

Synthesis and Biological Evaluation of Novel Schiff Base Derivatives

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Abstract In the field of medicinal chemistry, Schiff base derivatives are essential class of organic compounds because of its interesting structural flexibility, easy of synthesis and a variety of biological activities due to presence of imine or its derivatives which consists of characteristic C=N group in their molecules due to which such compounds possess strong electro donating power, hydrogen bond acceptability (in its neutral state) and can undergo metal coordination or interact with specific active site of the biological targets; these molecules attracted much attention from researchers working on medicinal field due to well-known antimicrobial, anticancer, antioxidant, anti-inflammatory, antiviral, enzyme inhibitory activities attributed from them and these compounds are found to be effective scaffolds for development of new drugs; however the rise in multidrug resistance development, some drawbacks of the available drugs, undesirable side effects and lack of efficacy may be due to decreased activity have been established, thus it becomes indispensable task to search new molecules with higher potential and better therapeutic properties and also due to constant requirement of new drug molecules, there has been an urge to identify novel pharmacologically active molecules with advanced benefits. Therefore, in this article a conceptual research is discussed concerning design, synthesis, characterization and biological assessment of Schiff base derivatives, based on rationally planned modification of the aldehyde and primary amine which may lead to diverse structures of imine containing molecules for designing novel chemical entities with possible pharmaceutical relevance; a synthetic strategy was designed on basis of condensation reactions among preselected aldehyde and amines followed by functional modification of resultant compound so as to achieve the desired property modification. Spectroscopic method such as FTIR, ¹H, ¹³C NMR and Mass Spectroscopy are conceptually included to characterize the compounds developed which are formed on the modification and thus will confirm presence of the functional group, structural features of the molecules and their molecular mass and weight. Computational molecular docking and ADMET study are then proposed to study behavior with biologically relevant molecules and thus predicts how the molecules behave when dosed as drug candidates through prediction

of molecular parameters and properties. Some of the biological activity screening like antibacterial, antifungal, anticancer, antioxidant, anti-inflammatory studies are theoretically planned which would help us to estimate some relation between structure activity. The anticipated outcome of this study would be the identification of compounds of the present class of Schiff base derivatives to serve as lead candidates for new drugs and exploration of the structure activity relations and designs.

Keywords: Schiff bases, Imine compounds, Condensation reaction, Medicinal chemistry, antimicrobial activity, Anticancer activity, Structure–activity relationship, Organic synthesis

I. INTRODUCTION AND BACKGROUND RELATED TO THE STUDY

Schiff base chemistry is an important area of organic and medicinal chemistry that has been thoroughly investigated due to unique structural characteristics, synthetic flexibility, and wide biological importance. Schiff bases are organic compounds defined by the C=N (imine) double bond functional group which arises from the reaction between primary amines and carbonyls (aldehydes or ketones). This type of compound was first described by Hugo Schiff in 1864 and originally believed to be simple condensation products. Now they are regarded as sophisticated building blocks with many potential applications ranging from materials science and coordination chemistry to catalysis and the medicinal world (Schiff, 1864; da Silva et al., 2011). Schiff base synthesis occurs via the nucleophilic addition of an amine N atom with the carbonyl C atom, and then the elimination of H₂O. This allows an imine functional group (C=N) to be formed; this unique property gives Schiff bases electronic features, and excellent conjugation properties and allows them to interact differently with biological components. Their inherent and highly tune able structural modification opportunities offer a means for researchers to develop

structures with improved drug-like and potent biological properties. The N, O, and S donor atoms on many Schiff bases attract a great deal of interest from scientist as these make it possible to interact and complexate with metal species as well as participating in hydrogen bonding as well as potentially interacting with enzymes, receptors, and cell components. Derivatives of Schiff base have received significant attention in the development of novel medicines due to their reported antimicrobial activity, activity against cancer, antioxidants, anti-inflammatory effects, anti-viral activity and inhibitory effects on enzymes and varied activities are known due to varying degrees of influence and binding in relation to specific components. This can be increased by modification and varying substitution to the various regions of the molecule to allow optimisation. Biological activity of various kinds has also been established against a plethora of applications; their antimicrobial and anticancer properties have been attributed to the ability of the Schiff bases to act as inhibitory entities on the enzymes found within a microorganism or cell. Cell membrane permeabilization, inhibition of protein, and DNA synthesis are other potential mechanisms of antibacterial and anticancer activity respectively. Furthermore, the electron withdrawing or donating nature that different substituent groups give to the Schiff base, has been cited as an ideal reason for an increase in or decrease of the Lipophilicity and or solubility of each variation. Such features in drug molecules are critical for efficient distribution around the body, and increase of activity of drugs etc, etc, however their relatively easy synthesis. The continued search for novel drugs is in some part driven by increased drug resistance, the complexity of some diseases and a general lack of 'lead' molecules to carry forward for future medicinal research. While therapeutic treatments have been a major focus within medicinal chemistry, an increasing drug resistance has also made it of paramount importance to develop novel bioactive molecules that not only have high efficacy but are also safe. Modern medicinal chemistry requires the creation of compounds that have good physicochemical properties, strong potency and specificity towards their target molecule, and high biological availability, and indeed modern science aims to produce better results over time and now this may be achieved with lead compounds created via organic synthesis and developed into a new, efficient

drugs. Therefore, the design, synthesis and the examination of novel Schiff base derivatives could have considerable application as potential pharmaceutical lead candidates.

II. IMPORTANCE OF SCHIFF BASES IN MEDICINAL CHEMISTRY

The significance of Schiff bases in medicinal chemistry has evolved tremendously since Hugo Schiff's observation in 1864 when imine compounds, synthesized via a condensation reaction of an aldehyde or ketone and a primary amine were synthesized thus forming a new family of biologically active nitrogen-containing organic molecules with characteristic structure and properties; what appeared to be simple products in those initial years soon assumed greater significance in a variety of fields of chemistry, and now Schiff bases are considered highly effective multi-functional molecular scaffolds because of ease of their synthesis, electrical and functional properties and varying biological and chemical activities which may be easily modified by changing aldehyde and amine components (Schiff, 1864; Patai, 1970); azomethine C=N moiety lends chemical characteristics such as conjugation, conjugation, electron conjugation, ability to participate in hydrogen bonding and act as a coordinating group and thus act as sites for chemical interactions with biological systems and metal ions enabling it gain importance beyond ordinary simple organic chemistry, and find relevance as pharmaceutical molecules and building blocks; coordination chemistry especially with transition metals is one area where Schiff bases are actively studied as diverse range of derivatives containing oxygen, sulfur, and nitrogen atoms can form stable metal complexes that show enhancement in biologically active properties such as biological, antimicrobial, anticancer, antioxidative and anti-inflammatory attributes by controlling activities of important enzymes and their resultant complexation can improve efficacy of a particular drug; thus these coordination traits have resulted in vast investigation as well as potential therapeutic agents and functional materials (Przybylski et al., 2009); Medicinal applications of Schiff base derivatives are also gaining increased interest and these compounds have demonstrated a wide array of biological activities such as their action against microbes that involves

inhibition of crucial microbial enzymes and destruction of biological cellular components through DNA binding (DNA, protein interactions), controlling inflammation mediated by control of release and activity of inflammatory mediators and anticancer activity via control over oxidative stress and initiation.

III. AIM OF THE STUDY

The present conceptual work focuses on development of an appropriate research framework, to design, synthesize, structurally elucidate and biologically evaluate new Schiff bases derivatives as lead drug molecules by means of incorporating all three major sub disciplines like organic synthesis, medicinal chemistry, spectroscopy and as well as computational as well as a pharmacological study; more emphasis will be laid on building diversity based imine contain compounds by strategic choice of suitable aldehyde and primary amines antecedents to develop molecules with enhanced biological activity, chemical stability and possible therapeutic utility (da Silva et al., 2011); concept of structure activity relationship will be utilized, to explore the link between molecular structure and biological activity by using structure-activity relationship concepts while focusing on how functional group modification affects their antimicrobial, anti-cancer, antioxidant and anti-inflammatory potential; another aspect to be focused in this article will be to optimize proper strategy to synthesis Schiff bases by means of condensation reaction, and these compounds will be structurally characterized through powerful techniques such as FTIR, NMR and MASS spectral studies; finally these compound will be computationally evaluated and predicted by carrying out molecular docking and ADMET prediction to gain initial insight into biological interaction, pharmacological potential and drug like properties of synthesized compounds before they have been synthesized; I strongly believe that this research article will contribute significant knowledge towards the identification of new Schiff bases based bioactive entities and lay a clear vision and strategy to the future drug design research.

IV. RESEARCH OBJECTIVES

1. To design novel Schiff base structures.

2. To propose synthetic pathways for derivative formation.
3. To evaluate structural properties using analytical methods.
4. To investigate predicted biological activities.
5. To establish structure–activity relationships.

V. LITERATURE REVIEW

Their structural features and chemical nature of Schiff bases (SBs) are essentially defined by the presence of the imine functional group ($C=N$), which are structurally crucial for their specific electronic, conformational and biological characteristics. SBs generally are formed by condensation reaction of an appropriate carbonyl group with primary amine leading to molecular structure containing carbon-nitrogen double bond, which possesses remarkable molecular stability and conjugation, (Patai, 1970). The planarity of the imine moiety derived from sp^2 hybrid state on carbon and nitrogen atoms favors efficient overlap of atomic or molecular orbitals providing extension of conjugation to adjoining heterocyclic or aromatic fragments, in the plane containing double bond in imine functionality, influences rigidity of the molecule and thus their interaction with biological target molecules. The electron delocalization over the imine structure results in efficient electron communication, impacting the molecule in aspects such as color properties, chemical reactivity, antioxidant action and formation of chelates with metal ions. (da Silva et al., 2011). The presence of available donor atoms such as O, S, or N in the structure of the SBs make them good potential coordinating molecules to the transition metals. Formation of metal chelates leads to change in Physicochemical properties and enhances bioactivity. Structural modifications can be readily implemented due to the flexibility of SB framework in forming conjugates with selected therapeutic targets like biomolecules and their binding and interacting capability with their corresponding target at various possible mechanisms. (Przybylski et al., 2009).

VI. CLASSIFICATION OF SCHIFF BASE DERIVATIVES

A classification for derivatives of Schiff bases can be proposed according to the structural nature of their carbonyl and amine precursor moieties; changes in aldehyde and amine constitution may affect the

derivative's electronic behavior, its chemical activity, its coordinated capacities and also its biological activity. Classified according to the aldehyde source, one usually find a sub classification of aromatic aldehyde Schiff bases and heterocyclic aldehyde Schiff bases; aromatic aldehyde-derived structures that incorporates benzene or some substituted aromatic ring structures present higher stability since the effect is attributed to the electronic delocalization and been studied for activity as antimicrobial, antioxidant, anti-carcinogenic and enzyme inhibition agents (da Silva et al., 2011); the application of heterocyclic aldehyde Schiff bases which have ring structures including at least one heteroatom such as nitrogen, oxygen and/or sulphur offers added biological actionability in terms of hydrophilicity as well as ability to participate to the formation of hydrogen bonds, increasing thereby their potentiality as building structures in drug design (Przybylski et al., 2009); on the basis of the amine used, one can generally distinguishes aniline derived Schiff bases, amino acid derived Schiff bases, and hydrazine derived Schiff bases; aniline derived-derivatives consist in aromatic nitrogen-containing framework with an electron rich structure, they are therefore good candidates for activity screening; amino acid based Schiff bases are imine functionalities conjugated with biologically relevant molecular fragment and hydrazine derivatives represent Schiff bases that have the capability to acquire an extra-N donating center that will increase their metal-binding aptitude as well as their biological possibilities. In view of the great variation of both functional groups, it seems logical that this approach could lead to the formation of the widest range of structures, allowing us to correlate their structures with their functions by establishing structure-activity relationships.

VII. BIOLOGICAL ACTIVITIES OF SCHIFF BASE COMPOUNDS

The wide range of biological activities observed in Schiff base compounds of medicinally significance is attributed to some distinctive features such as the compound structure, distribution of electron density, chelation of metals, as well as interactions with the biological targets; among all pharmacological properties demonstrated for the Schiff base derivatives, antimicrobial activity has been widely explored. Schiff

base derivatives have displayed inhibitory activity against wide variety of bacteria and fungi; possible modes of action by Schiff base derivatives on microbial species include cell membranes disruption, inhibition of crucial enzymes or pathways within cells, interference with cellular process or modification on nuclear acids functions (da Silva et al., 2011). In order to confirm biological screened compounds for their potential antimicrobial agents, the derivatives with potential effectiveness upon microbial strains were further investigated against various bacterial and fungi strains; typical biological screening methods were used to investigate preliminary effects upon microbial strain viability; they included agar diffusion assay for checking the inhibition of microbial strain and minimum inhibitory concentration (MIC) assay for determining quantitatively, the lowest concentration of derivative to inhibit visible microbial growth, that shows significant information's for the activity of bacterial and fungal effect (da Silva et al., 2011). Schiff base derivatives have been of great interest as potential anticancer agent since interactions with cellular components, balance of cellular oxidative status and macromolecules were regulated through binding onto biological macromolecules to modulate the mechanisms responsible of cell cycle control, proliferation, survival and apoptotic death (Przybylski et al., 2009); cell viability assay, cytotoxicity, and apoptosis investigation were routinely used to explore the anticancer capability of newly designed Schiff bases. Besides antimicrobial and anticancer agents, researches explored the potent antioxidant property in derivatives, such as conjugated structure, with electron-donating substituents has favored the stability toward free radical, to a level that may allow an adequate regulation on reactive oxygen species (ROS). The evaluation of potential antioxidant agents was based on chemical analysis, such as DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay and ABTS (2,2-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)) assay (ds Silva et al., 2011). The analysis show that they are able to neutralize the stable free radicals by diverse ways. These studies suggest that Schiff bases, as a class of compounds, play a fundamental role as lead structures in discovering potential pharmaceuticals via structure modification coupled with biological screening and SAR analysis.

VIII. SYNTHETIC METHOD RELATED TO THE STUDY

It has been based on an easily and classical condensation reaction between carbonyl compounds of aldehyde/ketones and primary amines, which is considered one of the most widely used methods in the field of organic and medicinal chemistry to construct imine based molecules due to it involves nucleophilic addition of the nitrogen atom of primary amine to the electrophilic carbon of the carbonyl group and subsequently dehydration to obtain C=Nazomethine link by water liberation (Patai, 1970). In general of this synthesis, aromatic/heterocyclic aldehydes react with selected primary amines to yield the corresponding Schiff bases including different structural fragments, that can be further utilized for further biological study; It must be concerned that reaction mechanism on the Schiff base formation can be affected by some factors such as electronic nature of substituents on aldehyde and amine components, reactional medium polarity, reactional temperature, reaction time, removal of water generated during the reaction etc; and consequently product's yield, stability and purification depend on them as reported in the literature (da Silva et al., 2011). Traditionally, reaction was carried out in polar protic solvents such as Ethanol or Methanol as they maintain good reactional environment, provide good solubility for many reagents, and also make the isolation of crystalline products possible. Often refluxing the reaction mixture at temperature below the boiling point enhances better interactions within molecule in reaction and increasing condensation rate, while weak acidic catalysis might be introduced to strengthen activation on the carbonyl moiety to attain high reaction rates as recommended, provided that no side-reactions or sensitive functionalities present in molecules were susceptible to such catalytic condition and degradation; The conceivable scheme of substituted Schiff bases synthesis can be achieved through the condensation reaction of aromatic aldehydes bearing an electron withdrawing or electron donating substituent(s) with substituted aromatic primary amines, heterocyclic primary amines, hydrazides or even amino acid components, giving in this way diversified imines. The suggested condensation based synthetic route would be useful for an efficient, straightforward, flexible and cost-

effective preparation of novel Schiff bases for biological activities including antioxidant, antibacterial and anticancer activity and some pharmaceutical effects.

IX. GREEN SYNTHETIC APPROACHES

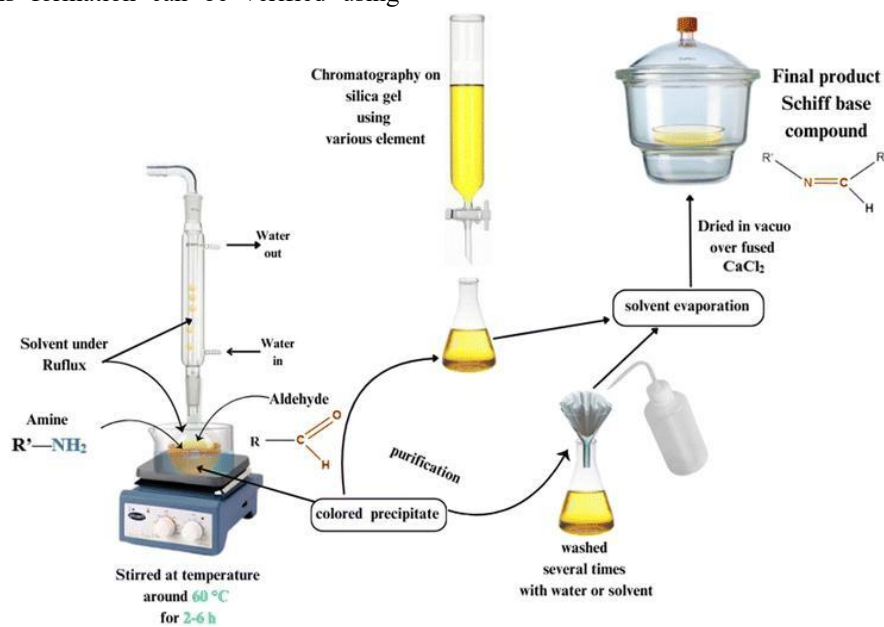
Among the synthesis strategies of various types of Schiff base derivatives (see Scheme1), the application of green synthetic methodologies is a key contribution in medicinal organic chemistry, in which this synthetic approaches is directed toward the enhancement of overall reaction efficiency and environmental considerations as well as a safer chemical transformations compare with conventionally organic synthetic method on use of great sum of organic solvent and huge energy needed during the reaction; solvent-free synthesis is a desirable green chemical approach since organic solvent has been eliminated, therefore reduces the volume of chemical waste generation and safety concerns and increase a sustainable characteristic in the condensation reaction that is applied on Schiff base formation, although there is an optional usage with minimum amount of organic solvent as media for the reaction or support phase (Anastas & Warner, 1998); microwave assisted synthesis that offers a fast and homogeneous heating, increase the rate of a reaction, raise the efficiency in product yield as well as reduce an enormous amount of energy are often used for synthesis process of the imine containing and other medicinally organic compounds since reaction condition are easier tunable compared with thermal assisted heating(Kappe, 2004); alternatively, ultrasound assistance strategy could significantly increase mass transfer, molecular mixing and rate kinetic under milder conditions due to generation of acoustic cavitation in the mixture which could increase effective inorganic organic transformation efficiency in many reaction under reduced time and better conditions (Suslick, 1998) and use of renewable and earth-preferable solvents like water, bio-based solvent, ethanol and other green solvent to replace hazardous organic solvent without significantly decline product yield has potential advantage to provide more efficiency to lab and industrial process and safer lab condition (Clark, 2018). This green approach is appropriate on synthesis process of Schiff base since the condensation reaction toward the formation of the azomethine functionality

(Scheme 1) could be adapted in the different conditions or environment. Consequently, green synthetic approach on the field research of Schiff base can be benefit for less waste, fast reaction time, efficient energy transformation, safety of reaction and even suit for industrially drug synthesis approach and novel Schiff base derivative.

X. DISCUSSION RELATED TO THE STUDY

The conceptualization to synthesize novel derivatives of Schiff bases provides a suitable model to understand that how the rational design, synthesis procedures, structural characterization and the biological evaluations may lead to potential drug candidates whereby the synthesis of the Schiff base derivatives could proceed through the efficient condensations reaction between judiciously selected substituted aromatic aldehyde (such as salicylaldehyde etc. If desired with substitution) and specific aromatic primary amine (where primary amine contains appropriate functional groups for enhancing various properties and is desired by design); which will yield fairly stable imines (azomethine molecules) featuring the presence of C=N functional group (as shown below). The formation of imine becomes a necessary step towards researches on Schiff base compounds since structural verification is required to ensure whether the designed molecule has successfully been formed; and this formation can be verified using

complementary analytical methods such as Fourier transform infrared (FTIR) spectroscopy, nuclear magnetic resonance (NMR) spectroscopy and Mass Spectrometry (MS) since these methods yield the information on functional groups, electronic structure, the atoms and molecule respectively, about it (Patai, 1970). Appearance of the appropriate imine stretching vibration (around 1600-1700cm⁻¹), presence of characteristic peaks for the imine proton and carbon atoms in NMR spectra, appearance of molecule ion peaks in MS spectroscopy etc. Confirms the structure, and thus development to the specific derivative. Evaluation of their biological activities following structural verification of Schiff bases allows screening to be carried out for identifying lead compounds, while systematic investigation has shown these compounds to possess several beneficial activities, such as antimicrobial, anticancer, antioxidant, and anti-inflammatory properties, depending on appropriate systemic evaluation (da Silva et al., 2011). The biological activity is found to be directly proportional to the structure of molecule and therefore various groups on the molecule could influence a property of its activity. Structure-activity relationship is important because researchers can analyze and quantify what modifications and specific features will improve potency, target selection and therapy profile (Przybylski et al., 2009).



Above image showing Synthesis and Biological Evaluation of Novel Schiff Base Derivatives

XI. SIGNIFICANCE OF THE STUDY

The study has importance due to scientific, pharmaceutical and Industrial relevance as it presents a conceptual guideline that enhances investigation and synthesis of imine based molecular systems with useful bio-active properties; Scientifically, the study contributes towards the progression of Schiff bases chemistry by investigating structural variation, synthetic strategies for modification and dependence of chemical and biological activities on molecular architecture thereby offering greater insight to rational molecular design as well as structure activity relationship in the designing of medicinal agent (da Silva et al., 2011); Different architectures derived from an aldehyde and an amine contribute to the understanding of the role of functionalization, electronic properties and interaction of molecules on the chemical reactivity of Schiff base compounds; Pharmaceutically the study serves to offer potential drug candidates by testing different novel derivatives in terms of antimicrobial, anti-cancer, anti-oxidant activity and etc that aid in the discovery of the next generation of therapeutic agents that may offer promising lead structures against the shortcomings found in drugs and the ever existing new health threat (Przybylski et al., 2009); Industry is positively impacted due to the fact that schiff base chemistry research benefits drug discovery, production process in the pharmaceutical manufacturing and development of medicinally valuable molecules as candidate molecules of lead drugs in further research, hence systematic investigation on its derivatives in synthesis, characterization, computational analysis and biological assessment will make headway research activities in medicinal chemistry coupled with advancement of new pharmaceutical technologies.

XII. LIMITATIONS OF THE STUDY

Despite their potential as ideal molecular templates for drug discovery purposes, Schiff base derivatives also have limitations that have to be kept in mind throughout development and investigation, as the proposed biological activities based on theoretical methods of Structural activity relationships analysis, computational approaches and molecule modeling still needed further validation in the wet lab and confirmation before being used as drug candidates. With applications in the area, computational approaches such as molecular docking and activity

prediction can render important preliminary results on target binding and the likely biological activity, although its complexity, metabolic effects and interaction with its cellular components cannot be fully simulated with laboratory-based methods (Sliwoski et al., 2014); hence appropriate biological activity investigation like antimicrobial, anticancer, antioxidant and so on is crucial to assess and reconfirm those properties with suitable laboratory investigations of appropriate models. Apart from these, toxicity evaluation is also important, since activity of a drug does not necessarily mean safe drug; this involves investigation in cytotoxic property, pharmacokinetic study and potential unwanted side effects. It has also been highlighted that some Schiff bases are limited on scale-up work from lab procedures to industrial production, since issues pertaining to reaction mechanism, scale-up potential of the method of preparation of the Schiff base, sourcing of Raw Materials, efficiency of the procedure, cost and quality control of the product when synthesized on a large scale could be significant problems. The difference in standard laboratory environment as compared to actual manufacturing environment may also impact the quality, quantity and feasibility as well in the production, therefore a thorough study from theoretical conceptualization and initial screening to experimental validation and scale-up strategy planning are required if these are to serve as drugs candidate in an industrially viable process.

XIII. CONCLUSION

Schiff base derivatives continue to represent important molecular scaffolds in medicinal chemistry because their versatile structural characteristics, synthetic accessibility, and diverse biological properties provide valuable opportunities for the discovery of novel therapeutic agents; the conceptual study entitled "Synthesis and Biological Evaluation of Novel Schiff Base Derivatives" highlights the significance of rational molecular design and structural modification strategies in generating improved bioactive compounds with enhanced pharmacological potential, where variations in aldehyde and amine components allow optimization of electronic properties, molecular interactions, and biological responses (da Silva et al., 2011); the systematic synthesis of Schiff base frameworks combined with advanced characterization techniques such as infrared spectroscopy, nuclear

magnetic resonance analysis, and mass spectrometry enables accurate structural confirmation and provides essential information for understanding molecular behaviour; furthermore, integration of computational chemistry approaches including molecular docking, drug-likeness prediction, and biological modelling with experimental evaluation strategies creates an effective multidisciplinary platform for identifying promising lead molecules and improving structure–activity relationships (Sliwoski et al., 2014); biological investigation of these derivatives through antimicrobial, anticancer, antioxidant, and other pharmacological assessments further supports their potential contribution to pharmaceutical development; therefore, the combined application of organic synthesis, spectroscopy, computational analysis, and biological sciences represents a powerful drug discovery strategy that can accelerate the identification of safer and more effective Schiff base-based therapeutic candidates while expanding knowledge in medicinal chemistry and molecular design.

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