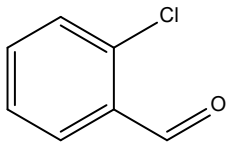
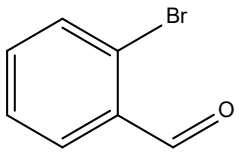
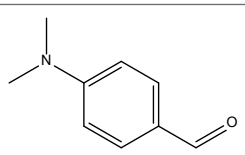
2.3. Synthesis of the Schiff Bases

To synthesize the Schiff bases, equal amounts of isoniazid and aldehydes were heated in methanol at 70°C with continuous agitation for 4–7 hours, as shown in Scheme 1. The first step in Scheme 1 involved dissolving isoniazid (0.274 g, 2.0 mmol) in 5.0 mL of warm methanol, followed by dissolving 0.258 g (2.0 mmol) of 4-(dimethylamino) benzaldehyde in 5.0 mL of warm methanol. The mixture was heated to 70°C and agitated continuously for 4 hours in a water bath, resulting in the formation of a yellow solution. Thin-layer chromatography (TLC) was employed to monitor the progression of the reaction using a solvent mixture consisting of 40% isopropyl alcohol and 60% hexane. Upon cooling, the solution underwent solvent evaporation, resulting in the formation of yellow crystals after two days[4] [17] [18]. The resultant product was filtered, treated with cold methanol, and desiccated in a desiccator utilizing anhydrous CaCl2. The compound was synthesized by subjecting isonicotinic acid hydrazide salt to reflux in an ethanol/water solvent mixture for 24 hours [17]. The purity of the compounds was assessed using analytical HPLC and measurement of melting temperature (Table 2). The aldehydes commonly employed in the synthesis of Schiff bases are shown in Table 1.



Scheme 1. General method of synthesis of Schiff bases

Table (2-1): Chemical properties of prepared hydrazones (M1-M11)

General structural formula					
Comp.	**-Ar**	**M.F.**	**M.Wt.**	**M.P.°C**	**Yield%**
M_1		$C_{13}H_{11}N_3O$	225.25	171 -169	97%
M_2		$C_{13}H_{10}N_5O_2$	268.26	280 -283	90%
M_3		$C_{13}H_{10}N_3O$	259.69	225 -230	79%
M_4		$C_{13}H_{10}BrN_3O$	304.15	230 -234	87%
M_5		$C_{14}H_{13}N_3O$	255.28	182 -186	80%
M_6		$C_{15}H_{15}N_3O_3$	285.30	131 -134	89%
M_7		$C_{13}H_{13}N_3O_2$	241.25	310-308	87%
M_8		$C_{13}H_{13}N_3O_2$	241.25	210-207	76%
M_9		$C_{13}H_{10}N_3O$	259.69	224-222	92%
M_{10}		$C_{13}H_{10}BrN_3O$	304.15	248-245	89%
M_{11}		$C_{15}H_{16}N_4O$	268.32	219-216	87%

2.4. Computational Study

Molecular characteristics of produced M1-M10 compounds, such as dipole moment, HOMO, LUMO, HOMO-LUMO gap, and certain electronic properties, were calculated using density functional theory (DFT) with (B3LYP) as a functional and the def 2-SVP as a basis set using the ORCA software program.

3. RESULTS AND DISCUSSION

3.1. Elemental Analysis

Table (2-1) presents the physical characteristics of the Schiff bases originating from isoniazid, which include their molecular weight, melting point, and elemental analysis. Elemental analysis values exhibit a high degree of agreement between experimental and theoretical data. The compounds exhibited distinct melting points that deviated from those of the parent materials, therefore verifying the formation of novel compounds. The high melting temperatures seen suggest that the molecules are bound together in a lattice structure by robust intermolecular hydrogen bonds.

3.2. Infrared

The compounds have an average stretching frequency of the N-H band ranging from 3139 to 3296 cm-1. The distinctive peak of C=N (imine) fluctuates between 1603 and 1550 cm-1. Resonance effects cause a little rise in the NH band of monosubstituted methoxy-aldehydes, with the substituted Schiff base exhibiting the greatest frequency and the m-substituted isomer the lowest. The compounds exhibit clustering of prominent bands within the 1500 cm-1 range, which can be attributed to the C=N and C=C bonds present in the pyridine/aromatic rings[19].

3.3. Computed Density Functional Theory

In general, molecules with small HOMO-LUMO gaps are reactive, while those with large gaps are stable and unreactive. Higher HOMO energies indicate easier electron donation for HOMO, while lower LUMO energies indicate easier electron acceptance for LUMO. Theoretical investigation revealed that generated M1–M10 with halogen substitution had minimal effects, except for M, which raised the LUMO energy level and made the molecule more stable in comparison to other compounds. The energy gap

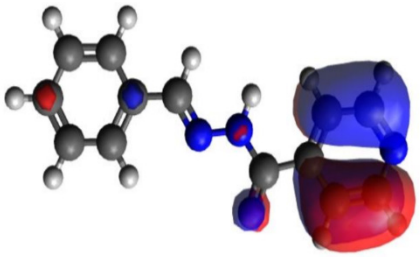
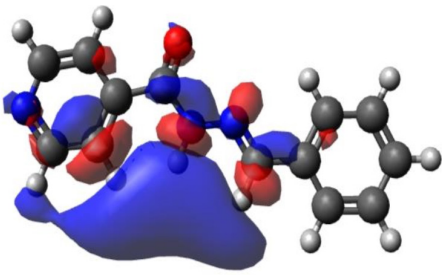
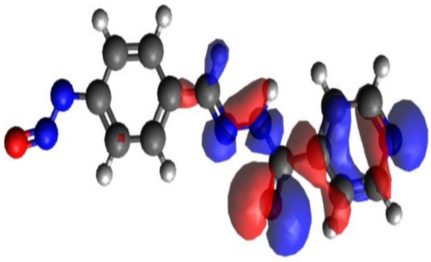
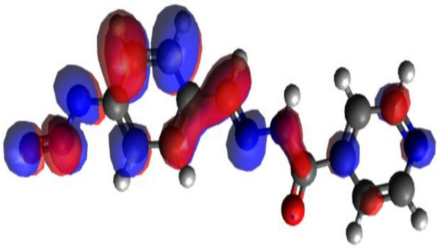
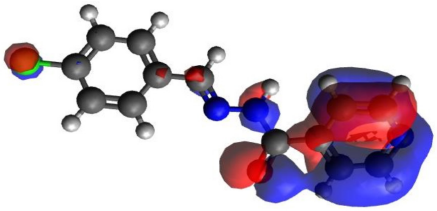
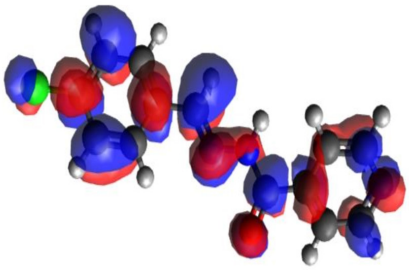
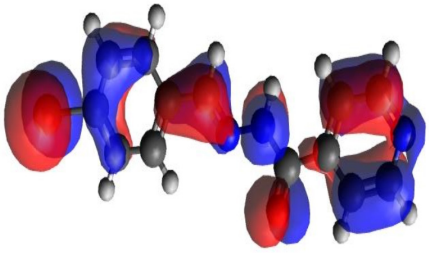
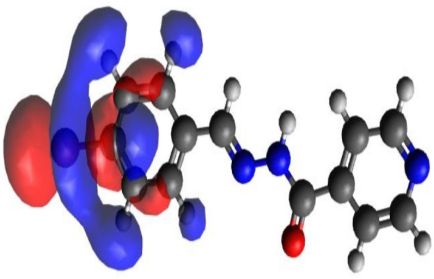
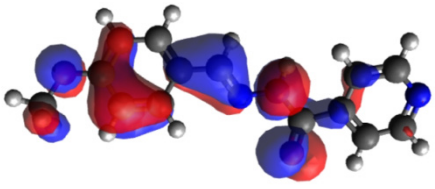
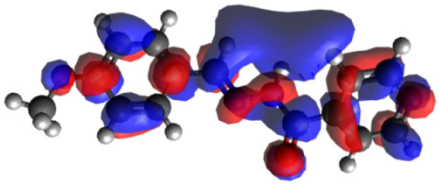
between the HOMO and LUMO orbitals in compounds M1–M10. The following formulas were used to compute the electronic characteristics, which include electron affinity A, Ionization potential I, absolute electronegativity μ, absolute hardness η, and electrophilicity ω. The findings are shown in Table 3.

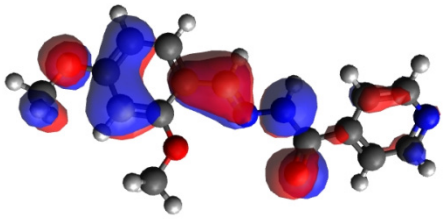
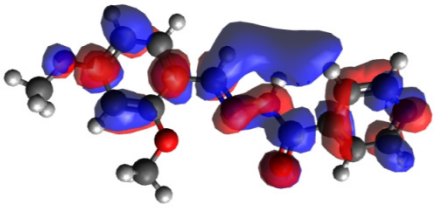
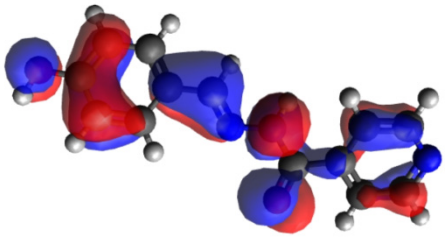
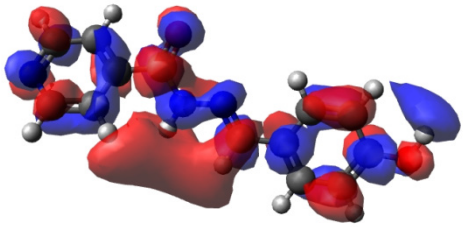
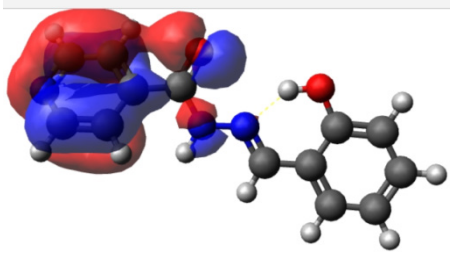
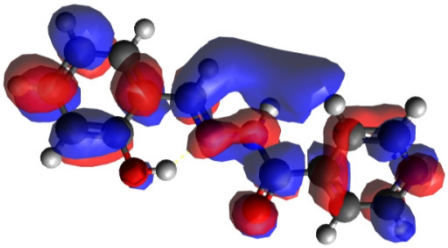
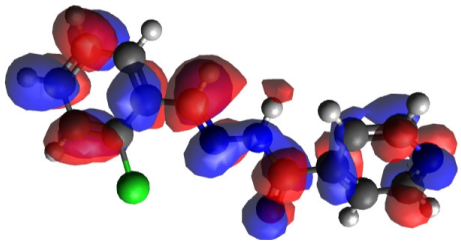
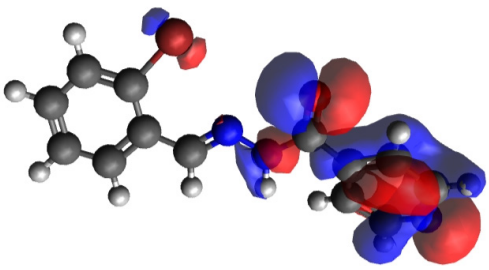
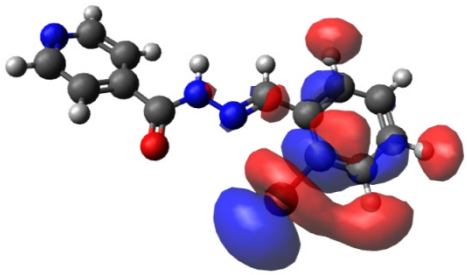
$$A = -(E_{LUMO}) \qquad I = -(E_{HOMO}) \qquad \omega = \frac{\mu^2}{2\eta}$$

$$\mu = \frac{E_{LUMO} + E_{HOMO}}{2} \qquad \eta = \frac{E_{LUMO} - E_{HOMO}}{2}$$

3.4. The border molecular orbitals

Frontier molecular orbitals include both the highest occupied molecular orbitals (HOMO) and the lowest unoccupied molecular orbitals (LUMO). The HOMO can give an electron, whereas the LUMO indicates the ability to absorb electrons. These orbitals are vital in determining the stability of a chemical molecule. The HOMO and LUMO energy levels were computed using the DFT technique at the B3LYP/def2-SVP level of theory, as indicated in the table2. One electron is transferred from the highest occupied molecular orbitals to the lowest empty molecular orbitals to mark the transition from the ground state to the excited state. The figure displays a schematic of the HOMO-LUMO energy values. The energy gap between HOMO and LUMO provides detailed interaction between the molecules and chemical stability. The HOMO electronic density distribution for Schiff bases is plotted in Fig. 3.

Code	HOMO	LUMO
M1		
M2		
M3		
M4		
M5		

Code	HOMO	LUMO
M6		
M7		
M8		
M9		
M0		

4. Conclusion

In this study, isoniazid-derived Schiff bases were successfully synthesized, characterized, and analyzed using both experimental techniques and DFT theoretical calculations. The elemental analysis, IR spectroscopy, and computational studies confirmed the structure and stability of the synthesized compounds. The results showed that the Schiff bases exhibit significant electronic properties, as evidenced by the HOMO-LUMO energy gap, indicating their potential for chemical reactivity and biological activity.

These findings suggest that the synthesized Schiff bases could serve as promising candidates for applications in pharmaceutical and material sciences. Future research should focus on exploring their biological activities and potential to enhance therapeutic properties, thereby contributing to advancements in drug design and development.

References

L. S. Goodman and A. Gilman, *The pharmacological basis of therapeutics*, vol. 230. Macmillan, New York, 1970.

A. S. Kolyva and P. C. Karakousis, "Old and new TB drugs: mechanisms of action and resistance," *Understanding Tuberculosis-New approaches to fight against drug resistance*, 2012.

F. A. R. Rodrigues, A. C. A. Oliveira, B. C. Cavalcanti, C. Pessoa, A. C. Pinheiro, and M. V. N. de Souza, "Biological evaluation of isoniazid derivatives as an anticancer class," *Sci Pharm*, vol. 82, no. 1, p. 21, 2013.

O. F. Akinyele, E. G. Fakola, L. M. Durosinmi, T. A. Ajayeoba, and A. O. Ayeni, "Synthesis, characterization and antimicrobial activities of heteroleptic metal chelates of isoniazid and 2, 2'-bipyridine," *Bull Chem Soc Ethiop*, vol. 34, no. 3, pp. 471–478, 2020.

Y. H. Ebead, H. M. A. Salman, and M. A. Abdellah, "Experimental and theoretical investigations of spectral, tautomerism and acid-base properties of Schiff bases derived from some amino acids," *Bull Korean Chem Soc*, vol. 31, no. 4, pp. 850–858, 2010.

A. S. Abu-Khadra, R. S. Farag, and A. E.-D. M. Abdel-Hady, "Synthesis, characterization and antimicrobial activity of Schiff base (E)-N-(4-(2-hydroxybenzylideneamino) phenylsulfonyl) acetamide metal complexes," *Am J Analyt Chem*, vol. 7, no. 03, p. 233, 2016.

A. T. A. Boraei, M. S. Gomaa, H. El Sayed, and A. Duerkop, "Design, selective alkylation, and X-ray crystal structure determination of dihydro-indolyl-1, 2, 4-triazole-3-thione and its 3-benzylsulfanyl analog as potent anticancer agents," *Eur J Med Chem*, vol. 125, pp. 360–371, 2017.

L. Wei *et al.*, "Synthesis, characterization, and antifungal activity of Schiff bases of inulin bearing pyridine ring," *Polymers (Basel)*, vol. 11, no. 2, p. 371, 2019.

S. Slassi, A. Fix-Tailler, G. Larcher, A. Amine, and A. El-Ghayoury, "Imidazole and Azo-Based Schiff Bases Ligands as Highly Active Antifungal and Antioxidant Components," *Heteroatom Chemistry*, vol. 2019, no. 1, p. 6862170, 2019.

F. K. Camellia, M. Ashrafuzzaman, M. N. Islam, and L. A. Banu, "Synthesis, characterization, antibacterial and antioxidant studies of isoniazid-based Schiff base ligands and their metal complexes," *Asian Journal of Applied Chemistry Research*, vol. 11, no. 3, pp. 8–23, 2022.

R. Gavadia, J. Rasgania, M. V. Basil, V. Chauhan, S. Kumar, and K. Jakhar, "Synthesis of isoniazid analogs with promising antituberculosis activity and bioavailability: biological evaluation and computational studies," *J Mol Struct*, vol. 1283, p. 135325, 2023.

M. A. Shah *et al.*, "Synthesis and characterization of novel hydrazone derivatives of isonicotinic hydrazide and their evaluation for antibacterial and cytotoxic potential," *Molecules*, vol. 27, no. 19, p. 6770, 2022.

S. Gupta *et al.*, "Experimental, spectroscopic, and theoretical investigation on structural and anticancer activities of Schiff bases derived from isonicotinohydrazide," *J Mol Struct*, vol. 1293, p. 136212, 2023.

M. A. Islam, F. Tasnim, M. S. Hossain, M. F. Hossen, M. K.-E. Zahan, and M. A. Ashraf, "Experimental and computational insights into antibacterial and antioxidant properties of metal complexes with isoniazid-based Schiff base ligands," *J Mol Struct*, p. 140916, 2024.

S. Gupta *et al.*, "Experimental, spectroscopic, and theoretical investigation on structural and anticancer activities of Schiff bases derived from isonicotinohydrazide," *J Mol Struct*, vol. 1293, p. 136212, 2023.

R. S. K. Sachan *et al.*, "Overcoming Mycobacterium tuberculosis drug resistance: novel medications and repositioning strategies," *ACS Omega*, vol. 8, no. 36, pp. 32244–32257, 2023.

H. Sahebalzamani, N. Khaligh, S. Ghammamy, F. Salimi, and K. Mehrani, "Crystal structure and density functional theory study on structural properties and energies of an isonicotinohydrazide compound," *Molecules*, vol. 16, no. 9, pp. 7715–7724, 2011.

J. Parekh, P. Inamdhar, R. Nair, S. Baluja, and S. Chanda, "Synthesis and antibacterial activity of some Schiff bases derived from 4-aminobenzoic acid," *Journal of the Serbian Chemical Society*, vol. 70, no. 10, pp. 1155–1162, 2005.

M. I. Choudhary *et al.*, "Substituted benzenediol Schiff bases as promising new anti-glycation agents," *J Enzyme Inhib Med Chem*, vol. 26, no. 1, pp. 98–103, 2011.